National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Problems of Drug Dependence, 1992: Proceeding of the 54th Annual Scientific Meeting

The College on Problems of Drug Dependence, Inc.

132

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • National Institutes of Health

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Editor:

Louis Harris, Ph.D.

Research Monograph 132
1993

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

ACKNOWLEDGMENT

The College on Problems of Drug Dependence, Inc., an independent, nonprofit organization, conducts drug testing and evaluations for academic institutions, government and industry. This monograph is based on papers or presentations from the 54th Annual Scientific Meeting of CPDD, held in Keystone, Colorado in June 1992. In the interest of rapid dissemination, it is published by the National Institute on Drug Abuse in its Research Monograph series as reviewed and submitted by the CPDD. Dr. Louis S. Harris, editor of this monograph, is Professor of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth.

National Institute on Drug Abuse
NIH Publication No. 93-3505
Printed 1993

NIDA Research Monographs are indexed in the Index Medicus. They are selectively induced in the coverage of *American Statistics Index, BioSciences Information Service, Chemical Abstract, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.*

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The following organizations have generously supported the work of the College on Problems of Drug Dependence during the past year:

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POSTER SESSION I

OPENING REMARKS TO THE 54TH SCIENTIFIC MEETING OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE

K. F. Killam, Jr.

I bid you welcome to the 54th Annual Scientific Meeting of CPDD. This is a very special occasion in as much as it is the first under the auspices of the College and it is a joint meeting with INRC - the International Narcotics Research Conference. Drs. Mary Jeanne Kreek and Martin W. Adler of CPDD joined with Drs. Huda Akil and Alan North to put together the program.

The program melds the interests of the two groups on Tuesday and Wednesday. The special interest of CPDD and its constituents are organized for the early part of the week, and those of INRC for the latter part of the week.

For the College, this year has represented a year of "bootstrapping". The conversion of the committee formatted organization to an open membership college is well underway. The Charter Fellows have been contacted with an excellent response. The Charter Fellows include those persons who have previously served on the Committee or who have been recipients of the Nathan B. Eddy Award. Those contacted are listed in the current issue of Newsline and are posted in a list at the registration desk. This is important information for those of you interested in joining the College in as much as the Charter Fellows serve as the initial conduit to build the body of the College. I join with the Charter Fellows in encouraging and welcoming you for membership.

The program of collaborative outreach to Eastern European countries, under the leadership of Dr. Arthur Falek of CPDD and Dr. W. Lindblad of NIDA, is progressing toward a meeting in Hungary during the next year. In addition, the program is supporting six visiting scientists at this meeting: Drs. J. Rasz, H. Furgen-Baren, L. Csemy, O. Burda, A. Borsodi and M. Krsiak. A warm welcome is extended on behalf of the College.

Beginning this year, CPDD is formalizing a program to encourage the entrance of under-represented groups into the field of substance abuse research and clinical service. A committee, co-chaired by Drs. Jack Henningfield and Lawrence Brown, will be taking the lead in formulating the program in this very important area.

In the policy and political arena, the College has been very active. As should be expected, with the compromise format of the process - successes are tempered with non-successes. Dr. William L. Dewey and Dr. Louis S. Harris have carried the heavy load. The College and the field owe them a great deal of gratitude for their effort. Dr. Dewey has taken the lead with respect to formulating and espousing the needs of the field. Dr. Harris has taken the lead in presenting appropriate positions in the delicate matter of the possible reorganization of ADAMHA and NIH. The College's positions on both matters have been advisory as to the structures and supports needed to consolidate the real progress and to go forward in all aspects of substance abuse.

I would now like to recognize the contributions to the Committee and College of the following retirees from the Board of Directors: Loretta Finnegan; Louis Harris; Donald Jasinski; James Kulikowski; Jack Mendelson; Kenner Rice; Eric Simon and E. Leong Way.

As the retiring President, my personal thanks go to Dr. Martin W. Adler and his staff - Marie Brown and Ellen Geller. It simply would not get done without them. In addition special kudos go to Marilyn Waranch for her devotion and imagination. Finally, thanks go to Fred Graefe who made some impossible things possible.

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TECHNOLOGY TRANSFER: KNOWLEDGE FOR HELPING

E. M. JOHNSON

Thank you and good morning! It is a special pleasure to have the opportunity of addressing this meeting of the College on Problems of Drug Dependence. I feel that I know many of you from my years in NIDA and as the Director of the Office for Substance Abuse Prevention.

I come before you today in my role as the Acting Administrator of ADAMHA and want to share with you my observations from that perspective. I will bring to you a concern that has evolved over the years that I might not otherwise share, were it not for the fact that I know of your dedication to research and to its application.

I have an enormous appreciation of the significant contributions that the research community has made, and is making, to the advancement of knowledge in the addictions. You have given us new insights into fundamental questions about how the brain works and the etiology of disorders.

The area of applied science has brought us new medications and new understandings of interventions on an individual, group and community level---to name just a very few of the enormous range of contributions that have been made.

The current level of excitement in the research community portends the promise of continued accomplishments. But what are we to do with this knowledge?

It is increasingly evident that a gap exists in the transfer of knowledge from laboratories and academic settings into the communities where problems exist and need to be addressed. Likewise the research community has been slow to embrace some of the more complex social problems that do not lend themselves to the usual research methodologies.

While such global statements are risky to make, I make them more as a challenge to the entire public health field than as an indictment of the College. How can we find the means to improve technology transfer, and the translation of community problems into research agendas?

We must find ways to improve information dissemination. How can we devise the means to carry out research and facilitate the dissemination of what is learned in the most rapid and effective means possible so that the practitioner can understand and incorporate findings?

Can new methodologies or approaches to research be developed? Can new partnerships for research be developed? Can prevention research find its place in the current climate of emphases on molecular biology? The fact of the matter is that I am optimistic about all of these possibilities.

As the Acting Administrator of ADAMHA and as an individual who has gained over the past 20 years a broad perspective on the activities of the NIMH, NIDA, and OSAP from having worked in those agencies, I see some creative opportunities to stimulate the very types of interchange and development that I am suggesting.

Why do we need to do this? From the ADAMHA perspective, it is evident that the problems we face today require an appreciation of the complexity of the interactions in communities that cannot be duplicated in laboratory settings.

Research findings need to be applicable to the problems as they are seen in the community---whether it be in the area of preventing HIV transmission, the curbing of youth violence, or decreasing the victimization of children and women. All of these problems, as you know, are often associated with substance use and abuse.

The extensive knowledge development that has come from the work of the NIMH, NIDA, and NIAAA has furthered our understanding of risk factors, protective factors, individual differences, and mediating factors. However, when we are faced with dealing with violence in communities or gaining compliance with treatment for HIV-infected substance abusers, we are less than successful. These types of frustrating problems must be addressed or we run the risk of having our most valuable contributions invalidated.

Too often we are not passing the test---"What works?" Increasingly, it is this test that must be passed in order to secure funding in both the Federal and non-Federal arenas.

An additional challenge from the ADAMHA perspective, and I believe also from my knowledge of the foundation perspective, is the increasing sense that research in the areas in which we are concerned must be tied to interventions.

The development of research programs in substance abuse that relate to prevention, in the absence of intervention, are harder to justify in this very difficult fiscal climate. This does not mean that prevention is any less important---far from it.

As many of you know I have been a staunch supporter of prevention research and prevention efforts in general, but the "What works" criteria forces us into translating more theoretical constructs to real life settings. Shifts in dollars over the past few years have underscored this trend.

I have been heartened by the recent recognition on the part of the public health service that, when it comes to complex medical problems with a significant behavioral component, ADAMHA is recognized for its capabilities of mounting programs that can be effective.

Most recently we have been given responsibility for pursuing a major increase in efforts to reach HIV-infected injecting substance abusers and their partners.

This initiative is made possible by the demonstrated capability of drug treatment programs to reach and retain injecting drug users. This provides a means to build a program that will demonstrate potentially more effective means for accomplishing HIV testing, counselling, and the involvement of partners who may be at risk.

This initiative would not be possible if the research community had not worked on the means for enhancing drug treatment. The future holds even more promise with the

development of new medications for drug treatment, additional strategies for relapse prevention, and a refinement of our diagnostic capabilities.

Similarly, in the area of violence, the significant contributions in the understanding of risk factors and protective factors will allow ADAMHA programs to play a significant role in the development of new initiatives to address violence in the community. An example of an already operative aspect of this approach is in the High-risk Youth Demonstration Grant Program of OSAP.

This increasingly sophisticated program now actively seeks to infuse its programs with the latest research on the contribution of conduct disorder and substance abuse to the evolution and support of violence and to attempt to understand the ways in which to prevent it.

For example, the community, as a laboratory, shows us that church, schools, the family, and peers all can influence outcome in those viewed as being most at risk. We have much to learn.

The future holds great promise for basic research on brain functioning to pinpoint ever more precisely predisposing conditions that might be remediated in newer ways through behavioral techniques, medications or the manipulation of environments.

Demonstration programs have for the longest time supported evaluation as a key means for ascertaining what works. Sophisticated evaluation that takes into account the determination of proper and complete baseline data and has appropriate measures can advance our understanding of what works.

Many individuals with research interests have become involved in the evaluation efforts supported by the OSAP and OTI demonstration grant programs. The support offered for the evaluation of these programs has often laid the groundwork for further research or helped to answer questions about the applicability of techniques developed in other areas of investigation.

This is a legitimate use of the substantial financial resources devoted to the evaluation of ADAMHA programs. I invite you to participate in these activities. Increasingly, though, we are needing to find additional strategies.

While we have made strides in knowledge development in community settings and identified strategies that may hold promise for integrating research and services, we must also look at additional research strategies for answering that ever critical question of "What works."

The concept to be embraced in this endeavor is not new; we are in fact going back to the 1940's and the concept of "action research." Action research for those of you too young to remember is an interactive partnership between practitioners and researchers---information sharing to help improve the effectiveness of social programs.

By soliciting the participation of those individuals served by the program, researchers and community members work together to develop evaluation mechanisms, provide feedback, and disseminate gathered information. Multi-disciplinary in its approach, action research "plants the seeds" for systemic change in the incidence/prevalence of alcoholism, drug abuse, and mental illness.

ADAMHA has begun to use action research in the evaluation of its ADM prevention and treatment programs. In OSAP's National Training System (NTS) evaluation, an action research approach has been adopted. During the evaluation, target groups participate in event monitoring/tracking, outcome/impact analysis, and feedback analysis.

Evaluation results, and the input of those served, are then used to revise the content of trainings; the types of training and technical assistance offered; and the delivery of services. A primary intent of the national training system evaluation is to enable service recipients and other community representatives to understand the options/strategies available to them and to respond to the issues being faced.

Instead of simply asking if the program has achieved some desired impact, the NTS evaluation attempts to answer a dual-fold question: how does the training and/or technical assistance enable/affect the actions of the recipient? And how does the recipient's actions impact upon the community? An action research model will also be used to evaluate our new HIV prevention/intervention initiative.

This action research approach is also being used for OTI's Campus Treatment Demonstration Programs. The term "campus" means a setting where several providers, sharing certain common resources (such as intake and assessment, medical services, drug testing, etc.), deliver residential treatment services for drug abuse. The campus model presents researchers with a unique opportunity, that of being able to study five different treatment models under one "roof."

Its goals include evaluating the efficacy and efficiency of alternative approaches to treatment using scientifically valid methods of comparison; determining whether increased medical and psychological services can increase retention in residential treatment; and providing an effective approach to the provision of medical services to HIV-positive addicts, pregnant women, and female addicts with children.

The attainment of these goals will be measured through an evaluation that is being conducted by NIDA. A series of interrelated studies will be used to evaluate the campus projects and will be designed to test hypotheses related to self-selection bias, retention and dropout, duration of treatment, and impact of shared facilities and services. In the latter stages of the project, NIDA plans to test specific treatment delivery models comparing different approaches to residential treatment.

What of the future for research within ADAMHA, especially as it relates to the multi-faceted problem of substance abuse? As many of you know, reorganization of ADAMHA is being considered by Congress.

As presently conceived, the reorganization would see the NIMH, NIDA, and NIAAA move to NIH as three intact individual entities, with the substantial portions of their research portfolios. The institutes would retain the authorities necessary to continue their research, and, for a period of four years, would be allowed to use their existing peer review and advisory council systems.

Concomitantly, the merging of NIMH, NIDA, and/or NIAAA with each other or with any other NIH institute would be prohibited for a period of 5 years. Each institute would retain its direct budget authority and be required to spend at least 15 percent of its research funds on services-related research.

In addition, the pending legislation would create an Associate Director for Prevention in each of the three institutes, and an Office of AIDS at NIDA and NIMH. NIDA would also be given a new authority with an appropriation of $85 million in fiscal year 1993 for medications development.

Further, the reorganization would enhance services delivery and strengthen federal government leadership in the ADM service area. The new agency would be named SAMHSA---Substance Abuse Mental Health Services Administration. And while this new agency would have a focus on services development, it will both have a mandate and a commitment to the support and integration of research into those initiatives. SAMHSA will foster and maintain strong linkages to the institutes and develop the needed mechanisms for technology transfer.

The same mechanisms that have existed in the past for collaboration in the funding of programs having relevance for service, such as the NIMH prevention of conduct disorder research that has been partially supported by OSAP, can be supported by SAMHSA. The findings from that research can be incorporated into the clinical programs supported by the new agency.

The same is certainly true of the very relevant research in medications development, risk factor identification, epidemiology, and general psychosocial research that is supported by the institutes.

Likewise, the clinical programs of SAMHSA can provide the community "laboratory" for the institutes to test their findings in real life settings. Hopefully, SAMHSA will stimulate the institutes and other science organizations to explore new clinically relevant questions. Every effort will be made to coordinate the programs of SAMHSA and the institutes.

In addition to the reorganization of the agency, ADAMHA's reauthorization legislation requires several studies to be carried out. These include:

1. An Institute of Medicine (IOM) study on the role of the private sector in medications development;

2. An NIMH study to examine barriers to insurance coverage of mental illness and substance abuse;

3. A Center for Mental Health Services study to evaluate the most effective ways to provide mental health services in correctional facilities;

4. A study by the Secretary of DHHS on the prevalence of fetal alcohol syndrome and fetal alcohol effects in the U.S.;

5. A National Academy of Sciences study on the effectiveness of distribution of sterile needles and bleach for the prevention of acquired immune deficiency syndrome (AIDS); and

6. A SAMHSA report on the barriers to insurance coverage for ADM disorders.

A corollary issue---that of improvements in the quality and rigor of health services research, including evaluations of prevention and treatment services---is an essential element in efforts to improve the drug treatment system.

NIMH, NIDA, and NIAAA will continue to conduct rigorous services research programs in coordination with SAMHSA, as well as controlled trials of new treatment strategies and their delivery systems.

Elements of a broadly defined services research component will remain in each agency, as demonstrated by the requirement that each institute dedicate at least 15 percent of its research funds to areas related to services research. There is a possibility that SAMHSA will be given the responsibility for conducting services systems assessments to help inform and direct the delivery of treatment and prevention services.

SAMHSA will retain responsibility for disseminating evaluation findings to the services field and will undertake community-based replication of proven models.

When they transfer to the NIH, NIDA and the other research institutes will continue undiminished in their ability to pursue the kinds of broader research needed to improve understanding of the nature of drug dependence, and in fact, will be enhanced the ability of NIDA and other institute investigators to interact with NIH research in other institutes, centers, and divisions, that also have behavior and prevention research experience.

In conclusion, I hope this opportunity to speak with you will be the beginning of a dialogue that will enable us to forge an even more improved method of bringing the research and services community into as close a working relationship as possible. I truly believe that neither enterprise will fare well in the future in the absence of the other.

Our common interest in finding solutions to problems will hopefully bond us in a strong and vital partnership to expand knowledge and provide the best services possible for those in need.

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The National Institute on Drug Abuse 1992 -- Focus on the Future: A Steadfast Commitment to Research

Richard A. Millstein

It is indeed a pleasure and a privilege for me to have this opportunity to address the College on Problems of Drug Dependence (CPDD) -- the oldest and most prestigious society in the United States concerned with the problem of drug abuse. In addition to the many other functions of the College, this meeting, the 54th in an annual series, provides both a showcase of our accomplishments within the field of drug abuse research and a vital forum for the exchange of information which stimulates new and innovative research. I understand there are some 800 of us in attendance at this meeting -- 800! -- further evidence of the vitality and vibrancy and vigor of our field.

I have been looking forward to meeting as many of you as I can and to participating in and learning from these presentations and symposia -- because the more I know and learn the better I can advocate and be a stronger voice within the Federal government for drug abuse research. One cannot help but be impressed, and perhaps somewhat overwhelmed, by the diversity and range of research to be presented -- from the molecular, biological and behavioral to the clinical, epidemiologic, and ethnographic. But on second thought, such diversity and range demonstrates an accurate and necessary spectrum of research on the complex social, biomedical, and behavioral problems that underlie drug addiction. Advances in these areas have provided -- and will continue to provide -- us with the knowledge that increasingly promises to allow us to significantly reduce drug abuse and dependence and its consequences. And the rate of these advances has been catalyzed by the dramatic increases in NIDA funding over the last half-decade --years, I might add, which coincide with the tenure of my friend and colleague, Bob Schuster. I know that at last year's meeting he -- with tongue firmly in cheek -- took full responsibility for the increases in NIDA's funding that overlapped his years as Director. But let me say with sincerity how much NIDA, the research fields -- and the treatment and prevention of drug addiction -- have benefited from his stewardship.

This morning I would like to give you a status report on the Institute, share with you some of the significant events of the past year that have impacted or will impact NIDA, and then give you my sense of where NIDA and drug abuse research are going in the future. My working title for this talk was "Focus on the Future: A Steadfast Commitment to Research". One thing I would like for everyone to take home from this meeting is an understanding that in spite of reorganization, in spite of budget disappointments, and in spite of cost-containment policies which requite us to limit increases on grant awards, NIDA is now positioned to support research as it has never been before. We have the largest budget in our history; we are supporting more grants, contracts, and intramural research projects than ever before; and all indications are that we are entering a period of budget stability which will allow us, for the first time, to realistically and strategically plan for the future. It is the future that I want to spend most of my time discussing with you today; but first let me retrace some of the recent events which arc shaping that future, and perhaps give some of you a justifiable feeling of deja vu.

REORGANIZATION

This time last year it seemed a near certainty -- that ADAMHA was on the brink of a major reorganization which would separate its research and services components. MDA, NIAAA and NIMH were soon to join the NIH as separate research institutes, and the services components -- OSAP, OTI, and a to-be-formed Mental Health Services organization -- would comprise the new ADAMHSA -- the Alcohol, Drug Abuse and Mental Health Services Administration. Now, one year later, after several fitful starts and stops, we remain on that brink - only this time the ADAMHSA is a SAMHSA. The bill has been passed by the Senate and awaits consideration by the House and appears, by most observers, to be finally nearing resolution.

Dr. Johnson has described the major provisions of the reorganization. The question is, "what does it mean?" For NIDA, on a narrow level, it means transfer of some of our services-related activities, primarily those involved in the collection of data on the treatment services system. But on a broader level it will also mean a significant enhancement and expansion of the growing relationships we have developed in recent years with many of the Institutes within the NIH. We know NIH; and NIH knows us; and that is good. We have always had relationships with NIH. Most recently, these have included a variety of intramural and extramural activities at NIH, including the accrual of injecting drug users into HIV therapeutics and AIDS vaccine clinical trials with the National Institute of Allergy and Infectious Diseases (NIAID); neonatal and infant health programs with the National Institute of Child Health and Human Development (NICHD); pain and analgesia work with the National Institute of Dental Research (NIDR); and anabolic steroid research with a number of NIH institutes. So whether at NIH or ADAMHA, drug abuse research will fare well. NIDA -- and the field's -- direction and momentum are on the right track. And the reorganization has made us more aware of the links between research and practice, links which, perhaps paradoxically, the talk of reorganization has helped to strengthen. In NIH, and cooperatively with SAMHSA, NIDA will maintain -- and expand -- the progress we have made in fulfilling our research mission in the service of the improvement of the nation's public health. The critical importance now is to grasp this opportunity and challenge for a strengthened scientific foundation that, as in the past, will continue to undergird and justify the prevention and treatment programs of OSAR and OTI. And it is those service organizations -- and, through them, prevention professionals and treatment practitioners -- who, by utilizing the findings of our research, keep our science relevant. I am committed to ensuring the maintenance and strengthening of the essential connection between research and practice. It is a major thematic priority for the Institute.

Fortunately, the political debate surrounding our future organizational ties has done nothing to impede the progress of our research and planning processes. Rather, it has given us occasion to reflect on the characteristics that make NIDA unique and the methods we can most effectively utilize to strengthen the foundation on which NIDA's successful programs have been built. I think we have a unique opportunity -- and responsibility -- to move forward aggressively to identify and deliver more effective prevention and treatment technologies and to increase the capacity to turn research findings into practice.

As the Federal agency responsible for leading and directing the Nation's drug abuse research program, NIDA has been the primary force behind many advances in the field, funding an estimated 88% of all research on drug abuse in this country. Since 1986, NIDA's budget has increased five-fold -- from $85 million to more than $400 million in 1992 -- allowing the diversity of NIDA's programs to increase accordingly -- expanding into new areas such as drug abuse related AIDS and HIV infection. The Institute also has extended its research to include such areas as medications development, maternal and fetal effects, anabolic steroids, and drugs in the workplace. As we move to

the NIH I remain committed not only to maintaining the direction and momentum that are well underway, but to enhancing and expanding this vital and vibrant national research enterprise.

Today, the Institute's scientific activities are based on a strong programmatic mix of intramural programs, research project grants -- which remain the primary and fundamental mechanism of research support -- as well as research and development contracts and cooperative agreements. Allocation of this year's research budget was divided approximately equally between the basic biomedical and neuro-behavioral research portfolio and for prevention, treatment, and epidemiology research. This represents the culmination of a planned change of some years in the making, from a balance that was approximately 2/1 to 1/1. Happily, the five-fold NIDA budget increase over that last half dozen years has allowed this greater attention to prevention, treatment, and epidemiology research to occur while allowing concurrent growth in our basic biomedical and behavioral research program. Now we -- like most of the country -- have entered a new era of economic and budgetary realities. For NIDA, this represents a period of stabilization that brings with it challenges as well as opportunities.

The coming years will hopefully enable us to work from this stable foundation to effectively maintain our base of programs and to target research toward emerging areas of need and opportunity. Our overriding objective throughout this period of stabilization will be to assure the continued vitality and strength of the Institute's programs as they have been shaped in response to the revolutions in neurobiology, molecular medicine, and biobehavioral and psychosocial research and to value the contributions of the biological, behavioral, and social mechanisms involved in drug addiction and the various perspectives brought to bear in the analysis of the problem.

LEADERSHIP

The process for filling the vacancy of Institute Director is well underway. The formal vacancy announcement, issued in late March, is being published in a wide variety of journals and will remain open until July 2. A committee of experts appointed by Dr. Goodwin to facilitate this search process will review the applications of those candidates deemed by ADAMHA personnel to meet the minimum qualifications set forth. It is anticipated that by October, the Qualifications Review Board, comprised of the search committee members and several other NIH Institute Directors, will determine which of the applicants are most highly qualified, conduct interviews with these individuals and forward the results to the selecting official. Once formulated, the selecting official's recommendation will be sent to the Assistant Secretary for Health and then to the Secretary of Health and Human Services for concurrence. In the most optimistic of scenarios, we could potentially have a permanent NIDA Director in place somewhere between November and January.

I would also like to make special mention of Secretary Sullivan's approval of my request to name Dr. Marvin Snyder as Acting Deputy Director. Marvin is, I know, familiar to many of you as a long time NIDA scientist and administrator who has served the Institute and the drug abuse field in several key policy and research administration positions. I am fortunate to have such an experienced individual to assist me while I serve as Acting Director -- and I encourage anyone who has any problem to call him. (Isn't that what deputies are for?)

RESEARCH PRIORITIES

As reported to you last year, NlDA has developed and continues to update its research priorities. This process is iterative and incorporates advice from outside Government -- our advisory boards -- the National Advisory Council on Drug Abuse (NACDA), the Extramural Science Advisory Board (ESAB), and the Board of Scientific Counselors

(BSC); as well as ad hoc groups of extramural scientists (5 year plans). Indeed, involvement of the field in guiding our plans and deciding upon directions is a basic, underlying principle. In addition, NIDA staff make recommendations and participate in developing long-term goals. For example, some months ago we convened a mini-retreat of senior NIDA staff with the goal of targeting of efforts in a balanced and effective way on existing and emergent drug abuse related issues. Out of these various sources has emerged the blueprint detailing Institute priorities. And that positions us well as senior NIDA staff and I increasingly have become involved in the evolution of the NIH Strategic Plan.

Over the next several years special areas of emphasis will include epidemiology and drug abuse prevention; drug abuse related initiatives in neuroscience; maternal and fetal effects of drugs of abuse; drug abuse treatment research, including medications development; HIV infection and AIDS and the drug abuse connection; the training of new scientists in the drug abuse field; and activities focused on underrepresented populations. Let me now speak to each of these.

Epidemiologic research starts simply by posing four easy-to-state questions: Is there a problem? How large is it? Who is most at risk? Why? But the answers are anything but simple. Now as the reorganization of ADAMHA makes clear, data collection is a tool, and is appropriately conducted both in a research and a services agency. But epidemiology is much more than data collection. The hallmark of what NIDA's epidemiology program will be doing is formulating and testing research hypotheses, improving survey methodologies, refining measures of the nature and extent of drug abuse in the general population, and analyzing determinants of vulnerability and progression of use.

Our epidemiological research program is thus much more than surveillance of drug use patterns and trends. It consists of a multi-dimensional, comprehensive, and integrated set of studies that help us, through research analyses, to accurately characterize the current drug situation and its many complex parameters. Perhaps best conceptualized by the questions we ask, our program seeks to define the extent of drug using behaviors, including factors associated with the initiation of drug use and the progression to drug abuse and dependence; and to better understand the nature and pattern of these drug using behaviors as well as the characteristics of persons who use drugs. Identifying factors which predispose or render an individual vulnerable to serious drug abuse problems and factors that influence the onset of drug using behaviors and dependence are instrumental in the design of new and improved prevention interventions.

Our prevention intervention research portfolio, providing a natural and vital bridge between the important program components focused on etiology and epidemiology, will develop and test innovative preventive practices and programs. Epidemiological research is critically informative for NIDA's other research agenda, biomedical and clinical. Each discipline informs the other: biomedical, behavioral, epidemiological, prevention and clinical.

Of course, it is our basic research which has been and will continue to be the bedrock foundation of NIDA's research programs. The explosion of information on the workings of the brain is driving forward the frontier of our knowledge about drug-receptor interaction and the cascade of subsequent events which are ultimately reflected in behavior, and will lead to a better understanding of drug dependence and addiction. NIDA intends to further capitalize on the opportunities offered in this "Decade of the Brain" by expanding our efforts in a number of areas. But, to reemphasize my earlier comment, we must reduce the "disconnection" between basic drug abuse research and clinical practice in the field of drug treatment.

One area is exploring the role of genetic factors in the use of drugs, employing many of

the techniques that recent advances in molecular medicine have made possible. Another area involves the brain-behavior-environment interactions, as well as the mechanisms by which drugs act as reinforcers and how their reinforcing properties can be altered by biological or environmental factors. Importantly, an expansion of studies using imaging techniques in animals and humans as well as other studies that interface biology with behavior are planned to provide the information on the mechanisms of addiction which will enable us to design more effective treatments. To this end, NIDA hopes to establish a number of multidisciplinary research centers, and we arc currently considering innovative ways to establish within these centers several brain imaging facilities employing both human and animal research to study clinical problems central to improving the prevention and treatment of drug abuse and addiction. We believe that imaging holds great promise for our field, since through imaging we can observe how the brain changes in response to abused drugs, medications, and behavioral therapies.

NIDA's expanded neuroscience efforts in this "Decade of the Brain" are also evidenced by our role in the Institute of Medicine (IOM) recommended Human Brain Project. This Brain Mapping Initiative has as its long-term objective the development of three-dimensional computerized maps and models of the structure, functions, connectivity, pharmacology, and molecular biology of human, rat, and monkey brains across developmental stages and reflecting both normal and disease states. NIDA is joining the NIMH. the National Science Foundation and other NIH Institutes in a program announcement seeking applications to undertake the necessary pilot projects.

One area of high priority which has emerged rapidly over the last several years is the area of drug-exposed infants. NIDA has responded to fill the gaps in our knowledge about the extent of pre-natally exposed infants as well as the acute and long term consequences of such exposure. Although there are many confounding variables involved in this research, our efforts will attempt to delineate, to the extent possible, the effects of maternal drug use on development, including the relationships between a number of maternal drug use variables such as drug dose, timing, and route of administration and an array of outcome variables in order to better understand the medical complications of drug effects on the neonate. Our agenda in this area also calls for an examination of the seldom studied effects of paternal drug use on the fetus at conception and during gestation, including subsequent genetic or biological abnormalities.

Our program is broader than the infant. Our research seeks to respond to needs of the infant, but also of the mother and of the mother/infant dyad. Accordingly, we also will be examining the effectiveness of drug treatment and intervention programs for pregnant women and will attempt to develop the appropriate biological and other assessment tools to better diagnose the effects of prenatal drug exposure. Urgently needed studies to identify and eliminate barriers to increased participation in prenatal care, medical care, drug treatment, and related support system services am also a priority. In this area, our "Perinatal 20" program is currently underway. The goal is to scientifically evaluate the effectiveness of each of 20 comprehensive therapeutic programs designed for drug abusing women of childbearing age and their offspring. The importance of this area is also reflected in the establishment of a new NlDA IRG -- the "Human Development Research Review Committee" -- to provide peer review for the growing number of proposals in this area.

I see a two-pronged approach in the area of treatment research, with efforts to develop and test psychosocial interventions, new medications, and their combination. Our efforts toward the development and testing of new psychosocial treatment approaches include: drug counseling, behavioral approaches and psychotherapies; the development of therapy-specific diagnostic approaches to successfully match clients with the most appropriate treatment modality; and improved integration of psychosocial and pharmacological treatments. NIDA is making a special effort to highlight research regarding the appropriate use and dosing of methadone and will examine ways to increase physician

knowledge and use of other therapies. including naltrexone and clonidine. Our plans also include the identification of factors which increase client compliance, increase retention, and influence completion of treatment programs, as well as research to clarify the interpersonal and environmental factors associated with treatment entry, recovery, and relapse.

A major development in this area of research is the provision in the reorganization bill which requires 15% of our research dollars be spent on services research. Health services research is defined as research on the impact of the organization, financing, and management of health services on the quality, cost, access to, and outcomes of care. This must be distinguished from service systems evaluation with respect to their placement within the reorganization. The services organization, SAMHSA, will collect information to monitor the status of the drug abuse service delivery system, while NIDA will continue to support research.

Let me take a moment here, as I have briefly returned to the topic of reorganization and its impact, to describe what I see as NIDA's role in supporting research demonstrations. NIDA will continue to fund research demonstrations: where a research hypothesis is being studied, where there is random assignment of individuals, where clinical service is integral and essential to the research design, wherein the aim is to demonstrate an improvement over current care. By contrast, services demonstrations seek to expand the best and highest level of care demonstrated through research. Put another way, the responsibility of services demonstrations is to bring all service programs, prevention as well as treatment, up to the current state of the art as developed through NIDA efforts; while NIDA's responsibility is, through research demonstrations, to improve upon the state of the art.

Our Medications Development program has made great strides in the past year toward the goal of identifying compounds for the treatment of opiate and cocaine addiction. And the identification and cloning of the "cocaine receptor"/dopamine transporter site by Dr. George Uhl and his colleagues at the ARC was a major achievement. In the coming years, this program will continue its efforts to identify pharmacological treatments for cocaine addiction; to develop non-dependence producing maintenance treatments for opioid addiction; and to develop medications for the treatment of audictine disorders that have few or no effects on the developing fetus. The development of drug delivery systems that will increase patient compliance is also a priority, and includes the development of implantable depot systems, oral controlled-release systems, transdermal delivery systems, and triggered-release or self-regulated drug delivery systems.

We are also continuing to evaluate and clinically test LAAM, buprenorphine, and depot naltrexone for their utility in treating drug dependence. The approval of LAAM for maintenance of opiate dependence has been one of our Medications Development Division's top priorities this year. Combining the wealth of preclinical and clinical information generated over the past several years with current clinical and manufacturing data, we are developing a New Drug Application (NDA). The Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), NIDA, and BRI -- the company which will market LAAM -- are cooperating in an expedited review of the LAAM New Drug Application. Much of the data for the New Drug Application was presented to the FDA's Drug Abuse Advisory Committee earlier this year, and we are confident that the LAAM NDA will meet current regulatory requirements for marketing approval. Assuming an uncomplicated review, LAAM should be approved and commercially available during 1993.

Currently, AIDS related to injecting drug use accounts for nearly one-third of all adult cases reported -- as well as perhaps two-thirds to three-fourths of cases in women and children. Clearly, our best hope of reducing and ultimately eliminating drug abuse related AIDS cases lies in improving the efficacy of drug abuse treatment and preventing drug

abuse. To maximize drug abuse treatment's potential for AIDS prevention, recruitment strategies must be extended; treatment capacity must be expanded; and treatment quality must be enhanced. There is also an urgent need for outreach efforts and AIDS risk reduction education; for the training of drug abuse personnel; and for the acquisition of drug abuse treatment data which is sorely needed in AIDS prevention planning. And it is imperative that our efforts target not only drug abusers but their sexual partners as well. Although some of these activities will be focussed in the programs of the new SAMHSA, NIDA will continue to conduct research to inform and guide the development of improved treatment strategies.

NIDA is also working with the National Institute of Allergy and Infectious Diseases (NIAID) to enroll more HIV-infected injecting drug users in the AIDS Clinical Trials Group studies. This initiative makes it easier for injecting drug users to gain access to investigational AIDS medications, and encourages linkages between NIAID's AIDS Clinical Trials Units and MDA's Treatment Research Units.

There is also excitement about potential field trials to test the efficacy of one or more vaccines to prevent HIV infection which are likely to begin within the next two years. Because injecting drug users are known to be at high risk of HIV infection, may present special issues related to compliance, and could benefit from a vaccine; they are likely candidates for such future vaccine trials. Through a joint NIAID/NIDA vaccine preparedness initiative, supplemental funding is being made available to NIDA grantees to examine the feasibility of conducting HIV vaccine trials in injecting drug users.

Diseases other than AIDS am also closely associated with substance abuse, including hepatitis, endocarditis, and tuberculosis. For example, HIV-infected injecting drug users are among the populations hardest hit by the dramatic comeback of tuberculosis. Tragically, the incidence of active TB in HIV-infected patients is almost 500 times that in the general population. In those whose immune systems have been weakened by the HIV infection and AIDS, TB's detection is far more difficult and its progression is far more rapid. The situation is made more ominous by the development of multiple drug resistant tuberculosis, and the general lack of access to good health care by drug abusers. TB, unlike AIDS, is highly infectious, and large portions of the population may be placed at risk unless it is controlled. Recognizing the importance of early identification of drug abuse and its associated problems, NIDA, in concert with the Health Resources and Services Administration (HRSA), has been actively supporting a community-based program to implement and assess models for linking drug abuse treatment and primary health care to reduce the spread of AIDS.

Apart from specific promising areas of science, yet another area of critical importance to NIDA and to the research community at large is research training. The ultimate success of our programs is directly tied to our ability to assure that an adequate number of trained and qualified research scientists is working on drug abuse issues. The challenge this represents to the field of drug abuse grows steadily in magnitude and complexity as the youth of our nation continue to pursue other career paths and as the pool of scientific talent continues to shrink. Allowing this critical population to shrink will, in the long term, seriously threaten our Nation's ability to compete, and certainly will be reflected in serious curtailment of research progress. While this problem is certainly broader than drug abuse, and is being addressed at several levels within the government, NIDA continues to seek new ways of recruiting scientists into the drug abuse field, and to develop and implement methods of attracting students to science and facilitating their smooth transition from research trainee to established investigator in an effort to maintain stability within our resource pool. Through a variety of individual and institutional training and career development mechanisms we remain firmly committed to these recruitment and engagement efforts. In particular, NIDA has designated clinical research training and epidemiologic research training as its highest priorities because of shortages of trained scientists in these areas. We are developing a comprehensive plan, including science

education, to expose young students to research, to encourage them to undertake science careers, and to provide a continuum of support from the pre-baccalaureate, pre-doctoral, post-doctoral, and transition to independent research scientist. This year, with a training budget totaling $6.8 million, NIDA is sponsoring 275 trainees, including a number of minority focused programs, and we will strive to expand this program in the coming years.

Finally, another factor which seriously threatens our scientific vitality is the shortage of minority scientists. As Secretary Sullivan has said, "The training of future minority biomedical scientists must be achieved if our Nation is to have the critical supply of future researchers and teachers in the next century." Accordingly, NIDA is reexamining its minority activities portfolio. As you know, NIDA's efforts for special populations are infused into the workings of all Institute activities and programs including research, outreach, education and training. In addition, NIDA supports a focused minority training strategy, based on several principles, including the development and support of a variety of mechanisms to reach students at all stages of their education. This year our direct Minority Health and Assistance Budget for these focused activities totals over $3.5 million. Among the ongoing initiatives are many familiar to you -- the Minority Access to Research Careers (MARC) Program providing training to undergraduates to encourage them toward research careers; the Minority Institutions Research Development Program (MIRDP), through which we award grants to institutions with substantial minority enrollments for supporting research, enhancing research infrastructure, and providing advanced training of faculty; and the Minority High School Apprenticeship Program, which provides stipends for promising students. Others may not be as well known to the research community. We have placed a special focus on the Minority Research Supplement Program, and have instituted a major enhancement in our special populations activities. Just this past year, through the Minority Research Supplement, we were able to support some 30 minority researchers at various points in the training pipeline. And with the goal of improving access of minority scientists to scientific and research training opportunities, NIDA has been actively involved with symposia with key organizations such as the National Medical Association and the Presidents of Historically Black Colleges and Universities, to help us work with them.

In closing, let me reiterate the imperative that we maintain the breadth and scope of what NIDA supports -- basic, behavioral, epidemiologic, clinical and applied research, on a wide range of drug abuse related issues, with the common element being support of science of the highest quality. I can assure you that during my tenure as Acting Director I will continue to support rigorous scientific research, whatever the discipline, and knowledge development that will form the basis for generating a better understanding of drugs of abuse, their actions and interactions, from the molecular to the individual level. And, as an integral part of our mission is making certain that the research we conduct and support is translated into the most effective prevention and treatment strategies and approaches to be applied, I am committed to strengthening the linkages between the research and practitioner communities, linkages which are as critical as those between the various research disciplines, and serve to assure the success of the fundamental goal of addiction research: improvement of the lives of citizens through safer and more effective prevention and treatment measures.

NIDA is a research agency, and the advancement of scientific knowledge is our fundamental and defining mission. But we are also part of the Public Health Service, committed to improving the health and well being of all Americans. So we cannot just support research; we have to make sure that it is appropriately translated for others to understand, apply, adopt, and adapt as necessary. And let me make it clear that I see knowledge transfer as a two-way street. Not only will researchers transmit their study findings to prevention and treatment practitioners; but these practitioners will transmit to researchers their clinical knowledge, wisdom, and judgment -- and these insights will serve to improve new research proposals as they are developed. So, I see the criticality of

strengthened cooperation and collaboration between a NIDA in the NIH and prevention and treatment services in SAMHSA, because our agencies can serve to bring our constituencies -- researchers and practitioners -- together.

Finally: it is my passionate belief -- and I hope I have made it clear -- that we as a country will not be able to make any real progress in improving primary health care, in reducing infant mortality, against TB, hepatitis, HIV infection and AIDS or other STDs; or to make progress in promoting mental health or advancing health care for women and minorities and the underserved -- if we do not understand and attend to the major contributing role and connections of drug abuse to these conditions. It is from this conviction, and the belief that research is the key to progress, that the broad, yet focused, research agenda which I have outlined this morning and the dogma of strengthening the linkages: among researchers; between researchers and practitioners; and from the substance abuse to the primary health care system, have emanated.

I hope this morning I have given you not only a "state of the Institute, 1992" mini-report, but also some insights into me, what makes me resonate, and my sense of obligation, opportunity, and optimism.

I thank you for all you have done . . . and all you continue to do.

AFFILIATION: National Institute on Drug Abuse, Rockville, MD 20857

PRESENTATION OF THE MORRISON AWARD

LOUIS S. HARRIS, PH.D.

The Morrison Award was created by CPDD to honor the memory of Michael Morrison, who for many years, was an exemplary Executive Secretary of a NIDA Study Section. His dedication and service to the drug abuse research community was remarkable even during his terminal illness. The award is to honor an individual with an outstanding record of public service.

It is both a great personal pleasure and honor for me to introduce this years' awardee, Professor Hans Halbach.

Dr. Halbach was born in Herde, Germany in 1909. After graduation in chemistry from the Technical University of Munich, he spent three years in Han Fishers' Institute doing analytical and natural product chemistry. He then went on to obtain his medical degree, again from the University of Munich. After the war he became a lecturer and then Assistant Professor of Pharmacology at Munich carrying out pharmacological research on anesthetics.

In 1954, he began his distinguished public career with the WHO as Chief of the newly created, Unit of Addiction Producing Drugs (later Drug Dependence). During this period he published, along with Olaf Braenden and Nathan Eddy, a series of three Seminoles Monographs on substances with morphine like effects.

He served as the Secretary of the 6th to 15th meetings of the WHO Expert Committee on Drug Dependence, as well as several other study groups. He was the WHO representative to the U.N. Commission on Narcotic drugs for two decades. He participated in the development of both the U.N. Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances. His encyclopedic knowledge of the Conventions and their Commentaries have proven invaluable to those of us who have led to serve as Chairman or Rapporteurs on later Expert Committees. He is also Hans, Professor of Pharmacology, University of Munich and Honorary Member, British Society for the Studies of Addiction.

Finally, Dr. Halbach was the founder and editor of the journal, "Drug and Alcohol Dependence". This year CPDD has become a sponsor of the journal.

Personally, Dr. Halbach is a gentleman of the old school, always considerate of others despite his strong advocacy for research in and prevention of the chemical dependencies.

AFFILIATION:

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WHAT'S A RADICAL BEHAVIORIST LIKE YOU DOING IN A NICE PHARMACOLOGY CLUB LIKE C.P.D.D.?

J. V. Brady

INTRODUCTION

It is truly an unexpected pleasure to be the recipient of an award I have long regarded as beyond the reach of mere mortals. Indeed, even a cursory review of the distinguished predecessors who have been so honored, not to mention the numerous individuals in this audience that I would have judged more deserving, suggests that there has been a change in traditional selection criteria. Perhaps the prize can now be awarded to the individual who learned the most during a quarter century association with this community of multidisciplinary scholars or to the individual who had the most to learn. It was only recently for example, that I learned the definition of a drug -- a chemical substance that, when put in the hands of a pharmacologist, results in a paper!

But whether or not there has been a change in the Eddy Award, a great many changes have certainly taken place as a result of the holy alliance between pharmacologists and behaviorists fostered by this Committee-Cum-College over the past 20 to 30 years. In this latter regard, I would like to address the interplay between these two disciplines in producing the conceptual and methodological developments that have been responsible. at least in part, for bringing about these changes. This account make no pretense to objectivity or completeness as it is my intention to simply talk for awhile about the events and of course, the people who have contributed importantly to these developments. And to keep this light and lively, I will approach what I have to say answering the question that provides the title for this presentation. This somewhat facetious variant on the pre-1960 male chauvinist quip, "What's a nice girl like you doing in a place like this?" was suggested by the comic reversal, "What's a girl like you doing in a nice place like this?"

THE SHORT ANSWER

The short answer to the title question is that drugs interact in profound and broad-ranging ways with the transactions between individuals and their environments -- the unique domain of the behavioral sciences and the root subject matter of radical behaviorists. But let me reassure you about radical -- not to worry, neither violent nor terrorist proposals are in the offspring. Simply defined, radical means root and calls attention to an important difference between behaviorists, all of whom are not created equal. There are many, perhaps, most, whose interest in behavior is primarily methodological in the sense that what goes on at the interface between individuals and their environments is of concern primarily if not solely as a reflection of other activities of presumably greater import like central nervous system functions or so-called cognitive processes. Without denying these methodological claims to the territory, root behaviorists view the transactions at the interface between individual and environment as a legitimate subject matter in its own right and the source of an orderly and systematic body of empirical knowledge that does not require reduction to other levels of analysis or appeals to other levels of explanation.

It follows of course, that card-carrying root behaviorists tend to favor alternatives to the dominant "inner states" orientation of the "psych" disciplines. Among the most compatible of these alternatives is environmentalism which has two main tenets. The first of these is that knowledge comes from experience rather than from innate ideas, divine revelation, or other obscure sources. And the second is that action is governed by consequences rather than by instinct, will, beliefs, attitudes, or even the currently fashionable congnitions. These two constructs about the nature of human conduct -- the experimental basis of knowledge and the governance of action by consequences -- define a philosophy of social optimism that says if you want people to do certain things or to manage their lives in certain ways with respect for example, to drugs and alcohol, circumstances can be arranged. These two features of environmentalism also provide a productive framework for the analysis of drug-behavior interactions as well as an operational basis for the development of effective drug abuse treatment and prevention.

THE LONG ANSWER

That's the short answer. The long answer to the question of both how root behaviorists got into this once-exclusive opioid club in the first place and how they have managed to stay around so long requires a somewhat more involved explanation. In the first instance, it is now abundantly clear that an adequate characterization and evaluation of pharmacological agents in general, and drugs of abuse in particular requires assessment of their behavioral functions. And while this is not exactly a new idea -- Abe Wikler's studies at Lexington were early alerts -- there have been a number of conceptual and methodological developments over the past several decades that were less than well defined when the hustling behavioral of addicts was first described by Wikler (1955) and the classic monograph on drugs and human behavioral appeared two years later (Wikler, 1957).

In many respects, of course, both the short and long answers to the title question can be seen to have common historical antecedents and familiar contemporary elements that feature the interplay of conceptual and methodological developments in the behavioral pharmacology of drug abuse. In the early 1950's for example, an important conceptual change occurred when long-unwanted drug side effects became the focus of medication development programs in virtually every major pharmaceutical company with discovery of the tranquilizers, reserpine and chlorpromazine. Although it was not obvious at the time, this new focus on behaviorally active drugs was to considerably broaden the arena of drug dependence and abuse as the plethora of available hypnotics, anti-depressants, and anxiolytics, not to mention coming generations of so-called cognitive enhancers, now convincingly demonstrates. But this conceptual shift also set the stage for some very influential methodological developments in response to the need for effective behavioral screening and evaluation of the numerous candidate compounds already on the pharmacologist's shelf, as well as those that were to continue to flow from the chemist's bench.

An Early Research Finding and It's Consequences

It was in this fortuitous 1950's climate that a report of one of the first behavioral pharmacology experiments appeared in Science, the century-old interdisciplinary publication of the American Association for the Advancement of Science. This single animal, single dose study contrasted the behavioral effects of amphetamine and reserpine on a "conditioned emotional response" defined by the disruption of a thirsty rat's water-rewarded lever pressing by presentation of clicking noise that had previously been paired with electric foot shock (Brady, 1956). While amphetamine (2 mg/kg) accentuated the conditioned emotional response by increasing the lever pressing rate in the absence of the

clicking noise and decreasing the lever pressing rate below even the saline control rate during the clicker, reserpine had the opposite effect. Reserpine (0.2 mg/kg), while decreasing the lever pressing rate in the absence of the clicking noise, actually increased the lever pressing rate during the clicker as compared to the effect of the clicking nose on lever pressing under amphetamine and saline control conditions.

It was this selective attenuating effect of reserpine on the conditioned emotional response that produced two rather surprising and far-reaching consequences. On the one hand, there was a laboratory visit from Abe Wikler and Dick Belleville from the Addiction Research Center in Lexington, and on the other hand there were several calls from people like K.K. Chen of the Lilly Laboratories and Karl Beyer of Merck. In the first instance, Wikler and Belleville were involved in investigations of the "anxiety reducing" effects of morphine, and the behavioral pharmacology laboratory was brought into early contact with drugs of abuse. In the second instance, the calls from K.K. Chen and Karl Beyer, among others launched a rather extended series of lectures and visits to pharmaceutical company research laboratories and inquiries about the availability of behaviorally trained laboratory scientists who might join forces with the pharmacologists at Lilly, Merck, and elsewhere. Len Cook at Smith, Kline, and French was among the pharmacologists making early moves in this direction, and more than a few of the behaviorists associated with drug abuse research including Roger Kelleher, John Boren, Irv Geller, and Larry Stein, among others, received their baptism of fire in pharmaceutical company laboratories responsible for behaviorally significant methodological advances.

While most of the action in these early days was clearly centered in the drug houses, at least a few academic behavior laboratories -- the hens that laid the golden eggs -- became the beneficiaries of pharmacology's largesse. Not the least among those was Fred Skinner's laboratory at Harvard where Peter Dews had found his ways across the river of Cambridge from Otto Krayer's Pharmacology Department at the Harvard Medical School. The enduring effects of that productive liaison between pharmacologists and behaviorists continues to be reflected in the contributions of Bill Morse, Larry Byrd, and Don McMillan, among others, to drug abuse research. In addition, the laboratories at the University of Maryland in College Park became the site of the first NIMH Behavioral Pharmacology Program Project Grant -- $250,000 was a lot of money in the 1950's -- and the training ground for several more noteworthy drug abuse research contributors. And while many behaviorists were leaving academia for industry, at least one significant move in the opposite direction can now be seen to have had far reaching effects upon behavioral pharmacology in general and the behavioral pharmacology of drug abuse in particular.

Charles R. Schuster was the first to make this move from Len Cooks laboratory at SKF to upgrade our budding behavioral pharmacology initiative at the University of Maryland. At about the same time, he was joined in College Park by our first behavioral pharmacology post-doctoral trainee, Travis Thompson, and the rest is history. Within a few years, they jointly authored the first behavioral pharmacology textbook and they and their students have for all practical purposes defined the behavioral pharmacology of drug abuse over the past several decades.

The Zeitgeist and Drug Abuse Research

In many respects, it was the tenor of the times that set the stage for many of the conceptual and methodological developments of which drug abuse research was to become the beneficiary. As the decade of the 1950's drew to a close, reports were emanating from widely scattered sites in Montreal, Canada, Kalamazoo, Michigan, Washington, D.C., and College Park, Maryland, about the strange behaviors of

laboratory animals pressing levers to electrically stimulate themselves through implanted brain electrodes on the hand, and to self-inject drugs through intravenous catheters, on the other. In the latter case, it was the publication of drug self-administration reports in quick succession from College Park, Maryland with monkeys (Clark and Schuster, 1961) and Kalamazoo, Michigan with rats (Weeks, 1962) that launched a new era in the behavioral pharmacology of drug abuse. But despite the enthusiasm with which these findings were greeted by the behaviorists, early offering based upon this animal drug self-administration model were not always warmly embraced when presented before CPDD gatherings like the one that took place some quarter century ago in Chapel Hill, North Carolina.

The events leading up to that fateful occasion included the virtually simultaneous publication of the monkey studies describing the reinforcing effects of self-injected drugs and some experiments by a young Walter Reed behaviorist, Bill Hodos, introducing the innovative progressive ratio procedure for comparing the reinforcing effects in laboratory animals of electrical stimulation through electrodes implanted in several different brain structures. By measuring the amount of work -- i.e. number of lever presses -- animals performed for electrical stimulation, Hodos demonstrated that there were marked differences in the reinforcing functions mediated by the several different brain sites tested (Hodos, 1962). It was just about 30 years ago that this paper by Hodos and the Schuster jugular self-infusion paper appeared almost simultaneously in the widely circulated house organ of the AAAS -- in those days Science was publishing something other than gene sequences!

The experiment reported at that first CPDD presentation over 20 years ago purported to demonstrate that the progressive ratio procedure could be used to compare -- rank order, if you will -- a range of self-administered drugs with respect to the relative strength or efficacy of their reintorcing functions. The results showed for example, that higher ratios of responding -- more lever presses -- could be maintained for a self-injection of cocaine than for self-injections of amphetamine, methylphenidate, phentermine, or fenfluramine. Amphetamine in turn, maintained higher ratios of lever pressing than methylphenidate, phentermine, or fenfluramine, and so forth. There was no argument with the behavioral procedure -- systematic increases in the required number of lever presses for successive drug injections until a "breaking point" was defined when the work required exceeded that which the animal would do for access to a self-injected dose of a particular drug. But the pharmacology was indeed a bit naive. A single animal combined with a single dose of a drug like amphetamine hardly made a convincing case for the validity and reliability of a comparative analysis of reinforcing functions.

The hard lession learned on that occasion was to pay dividends however, with the welcome and generous assistance of the Thompson/Schuster behavioral pharmacology training sites at Minnesota, Michigan, and Chicago. Within a few years following the arrival of George Bigelow and Roland Griffiths in Baltimore, several published reports from the Johns Hopkins laboratories helped to redeem that inept performance characterizing our initiation to the club. Of particular significance in is regard were a series of within and between animal studies with a half-dozen or more baboons over a range of doses with several stimulants including cocaine, in a Psychopharmacology paper (Griffiths and Brady, 1978) and those described in a a Biological Psychiatry publication (Griffiths and Brady, 1978) comparing the reinforcing functions of such stimulant drugs confirmed a rank ordering of these compounds that was quite consistent with their relative reinforcing efficacy as suggested by the offending CPDD presentation some 10 years earlier. All of which goes to prove that you can be right for the wrong reasons!

A Seminal Behavioral Observation and Conceptual Impact

Of far greater import however, was the seminal behavioral observation that laboratory animals would repeatedly self-inject pharmacological agents and that substantial and extensive drug-seeking and drug-taking performances could be maintained on the basis of such animal drug self-administration. This methodological development can now be seen to have contributed importantly to a decisive shift in the traditional conceptual focus upon the reactive features of drug and alcohol abuse. W.C. Fields' classic comment that "it was a woman who drove me to drink, and I never got a chance to thank her," aptly expressed these prevailing views. As even this comic reference suggests however, and Abe Wikler's early contributions convincingly documented, powerful reinforcing functions emphasized the more active, consequential control that can now be seen to characterize drug abuse disorders. Subsequent research has confirmed the cross-species and cross-substance generality of these findings and provided evidence of a remarkable concordance between the range of chemical substances self-administration by laboratory animals and those abused by humans (Brady, et al., 1975, Griffiths and Balster, 1979; Griffiths, et al., 1980).

As a result, laboratory procedures for the generation and maintenance of drug self-administration have become the hallmark of abuse liability assessment based upon the kind of functional models that have proven most useful and productive in the experimental analysis of behavior. The most important conceptual and methodological consequence of this interactive research has been the analysis of relationships between the biochemical/pharmacological properties of drugs and their environment/behavioral stimulus functions. And while investigative attention has continued to focus upon reinforcing stimulus functions, an ever expanding data base on the discriminative stimulus functions of drugs has provided a more comprehensive basis for characterizing a drug's spectrum of action and evaluating its abuse liability. There is now abundant evidence for example, that both laboratory animals and humans can be trained to respond differentially to the "signalling" functions of stimuli whether the stimulus "signals" are presented exteroceptively (e.g., vision, audition) or interoceptively as in the case of drugs. It is hardly necessary to detail the contribution of behavioral pharmacologists in an area that has been so strongly represented in the CPDD scientific programs over the past decade. But the impressive range of applications involving drug discrimination methodologies in substance abuse research is worth emphasizing. Beside implications for a more operational approach to comparisons involving so called "subjective effects", analysis of a drug's discriminative functions has helped to refine the definition of drug categories and subcategories, to identify active metabolites, analogues, and new drug effects as well as to enhance drug evaluation at both the clinical and preclinical levels. And the explosive advances in new knowledge of neurotransmitter and receptor dynamics combined with the demonstrated specificity of action and good correspondence with drug discrimination generalization profiles now provide a more precise behavioral reflection of neurochemical mechanisms (Barrett, 1991).

These increasingly visible contributions to substance abuse research have as well been complemented by advances in the more traditional province of the behavioral pharmacologist's concern with direct effects on performance, more technically referred to as the eliciting stimulus functions of drugs. These long-recognized "side-effects" have received increasing experimental attention as "behavioral toxicity" has become a prominent defining feature of drugs with abuse liability. Substances with only minimal if any disruptive physiological/behavioral effects are generally not regarded as having significant abuse liability even though their use may be widespread and some degree of physical dependence can be demonstrated (e.g. caffeine in coffee, tea, and soft drinks). In contrast, compounds self-administration even sparingly that are associated with

disruptive behavioral/physiological changes are considered highly abusable (e.g. lyserigic acid diethylamide, LSD). At the most basic level, it has been possible to develop a body of knowledge on the sensorimotor effects of a range of abused drugs by a methodological tour de force combining classical psychophysics, behavior analysis, and experimental pharmacology (Heinz and Brady, 1981). Sensitive and reliable laboratory models for evaluating the unique patterns of change induced by drugs of abuse in auditory and visual thresholds and reaction times have now been extended to assess the effects of such substances on speech sound discriminations to include analyses of dose dependence and time course (Hienz and Brady, 1987).

The conceptual fallout from these methodological developments has provided the basis for a quantitative analysis of the relationship between the behaviorally toxic eliciting effects of abused drugs and their reinforcing functions. The resulting reinforcement/ toxicity ratio (Brady et al. 1982) compares the relative potency of a drug as a reinforcer with its relative potency in impairing sensorimotor function. A drug with potent reinforcing functions (i.e. maintains self-injection at relatively low doses) but which impairs sensorimotor functions only at relatively high doses would have a low reinforcement/toxicity ratio, whereas a drug that maintains self-injection only at relatively high doses but impairs sensorimotor function at relatively low doses would have a high reinforcement/toxicity ratio. Such an interactive analysis can provide an assessment at the preclinical level of the extent to which self-administration of a given drug will impair basic sensorimotor functions.

These advances in research technology and the consequent enhancement in our understanding of drug action have also provided the basis for a more operational approach to some of the conceptual problems associated with the quasi-technical use of such terms as "addiction", "dependence" and "abuse" as referents for a bewildering range of phenomena and experiential pseudo-phenomena (Brady and Lukas, 1984). At least some definitional clarity can be approximated by dividing the vast array of relevant observations that characterize the domain into two operationally identifiable categories defined by the events that occur before and those that occur after the actual substance intake. As a first approximation, the defining operations of the "before" class would include proactive drug-seeking behaviors and the rituals associated with drug-taking, while defining operations of the "after" class would focus upon the reactive biochemical, physiological, and behavioral changes associated with tolerance and the abstinence syndrome when a repeatedly-used drug is withdrawn. The relevance and importance of this distinction between proactive "abuse" and reactive "dependence" resides in the fact that the defining properties of the two classes are not coextenstive, they do not invariably occur together, and the methods by which they are evaluated differ. Proactive drug-seeking and drug-taking s cardinal signs of abuse for example, can be maintained in strength by use patterns and doses of compounds (e.g. cocaine) that produce no significant tolerance or withdrawal -- the reactive changes traditionally associated with physiological dependence. In contrast, there are compounds (e.g. propranolol) that produce tolerance and physiological dependence but that neither generate nor maintain drug-seeking or abusive drug taking.

Interaction between these proactive and reactive features of substance use and misuse are of course commonplace. Changes in drug-seeking and drug-taking often occur as sequelae to both the acute effects of pharmacological agents and to the tolerance and withdrawal effects that follow more chronic drug exposure. Conversely, the chemical and physiological changes that define dependence can as well be sequalae to the repeated self-administration of abused drugs. But the relative contributions of these distinguishable processes to substance-related problems can vary widely with different pharmacologic agents as a function of dose, environmental circumstances.

Gifts of Fortuitous Environment

All the methodological and conceptual developments from which drug abuse research has benefited have not originated in laboratories of either biochemical or behavioral pharmacology. On occasion, the fortuitous methodological requirements of quite unrelated areas may prove useful in disciplines that seem far afield. One example of such conceptual and methodological generalization of which research on the behavioral pharmacology of drug abuse has been the beneficiary is the fallout from behavioral research on small groups confined microsocieties undertaken in support of the flight programs of the National Aeronautics and Space Administration. In conjunction with both animal pretests and human extended space flight requirements, procedures were developed for establishing and maintaining performance repertoires in the context of behavioral programs under total and continuous environmental control. The ground-based programmed environment laboratory methodologies developed for this research have proven useful and productive for the study of abused drugs in a context that provides access to more complete repertories of human behavior by combining the conceptual framework of an experimental analysis with the naturalistic goals of ethological observation.

This unique combination of ethological richness and precision of experimental control has been the basis of a human residential laboratory analysis of some of the more elusive behavioral changes attributed to one of the most widespread drugs of abuse, marijuana (Brady, et al. 1986). Without belaboring the details of a research initiative that has been described on numerous occasions over the past decade before these CPDD meetings, it is worth emphasizing the methodological advantages of a laboratory capable of assessing the human performance repertoire as the fabled amotivational effects of marijuana were dissected under experimental conditions that provided continuous behavioral observation and recorded measurement 24 hours a day for periods of several weeks. Using a time based measure of value, it was possible to establish hierarchies of preferred, less preferred, and non-preferred work, recreational, and social activities with multiple groups of volunteer participants and to arrange contingent relationship between these performance such that the relative strength of behavioral dispositions to engage in such performances (i.e. an operational measure of motivation) could be compared under conditions of active and placebo marijuana smoking. Under contingent work conditions for example, performances on non-preferred work tasks required for access to more preferred work tasks were actually enhanced by smoked marijuana. These effects contrated with those found with recreational and social contingencies where the time spent engaged in less preferred recreational and social activities to gain access to more preferred recreational and social activities was observed to decrease following active marijuana smoking as compared to placebo marijuana smoking. This somewhat paradoxical but robust finding replicated under a range of conditions with several different groups of subjects, effectively demonstrated the sensitivity of the behavioral programmed environment methodology to the more subtle and evasive effects of drugs expressed under conditions that differentiate aversive and appetitive environmental influences (Brady, 1992a).

Technology Transfer and Mobile Drug Abuse Treatment

The sensitivity and precision of these laboratory methods notwithstanding, root behaviorism faces its greatest challenges in the transition from confined microsociety experiments to research in the unconfined macrosocieties that characterize the natural ecology of drug abuse treatment. In perhaps the most ambitious of behavioral pharmacology undertaking in this arena, a recent research demonstration study has been initiated with the objective of determining the feasibility and comparative effectiveness of

delivering drug abuse treatment within the context of a mobile health service in the city of Baltimore (Brady, 1992b). While some mobile drug abuse treatment precedents are to be found in the Amsterdam methadone bus and the Boston suburban methadone vans, the Baltimore project aims to provide an expanded mobile treatment program to include both medication and counseling delivered on site in center city communities with a high prevalence of substance abuse and other poor health indications.

The research evaluation design of this demonstration project provides for one pair of mobile units -- a medication van and a modified house trailer for drug abuse counseling and the delivery of ancillary health services including blood pressure, diabetes, and breast cancer screening, as well as health education -- that makes daily rounds at several predetermined sites in a center city community on the west side of Baltimore. A second pair of units made up of a medication van and counseling trailer offers identical services at a single fixed location in a center city community on the east side of Baltimore. The "yoked control" research plan calls for operations at these sites to continue for a period of a year to 18 months at which time the stationary units will begin to make daily rounds at several selected sites on the East side and mobile units on the West side will become stationary at a single site in that community. Despite the inevitable tradeoffs between service delivery imperatives and essential research procedures, substantial progress has been made over the past year in establishing and maintaining a mobile system that presently provides treatment for over 100 intravenous drug abusers on site in their local residential areas and offers ancillary health services to the community at large. There are on the project's waiting list over 200 applicants whose request for enrollment in the program were made through initial contact with the mobile drug abuse treatment units, and enhanced outreach services await only the availability of resources to support effective expansion.

The data available at this early stage of the program is limited to descriptive demographics and a few early probes regarding program effectiveness in the form of follow-up urine samples from patients over several initial months in treatment and a questionnaire evaluating client satisfaction with the program. In the latter case, the results are quite favorable, not surprisingly because of the high ratings the program receives on "convenience" and "scheduling" items. The urine sample results however are less encouraging although probably not surprising to those more experienced in drug abuse treatment research. While a not unexpected 40-50% of the urines were positive for opiates other than methadone, some 80-90% of the samples were positive for cocaine and 70-80% were positive for quinine -- that's a lot of gin and tonics! One redeeming feature of the data analysis to date however, is the low drop-out rate. Compared to attrition rates approximating 40% for the standard methadone treatment clinics in the city of Baltimore, the drop-out rate for the mobile drug abuse treatment program has averaged only 13% to date.

While these preliminary findings constitute only an initial 6-month progress report, they do generate some optimism with respect to at least the first aim of this research demonstration project. With regard to the question of whether it is feasible to establish and maintain a drug abuse treatment program within the context of a mobile health service, experience to date would certainly seem to suggest that the answer is yes. But it ain't easy and its certainly no business for an experimental laboratory perfectionist! One product of a pre-1960 Jesuit education however, is a certain detachment that views the world as a vale of tears with its problems never really solved this side of the grave. But you do what you can and what you must, taking it for granted that most of the effort will go for naught and most of the good intentions will backfire, so you get a few laughs from it all while you can!

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The experimental work described and the preparation of this manuscript was supported by National Institute on Drug Abuse Grants DA00018 and DA 06949.

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INTRODUCTION

E. M. Johnson

Good Afternoon. In this afternoon's session, we will examine the issue of alcohol and other drug addictions in women. In my work as the Acting Administrator of ADAMHA. I can assure you that this issue is one of great concern to us, especially as it relates to substance abuse by pregnant and postpartum women. I am proud to say that ADAMHA has been at the forefront of supported research in this area. Through supported research from NIAAA, we have established that alcohol may be acutely toxic to the fetus and that it can produce a range of devastating life-long effects, including mental retardation, cognitive-behavioral deficits, facial disfigurement, and hyperactivity as well as speech and hearing impairment.

We know that illegal drug use during pregnancy, especially the use of cocaine and opiates, is associated with poor infant health and developmental problems, as well as complicated pregnancies. And we know from ADAMHA's statistical surveys that drug use among women has been on the increase.

During a recent meeting between ADA MHA officials and six State and local area experts, shared data based upon DAWN and the States' own data collection methods revealed an increase number of female intravenous drug users entering treatment. Among female intravenous drug users, sadly, only a very small percentage enter treatment programs. Consequently, this population is not well understood, nor can education and prevention programs be easily designed and implemented for them.

ADAMHA has taken several very important steps to ensure that targeted research, treatment, and prevention are sensitive to the special needs and conditions of women. Some of you may already be familiar with the initiatives established by NIDA, OSAP, and OTI in support of pregnant and postpartum women and their infants.

ADAMHA has recently launched the National Resource Center for the Prevention of Perinatal Abuse of Alcohol and Other Drugs which will stimulate policy; disseminate new research findings; and provide information, training and technical assistance to the field. OTI is preparing a "Treatment Improvement Protocol" which will offer basic principles and guidelines for programs to use in providing supportive comprehensive care for pregnant, substance-abusing women and their children. And under the reauthorizing legislation, OTI will be assuming an even larger role in serving this population. And, although much remains to be accomplished, we will learn today from our speakers that very excellent and rigorous research is being done that will help to improve the research, treatment, education, and prevention of substance abuse.

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ALCOHOL USE AND ALCOHOL PROBLEMS IN WOMEN: EPIDEMIOLOGIC TRENDS

S.C. WILSNACK

Approximately 13 1/2% of American men and 4 1/2% of American women meet diagnostic criteria for alcohol abuse or dependence. There do not appear to have been any dramatic changes in levels of drinking or drinking problems among women between the mid-1960s and the mid-1980s. Public and media alarm about "epidemics" of alcohol problems in women during that period appear to reflect a delayed response to a previously neglected problem, and/or increased visibility of problem drinking women. Despite the lack of overall changes in drinking among women as a group, some change may be occurring within specific subgroups. These include the possibility of increased heavier drinking among women in their 20's and early 30's (which may be leveling off or declining in the most recent surveys), and the possibility of increased drinking (nonabstention) among older women socialized to alcohol use after the era of Prohibition. More women than men with alcohol disorders also meet diagnostic criteria for other drug disorders. Concurrent use of alcohol and prescription drugs is common among middle-aged and older women, combined use of alcohol and illicit drugs may be increasing among younger women.

Our U.S. national longitudinal study of women's drinking interviewed 914 women nationwide in 1981, with followup surveys in 1986 and 1991. In contrast to research in the 1970s which focused on role conflict or role overload as risk factors for alcohol abuse in women, the 1981 and 1986 surveys found that women with fewer social roles were more likely to drink heavily and with adverse consequences. Recent findings from several countries, including our U.S. survey, suggest that heavier drinking may be more common among women employed in traditionally male-dominated occupations. Characteristics of women's marital or quasimarital relationships also influence their drinking. Having a heavy-drinking partner makes it more likely that a woman will drink heavily herself, and a discrepancy between a woman's own drinking pattern and that of her partner is associated with more adverse consequences of the woman's drinking. An unexpected finding of the U.S. national survey is that divorced or separation predicts remission of alcohol dependence symptoms over a five-year period; this effect is particularly pronounced where the relationship was characterized by sexual dysfunction and/or a frequent-drinking partner.

Findings from this national longitudinal study point to important linkages between women's sexual experience and their drinking behavior. A majority of U.S. women believe that alcohol reduces sexual inhibition and enhances sexual pleasure, with these positive expectancies more common among heavier drinking women. A history of childhood sexual abuse predicts the onset of problem drinking, and problems of sexual adjustment are a strong predictor of continued problem drinking over a five-year period. Some women may use alcohol to self-medicate sexual difficulties created by early sexual abuse and/or societal suppression of female sexuality. Further research is needed to discover ways of applying recent advances in scientific knowledge to facilitate early identification of and intervention with women substance abusers. **AFFILIATION:** Dept. of Neuroscience, University of North Dakota School of Medicine, Grand Forks, ND 58202

WORKING WITH A COMPLEXITY OF ISSUES: CO-MORBIDITY IN ADDICTED WOMEN

I.E. SMITH; C. RASKIND-HOOD; C.D. COLES AND D. SOWEMIMO

Among women presenting for treatment, alcohol and other drug use are often accompanied by significant cofactors which may affect intervention and treatment outcome and increase relapse risk. Cofactors include affective disorders, Post Traumatic Stress Disorder (PTSD), and other psychiatric illness as well as a lack of social support, social isolation and stress. Thus, depressive symptoms are a primary concern in treatment as well as the effects of sexual and physical abuse. In addition, cocaine use leads to extreme mood fluctuations, from euphoria to depression. Smith, et al. (in press) found that 38% of cocaine-using women not in treatment reported past suicide attempts compared with 14% of those seeking drug treatment, suggesting that cocaine users are at high risk for suicidal ideation and attempts.

The present study examined the prevalence of depressive symptoms, including suicidal ideation in a sample (n=217) of cocaine-abusing women who were either: (1) participants in an intervention program for pregnant and parenting women; or (2) subjects in a study on the developmental effects of prenatal cocaine exposure. More than 1/3 reported suicide ideation or attempts. Comparisons of subjects with (SH+) and without (SH-) a history of suicide attempts suggest that these constitute distinct groups of addicts. While groups did not differ demographically, SH+ subjects were significantly higher on the alcohol ($p < .05$). drug ($p < .0001$), family/social ($p < .004$). and psychiatric ($p < .001$) subscales of the Addiction Severity Index (ASI) and more often in the pathological range on the Psychiatric Symptom Checklist 90 (SCL-90). SH+ subjects were also more likely to be polydrug users with a longer history of CNS depressant use, including alcohol, and more likely to report family drug problems ($p < .02$).

Depression and suicide ideation in addicted women may be multi-determined by: drug use itself; chronic psychiatric illness; PTSD symptoms due to abuse; HIV positive status; limited resources and multiple stressors. The results of this study suggest the importance of a comprehensive psychiatric evaluation at intake and the development of individualized treatment plans.

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CRIMINALIZATION OF THE PREGNANT ADDICT: THE IMPACT ON FAMILIES AND CHILDREN

Sandra A. Garcia

Criminalization of prenatal drug abuse has resulted in a complex set of reactions and practices that demand close study as related to the rights and welfare of pregnant and postpartum drug abusing women and their families. When Jennifer Johnson, a twenty-three year old woman addicted to cocaine was convicted of the delivery of a controlled substance to a minor following the birth of her chemically exposed baby, a concerted effort by professionals from diverse disciplines such as law, medicine, sociology, and ethics was successful in slowing the number of similar prosecutions. However, prosecutors in some jurisdictions have continued to charge pregnant and postpartum drug abusing women with fetal abuse, child abuse and neglect, involuntary manslaughter, fetal endangerment and delivery of a controlled substance to a minor.

The criminalization of prenatal addiction has had far-reaching effects on women, children, and families, including stigmatization of the women, their fear of detection and punishment and subsequent foregoing of adequate prenatal care, an erosion of trust between doctor and patient due to reporting practices, and the displacement of children whose mothers are incarcerated, or who have lost custody while they are on probation.

In addition to the debate over addiction as a disease that should not be punished, and addiction as a punishable, volitional criminal act, the criminalization of prenatal addiction has evoked calls for some form of accountability for the women who endanger the health of their fetuses and children. Thus, prosecutors and treatment personnel in a growing number of jurisdictions has agreed to enforce laws that allow treatment in lieu of prosecution.

While opponents of this sort of compromise assert that the threat of punishment is legally and ethically suspect, and carries many of the same negative effects on the women as does actual prosecution, proponents of the practice, including some women, themselves, point out the validity and effectiveness of coerced treatment. People on both sides of this debate agree that women who seek and successfully complete treatment programs in lieu of prosecution need greater assistance in strengthening their families during and after treatment. Support must come from the legal system, social service agencies, and community resources.

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ADDICTION PROBLEMS IN WOMEN

I. E. SMITH

Addiction problems in women are associated with a broad spectrum of issues. Although, in recent years, we have focused a considerable amount of attention and resources on the issues of pregnancy and drug use, we are still falling short of meeting the needs of this population in a "gender relevant" and efficacious manner. Punitive social policies have created numerous barriers to quality care for addicted women. Moreover, we still have only limited understanding of the myriad factors which may predispose women to turn to alcohol or other drugs during pregnancy or at other times in their lives.

Despite the fact that alcohol may be the most widely used drug, we still have only limited understanding of factors which may precipitate alcohol problems in women or of trends in alcohol use among different populations and cohorts of women. The significance of historical factors such as changing roles of women in society, changing social values, relationship and sexuality issues in the etiology of alcohol problems in women all merit further investigation.

Social concern about fetal outcomes has led to increased funding for addicted women who are pregnant and the development of numerous programs to intervene with women in this particular sub-group. As intervention strategies have become more refined, we have realized the need for specialized psychosocial as well as pre and perinatal care for the pregnant addict. However, negative attitudes and punitive social policies continue to reinforce barriers to quality care for this high risk population. The complex inter-relationships between the medical and the psychosocial needs of the mother and the unborn child have highlighted a need for cross training between medical and social service personnel. Experience with this special population has also illuminated the need for more effective linkages between primary health care, prenatal care, mental health and social services.

The legal debate over the "conflicting" interests of the mother and her unborn child has also had some far reaching consequences. While the debate rages on, many states have enacted punitive legislation making drug use during pregnancy a criminal offense. We have directed much of our attention toward the very limited period of pregnancy and the immediate post-partum period, while failing to consider the impact of our policies and interventions on family systems, foster care, and children of drug using mothers.

The key to the prevention of congenital disorders associated with maternal drug abuse is effective intervention and treatment for addicted women. Women often present for addiction treatment with multiple problems, in addition to their drug use. The high prevalence of affective disorders in addicted women, particularly depression, also places them at high risk for suicidal ideation and attempts. The importance of comprehensive intake assessments and individualized treatment plans cannot be overstated. AFFILIATION: Dept. of Psychiatry, Emory Univ. Sch. of Med., Atlanta, GA

PHARMACOLOGY OF IRREVERSIBLE OPIOID ANTAGONISTS

J. WOODS

Dr. Richard Rothman presented an overview concerning the in vitro characterization of irreversible ligands. He defined an affinity ligand as a ligand possessing such high affinity that the receptor-ligand interaction is non-equilibrium while pointing out that such an interaction need not necessarily be of a covalent nature. He then described the basic procedure by which these affinity ligands can be identified in vitro. The first step is to determine apparent K_i values in standard "reversible" binding assays (i.e. competition studies vs. selective radioligands). This provides useful selectivity information which can then be used to study the putative affinity ligand in "wash-resistant" inhibition binding. This technique most commonly consists of multiple centrifugations ("washings") of a membrane preparation pretreated with an affinity ligand. After each step, the supernatant is tested for residual free ligand and the pellet is resuspended and subjected to binding assays. One fundamental characteristic of an affinity ligand is that, once present in a membrane preparation, repeated washing of the preparation should be largely ineffective in removing the compound from the receptor. In addition, Dr. Rothman emphasized the importance of measuring the contribution of supernatant inhibition to wash-resistant inhibition, since a wash-resistant inhibitor may appear to be irreversible but not actually be so.

Dr. James Woods presented an overview of the jn vivo characterization of opioid receptor alkylators. He discussed several criteria for determining whether an antagonist acts in a competitive or a noncompetitive manner in vivo. First, the shifts in an agonist dose-effect curve produced by a noncompetitive antagonist depend, in part, upon the intrinsic efficacy of the agonist. For example, in a series of agonists with similar selectivities for a particular receptor, a given dose of an irreversible antagonist would antagonize those agonists with lower intrinsic efficacies to a greater degree than those with higher efficacies. In contrast, a given dose of a competitive antagonist would antagonize all of the agonists to a similar degree, regardless of intrinsic efficacy. Second, if it can be assumed that irreversible antagonists permanently inactivate receptors, then it follows that new receptors must be synthesized for the antagonist effect to diminish. For this reason, irreversible antagonists usually have a longer duration of action in vivo than do competitive antagonists. Along these same lines, the percentage of receptors eliminated by an irreversible antagonist should be positively related to both the dose of the antagonist and the time it takes for receptor recovery to occur. The significance of protection experiments was also discussed. This refers to the ability of a competitive antagonist to protect against the actions of an irreversible antagonist when the reversible compound is administered first. This type of experiment is crucial in determining whether the apparent irreversibility is due to pharmacodynamic or to pharmacokinetic factors. He stressed that none of these criteria alone are sufficient to conclude that a compound acts in an irreversible fashion in vivo. All criteria

should be met and these results must be compared to data generated from in vivo studies such as those discussed by Dr. Rothman before an accurate determination of irreversibility can be made. Dr. Woods summarized this portion of the symposium by highlighting the importance of irreversible antagonists as pharmacological tools. For instance, they can provide valuable insights into receptor function. They can be useful for in vivo application of classical receptor theory such as the determination of pharmacologic constants (e.g. agonist affinity and intrinsic efficacy). Finally, they can be quite helpful in relating receptor occupancy to receptor function.

Next, Dr. Frank Porreca talked about the use of novel and selective irreversible ligands in opioid receptor differentiation. He presented several examples of their utility in defining opioid receptor subtypes. However, he also sounded a note of caution regarding the interpretation of results obtained with putative subtype-selective irreversible antagonists. An example of this occurred with the study of UPHIT, a benzacetamide derivative which contains an isothiocyanate electrophile. His laboratory found this compound to be an irreversible antagonist with an apparently high degree of selectivity for the kappa-1 receptor subtype. This conclusion was based on the finding that, in mice, UPHIT antagonized both the analgesic effects and the specific binding of U-69,593, a kappa-1 selective benzacetamide agonist, while having no effect on bremazocine, a kappa-2 selective benzomorphan agonist, in either assay. This seemed to be a straightforward assumption. However, since no kappa-2 selective irreversible antagonist was available, the question arose as to whether the differential antagonism by UPHIT of the analgesic effects of U-69,593 and bremazocine was due to the selectivity of UPHIT or to the intrinsic efficacies of the agonists. With regards to the latter, it could be argued on the basis of the above finding that bremazocine simply has a much higher analgesic efficacy than does U-69,593 and is capable of producing a full analgesic effect even when a substantial fraction of receptors is eliminated. In addition, this study contained what seemed to be a major inconsistency in that UPHIT had no effect on the analgesic response to CI-977, another kappa-l selective benzacetamide. Perhaps this was also a case of high intrinsic efficacy. Both of the above questions were assessed by making direct measurements of relative efficacy in a smooth muscle preparation. There it was found that CI-977 did have a much higher intrinsic efficacy than U-69,593 and that the efficacy of bremazocine was similar to that of U-69,593. These findings support the initial conclusion that UPHIT is a kappa-l selective irreversible antagonist. In contrast, he showed that such problems did not arise during the characterization of delta receptor subtypes. In this instance, irreversible antagonists exist for both the delta-1 (DALCE) and the delta-2 (5'-NTII) subtypes and a bidirectional separation of the effects of delta-l selective agonists (e.g. DPDPE) and delta-2 selective agonists (e.g. DSLET) could easily be demonstrated.

Dr. Timothy Burke then discussed some findings obtained in mice with clocinnamox (C-CAM), a novel irreversible opioid antagonist synthesized in the laboratory of Dr. John Lewis. He showed evidence that C-CAM is a systemically-active irreversible antagonist with no agonist activity at mu receptors. It was found to possess many of the predicted in vivo characteristics of an irreversible antagonist. For example, certain doses of C-CAM antagonized the analgesic effect of morphine to a greater degree than the analgesic effect of fentanyl or, to an even greater degree, etonitazene. In contrast, a single dose of the competitive antagonist naltrexone antagonized the analgesic effects of all of the mu agonists listed above to a similar degree, illustrating one major difference between the two types of antagonists. C-CAM also exhibited a substantially longer duration of antagonist action against the analgesic effect of morphine than did naltrexone. Furthermore, simultaneous administration of various

doses of the short-acting competitive antagonist naloxone with the highest dose of C-CAM tested blocked, or protected against, the antagonist effects of C-CAM versus morphine in a dose-dependent manner. He also described the results of a series of experiments in which the animals were pretreated with various doses of C-CAM at various times prior to their sacrifice. Cerebral membranes were then isolated from these mice for use in receptor binding experiments. These experiments showed that C-CAM pretreatment decreased the B_{max} of the mu-selective radioligand [^{3}H] DAMGO in a dose-dependent manner while not affecting its K_d, or affinity. Furthermore, the doses of C-CAM required to produce a complete or near-complete inhibition of [^{3}H] DAMGO binding in this assay were those that eliminated the analgesic response to morphine, but not to fentanyl or etonitazene. The duration of inhibition by C-CAM of [^{3}H] DAMGO binding was also similar to the duration of antagonism of morphine analgesia. Together, these results indicate that the ability of C-CAM to antagonize the analgesic effects of mu opioids is largely, but not completely, due to the elimination of mu receptors. Finally, it was shown that C-CAM also has affinity for kappa and delta receptors. C-CAM appears to be approximately twice as selective for mu receptors as for kappa and 10-20 times as selective for mu than for delta receptors. C-CAM should prove to be a useful and interesting tool for the study of opioid receptor mechanisms.

Dr. Jean Bidlack talked about her work with some novel irreversible opioid antagonists which were developed in the laboratory of Dr. Sydney Archer. The novel feature of these ligands is that they contain sulfhydryl groups which can form covalent disulfide bonds by oxidative coupling to a sulfhydryl group in the receptor protein. One of these compounds, TAMO, exhibited an analgesic effect immediately after administration which appeared to be mediated through mu receptors as it was blocked by the mu-selective irreversible antagonist beta-funaltrexamine. This agonist action diminished after approximately 2 hours, at which time TAM0 became a selective mu antagonist with a long duration of action against morphine analgesia. Another compound that she described was the N-cyclopropylmethyl analog of TAMO (N-CPM-TAMO). This compound did not exhibit any agonist activity and possessed a similar selectivity profile to that of the patent compound TAMO. It was also a long-acting antagonist of morphine analgesia. One problem with sulfhydryl-reacting compounds is that they react with glutathione, which contains a sulfhydryl group and is commonly present in membrane preparations. Competition with glutathione may therefore complicate the results obtained with sulthydryl-reacting compounds such as TAMO or N-CPM-TAMO in binding assays. Nevertheless, both compounds appeared to be irreversible mu-receptor antagonists both in vivo and in vitro.

Dr. John Lewis closed the symposium with a brief discussion of the role that structural characteristics of irreversible opioid antagonists play in terms of function. He pointed out that structural aspects contribute a great deal to the agonist/antagonist and specificity profiles of opioid alkylating agents. Furthermore, less reactive alkylating groups are more beneficial in terms of central availability after systemic administration than are highly reactive groups which can interact in an irreversible manner with any number of proteins en route to the CNS. Finally, he observed that some high affinity, non-electrophilic ligands, such as buprenorphine, can also interact with receptors in an essentially irreversible manner.

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CLINICAL RESEARCH METHODS FOR DRUG ABUSE MEDICATIONS DEVELOPMENT

C. V. GRUDZINSKAS AND G. E. BIGELOW

The effective and efficient development of new medications is guided by a series of well defined decision points -- beginning with a Medical Needs Assessment and ending with regulatory approval of the New Drug Application (NDA) and market introduction of the new pharmacotherapeutic agents.

Three medications for treating heroin abuse/dependence are currently approved (methadone, naltrexone, naloxone) and other (levo-alpha-acetyl-methadol, buprenorphine) appear well on their way toward approval. The development of medications to treat cocaine abuse/dependence lags considerably. Methods are needed for identifying promising pharmacotherapeutic agents for cocaine abuse/dependence and for assessing their likely therapeutic value so that efficient decisions can be made during this medication discovery and development process. This process of developing medications to treat cocaine abuse may benefit from the experience and the methods used with other types of substance abuse, or novel methods may be needed. At this time it is unclear which animal and/or human pharmacology models and procedures will have the necessary predictive validity.

This symposium provides an update on the current state of the art in clinical research on identification, evaluation, and development of medications for treatment of drug abuse and dependence. Special focus is placed on the predictive ability of the various clinical pharmacology models and procedures and on their value in guiding discovery and development decisions regarding anti-cocaine pharmacotherapies that might:

1. treat/reduce cocaine toxicity;
2. reduce cocaine use and/or aid initiation of cocaine abstinence;
3. prolong periods of cocaine abstinence.

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THE ROLE OF HUMAN LABORATORY STUDIES IN DRUG ABUSE MEDICATIONS DEVELOPMENT

G. E. BIGELOW

Human laboratory methods offer a powerful and sensitive technology for assessing the likely therapeutic efficacy of medications for treatment of drug abuse. It is advocated that human laboratory methods should be used to identify promising drug abuse treatment medications and to guide the selection of medications for further evaluation in clinical trials. At present, a variety of medications, with vastly different neuropharmacological mechanisms, are being studied or proposed for study as potential pharmacotherapies for cocaine abuse, often with little or no evidence of relevant behavioral pharmacological activity. Such activity can be detected most sensitively and efficiently in the well-controlled and precisely-measured laboratory setting.

Human laboratory studies also offer advantages from the perspective of safety assessment. Potential interactions of the treatment medication with the drug of abuse can be detected and managed most effectively in the laboratory setting.

A useful conceptual framework is to view the goal of drug abuse pharmacotherapy as being to reduce the abuse liability of drugs of abuse. An extensive and well-validated experimental literature exists concerning assessment of drug abuse liability in humans. A promising medications-development approach is to assess whether putative pharmacotherapies alter the effects of drugs of abuse in directions suggestive of reduced abuse liability. One recommended method is to evaluate the subjective, physiological and behavioral effects of laboratory challenges with drugs of abuse before, during, and after chronic treatment with gradually escalating doses of the test medication. Studies with buprenorphine treatment of opioid abuse have demonstrated sensitivity of laboratory measures to relevant effects not detected by more global clinical outcome indices.

The sensitivity and value of human laboratory procedures for evaluating potential anti-cocaine pharmacotherapies is illustrated by two recent studies. In one, dual abusers of opioids and cocaine were tested in the laboratory for response to 40 mg i.v. cocaine challenges before and during treatment with buprenorphine 9 mg/day. There was no evidence that buprenorphine treatment reduced cocaine's abuse liability. Rather, nonsignificant trends suggested enhancement by buprenorphine of cocaine's positive subjective effects and of cocaine craving. These data suggest buprenorphine to be a poor candidate as an anti-cocaine pharmacotherapy. In a second study, volunteer cocaine abusers in a residential laboratory were repeatedly challenged with cocaine (0, 20, 40 mg i.v.) before, during, and after chronic daily treatment with the serotonin uptake blocker fluoxetine (up to 40 mg/day). Fluoxetine treatment was associated with a dramatic and dose-related attenuation of the magnitude and duration of cocaine's positive subjective effects. These data suggest fluoxetine and, by implication, other serotonin uptake blockers be promising agents deserving further study as potential pharmacotherapies for cocaine abuse.

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THE ROLE OF SUBJECT CHARACTERISTICS: SYMPTOMATIC VOLUNTEERS VERSUS PATIENTS

E. M. SELLERS AND U. E. BUSTO

Traditionally severely dependent individuals have been used in studies of efficacy and safety of new therapeutic agents for the treatment of addictive disorders. The reasons for focusing on this group, which stands in contrast to most other areas of therapeutic development, are primarily social, political and economic, and to a much lesser extent pharmacologic or scientific.

In the area of abuse liability testing most studies to date have used post-addicts or current abusers. The few studies of "normal" volunteers and those with altered affect have generally found most individuals do not prefer sedative-like drugs such as the benzodiazepines over a placebo. We have recently been conducting abuse liability studies using individuals who arc familiar with psychotropic drug effects but have never used drugs. The strategy we have been following is to screen individuals prior to testing with a test dose of e.g. secobarbital 150 mg, and to select only those who can reliably and appropriately report the drug effects (about 60% of the screened population). We have used a novel clinical trial design to ensure that three pharmacologically comparable doses of the partial agonist benzodiazepine, bretazenil, could be compared to three doses of each of the full agonists, diazepam and alprazolam in 28 experienced drug users. These subjects could distinguish these compounds from each other with respect to time course of drug effects, magnitude of sedation, liking, euphoria and dysphoria. Their pattern of subjective reports were very similar to those of abusers except that they tolerated somewhat lower doses and experienced more dysphoria. Based on this study one could have drawn the same conclusions with respect to relative abuse liability of diazepam and alprazolam as has been derived from epidemiologic, and user and clinician surveys concerning abuse. These data suggest that the validity and reliability of subjective reports of drug effects are more important than a past history of drug dependence.

The issue of patient characteristics is obviously of importance for the medication development field to consider in order that subsets of patients who respond to specific medication alone and in combination with specific non-pharmacologic treatments, can be identified. The focusing of studies on the severely dependent and affected individuals fail to address the under-served patients who are mildly dependent. This group is important from a public health prospective, not only because they are common but also because they are likely to benefit from treatment. From a methodologic standards perspective the full characteristics of trial participants and non-participants should be reported. The treatment outcomes and characteristics of patients who are recruited, mandated and self-referred for treatment, stratified by extent of drug use and other psychopathology, need to be determined.

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THE ROLE OF CLINICAL PHARMACOLOGY IN PREDICTING CLINICAL EFFICACY

B. C.Y. TAI

Medications development is a highly focused activity which may be viewed as a sieving process for determining the efficacy of the potential medications. The current research efforts in the field of medications development are mostly directed toward the validation of the development rationale rather than the prediction of the clinical efficacy of the investigational compound. In light of this, the Medications Development Division (MDD) of the National Institute on Drug Abuse, proposed the establishment of a Clinical Decision Network whose near term goals are to 1) form a network with multi-disciplinary experts, 2) identify and evaluate issues relevant to the design and implementation of clinical trials, and 3) make recommendations on how to generate results that are unambiguous, comparable among trials and consistently predictive of clinical efficacy. The long term goal of this Decision Network is to develop a validated clinical decision tree which will effectively and efficiently move potential cocaine treatment medications into multi-center efficacy trials with an excellent likelihood of success.

The first Clinical Decision Network was held on April 20-21, 1992, in Rockville, Maryland. Experts from the FDA, NIDA's TRUs, the VA-CSP Advisory Group, the PMA Commission on Medications for the Treatment of Drug Dependence and Abuse, and various Divisions within NIDA met to examine critical issues pertinent to the initial clinical pharmacology studies that will yield efficacy predictive results. Elements missing from the current process were identified and the following proposals were made:

1) Missing element: Definition of treatment success. Proposal: In collaboration with DCR/NIDA, Dr. Betty Tai will coordinate the NIDA TRUs and the three NIDA VA clinical centers to develop a proposal defining treatment success criteria.
2) Missing element: Standards of measurements in clinical trials. Proposal: Drs. Charles O'Brien and Paul Fudala working with NIDA's VACSP Advisory Group will draft a proposal that would permit parametric comparison of trial results of the same compound and across compounds.
3) Missing element: The development of new pharmacological assessment methods as predictors of clinical efficacy, Proposal: Dr. Charles Gruzinskas will coordinate an initiative with the NIDA ARC, DCR and DPR to draft new methods proposals.
4) Missing element. Medication development decision network from preclinical to multi-site trials. Proposal: MDD will work with the PMC Commission's Clinical Committee (Dr. Scott Reines - Chair) to develop a medications development decision (Go/No Go) network. Future workshops are planned to review the progress.

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FDA PERSPECTIVE: IDENTIFYING INDICES OF EFFICACY

C. WRIGHT

The FDA regulates the pharmaceutical industry, judging new medications according to the claims to be made about their actions. For practical reasons face-valid short-term indices are frequently used in clinical trials intended to support such claims as surrogates for longer term outcomes.

Disease outcome in clinical trials usually have four dimensions for measurement. These consist of subjective reports by the patient, observer ratings of disease severity, relevant behaviors and various physiological measurements. Robust trials (trials with a high likelihood of success) sample all four dimensions of outcome for a given therapeutic objective. Currently, there is some consensual agreement that medications are needed to modify the cycle of use and abuse of a drug, to enhance therapeutic responses to the environment, and to promote rehabilitation.

Medications which affect drug use may deter initial use by hardening the host, altering the drug's subjective effects, blocking toxicity, modifying tolerance or dependence, treating withdrawal, reducing drug seeking behavior, supporting abstinence, or (perhaps most importantly) relieving suffering. Medications which alter the interaction between the addict and the outside world may help keep the patient (or the victims) alive by reducing down denial, helping to retain the patient in treatment, or supporting rehabilitation by promoting abstinence. Medications may specifically promote rehabilitation by supporting cognition, fostering normal impulse control, or preventing or treating dysphoric mood states.

Investigators may improve their trials by writing a hypothetical package insert before the protocol for a clinical trial of a new treatment. If it appears that the protocol will (if successful) support the desired claims, it is likely to succeed.

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MEDICATIONS DEVELOPMENT: MAXIMIZING THE YIELD OF RESEARCH RESOURCES

F. J. VOCCI

During the past eighteen months, the Medications Development Division (MDD) of the National Institute on Drug Abuse (NIDA) has incorporated business management techniques commonly used in the pharmaceutical industry to evaluate and develop areas of medications development for addictive disorders. A strategic planning process was initiated. A mission statement and goals and objectives for the Division were developed. A five year plan was developed and components of the plan have recently been initiated. The Division has concentrated on the development of pharmacotherapies for the treatment of cocaine and narcotic dependence. The cocaine pharmacotherapy program has both preclinical and clinical components. The preclinical component of the cocaine development program, the cocaine treatment discovery program, has evolved over the last year. This program has compound identification and acquisition teams. Compounds are evaluated through a decision tree in which go/no-go decisions are reached regarding further assessment and compound development. This program will develop substances which are both cocaine-like or cocaine antagonist. A similar process has been implemented in the clinical program with evaluations of the selection process and several compounds currently in testing.

The opiate development program has two New Drug Application (NDA) candidates, LAAM, and buprenorphine. In addition, a depot-injection form of naltrexone has been developed and is currently being tested. A preclinical opiate treatment discovery program has been discussed and will be implemented in the next year.

In addition to the programs, the MDD has made progress in developing regulatory interactions with the Food and Drug Administration (FDA), interactions with the private sector, interactions with grantees and contractors, and developed interagency agreements which can facilitate the development of new medications for the treatment of cocaine and narcotic addiction.

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USE OF DRUGS, TRANQUILLIZER AND ALCOHOL IN TWO NORWEGIAN POPULATION SAMPLES

I. Sandanger

The data to be presented are collected through personal interviews with two random samples in the populations of one part of Oslo and in four municipalities on the islands of Lofoten in Northern Norway. Each sample is 1000 individuals age 18 or older, chosen by the Central Bureau of Statistics. The aims of the investigation are better knowledge of resources and risks for health in the populations; to compare the urban Oslo-population with the rural coast-population; and to make suggestions for better planning in local societies and health services.

Pepresentativity. The respondent rate in Oslo is 75% and in Lofoten 79%. The samples are representative for sex and civil status. In the data used for this paper, only the age groups 20 - 49 will be used.

Use of alcohol, tranquillizer/sleeping pills and illegal drugs in these populations are related to demographic variables and some vulnerability - and risk - variables.

Results. Sex differences arc largest with alcohol: 1.7% women and 11.8% for men. 20 - 29 years have most cases, and there are twice as many cases in Lofoten as in Oslo. Drugs are used equal between men and women, and very seldom in Lofoten. Tranquillizers are used nearly twice as often by women than men, but if one considers daily use the sexes are equal. All three dependent variables increases in caseness as life strain last year or illnesses last year increase. They also increase with lowering social support. Having had parents with alcohol abuse increases use of tranquillizers, and parents treated for nervous problems increases taking drugs. There is a 14% overlap between hazardous alcohol consumption and drug-ever use. Two-thirds of those who use tranquillizers report psychiatric symptoms above caseness score at the Hopkins Symptom Checklist 25 items, 21% among the high alcohol consumers and 22% of the drug-takers. There are large sex differences in favour of more symptoms to women. There are also more psychiatric diagnoses last year as measured by the Composite International Diagnostic Interview. Compared internationally, use of alcohol and tranquillizers are relatively low in Norway, but with large differences within the country. Comparable figures for drugs arc not yet found.

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PEOPLE RECEIVING TREATMENT FOR DRUG AND ALCOHOL PROBLEMS IN AUSTRALIA

A. BAILLIE, R. P. MATTICK, P. WEBSTER AND R. CHEN

The first Australian national census of clients of substance use treatment agencies (COTSA90) was undertaken on Wednesday 21st March 1990. All agencies specializing in the treatment of drug and alcohol problems (n=506) were surveyed with 431 (85.2%) responding.

The results of this census indicate that 6,175 people were receiving services for drug and alcohol problems across Australia on the census day. Ten percent of people seen were collateral's or relatives or friends of a substance user. The mean age of the clients was 34.4 years and two thirds were male. The majority were Australian born with ten percent being Aborigines or Torres Strait Islanders. The majority of clients were not in paid employment. The most frequent presenting drug problem was alcohol (46% of clients) followed by opiates (24%) and poly-drug use (11%). Cocaine was reported as the principal drug problem in less than half a percent of clients.

In September 1989 NIDA and NIAAA conducted the National Drug and Alcoholism Treatment Unit Survey (NDATUS89). This survey of treatment units in the United States provides a point of comparison for the COTSA90 findings. If allowances are made for the methodological differences between COTSA90 and NDATUS89 estimates show the treated prevalence of substances use is between 1.4 and 2.2 per thousand in Australia compared with 2.9 per thousand in the USA.

Australians in alcohol treatment are older compared to NDATUS89 findings while those in treatment for opiate or other illicit drug use are younger in Australia. The age difference in alcohol treatment may be due to greater cultural acceptance of excessive alcohol consumption in Australian society.

A greater proportion of those in treatment for alcohol problems are women in the USA compared with Australia. However, the proportion of women in treatment for opiate and other drug problems in the same. Aborigines in Australia and blacks in the US are over-represented in treatment compared to the make-up of the general population.

A second national census has just been completed with about 5,700 clients currently receiving treatment in Australia.

REFERENCES: Available from the senior author on request.

ACKNOWLEDGMENTS: This research was funded by the Australian Government's Department of Health, Housing and Community Services as part of the National Campaign Against Drug Abuse

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PREVALENCE ESTIMATES OF PSYCHO-PATHOLOGY IN SUBSTANCE ABUSERS TREATED IN METHADONE-PROGRAMS IN THE NETHERLANDS

R. M. W. Smeets, J. Van Limbeek and X. Hofman

The prevalence of psychopathology in substance abusers in the United States of America is high. The main question in this paper is: "Does this also apply for the Netherlands?" An outline of the development of drug treatment programs in the Netherlands is given. The objectives of the coherent treatment program in Amsterdam are:

1. Reduction of negative social consequences of drug abuse 2. Improvement of physical and psychological conditions to bring about a more human existence. 3. To prevent young adolescents from using drugs.

The principles of continuity of care are implemented and priority is given to care instead of cure. Studies and data are presented from three methadone maintenance programs in the Netherlands:

1. A low-threshold program in Rotterdam aiming at stabilization. (n = 116).
2. A high-threshold program in the Hague, treatment oriented, offering counseling and psychotherapy. (n = 152). 3. A public health program in Amsterdam aiming at patients expelled from all other programs (n = 76)
The main results of three studies show that in all programs 75-80% are male. The mean age in the public health program is 37.2 years, 10 years more than in the other programs. Psychopathology was assessed within the first 10 days of admission using the NIMH-DIS-III-A. Current and life-time prevalence of at least one DSM-III-axis 1 disorder are in the low-threshold program, 26.1 vs. 40.0%; and in the high-threshold program, 40.0 vs. 67.8%. Current and life time prevalence of no DSM-III diagnosis are in the low-threshold program, 50.4 vs. 435%: and in the high-threshold program, 19.5 vs. 13.8%. Current and life time prevalence of A.S.P. do not differ significantly between programs. Life-time prevalence of dysthmic disorder ranges from 38.5% in the change-oriented program to 11.5% in the low-threshold program to 8.6% in the public health sample. The life-time prevalence of psychotic disorders ranges from 3.9% in the treatment oriented program to 4.5% in the low-threshold program to 17.3% in the public health program.

The results lend support to the following hypotheses:

1. The prevalence of psychopathology in substance abusers in methadone-maintenance programs in the Netherlands does not differ significantly from the U.S.A. 2. Substance abusers with higher levels of psychiatric co-morbidity are treated in high-threshold change oriented treatment programs. 3. The public mental health organization takes care of a hard to treat, most severely ill, and more psychotic group of substance abusers.
The clinical relevances of these results are discussed.

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PREVALENCE ESTIMATES OF SUBSTANCE ABUSE, SOCIAL FUNCTIONING AND DEMOGRAPHIC CHARACTERISTICS IN GENERAL POPULATION CASES, IN GENERAL PRACTITIONERS' CASES AND IN MENTAL HEALTH CARE CASES IN THE EAST/SOUTH CATCHMENT AREA OF AMSTERDAM

X. Hofman, J. van Limbeek, and L. Wouters

SUBJECTS METHOD: Data (1458 Subjects) of a research project in the Amsterdam East/South Catchment Area (80,000 inhabitants) are presented. Results from two studies were combined. The total study-population is divided in three strata:

I. General population: a representative sample of the register of population in the catchment area (410 subjects).
II. General practitioners: consecutive admissions of 41 general practitioners in the catchment area (938 subjects).
III. Psychiatric outpatient facilities: consecutive admissions of psychiatric outpatient facilities in the catchment area (110 students).

From each subject, a complete psychiatric history was obtained using the Dutch version of the NIMH-DIS Version III-A. Psychosocial functioning was assessed with the Sickness Impact Profile (The SIP). The SIP provides a measure of perceived health status.

RESULTS: The response rates were .52 for the general population stratum, .65 for the general practitioners stratum, and .70 for the psychiatric outpatient facilittes stratum. Results were not biased regarding demographic variables.

A significant increasing trend in prevalence rates of affective disorders, anxiety disorders and any DIS/DSM-III disorder across strata was found.

In a whole group analysis it was found, despite different prevalence rates of substance dependence in three strata, that the probability of psychiatric comorbidity in substance dependent persons does not differ across strata (Mantel-Haenszel Odds Ratios varied from 2.4 to 2.7 for different diagnostic categories). Alcohol dependent persons are less likely to have psychiatric comorbidity as drug dependent persons and the prevalence of psychosis does not significant differ between alcoholic and non-alcoholic persons.

Two other findings ought to be stressed: (1) psychiatric outpatient facilities are more likely to have substance dependent disorders as persons in lower strata and (2) a significant increasing trend across strata in mean number of days on sick leave, mean number of psychopathological symptoms and psycho-social dysfunction (SIP) was found. Therefore, although the differences are not impressive, these findings probably reflect the impact of psychiatric comorbidity in substance dependent persons over time.

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GENETIC APPROACHES TO UNDERSTANDING THE ACTIONS OF DRUGS OF ABUSE

R. J. MARLEY; A. C. COLLINS; G. I. ELMER; S K. SUDAKOV;
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Techniques from the fields of behavioral genetics, pharmacogenetics, quantitative genetics and molecular genetics have been used extensively for investigations of the actions of alcohol and nicotine. The use of these genetic approaches has contributed substantially to our understanding of individual differences in response to alcohol and nicotine and the mechanisms underlying the actions of these substances. More recently, these techniques have begun to be applied to studies of the actions of psychomotor stimulants and opiates. This symposium provided an opportunity for investigators, using a variety of genetic techniques to study problems related to drug abuse, to present their techniques and findings. It also served as an introduction to genetic techniques available for studying drug abuse.

A number of studies have presented evidence which suggest that tobacco use is regulated, in part, by genetic factors. It has been argued that environmental factors promote or inhibit the initiation of tobacco use, whereas genetic factors regulate its persistence. These genetic factors may influence sensitivity to the acute actions of nicotine, the development of tolerance to these actions, the development of dependence on nicotine or the reinforcing actions of nicotine. Studies conducted by Al Collins and colleagues utilizing inbred and selectively bred mouse strains have provided evidence concerning some of these measures as well as providing partial neurochemical explanations for variability in response to nicotine. Analyses of genetic influences on sensitivity to nicotine suggest that the number of brain nicotinic receptors partially regulates sensitivity to nicotine. These studies assessed the relative sensitivities of 19 inbred mouse strains to nicotine on seven behavioral and physiological measures. The strains varied 2-3 fold in their sensitivities to nicotine. Interestingly, the rank order of sensitivity varied depending upon the response measured. Principal component analyses suggested that a minimum of two separate response systems may exist; one characterized by nicotine effects on locomotor activity and body temperature and another characterized by nicotine-evoked seizures. Correlational analyses suggest that the Y-maze/body temperature responses may be regulated by a variant of the nicotinic receptor that binds [3H]-nicotine with high affinity. The seizure measures seem to be associated with a nicotinic receptor that binds α-bungerotoxin. Other studies have assessed whether genetic factors regulate the development of tolerance to nicotine. A recent analysis of nicotine tolerance utilized 5 inbred mouse strains that differ in sensitivity to an acute challenge dose of nicotine. These five strains were treated chronically by i.v. infusion of increasing doses of nicotine. Tolerance to nicotine was determined for several measures. The five mouse strains differed dramatically in the nicotine infusion dose that produced

detectable tolerance to nicotine. Those mouse strains that were most sensitive to an acute challenge dose of nicotine developed tolerance at the lowest infusion doses. Resistant strains developed tolerance only after chronic treatment with the highest infusion doses. This analysis also included an evaluation of the effects of chronic nicotine on the number and affinity of brain nicotinic receptors. Tolerance development correlated highly with nicotine receptor changes in strains that developed tolerance at low infusion doses, but no significant correlations were seen for those strains resistant to the development of tolerance. Tolerance development correlated with changes in the number of bungerotoxin binding sites only for the tolerance resistant strains. These results indicate that tolerance to nicotine is not inextricably due to receptor up-regulation. Preliminary data suggests that strain differences in the reinforcing properties of nicotine may also exist. Thus, initial sensitivity and the development of tolerance to nicotine and preference for nicotine appear to be genetically regulated with common genes regulating the number and functional status of brain nicotinic receptors.

The behavioral genetics model investigates individual differences in behavior as a function of an individual's genotype, environment and interactions between the two. Greg Elmer has been integrating behavior genetics methods and classical pharmacological techniques to determine genetic and pharmacological contributions to characteristics important in the acute effects of opioids. Potency, efficacy and genotype are important for the pharmacological effects of a drug. Genetic differences in opioid potency have been studied extensively, however, genetic factors important in the therapeutic efficacy of opioids have not been investigated. Genetic differences in the potency of morphine were determined in eight inbred mouse strains using the hot-plate technique. Genetic differences in morphine's' therapeutic efficacy were determined by administering an equi-active dose of morphine for each respective strain at increasing stimulus intensities on the hot-plate. Quantitative differences in potency and large quantitative and qualitative differences in therapeutic efficacy were found as a function of genotype. These results suggest that the factors mediating potency and therapeutic efficacy are genetically and possibly mechanistically unrelated. A second set of experiments determined genetic differences in relative y-receptor reserve and agonist affinity using an in vivo pharmacological method of partial irreversible receptor blockade. These studies suggest that u-opiate receptor reserve as determined in vivo is an important factor for sensitivity to morphine. Mu-receptor reserve was highly correlated with the potency of morphine across genotype. Conversely, agonist affinity and sensitivity to delta opiate antagonists appear to be important factors in differences in the therapeutic efficacy of morphine. The characterization of genetic differences in the therapeutic efficacy of opioids adds an important dimension to the investigation of genetic components in opioid-related drug effects. Behavioral pharmacogenetic techniques have also been used to investigate genetic influences on intravenous opioid self-administration behavior. Genetic differences in relative sensitivity to the acute analgesic effects of morphine and the development of tolerance and withdrawal severity from morphine are currently being investigated in several inbred rat strains known to differ significantly in general locomotor activity and response to acute stress. Large differences in morphine self-administration behavior, morphine intake

under two bottle preference procedures and locomotor stimulant effects were found as a function of genotype. In addition, genotype by environment interactions thought to be important in the complex behavioral effects of a drug have been investigated. Genetic variations in extinction patterns during self-administration studies suggested possible differences in conditioned drug effects. To this end, environmental conditioning studies using opioids demonstrate that genotype may be an important factor in conditioned drug-like effects and may play a role in drug-seeking behavior.

The range of individual differences in susceptibility to drugs of abuse is obviously enormous. Understanding the determinants of these individual differences is essential both for the purposes of identification of risk factors and for design of rational preventive or therapeutic interventions. Until recently, two general approaches have been available for studying the domain of genetic influence: (1) single locus methods when a single gene has powerful influence resulting in discrete phenotypic categories, and (2) methods appropriate to quantitative genetic analyses when there is clear evidence of resemblance of relatives, but a smooth, continuous distribution of the phenotype in the population. The single locus approach, when applicable, offers substantial advantages. These include prospects for characterization of individuals' genotypes for purposes of genetic counseling or pre-onset intervention and the possibility of identifying the primary gene product with consequent opening up of avenues for research on mechanism. However, the enormous range of "normal" individual differences in response to drugs is largely inaccessible to this approach. In these cases, statistical approaches can characterize the proportion of that variability which is due to genetic differences among individuals, and can describe the role of shared genes in determining correlations among pharmacological phenotypes. Just as the single locus approach is powerful in its clarity and simplicity, the quantitative genetic approach is powerful in its comprehensiveness. It can detect the effects of all genes, regulatory, as well as structural, that influence the phenotype in any way. The analytic models typically posit an indefinitely large number of genes of equal, indefinitely small, effects. The genes remain anonymous and largely inaccessible to mechanistic study. It has long been appreciated that for many continuously distributed phenotypes the involved loci may be unequal in magnitude of effect, with some having substantial influence. Methods of investigating these situations have been limited until quite recently when molecular genetics provided, in the form of restriction fragment length polymorphisms (RFLP), a method of "marking" mearly the whole of the chromosomal material. The availability of RFLP has inspired a burgeoning research effort on the topic of quantitative trait loci (QTL). QTL are loci that have a detectable effect on the variance of a quantitative phenotype although they are not so influential as to be found by conventional single locus approaches. This research has been remarkable in that QTL have been found for almost every phenotype studied and in that a substantial proportion of the phenotypic variance can be ascribed to these QTL. The systematic search for QTL in animals has only begun; in respect to pharmacogenetics, bare beginnings have been made in alcohol studies.

McClearn and other have begun utilizing a particularly powerful approach to QTL in drug-related processes which utilizes recombinant inbred (RI) strains

of mice. RI strains are inbred strains derived from the crossing of two parental inbred strains to produce an F1 and subsequent F2 generation. Several RI strains are then derived from the genetically segregating F2 generation by inbreeding. For each locus for which the alleles of the parental strains differ approximately half of the RI strains should be homozygous for the allele of one allele and half homozygous for the other allele. If a single gene is responsible for a trait approximately half of the strains should be like one parent and half like the other with no intermediate phenotypes. Conventional RI analyses permit the identification of single loci of major effect, and the assessment of heritabilities and genetic correlations among phenotypes. Adaptation and extension of the classical RI analysis to include QTL analyses, however, permits the identification of multiple chromosomal regions in which there are genes influencing a phenotype of interest. RI strains, thus, provide a valuable tool to identify QTL associated with quantitative traits that show continuous RI strain distribution patterns. QTL also offer an exciting prospect of selective breeding directly for genotype, rather than indirectly on the basis of phenotype, as has been necessary heretofore. Lines generated by QTL-based selection provide a powerful means of confirming the causal relationship of marker and phenotype and to provide "purpose-built" models for investigating neurochemical mechanisms.

Belknap and colleagues have used a QTL approach to assess associations between a quantitative trait (e.g. morphine sensitivity) and allelic variation at one or more previously mapped marker gene loci. For this purpose, a correlation coefficient between the BXD RI strain means for 4 morphine-related traits (hot plate-assessed analgesia, hypothermia, locomotor activity and Straub tail) and a series of 360 marker loci was calculated as an initial screen for candidate QTL chromosome sites. These RI strains were originally derived from a cross between C57BL/6J and DBA/2J inbred mice, and have been used extensively as a tool for chromosome mapping efforts. Each marker locus was scored as a zero if the C57 allele was present, and a one if the DBA allele was present, for each of the BXD RI strains. A significant correlation between a trait of interest and a marker locus suggests that a QTL affecting the trait of interest is located in the same chromosome region as the marker, i.e., they are linked. Strain sensitivity to morphine-induced analgesia, hypothermia and locomotor activity were all genetically intercorrelated with each other among the 20 RI strains, but not with Straub tail. Naloxone K_D was also correlated in the expected direction with the first three measures. QTL analysis revealed about a half dozen candidate chromosome sites for each sensitivity and naloxone binding measure. The one shared in common with naloxone K_D, Bmax, morphine analgesia and hypothermia was the *Mpmv-5* region of chromosome 10. Since naloxone K_D was strongly associated with this chromosome region, this binding parameter may be serving as a marker for one of the opioid receptor genes, which heretofore have not been mapped. If *so,* the *Mpmv-5* region may be the site of one of the opioid receptor genes, most plausibly the mu receptor gene(s).

Several methods are available for the analysis of complex human behavioral phenotypes such as substance abuse. These methods include family, twin, and adoption studies, as well as segregation, linkage, and association strategies. Although each method had its own implicit assumptions and

limitations, converging evidence obtained from such alternative research designs would provide evidence of a significant genetic etiology for substance abuse. Unfortunately, for substance abuse other than alcoholism, very few of these designs, other than family studies, have been utilized. The goal underlying family study designs is to determine the extent to which a disorder clusters within families. The prevalence of the disorder in relatives of affected individuals is contrasted against the prevalence of the disorder observed in relatives of a comparable group of unaffected individuals or a community sample. For example, Rounsaville and colleagues (1991) reported 38.4% of the relatives of a group of opiate addicts had a drug disorder compared with a community sample estimate of only 5.7% for drug disorder. The resemblance between family members may be due to both genetic and environmental factors; therefore, increased risk for drug abuse in family members of abusers is consistent with, but not proof of, a genetic etiology. Stronger evidence for a genetic component to substance abuse would come from twin and adoption studies, but there are few of these studies due, at least in part, to difficulties in obtaining enough of these rare individuals to ensure meaningful genetic analysis. Twin studies rely on the comparison of concordance rates in identical and fraternal twins and ascribe any increased concordance in identical twin pairs versus fraternal twin pairs to the greater genetic similarity of identical twins. The adoption method separates genetic and environmental effects by studying adopted-away offspring of affected biological parent(s). Cadoret and colleagues (1986) found that drug abuse in adoptees was predicted by having a biological parent with alcohol abuse. Furthermore, it was reported that divorce and psychiatric disturbance, but not alcoholism, in the adoptive family were associated with drug abuse in the adoptee. These findings suggest both genetic and environmental factors are important in the etiology of substance abuse.

Once evidence has been obtained to indicate a significant genetic etiology for a complex disorder, the next logical step in identifying the genetic factors is to determine the way in which the genetic vulnerability is transmitted. Segregation analysis is a statistical tool which compares the observed segregation patterns within affected families to expected segregation patterns under the conditions of random aggregation, a single major locus, multifactorial transmission, and a single major locus with a polygenic background. Likelihoods are compared for nested models in order to determine the model most consistent with the data. Segregation analysis of substance abuse has not been reported in the literature. Genetic linkage strategies utilize the information from segregation studies in order to analyze the co-occurrence of disorder and a genetic marker within related individuals. This co-occurrence is described by the lod score which is the log10 of the odds favoring linkage. Association studies, on the other hand, compare the presence of a particular marker in unrelated, affected individuals with the frequency of occurrence of the same marker in unrelated, unaffected individuals. In 1990, Blum and associates reported an allelic association of the D2 dopamine receptor gene with alcoholism. Although some studies have failed to replicate this association, 2100 subjects in 14 laboratories have been studied to date and a meta-analysis of these data suggest that the TaqI restriction fragment length polymorphism originally reported by Blum is found more frequently both in alcoholics and other drug abusers.

BEHAVIORAL ECONOMICS: A NOVEL APPROACH TO THE STUDY OF DRUG DEPENDENCE

W. K. Bickel, R. J. DeGrandpre, S. T. Higgins, and J. R. Hughes

Drug abuse and dependence are among the most important problems facing society today. Understanding the determinants of drug abuse has been advanced by a considerable quantity of research which has catalogued a variety of factors that control drug taking in the laboratory and in the real world. However, an integration of those various factors into a consistent parsimonius system has yet to be accomplished. Behavioral economics, which is the application of economics principles to the behavior of individuals, has the potential to integrate that research. In this presentation, the utility of behavioral economics for the study of drug dependence was addressed.

Specifically, we presented research that shows the utility of behavioral economics for 1) the integration of variables that control drug taking into singular terms via the economic notion of unit price; 2) the identification of a fundamental behavioral process previously unrecognized; 3) the quantification and subsequent prediction of drug consumption; and 4) evaluating the effectiveness of medications to treat drug dependence via application of the economic concept of elasticity (sensitivity of consumption to price).

We conclude that behavioral economics provides a novel conceptual framework for the study of drug dependence that is consistent, integrative, and parsimonius.

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BEHAVIORAL ECONOMICS AND DRUG CHOICE IN RHESUS MONKEYS

M. A. Nader and W. L. Woolverton

For several years, we have been investigating environmental determinants of choice between drug and non-drug positive reinforcers in monkeys. We have found, for example, that an increase in the magnitude of an alternative reinforcer can decrease the frequency of drug choice in a two-option situation (Nader and Woolverton, 1991). In another experiment (Nader and Woolverton, 1992), when monkeys were given a choice between cocaine and food, consumption of cocaine increased with dose as did the frequency with which it was chosen relative to food. When the response requirement for cocaine was increased, while the response requirement for food was held constant, the cocaine dose-response function shifted to the right and parallel. To examine the generality of the unit price model from behavioral economics to a choice situation, we reanalyzed data from that experiment. The dose-response data were initially analyzed using a linear regression model with three independent variables: response requirement, dose and number of pellets as the alternative. The r^2 using this model was 0.57 ($p<0.001$). The data were then reanalyzed using multiple regression with unit price and number of pellets as independent variables. Unit price combines response requirement and dose into a single independent variable, unit price (responses/mg/kg). As predicted, consumption decreased as a function of increasing unit price. The r^2 for this analysis was 0.48 ($p<0.001$). The difference between the r^2 treating dose and response requirement as separate independent variables and the r2 for the unit price analysis was significant ($p<0.001$). That is, the difference was greater than would be predicted based upon the decrease in independent variables from three to two. Thus, combining response requirement and dose into a single independent variable, unit price, significantly decreased the proportion of the variance that was accounted for by the regression analysis. This analysis suggests that the unit price model may require further refinement for use in situations involving choice.

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ACKNOWLEDGEMENTS

Supported by NIDA Grants DA-00259 and DA-00161

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ECONOMIC ANALYSIS OF THE INTERACTIVE EFFECTS OF FOOD AND DRUG INTAKE IN BABOONS

R. W. FOLTIN

A basic tenet of behavioral economics is that reinforcing function is a dynamic process dependent upon environmental circumstances which can be best understood by studying changes in responding as a function of changes in cost per unit of the reinforcer. Responding will increase with initial small increases in cost, but as cost continues to increase, responding will reach a maximum, and then decrease. The cost at which responding is maximal can be used for comparisons across commodities. Increasing the response cost for food pellets decreased pellet intake of baboons by 60%, but increased responding by 2400%. Maximal responding occurred at 100 responses/g. The availability of alternate commodities differentially affected the cost associated with maximal responding for pellets: maximal responding was observed at 8 responses/g when identical pellets were available, and at 30 responses/g when dextrose was available. Thus, these commodities functioned as substitutes for pellets. Acute amphetamine and fenfluramine decreased food intake at all costs without affecting the cost associated with maximal responding, indicating that, unlike dextrose and food pellets, anorectic drugs were not a substitute for food. Acute diazepam increased food intake at all costs without affecting the cost associated with maximal responding. Self-administered amphetamine decreased the cost associated with maximal responding for pellets, indicating that it did substitute for food. Increasing the cost for pellets increased amphetamine, but not vehicle, self-administration. The cost at which responding for amphetamine was maximal was greater than that for vehicle or flavored dextrose. The emphasis on responding, rather than on consumption, highlights the fact that a commodity that is only taken occasionally may engender more behavior than a commodity that is consumed more frequently. Economic models of behavior will be useful in understanding drug-maintained behavior.

ACKNOWLEDGMENTS: This research was supported by grant DA-04130 from NIDA.

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THE ECONOMIC CONTEXT OF DRUG AND NONDRUG REINFORCERS AFFECTS ACQUISITION AND MAINTENANCE OF DRUG-REINFORCED BEHAVIOR AND WITHDRAWAL EFFECTS

M. E. CARROLL

A review of the drug self-administration literature indicates that alternative non-drug reinforcers reduce drug intake in animal and human studies. Goals of the present study were to: 1) examine the effects of alternative reinforcers on acquisition of drug self-administration and on disruptions in operant behavior during drug withdrawal and, 2) to determine the optimal economic conditions under which non-drug reinforcers suppress ongoing drug self-administration. An autoshaping procedure was used with rats to objectively quantify acquisition of i.v. cocaine self-administration. Concurrent access to a glucose and saccharin solution prevented acquisition in half of the rats for up to 30 days. In a control group that received only water there was 100% acquisition. Unlimited access to food also prevented cocaine acquisition in several rats. There was a significant negative correlation between the amount of food consumed and rate of cocaine acquisition.

In monkeys trained to self-administer orally delivered phencyclidine (PCP), PCP consumption was plotted as a function of unit price (response/mg) in a positively decelerating function (demand curve). When saccharin was concurrently available (vs water) greater decreases in PCP-reinforced behavior were found with higher PCP unit prices. A similar finding emerged when unlimited food or ethanol (8% wt/vol) were concurrently available. Thus, alternative reinforcers most effectively reduce drug intake when unit price of the drug is high due to either a high response requirement or low concentration. In another study the effect of saccharin on PCP-reinforced behavior was compared under two income (session length) conditions. When session length was reduced from 3 to 1 hr, saccharin intake was also reduced by two-thirds while PCP intake was unchanged. Thus, income is another economic variable that modifies the effect of a non-drug reinforcer.

The withdrawal studies were conducted with 17.5 hr daily access to PCP and water self-administration and a fixed-ratio (FR) schedule for food deliveries. When water was substituted for PCP, food-maintained lever pressing decreased by at least 50%, and it recovered to about 80% of baseline over eight days of withdrawal. When the food FR was increased over a range of 64 to 1024, the severity of withdrawal increased until the food FR was so high that body weight decreased, then the effect of withdrawal on operant behavior diminished. A subsequent study compared PCP withdrawal in an open economy (earned food is supplemented) and a closed economy (all food is earned). A marked suppression in responding occurred in the open economy, but there was no withdrawal effect in the closed economy. These results suggest that alternative reinforcers have a biphasic effect on the expression PCP withdrawal. As cost of food increases, withdrawal severity increases; but as cost of food continues to increase, the withdrawal effect dissipates. This research was supported by R01 02486 and R37 03240

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MOUSE STRAIN DIFFERENCES IN SUPPRESSION BY IN VIVO MORPHINE OF IN VITRO IMMUNE RESPONSES

T. K. EISENSTEIN[1]; J. L. BUSSIERE[1,2]; T. J. ROGERS[1] AND M. W. ADLER[2]

We have investigated the effect of subcutaneous implantation of morphine pellets (75 mg) on the capacity of dissociated spleen cells to make a primary *in vitro* antibody response to sheep red blood cells. Responses in treated mice were compared with those observed in control mice which received no treatment, sham animals which were subjected to the operation but received no pellet, placebos which were implanted with a placebo pellet, mice given a naltrexone pellet alone, and mice given a naltrexone pellet in addition to a morphine pellet. The effect of mouse strain and sex were evaluated. It was found that morphine dramatically suppressed (>70%) the *in vitro* plaque-forming cell (PFC) response in both male and female mice of the C3H lineage (C3HeB/FeJ and C3H/HeJ), and that the suppression was reversible by naltrexone. Similar levels of morphine-induced immunosuppression were observed in C57BL/6 mice, but in this mouse strain suppression was not reversed by naltrexone. Beige mice (C57BL/6/bg/bg), which have depressed analgesic responses to morphine as well as defects in natural killer cell function and in polymorphonuclear leukocyte granule formation and function, also showed markedly suppressed PFC responses following morphine treatment. Their heterozygous littermates (C57BL6/bg/+) were also immunosuppressed. Suppression was not reversed by naltrexone in either mouse strain carrying the bg gene. BALB/c mice gave poor primary responses to sheep red blood cells, making evaluation of suppression difficult. CxBk/ByJ mice, which have reduced numbers of p-receptors and fail to respond to the analgesic effects of morphine, were not suppressed by morphine pellet implantation.

Morphine pellet implantation caused significant splenic atrophy. However, highly significant immunosuppression was observed when the number of PFCs was calculated per spleen or per 10^7 cells. In C3H lineage mice and BALB/c mice splenic atrophy was reversed by naltrexone, but in C57BL/6 lineage mice it was not, substantiating the mouse strain differences observed in the ability of naltrexone to reverse immunosuppression. C3H lineage mice, but not other mouse strains, showed significant mortality (30%) in response to morphine pellet implantation.

The main conclusions from these studies are that 1) morphine administered *in vivo* is immunosuppressive in a panel of mouse strains in both sexes, and 2) in some mouse strains, but not others, the mechanism involves naltrexone-sensitive opioid receptors.

ACKNOWLEDGEMENTS
This work was supported by NIDA grants DA06650 and T32DA07327

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MECHANISMS OF IN VITRO IMMUNE SUPPRESSION BY OPIOIDS IN MURINE MODELS

T. J. ROGERS, S. BELKOWSKI, C. ALICEA, T. K. EISENSTEIN AND M. W. ADLER

Results reported by a number of investigators have established that immune function may be significantly modulated by opioid compounds. We have previously found that kappa agonists inhibit antibody responses both in vivo and in vitro. Mu agonists were found to exhibit a similar effect but at higher concentrations. The alteration in immune function was found to be naloxone-sensitive, stereospecific, and sensitive to the kappa-specific antagonist Nor-BNI. We have recently extended these studies in an effort to define the immune cell population(s) which are directly altered by these opioid agonists. Our first approach has involved the use of cellular fractionation techniques to isolate the accessory cell, T cell, and B cell populations. These isolated populations were individually treated with the kappa-selective agonist U50,488H for period for 4 hours. After the removal of unbound agonist, the other (non-treated) cell populations were added back in an effort to reconstitute the three components of the immune system. Our results show that treatment of accessory cells, but not B cells or T cells, with U50,488H leads to significant inhibition of the antibody response. These results suggest that the accessory cell component of the immune system represents a direct target for the effects of kappa opioid agonists.

In an effort to examine the mechanism of the effect of the opioid agonists on accessory cell function, we have carried out experiments with purified primary murine macrophages. Our results show that these cells fail to produce normal levels of either Interleukin 1 (IL-1) or Tumor Necrosis Factor-alpha (TNFα)) following treatment with either morphine or U50,488H. We have also observed that the murine macrophage cell line P388D1 is unable to synthesize normal levels of these cytokines following treatment with the kappa agonist U50,488H. Our current research objectives include a more extensive analysis of effects of kappa-specific agonists on macrophage function on both a cellular and molecular level in vitro. These studies should yield a better understanding of the molecular basis for opioid modulation of immune function.

ACKNOWLEDGEMENTS: Supported by NIDA grants DA 06650 and T32 DA07237.

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DIRECT VERSUS INDIRECT EFFECTS OF OPIATES ON THE MOUSE IMMUNE SYSTEM IN VIV0

H. U. BRYANT

Chronic treatment of mice with 75 mg morphine pellet implants results in the suppression of a number of immunologic parameters including responses typically assessed *ex vivo,* such as lymphocyte proliferation, antibody production, natural killer cell activity and macrophage function. Immunologic assays conducted entirely *in vivo* are also suppressed following morphine pellet implantation. The delayed type hypersensitivity response, graft versus host (GVH) reaction and survivability against bacterial infection are *in vivo* immunologic model systems sensitive to the inhibitory effects of morphine. These immunosuppressive effects of morphine are prevented by co-implantation of a naltrexone pellet and display a unique temporal profile with maximal immunosuppressive effects observed 48 to 72 hr after morphine pellet implantation.

Chronic opiate administration affects a variety of neuroendocrine parameters. In view of the well documented immunosuppressive effect of glucocorticoids, the stimulatory effects of morphine on ACTH and corticosterone release represent one possible mechanism for chronic-morphine induced immunosuppression in mice. Consistent with this hypothesis is the observation that the immunosuppressive effects of morphine pellet implants are accompanied by adrenal hypertrophy, and relatively selective atrophy of the thymic cortex (a glucocorticoid sensitive region). Further studies in immunosuppressed, morphine pelleted mice demonstrate a marked increase in circulating corticosterone levels which peak 48-72 hrs post-implantation. In adrenalectomized mice, an attenuation of the inhibitory effects of morphine pellet implants on proliferative responses and the GVH reaction suggest a role for an adrenal component. Studies with the anti-glucocorticoid, RU-486, indicate that blockade of glucocorticoid receptors attenuates the immunosuppressive effect induced by chronic morphine. Also, Weber and Rice (1989) have demonstrated that micro-injection of morphine into discreet brain nuclei in the hypothalamus is directly associated with an inhibition of natural killer cell activity. These studies imply that morphine-induced immunosuppression is at least in part mediated by activation of the HPA axis after implantation of the morphine pellet.

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ACTIVATION OF THE HYPOTHALAMO-PITUITARY-ADRENAL AXIS BYCYTOKINES

B. M. SHARP AND S. G. MATTA

Hormones of the hypothalamo-pituitary-adrenal (HPA) axis, such as ACTH,β--endorphin and glucocorticoid, regulate immune responses by direct effects on immune cells. In turn, activated immune cells secrete cytokines which influence neuroendocrine function. Our investigations have identified sites and mechanisms underlying the effects of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF) on ACTH secretion.

IL-1 is a potent secretagogue for hypothalamic CRF, both in vivo and in vitro, and CRF mediates the pituitary ACTH response to systemic IL-I (Berkenbosch et al. 1987). We have shown that catecholamines (CATs) are required for this response. Moreover, IL-1β, instilled into the hypothalamic median eminence (ME), stimulates ACTH secretion that is dependent on local CAT secretion (Matta et al. 1990). Prostaglandin (PG) secretion is also required for HPA activation by IL-1 (Katsuura et al. 1988). We have observed that indomethacin inhibits ACTH responses to intra-ME IL-1β. Studies indicate that IL-1β is more potent than IL-1α with respect to HPA activation. Our studies comparing IL-1β vs. α, delivered intra-ME or i.v. in the rat, are in agreement. Using equieffective doses of IL-1β vs. α, we found similar $1C_{50}$s for inhibition of ACTH secretion by IL-1 receptor antagonist protein (Matta et al. 1992). Thus, a similar receptor(s) mediates the ACTH response to both IL-1s. This receptor is similar to the rat peripheral type I. Indeed, mRNA for the type I receptor has been detected in the ME (Cunningham et al., 1992). Thus, i.v. IL-1 may bind to ME receptors, initially inducing PG secretion, followed by CAT and CRF release.

TNF-α is also a potent ACTH secretagogue at doses similar to IL-1β, which do not cause hypotension (Sharp et al. 1989). Its proximate target with respect to HPA activation has not been identified, although it is not active at the median eminence nor the anterior pituitary in vitro. We have found that indomethacin inhibits the ACTH response to i.v. TNF in sham and adrenalectomized rats (McCoy et al. 1992). The role of catecholamines has not been clarified. However, TNF receptors are present in the brainstem (Kinouchi et al. 1991) and catecholaminergic afferents to the hypothalamus originate from this brain region.

We observed that IL-6, given i.v. or intracerebroventricularly, is a considerably less effective ACTH secretagogue than IL-1 (Matta et al. 1992 b). Its interaction with IL-1 or CRF is not synergistic, and IL-6 shows modest effects on ACTH secretion from anterior pituitary cells in vitro. IL-6 induces ACTH secretion when instilled intra-ME, although the kinetics are delayed compared to i.v. administration. Thus, IL-1 does not activate the HPA axis via IL-6 appears to stimulate ACTH secretion by a central mechanism involving CRF, rather than releasing other hypothalamic ACTH secretagogues.

In summary, IL-1, TNF-α and IL-6 activate the HPA axis; the first two stimulate PG synthesis. The proximate target of IL-1 appears to be in the median eminence, whereas the site(s) of action of the other two cytokines is not known. All three appear to effect CRF secretion, although the precise mechanisms differ. Thus, the peripheral immune system can modulate the HPA axis through the central effects of different cytokines on CRF secretion.

(Supported by NIDA DA-03977 and DA-04196 (References available upon request)

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OPIOID-CYTOKINE INTERRELATIONSHIPS

N. R. HALL, M. P. O'GRADY AND R. A. MENZIES

A number of investigators have described links between interferon alpha and opioids. These include 1) the induction of naloxone reversible antinociception in mice (Blalock and Smith, 1981), 2) the attenuation of naloxone precipitated morphine withdrawal symptoms in rats (Dafny, 1983), 3) enhanced excitability of cultured neurons (Gresser, 1979), and 4) changes in activity of temperature and of glucose sensitive neurons (Kuriyama et al. 1990). Our own studies have been designed to further characterize the ability of interferon alpha to attenuate morphine symptoms and to bind with opioid receptors within the rat brain.

In the withdrawal studies, 75 mg morphine pellets were implanted subcutaneously beneath the scapula. Naloxone was administered at a concentration of 1 or 2 mg/kg 72 hours later. Withdrawal behavior was scored immediately following the naloxone injection and for a period of 10 minutes. Human recombinant interferon alpha was administered at a concentration of 150 Units per gram of body weight. While interferon administration did attenuate certain behaviors associated with withdrawal, this was not as robust a phenomena as has been reported in the literature. Wet-dog shakes were reduced by over 50% in animals receiving the cytokine, however, other behaviors such as jumping and teeth chattering were not always affected. Furthermore, there were inconsistent effects of interferon alpha upon withdrawal-induced decreases in body weight. Although withdrawal behavior was only mildly affected by the cytokine, open-field activity levels were significantly increased following either intracerebroventricular injection in rats or continuous sc infusion using mini-pumps in mice. The possibility that some of these behavioral effects may be mediated by opioid pathways within the brain is suggested by the observation that human recombinant interferon alpha is able to inhibit the binding of tritiated naloxone to rat brain membranes in vitro. This inhibitory effect was concentration dependent over the range of 500 to 6000 antiviral units per ml with 500 μg of membrane protein (Menzies et al. 1992).

In a related series of experiments, we have either injected cytokine preparations or induced endogenous cytokine production by the administration of viral antigen. In adult animals, this results in increased turnover of brain norepinephrine and stimulation of ACTH, beta-endorphin and corticosterone release. These effects are time and dose dependent. We have also determined that both Newcastle Disease virus and rat cytomegalovirus (CMV) can exert long term influences upon the pituitary-adrenal axis when they are administered to neonatal rats. In the case of CMV, significant increases in corticosterone release can be detected during the so called "stress-hyporesponsive" period. The possibility that some of these effects may be due to viral-induced interferon and other cytokine production is currently being investigated.

ACKNOWLEDGEMENTS: We thank Hoffman La Roche, Nutley, NJ for providing human recombinant interferon alpha. Portions of these studies were supported by grants from NIDA (DA05723), NIDDK (DK41025) and the USF Creative Scholarship Award Program. N. Hall is supported by a Research Scientist Development Award from NIDA (DA00158). The technical assistance of Janelle Oliver and the editorial assistance of Cecilia Figueredo are greatly appreciated. AFFILIATION: Depts. of Psychiatry/Behav. Med., U. of South Florida, Tampa, FL

REGULATION OF THE EXPRESSION OF PROENKEPHALIN-A (PEA) MRNA IN MURINE THYMOCYTES

K. M. LINNER AND B. M. SHARP

We are studying the regulated expression of PEA mRNA in murine thymocytes. In kinetic and dose-response studies we found that PEA mRNA is maximally expressed (15-fold over background) in adult murine thymocytes following 72h of culture with the T cell-specific mitogen, concanavalin-A (Con-A), at 5 or 7.5 μg/ml. Thymocytes cultured without Con-A or with a high concentration of Con-A (10 μg/ml) did not express PEA mRNA at 24,48 or 72h. In addition, no PEA mRNA was induced in murine splenic mononuclear cells at any time with any dose of Con-A. Further characterization of the maximally stimulated expression of PEA mRNA in thymus by Con-A led to the discovery that such expression was occurring in the mature, single positive CD4 subset of thymocytes.

The expression of PEA mRNA in adult thymocytes was found to be regulated by the cytokine mIL-1β in a biphasic dose-dependent manner. Concentrations of mIL-1β of 10^{-14} M and 10^{-13}M enhanced the Con-A-induced expression of PEA mRNA 1.5 - 2.5 fold over that of Con-A alone, whereas concentrations of 10^{-11}M and 10^{-10}M inhibited its expression 60 and 85%, respectively. Both the enhancing and inhibiting effects of mIL-1 β were completely reversed by the interleukin-1 receptor antagonist protein (IRAP) at concentrations 100X the concentration of mIL-1β in the culture, demonstrating the specificity of the response to mIL-1β. A lower concentration of IRAP (10X) did not reverse the effects of IL-1β.

Finally, PEA mRNA was found to be regulated during fetal thymic gestation. That is, it was constitutively expressed early in gestation (day 15). This constitutive expression of PEA mRNA was turned off later in gestation (by day 18); however, it could be induced at this time following 72h of incubation with Con-A 5 μg/ml, similar to the situation seen in the adult thymus.

It is concluded that the physiologically regulated expression of PEA mRNA in adult CD4 thymocytes and during gestation, as well as the absence of its expression in adult splenic T cells, suggest that PEA mRNA and enkephalin peptides may play a role in the maturation of thymic T cells, and thus, in the subsequent establishment of normal cell-mediated immune responses. These data also suggest an autocrine/paracrine role for enkephalin peptides in the thymus.

ACKNOWLEDGEMENTS
This work was supported by NIDA grants DA07068-01 and DA003977

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SMOKED COCAINE EFFECTS: AN ANIMAL MODEL

B. R. Martin

For centuries, smoking has been the preferred route of administration for many substances. In recent times, phencyclidine and cocaine have been added to this list. The choice of smoking or inhalating a substance is thought to be due to the rapid absorption which results in a rapid onset of the behavioral effects that are deemed pleasurable. Despite the fact that many substances are abused either by smoking or inhalation, they are frequently administered by other routes of administration when they are characterized experimentally. Obviously, smoking or inhalation studies are fraught with difficulties that can be avoided by simply injecting the drug. In order to understand the fate of abused substances during the smoking process as well as the absorption, biodisposition and metabolism of these substances by the inhalation route, we have developed an apparatus and procedures that allow us to 1) produce smoke or drug vapor in a way that mimics the drug abuser and 2) expose animals to this smoke or vapor in sufficient quantities to produce a pharmacological effect. The essential components of the apparatus consist of a furnace which is used to heat the drug to a predetermined temperature, a nose-only exposure apparatus for either mice or rats, and a vacuum source which provides a constant flow of vapor. Initially, we determine the extent of pyrolysis that occurs and identify the pyrolysis products.

We have recently completed a series of studies in which the pharmacokinetics and pharmacological effects of cocaine were determined by the inhalation route. Cannulated, male Sprague-Dawley rats were exposed to a constant concentration of cocaine vapor (13.6 ± 0.4 μg cocaine per ml mainstream air). The bioavailable doses of cocaine were 0.26 ± 0.05 and 1.54 ± 0.46 mg/kg after 1.5- and 5.0-min exposures, respectively. Peak cocaine plasma concentrations of 95 ± 26 and 205 ± 58 ng/ml, for the 1.5- and 5.0-min exposures, respectively, occurred after 1 min of exposure. Transient changes in heart rate and arterial blood pressure were generally dose-dependent and correlated with cocaine plasma concentrations. During exposure, 70 % of the animals demonstrated atrial arrhythmia and incomplete heart block. These findings suggest that a direct cardiotoxic effect results from inhalation of cocaine in rats. These results demonstrate the feasibility of conducting inhalation studies and underscore the importance of evaluating drugs under conditions which are relevant to their mode of use by humans.

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SELF-ADMINISTRATION OF SMOKED COCAINE BY HUMANS

R. W. FOLTIN AND M. W. FISCHMAN

The present study investigated the relative reinforcing effects of doses of smoked and i.v. cocaine and compared changes in subjective-effects measures with dose choice to estimate the relationship between cocaine self-administration and the self-reported effects of cocaine. Healthy adult male research volunteers reporting smoked and intravenous cocaine use resided on a Clinical Research Center for two-weeks, and participated in nine daily sessions, each of which consisted of seven-choice trials. The first two trials were sampling trials in which subjects received one dose each of i.v. cocaine hydrochloride (0, 16, 32 mg), and smoked cocaine base (0, 25, 50 mg). Each of the remaining five trials was a choice-trial, in which subjects could choose to self-administer either of the doses received in the initial two trials. Subjects a) reliably chose active doses of cocaine compared to placebo, b) chose to self-administer the low-smoked cocaine dose about as often as either the low or high i.v. cocaine doses, and c) reliably chose the high-smoked cocaine dose when compared to either active i.v. dose. With few exceptions, both low doses and both high doses produced similar subjective and cardiovascular effects after the initial dose, regardless of the route of administration. This suggests that initial effects were not predictive of subsequent choice. Cumulative doses of smoked cocaine increased scores on a number of subjective-effects measures that were not similarly increased by cumulative doses of i.v. cocaine. These differences were predictive of smoked cocaine self-administration. After-session ratings of drug "Liking" and "Quality" differentiated smoked from i.v. cocaine, reflecting route choice. However, there were no significant differences between these ratings for low and high doses. These results provide information about the relationship between subjective drug effects and drug self-administration, and demonstrate the utility of a choice procedure in analyzing these relationships.

ACKNOWLEDGMENTS: This research was supported by grants DA-03818 from NIDA, and MOI-RR-00035 from NIMH.

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BEHAVIORAL INTERVENTIONS IN THE PREVENTION AND TREATMENT OF DRUG AND ALCOHOL ABUSE: AN INTRODUCTION

S. T. HIGGINS

A behavioral approach has much to offer in the development of effective interventions for the prevention and treatment of substance abuse. The presentations in this symposium illustrate effective use of behavioral interventions across a variety of drugs, populations, and treatment settings. At a more conceptual level, I have listed below what can be considered five core strengths of a behavioral approach to this topic area:

1. **Conceptual clarity.** A behavioral approach emanates from an organized set of basis scientific principles, methods and concepts; i.e., a scientific paradigm. As such, it can bring conceptual clarity and organization to a broad set of empirical observations ranging from the preclinical laboratory to the clinic, and cutting across the various abused substances. Importantly, operating within this paradigm is not simply an academic exercise, but, rather, can suggest specific strategies and tactics for use in prevention and treatment efforts.
2. **Explicit commitment to empiricism and operationism.** The primacy of empirical data is a well known characteristic of a behavioral approach, and certainly a welcomed feature in the area of substance abuse treatment. Regarding operationism, behavioral interventions typically involve well specified techniques and outcome measures, which improves the possibility of successful replication and dissemination of research findings.
3. **Compatibility with pharmacotherapies.** There is a relatively extensive literature demonstrating the efficacy of combined behavioral and pharmacological interventions for substance abuse.
4. **Clinical breadth.** Substance abusers are a heterogeneous group with many and varied problems. Importantly, there is an extensive behavior therapy literature consisting of empirically validated interventions for many of the problems with which substance abusers commonly present (e.g., affective disorders, insomnia, chronic unemployment, marital problems). Those treatments often can be integrated with behavioral interventions for substance abuse for the purposes of providing a comprehensive treatment intervention.
5. **Demonstrable efficacy.** Last, and most important, the efficacy of behavioral interventions for drug dependence have been demonstrated empirically. To be sure, there are no magic bullets or "cures" to be found in this approach, but there is clear, demonstrable efficacy, as is illustrated by the presentations in this symposium.

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PHARMACOTHERAPEUTIC ENHANCEMENT OF BEHAVIORAL TREATMENT FOR ALCOHOL PROBLEMS MAY BE AFFECTED BY BELIEFS ABOUT WHETHER DRUGS OR PLACEBO HAS BEEN ADMINISTERED

T. Toneatto and E. M .Sellers

Effective pharmacologic treatments of alcohol dependence continue to be sought after. Pre-clinical studies have shown that increasing synaptic availability of serotonin can reduce alcohol consumption. Clinical trials have demonstrated a modest effect of serotonin re-uptake inhibitors in individuals with non-severe alcohol dependence. While pharmacological treatments are still elusive, cognitive-behavioral treatments for alcohol abuse have been developed, particularly for such individuals. The purpose of this study was to evaluate the effectiveness of combining a novel serotonin-uptake inhibitor, ondansetron (OND), and a brief psychological treatment in a randomized, double-blind, placebo controlled, study. Seventy-one male, alcohol abusers, ranging in age from 24 to 62 years, were screened by telephone. Suitable subjects entered a two-week baseline period and then randomly assigned to 6 weeks of 0.25 OND (n=23), 2.0 mg. OND (n=25) or placebo (n=23). All subjects received a psychological treatment consisting of an assessment and written materials emphasizing functional analysis and relapse prevention. The dependent variable was drinks/drinking day. The two independent variables were DRUG ADMINISTERED (placebo or OND) and DRUG PERCEIVED (subjective belief as to whether drug or placebo had been administered). ANCOVA was used with baseline drinking as the covariate. A main DRUG PERCEIVED effect, $F(1,64)=4.03$, $p=.049$, was obtained showing greater improvement regardless of which drug had been administered over the 6 weeks. Post-hoc means test showed that subjects receiving the high dose of OND, and also believing that they were receiving active drug, reported fewer drinks/drinking day (M=5.4) than those who received 2.0 mg. OND but believed that they had received placebo. Not taking into account subjective perceptions of which drug had been administered would have overlooked this interaction between drug reception and perception. While this study has several methodological problems (i.e., correlational, unequal, small sample sizes) subjective beliefs of whether drug or placebo has been administered had an impact on treatment outcome. OND produced effects greater than that achieved by the placebo groups, demonstrating the additional efficacy attributable to the medication. Randomizing subjects does not insure that subjects will believe that they are receiving the assigned treatment, with such beliefs possibly affecting the results obtained.

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Behavioral Interventions in the Methadone Clinic: Contingent Methadone Take-Home Incentives

M. L. Stitzer, G. E. Bigelow and M. Y. Iguchi

Introduction: The continuing use and abuse of supplemental drugs from non-opiate pharmacological classes, most notably cocaine and benzodiazepines, is recognized as a significant clinical problem in contemporary methadone programs. The purpose of the present controlled study was to determine whether methadone take-home privileges, when offered contingent upon drug-free urinalysis test results, would influence treatment outcomes of methadone maintenance patients. The study is of clinical importance because it emphasizes the use of take-home privileges as a means to shape behavior with the goal of improving outcomes for polydrug abusing patients.

Methods: Subjects were fifty three new intakes to a maintenance treatment research clinic whose average age was 34 years (±6.7 yrs) and who reported on average a 15 year history of opiate abuse. 66% were male, 34% were while, the remainder being black, 34% were employed and 23% were married at treatment entry. Subjects were randomly assigned to a contingent procedure (n = 26) where methadone take-home privileges could be earned on the basis of consecutive weeks of drug-free urines (minimum of two clean weeks to earn the first take-home) or a noncontingent procedure (n = 27) in which take-homes were delivered independently of urine test results. The intervention was implemented after a three-month baseline period and evaluated for six months.

Results: Mean treatment retention was 23.1 weeks for the contingent group and 22.8 weeks for the noncontingent group (t=0.13, n.s.). In the contingent group, 32% improved urine test results by 10% or more and exhibited at least four consecutive weeks of abstinence during the intervention, while only 8% of noncontingent subjects showed this outcome pattern ($z=2.12$, $p < .05$). Among subjects whose baseline urine test results could get worse (n = 20 or 21 per group), twice as many subjects in the noncontingent as compared with the contingent group showed a decline in drug-free urines during the intervention (62% vs 35%, z=1.72, n.s.). Lower baseline rate of drug-free urines and lower rates of urines containing multiple drugs were strongly associated with successful outcome, while the type of drug abused (cocaine versus benzodiazepines) did not influence outcomes.

Discussion: This study demonstrated that the methadone take home privilege, awarded after two consecutive weeks of drug free urines, was effective in promoting abstinence from cocaine and benzodiazepines during methadone maintenance treatment. Drug use for patients receiving noncontingent take-homes tended to worsen while 30% of contingent patients clearly improved. Study findings support a recommendation for routine use of contingent take-home incentives to motivate abstinence from supplemental drug use during methadone treatment but suggest that additional interventions may be needed for the more severe polydrug abusers. Since lower rates of baseline polydrug use predicted positive clinical response, this may constitute a good screening criteria for selecting patients who are likely to have a favorable response to incentive procedures. **AFFILIATIONS:** 1) Johns Hopkins Univ. Sch. of Med., Francis Scott Key Medical Center, Baltimore, MD and 2) Hahnemann University School of Medicine, Philadelphia, PA

A Behavioral Approach to Achieving Initial Abstinence

S. T. Higgins; A. J. Budney; W. K. Bickel and J. R. Hughes

Our group has been researching a behavioral approach to outpatient treatment of cocaine dependence. The treatment we developed is a multicomponent intervention involving contingency-management procedures and aspects of the Community Reinforcement Approach (CRA). We have conducted two consecutive treatment-outcome trials comparing this multicomponent treatment versus standard outpatient drug and alcohol counseling from a disease-model orientation. Our rationale for using standard outpatient drug counseling as a comparison treatment was a pragmatic one; if our multicomponent intervention did not engender better outcomes than a counseling approach that was already widely available throughout the U.S., then it was not worth the extra efforts involved in providing the novel treatment. The singular purpose of the studies was to determine whether the outcomes achieved with this multicomponent treatment were superior to outcomes achieved with what we deemed to be standard outpatient care. In the first trial, 13 consecutively admitted cocaine-dependent patients received the behavioral treatment and the next 15 patients received drug counseling (Higgins et al., 1991). In the second trial, 38 cocaine-dependent patients were randomly assigned to the two treatments (19/group); under review for publication. Across both trials, treatment outcome was significantly better with the behavioral than the standard treatment. In the randomized trial, for example, 58% of patients in the behavioral treatment versus 11% in standard counseling completed 24 weeks of counseling, and 68% and 42% of patients in the behavioral treatment achieved at least 8 and 16 weeks of documented (i.e., verified via urinalysis) continuous cocaine abstinence versus 11% and 5% in standard counseling. We feel this behavioral treatment represents an effective intervention for retaining cocaine-dependent individuals in outpatient treatment and for establishing initial but clinically significant periods of cocaine abstinence. Currently we are conducting prospective and retrospective studies to dismantle this multicomponent behavioral treatment package to identify which components are necessary to obtain positive outcomes.

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COORDINATED FAMILY AND SCHOOL BEHAVIORAL INTERVENTIONS TO PREVENT AND REDUCE ADOLESCENT SUBSTANCE ABUSE

B. H. BRY AND K. E. KRINSLEY

The current study assessed the preventive impact of adding behavioral family therapy to a school-based preventive intervention (Bry, 1982). High risk (Bry, et al., 1982) black, white and Hispanic male and female lower and middle class sixth, seventh and eighth graders were randomly assigned to school-based intervention alone or to coordinated family and school-based intervention. Results one year post treatment indicated that, compared to adolescents who only received school-based intervention, adolescents who received both the school and family components had used substances significantly less and had performed significantly better in school (Krinsley, 1991). Not one of the adolescents who received both the school and family intervention increased or initiated substance use during the 1 1/4 years of the study, while a significant number who received only the school intervention did.

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ACKNOWLEDGEMENTS

Supported by NIDA research grant DA 05112 to Brenna H. Bry.

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OPIATES AND THE PATHOGENESIS OF INFECTIOUS DISEASE

P. K. Peterson, J. Risdahl and T. Molitor

Although the infectious disease complications of opiate addiction and the contribution of opiate-induced immune dysfunction to pathogenesis have been recognized since the 19th century, the impact of opiate use on the course of natural infection rarely has been demonstrated. Because of the confounding variables in studies of addicted humans, we have evaluated the effects of chronic morphine administration in a swine model of a herpes virus infection. Swine were selected as an animal model because of the similarity of the immune system of humans and pigs, the ability to monitor clinical signs in pigs, and the capacity for obtaining frequent blood samples. Suid herpesvirus (SHV)-1, an important animal pathogen closely related to human herpes simplex virus (HSV), causes serious central nervous system (CNS) and pulmonary disease, and like HSV, latent SHV-1 can reactivate when cell-mediated immunity (CMI) is suppressed. Chronic morphine administration in male outbred Yorkshire swine was associated with development of profound impairment of delayed type hypersensitivity (DTH) skin test responses to DNFB and BCG, an in vivo measure of diminished CMI. This impairment of DTH occurred when the priming dose of antigen was given 7 days before or 7 days after initiation of morphine. Contrary to the expected result, morphine addicted pigs had a decreased mortality following infection with a high viral dose. The increased survival of morphine-addicted pigs was due to a reduction in SHV-1 CNS disease. The pathogenesis of pneumonia, however, was markedly increased in opiate-addicted animals as evidenced by both gross pathological and histopathological assessments. Using polymerase chain reaction for the detection of RNA transcripts in the trigeminal ganglion, reactivation of latent SHV-1 was observed in morphine-treated animals, but not in vehicle-treated controls. These findings demonstrate that morphine addiction can significantly impair CMI and alter the course of a natural herpesvirus infection. Understanding the mechanisms of these opiate-mediated effects in this swine model may provide insight into the pathogenesis of acute viral infections of the lungs and CNS as well as reactivation of latent viral infection in the heroin addict.

This work was supported by NIDA grant 271-89-8155.

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COORDINATE EFFECTS OF STRESS AND OPIATES IN MODULATING IMMUNITY AND SIVSMM INFECTION IN RHESUS MONKEYS

R. M. DONAHOE; L. D. BYRD; H. M. MCCLURE; P. FULTZ;
M. BRANTLEY; F. MARSTELLER; A. A. ANSARI AND M. ACETO

We have employed a monkey model of opiate dependency to study the immunomodulatory capacity of opiates. Several groups of monkeys were studied over nearly 2 yr: one injected with morphine (3mg/kg body wt every 6 hr) and infected nearly similtaneously with simian immunodeficiency virus (SIVsmm); others injected only with morphine, or saline as placebo. Repeated immunological, behavioral, endocrinological and virological assesments were performed before and after morphine/placebo administrations as well as within the context of the administration of several discrete forms of experimental stress to opiate-dependent animals and their controls.

The introduction of the 6-hr injection paradigm itself was a significant stress for the animals. Varying differences in in immune responses were evident between test and control groups in the non-viral infected monkeys throughout the first 6-8 mo of the study. Cell-mediated responses only differed significantly within the first 2 wk after opiate injection while circulating levels of IgM were depressed throughout the study. Changes in patterns of circulating leukocyte subtypes normalized after about 6 mo of opiate exposure. Immune responses of opiate-dependent monkeys differred significantly from controls after exposure to a mild social stress 8 mo after initiation of opiate exposure, while differring markedly 48 hr (but not 2 and 10 wk) after naloxone-precipitated withdrawal from opiates, which occurred 84 weeks after initiation of opiates.

For 6 opiate-dependent monkeys infected with SIVsmm, opiate exposure did not exacerbate AIDS symptoms. In fact, such symptoms appeared to be ameliorated in these monkeys despite evidence for normal progression of viral infection. Notably, SIVsmm appeared to be induced transiently by stressful opiate-withdrawal in 3/5 monkeys in which SIVsmm infection had become latent in respect to an inability to isolate virus by co-culture techniques.

These studies link stress with opiates in modulating viral latency and immunoresponsivity. Through stress reduction, well-compensated opiate addicts may be protected from induction of viruses and from immune liabilities commonly associated with stress. Alternatively, addicts subject to repeated episodes of opiate withdrawal may be abnormally vulnerable to immune breakdown and infection. Such suppositions indicate that stabilization of addict physiology with drug replacement therapy is likely to have favorable immunological impact. The data also illustrate the importance of the neuroimmune axis in mediating immunological and virological effects of opiates.
(Supported by NIDA grant DA04400 and DRR grant RR00165) Affiliation: Yerkes Regional Primate Research Center, Emory Univ., Atlanta, GA and The Medical College of VA., Richmond, VA

SIMIAN OPIOID DEPENDENCY, IMMUNE FUNCTION AND SAIDS

R. Y. CHUANG; D. J. BLACKBOURN; L. F. CHUANG; Y. LIU AND K. F. KILLAM, JR.

A vast portion of today's AIDS-afflicted population consists of opioid addicts who use shared needles. Previous studies show that various opioids are themselves immunomodulatory, suggesting that opioids in HIV-infected patients may accelerate the process from viral exposure to the development of full-blown AIDS. Through the use of a simian model of AIDS (SAIDS), and the opioids morphine sulfate and LAAM, the present investigation was conducted as a controlled, longitudinal study to evaluate the correlation between the chronic administration of opioids and its compromising effects on antimicrobial host defense mechanisms and cell-mediated/humoral immune functions before and after simian immunodeficiency virus (SIV) infection.

PMN cells from pre-SIV-infected, morphine-treated animals showed a marked, transient reduction in their ability to kill ingested yeast blastospores. Initial (first week) administration of morphine sulfate to uninfected rhesus monkeys was found to activate the quiescent lymphocytes for proliferation and induce a transient increase in the T cell proliferative response to mitogens. IL-2 release from the mitogen-stimulated limphocytes was also enhanced following morphine treatment. However, prolonged treatment of morphine or LAAM to the animals has revealed an overall immunosuppression of T helper cell functions.

Between 12-21 weeks post-SIV infection, 2/3 morphine-treated monkeys showed decreased phagocytosis activity, while the control monkeys did not. Innoculating the monkeys with SIV reduced both the PMN chemotaxis activity and the T cell mitogen response of all animals up to 3 months post-infection. These activities recovered gradually, coinciding with the appearance of antibodies against the intrusive virus. Nevertheless, a constant decline in the ratio of CD4+/CD8+ cells in the infected animals was evidenced. While autologous CD8+ cells of all animals were found to suppress SIV replication, the CD8+ lymphocytes of the morphine-dependent animals exhibited less ability for blocking SIV growth. Our experiments also showed that the opioid-dependent monkeys have a lower titer of neutralizing antibodies than non-dependent monkeys. Furthermore, our studies revealed the surprising result that the presence of anti-SIV antibodies could not be detected by standard western blot analysis in one morphine-dependent, SIV-infected monkey, suggesting that the animal was seronegative. However, antibodies against an autologous SIV strain could be detected as early as two weeks post-infection. These results indicate that the initial infecting virus had undergone rapid mutation in this animal, implicating severe consequences, from false negative diagnoses due to acute virus mutation, for the currently accepted forms of immunodeficiency virus screening programs. Supported by NIDA Research Grant DA05901. Affiliation: Department of Pharmacology and Toxicology, University of California, Davis, CA 95616.

IMMUNE FUNCTION IN HUMAN IVDU's

M. J. Kreek

Many studies from our group and others have shown profound disruption of immune function during cycles of heroin addiction. These findings include significantly reduced natural killer cell activity, possibly of great importance, since natural killer cells are involved in the first line of host defense against a variety of viral diseases as well as in surveillance against tumor spread. Although it is not yet known whether or not the natural killer cells play any role in the initial events of HIV-1 virus infection, natural killer cells would be expected to play significant roles in the progression from HIV-1 infection to AIDS as defined by the advent of a variety of diseases, events in which natural killer cells may play an important role. In the heroin addict population, other immune abnormalities have been defined by our group and others, including elevated levels of T cell numbers, total absolute numbers of CD3, CD4, and CD8 cells in those populations not infected with the HIV-1 virus, coupled with abnormal T-cell activity and abnormal B-cell activity as reflected by significantly elevated levels of IgM and IgG. Most of these abnormalities are probably due to the exposure and infection with a wide variety of diseases, coupled with the chronic exposure to foreign substances.

Many laboratories, including our own, have shown that opiate drugs and the endogenous opioids, the enkephalins, the endorphins, and, by our laboratory, the dynorphins, may alter specific indices of immune function. The effects of both opiates and each of the endogenous opioids are very specific. For instance, as reported in the preliminary studies from our laboratory, dynorphin peptides 1-17, 2-17, 1-13, 1-10 and 1-10-amide may each have very different effects on natural killer cell activity as studied in vitro. These findings, coupled with other findings on the effects of beta-endorphin and enkephalin peptides on specific indices of immune function suggest that the endogenous opioid system may be involved in modulation of immune function in humans and yet, this involvement may be very complex, with peptide processing yielding variable availability of specific neuropeptides to targeted sites of action to modulate immune function. Our group is also performing basic clinical research studies to determine further the effects of neuroendocrine function in the setting of normal as well as altered physiology in specific indices of immune function. One of the most provocative findings to date has been the finding that there is a normal circadian rhythm of natural killer cell activity, and that this circadian rhythm seems to follow the circadian rhythm of hormones of the hypothalamic-pituitary-adrenal axis. In a recent study of patients with post-traumatic stress disorder, we have shown that there is a significant disruption of normal circadian rhythm of the hypothalamic-pituitary-adrenal axis, and that this is paralleled by abnormalities in the circadian rhythm of natural killer cell activity. These findings provide further support of our earlier hypothesis, that some of the disruptions of immune function seen in heroin addicts may be related directly to the abnormalities of neuroendocrine function caused by chronic heroin use, and that normalization of these functions may occur during chronic methadone maintenance treatment.

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THE BRAIN AS AN HIV-1 RESERVOIR: FACTORS AFFECTING HIV-1 INFECTIVITY

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The central nervous system (CNS) is infected by HIV-1 early in the disease. HIV-1 possibly infects neurons but remote effects due to other factors may be involved. The mechanism of the onset and progression of AIDS Dementia Complex (ADC) is still enigmatic. The effects of illicit drug use such as cocaine, alcohol, and opiates on progression of HIV-1 disease, early cognitive changes, ADC, and on HIV-1 replication are not fully described. Several mechanisms have been proposed for possible acceleration of progression, including direct effects of macrophage-tropic strains of HIV-1 on the brain, virus load in blood and CSF: viral protein, gp120, is toxic for neurons. Remote effects include nutritional deficiencies (vitamins B6 and B12). quinolinic acid levels, autoimmunity, psychosocial factors, HTLV-I/II, and toxic cytokine release (neuroimmune axis). The syringe, an etiological vector for the transmission of HIV-1, may be associated with increased mortality. Antiviral drugs such as AZT produce resistant strains of HIV-1. The effectiveness of Peptide T on HIV-l disease, cognition, ADC, and peripheral nervous system (PNS) disease are being studied in Phase II trials (C. Pert; P. Bridge; J. Berger; K. Goodin, 1992). Peptide T prevents neuronal death in vitro. Inflammatory events are also associated with CNS and PNS disease during HIV-1 infection. HIV-1 is predominantly found in macrophagaes in the CNS and the macrophage is a source of several cytokines. We are also investigating this in PNS tissue. We showed that cytokines (TNF-alpha, IL-1β, and IL-6) may be involved in pathogenesis in AIDS CNS and PNS tissues. These factors may modulate HIV-1-1 replication resulting in a cybernetic or feed-back mechanism. Morphine, cocaine, and cocaethylene stimulate HIV-1 replication. Cytokines and herpes viruses (including CMV) stimulate transcription of the HIV promoter (LTR) and CMV stimulates HIV-1 replication in vitro. However, in terms of pathogenic mechanisms in the CNS, HIV-1 and not CMV was associated with encephalitis in post-mortem AIDS brain. Brain tissues were from the Univ. of Miami Brain Bank, Nat. Neurol. Res. Bank, Broward and Dade County Med. Examiners Officers. Supported in part by grants: DA04787, DA06227, DA06910, NS25569, CA1439518A, MH/DA42455, Helen Dowling Inst. for Biopsychosocial Med., the Netherlands.

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THE ETHNOGRAPHY OF HIGH RISK DRUG USE

S. KOESTER

By examining drug users on their terms and in their settings, ethnographers have described the context in which drugs are used and the lives of the people who consume them. This paper discusses ethnographic contributions to drug research by illustrating ethnographic data regarding the behavior that places drug injectors at high risk for HIV. Observation of drug use and open-ended interviews with users has led to findings challenging one dimensional views of high risk drug injecting. Three of these are discussed.

First, the term "syringe sharing" does not encompass the multiple ways a single syringe can be used by two or more people, and it does not necessarily reflect the way users themselves interpret this behavior. Needles are often exchanged anonymously, and often there is a time lapse between the exchange. Sexual partners or individuals who share the cost of a needle may not consider their joint use of it as sharing.

Second, the use of a common syringe is not due to some maladaptive cultural trait. Factors including availability, cost, a user's physical state, they type of drug being injected and the setting where injecting occurs all affect needle exchanges between users. The use of a common syringe is encouraged by laws making their possession illegal. Fear of arrest discourages users from carrying syringes, especially when they are holding drugs. As a result, they use whatever syringe is available.

Third, the use of a common syringe may not be the only high risk activity associated with drug injecting. Injectors risk HIV infection even when using their own syringe or disinfecting a common one. This occurs because they share other items when preparing to inject, including water used for liquefying the drug and rinsing syringes, and the filter and container used for mixing drugs. Injectors also place themselves at risk by "backloading", a procedure used for transferring the drug from one syringe to another. It is employed when measuring a jointly purchased drug, or when a syringe becomes clogged or broken.

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LONGITUDINAL ETHNOGRAPHY: CAREERS IN DRUG TRAFFICKING

P. A. Adler

Survey and other epidemiologic methods of studying people involved in highly deviant activities have had limited success in obtaining depth or longitudinal data on such hidden populations. Ethnographic research, with its personal involvement between researchers and their subjects, offers the only avenue whereby we can catch a glimpse into the depth rewards, problems, motivations, interpretations, and range of experiences deviants undergo. After briefly discussing the methods whereby I first came to develop trust and rapport with a group of upper-level marijuana and cocaine dealers and smugglers in the 1970s, I offer some longitudinal insights into the deviant and legitimate careers of these people. I briefly discuss how their involvement with drug trafficking evolved in character, and the factors affecting their reintegration, in the 1990s in to the conventional society and legitimate economy.

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BORROWING, BURNING AND PUBLIC POLICY

T. MASON

In recent decades, the study of illegal drug use has increased in significance beyond the interests of specialists to include broader policy spheres. Ethnographic research has become ever more useful as a means of understanding everyday drug use in the context of larger cultural and economic realities. The author conducted ethnographic research among injectors of illegal drugs in two poor neighborhoods in Baltimore, Maryland from 1988-1990. One neighborhood was a public housing project, with predominately African American residents, the other a primarily Anglo-American neighborhood of mixed residential and commercial establishments. Both had long histories as copping areas for illegal drugs, including heroin and cocaine. The research was part of a NIDA funded HIV prevention effort utilizing the indigenous outreach model associated with Dr. Wayne Wiebel of the University of Illinois at Chicago.

One focus of the research was on the variety of street transactions involving exchanges of skills and resources to get drugs. The social dimension of giving someone drugs or "works" in exchange for other goods or for similar favors in future is only one part of most such trades. Street transactions inevitably involve a commercial dimension, and maximizing one's gain at the expense of others is a common theme in street hustles. However, concepts such as "maintaining", also emphasize the survival value of guarding one's reputation for fairness by strategically minimizing the practice of "burning" people. Proper street etiquette recognizes that one's survival ultimately depends on the respect of others.

The study of street exchanges has clear relevance for the design of public health messages by revealing the survival principles to which they can appeal. However, evidence from these two communities suggests that with the expansion of drug sales and use, such principles may be breaking down in some areas. Younger people and those more recently drawn to the drug scene in these neighborhoods marked by deteriorating economic and social conditions appear less likely to have been schooled in the etiquette and skills of street hustling described by older addicts. This provides additional evidence of the serious policy challenges offered by the circumstances which have encouraged the expansion of drug sales and use in many neighborhoods around the country.

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ACCURACY IN SUBSTANCE ABUSE RESEARCH: AN ETHNOGRAPHIC PERSPECTIVE FROM EL BARRIO

P. Bourgois

By definition substance abuse research probes socially taboo information that drug users strive to hide or distort. Illegal drugs are especially concentrated among socially marginalized sectors of the population who have often had negative experiences with mainstream institutions. Many drug users rely on illegal activities to generate income and to survive. They are not likely, therefore, to be forthcoming with accurate information when questioned about the details of their lifestyles. It is unrealistic to assume that the data that we obtain via our traditional survey methods are accurate. In our pursuit of "hard data," consequently, we need systemically to incorporate alternative ethnographic methodologies with our statistical survey techniques.

The potential contribution of ethnography towards a deeper understanding of the substance abuse field extends beyond merely collecting accurate numbers. Most importantly, ethnographic research provides access to the more fundamental and contradictory dynamics which underlie and define drug abuse. By suspending moral judgement and delving into the "common sense" of drug users in their indigenous contexts, the ethnographer translates a world and a culture which is otherwise wholly inaccessible to mainstream society and to professional academic researchers.

Specifically, to make sense of the dramatic crack epidemic that overwhelmed US inner cities in the late 1980s/early 1990s, we need to explore the economic, social, and psychological logics of structural marginalization which has made substance abuse so tragically attractive to such a large proportion of inner-city youth. Unfortunately, without a prolonged social immersion among the people participating in the "drug culture" we cannot even ask the right questions, let alone understand and analyze the crucial context of social marginalization that defines substance abuse. In order to contribute to coherent prevention and intervention strategies, therefore, we need a creative analysis of the political, economic and intimately personal dimensions of the lives of drug users and the society engulfing them.

Combining this kind of deeply probing, non-traditional research methodology with more routine survey techniques is difficult, but it has tremendous potential. It can increase the accuracy of our data banks and reinvigorate the parameters of substance abuse research.

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SMOKING AND NICOTINE DEPENDENCE: RECENT FINDINGS

M. M. KILBEY; J. HENNINGFTELD; N. BRESLAU; P. B. S. CLARKE AND J. HUGHES

INTRODUCTION:
M. Marlyne Kilbey

1994 will mark the 30th anniversary of government recognition of the leading form of drug abuse: smoking. Since the 1964 Report of the Advisory Committee to the Surgeon General which termed tobacco use "habituating", data have been compiled to show that tobacco use is addicting, nicotine is the active agent responsible, in large part, for the addiction, and that the biopsychosocial processes underlying tobacco addiction are similar to those underlying heroin and cocaine addiction. Over 50 million Americans smoke cigarettes and rates of initiation of smoking among young women continue to increase. Yet smoking cessation is one of the bright spots in America's war on drugs. Better information about smoking consequences and the nature of nicotine addiction as well as better treatment for nicotine dependence have enabled over 38 million Americans to quit smoking. This is nearly 1/2 of all living adults who ever smoked. Smoking has long been associated with physical health risks and recent work has shown that it is associated also with mental health risks. Our purpose today is to review recent findings from the molecular to the molar which address issues of smoking and nicotine dependence as well as smoking cessation.

NICOTINE AND SMOKING: PERSPECTIVE FROM ANIMAL STUDIES
Paul B.S. Clarke

Many findings suggest that nicotine is critical to smoking behavior. Habitual smoking is thought to occur because smokers become dependent upon the central effects of nicotine. Precisely which action or actions of nicotine are involved in this behavior is not clear and some of the possibilities are outlined below.

Nicotine has powerful effects on behavior in animals. For example, nicotine initially decreases locomotor activity in drug-naive rats, but with repeated administration it increases activity. The stimulant effect is dose-dependent, stereospecific, and is due to a central action of nicotine. These properties suggest that nicotine acts through central nervous system receptors to produce this behavioral effect.

Where are the nicotine receptors in the brain that may mediate the behavioral effect described? There are actually several subtypes of nicotine receptors present in nervous tissue. An important and prevalent subtype can be labelled with ^{3}H-nicotine. Binding of ^{3}H nicotine in brain shows characteristics expected of a receptor: binding is saturable, of high affinity, steroselective, and has a discrete neuroanatomical distribution. Another subtype of nicotine receptor is labelled by the snake venom extract, alpha-bungarotoxin. However, we do not yet know if this subtype plays a role in smoking.

Several drugs of abuse are thought to derive their rewarding effects from their ability to activate the mesocorticolimbic dopamine system. Nicotine receptors labelled by ^{3}H-nicotine are present on neurons in this system in rats and presumably in humans too. Nicotine can promote mesolimbic dopamine release through a direct action on cell bodies or

terminals (for review see Clarke 1990).

This mesolimbic dopamine activating effect seems to underlie the locomotor stimulant action of nicotine in rats. We have shown that nicotine increases locomotor activity and mesolimbic dopamine utilization concurrently. Both effects were dose-dependent and stereoselective. Nicotine's locomotor stimulant effect could be blocked by 6-hydroxydopamine lesions of the nucleus accumbens. These lesions extensively depleted the mesolimbic dopamine terminals while having only a minor effect on those of the nigrostriatal system.

The ability of nicotine to activate mesolimbic dopamine neurons also seems to underlie its rewarding effects in rats (Corrigall et al. in press). Thus, intravenous self-administration of nicotine in rats was greatly reduced by extensive depletion of mesolimbic dopamine. It would appear that motor impairment was not involved, since the lesioned subjects could still respond at a fast rate for food reward.

Thus in rats, nicotine can activate the mesolimbic dopamine system, and this action seems to contribute importantly to the drug's stimulant and rewarding effects. Whether the same is true in man seems difficult or impossible to test at present.

Current aids to smoking cessation are not particularly successful in the long term, particularly those involving pharmacological intervention. This is perhaps surprising given the consensus that tobacco smoking is a form of nicotine dependence. However, to date, there have been very few published attempts to influence tobacco smoking with nicotinic receptor blockers. We have found that the nicotinic antagonist chlorisondamine antagonizes the stimulant effect of nicotine on locomotor activity in rats in a dose-dependent fashion. It also reduces i.v. self-administration of nicotine, but not cocaine in rats (Corrigall et al. in press). Thus, these data suggest that nicotinic receptor blockers may provide a pharmacological treatment for nicotine dependence (for review see Clarke 1991).

CIGAPETTE SMOKING AMONG OTHER DRUG DEPENDENCE DISORDERS
Jack Henningfield

Cigarette smoking is described as a prototypic drug dependence disorder. The clinical course of nicotine dependence is that of a progressive, chronic, relapsing disorder in which use typically begins during adolescence, is followed by an escalation over several months or years, and is occasionally interrupted by quitting attempts which usually lead to relapse within a few days or weeks. The pathophysiology of smoking involves the reinforcing effects of nicotine in the central nervous system as described by Dr. Clarke, effects of nicotine on hormonal and peripheral nervous system functions, which may also reinforce cigarette self-administration, and the development of tolerance and physical dependence to nicotine.

It has long been known that cigarette smoking is among the first instances of psychoactive drug use, and that for a portion of the population use of cigarettes precedes abuse of other drugs. such observations led to the designation of tobacco as a "gateway" drug. Consistent with this designation, population based studies of the National Institute on Drug Abuse show that compared to cocaine and alcohol, initial use of cigarettes is much more likely to lead to problems of dependence. Moreover, adolescents who take up tobacco use are more likely than their classmates to take up the use of alcohol, marijuana and cocaine. When non-smoking adolescents use alcohol, marijuana and cocaine, those who go on to initiate tobacco use are found to increase their use of the illicit substances and alcohol over the level used by those who remain non-smokers.

There is a direct relationship between amount of smoking and likelihood of illicit drug use and, in adolescents, binge alcohol drinking. In adults, the relationship between cigarette smoking and other psychoactive drug use continues with the relationship between amount of

smoking and amount of other drug use being strongest for alcoholic and caffeinated beverages and weakest for heroin and cocaine. Although more than 80% of alcohol and heroin abusing persons smoke cigarettes, the predictive value of tobacco use is strongest with respect to alcohol use in which epidemiologic data suggest that as many as one in three heavier cigarette smokers are at risk for the development of alcoholism. Taken together, such observations suggest that tobacco is not only a gateway substance to alcohol and illicit drug abuse, tobacco use is a preventable risk factor for other forms of drug addiction.

NICOTINE DEPENDENCE AND MAJOR DEPRESSIVE DISORDER
Naomi Breslau

Although there is scientific evidence that smoking is widespread and highly addictive as indicated in Dr. Henningfield's and Dr. Clarke's presentations, distinctions between smoking and nicotine dependence (ND) have been made rarely and the relationship between ND and other substance abuse disorders and affective disorders has received little attention. We present here results from a recent study of these associations.

A random sample of 1007 young adults enrolled in a large Health Maintenance Organization in the Detroit, MI metropolitan area was interviewed using the National Institute of Mental Health Diagnostic Interview Schedule (DIS), revised according to DSM-III-R. DIS modules for substance use disorders and affective disorders were administered. DIS systematic coverage of DSM-III-R criteria of ND allows identification of persons who met criteria for dependence among all smokers.

Substance dependence is conceptualized as a unitary process with cardinal characteristics indicative of impaired control of use of the psychoactive substance and continued use despite adverse consequences. Symptoms of the dependence syndrome also include tolerance and withdrawal.

In our sample of 1007 young adults, 394 or 39.1% smoked daily for a month or more in their lifetime. The lifetime rate of ND among smokers was 51%. Among persons with ND, 62% met criteria for mild dependence and 38% met criteria for moderate dependence. None met criteria for severe dependence. The rate of current smoking, i.e. within the last year, was 29% (n=292) and ND was 16%. Rates of smoking and ND were higher in whites than blacks and were inversely related to level of education (Breslau et al. 1991).

In examining the relationship between ND and other substance use disorders and affective disorders we estimated the relative lifetime prevalence of these disorders in persons with mild and with moderate ND, using the subset of persons with no ND as a reference. This latter group included 613 persons who had never smoked daily for a month or more in their lifetime (non-smokers) and 192 who smoked but did not meet dependence criteria (non-dependent smokers). With moderate ND, rates of all other substance dependencies, i.e. alcohol, cannabis, cocaine and miscellaneous drugs, increased significantly. With mild ND, rates of cannabis and other miscellaneous drug dependencies were significantly increased. The associations of ND and psychiatric disorders were estimated using an odds ratio adjusted for other substance use disorders and sex. The results indicated that the odds for major depressive disorder (MDD) were 4.7 times higher and the odds for any anxiety disorder were 4.2 times higher in persons with moderate ND compared to persons without ND. In persons with mild dependence, the odds for MDD were 1.86 times higher, and the odds for any anxiety disorder were not increased significantly.

In a second analysis we compared non-dependent smokers with non-smokers on these variables. Compared to non-smokers, non-dependent smokers had significantly increased rates of alcohol, cannabis, and cocaine dependence and any anxiety disorder, but their rate of MDD was not increased significantly. When other coexisting dependence disorders

were controlled, the relationship between any anxiety disorder and ND was not significant.

A follow-up interview with 995 of the respondents 14 months later allowed us to examine (1) whether or not smokers with a history of MDD progressed to ND and more severe levels of dependence at a higher rate and (2) whether or not persons with a history of ND were at increased risk for MDD. A history of MDD at baseline increased the risk for progression to ND and more severe levels of dependence two fold. Persons with a history of ND, at baseline, had a significantly higher rate of first incidence MDD (7.5%) than persons without such history (3.2%).

Of the 1007 respondents, 239 persons had tried to quit or cut down smoking unsuccessfully at some point in life. Persons with a history of MDD or any anxiety disorder reported more severe withdrawal compared to persons with neither of these disorders. However, neither severity of withdrawal or any specific withdrawal symptom accounted for the association between history of MDD and continued smoking (Breslau et al. 1992).

The association between ND and major depressive disorder observed in both the cross-sectional and prospective studies may reflect either causal influences between depression and ND or the effects of processes common to both disorders.

SMOKING CESSATION AMONG ALCOHOL/DRUG ABUSERS
John R. Hughes

Across several samples of alcohol/drug abusers vs the general population, the median prevalence rates for smoking status are 72% vs 9% heavy smokers (>20 cigarettes per day), 11% vs 19% light smokers, 17% vs 27% ex-smokers and 8% vs 55% never smokers. Alcohol/drug abusers also smoke more cigarettes per day and smoke each cigarette more intensely than smokers in the general population. The prevalence of smoking in males in the general population fell from 60% in 1965 to 33% in 1990. However, the prevalence of smoking in male alcohol/drug abusers in treatment fell only from 90% to 82% over this time period. In summary, smoking is highly associated with alcohol/drug abuse and this association will likely become stronger over time. In fact, at present, heavy smoking can be used as a marker for alcohol/drug abuse; e.g. 38% of nicotine dependent smokers have a lifetime history of alcohol dependence (Hughes et al. 1991).

Smoking is a major cause of death among alcohol/drug abusers. Mortality risks from alcohol and smoking are additive and, in some disorders, synergistic.

Two-thirds *of* patients and drug abuse counselors are interested in or recommend smoking cessation. The large majority of patients and counselors view immediately post-treatment as the best time to stop smoking. Many successfully recovering alcohol/drug abusers stop smoking (27-63%). The scientific evidence available suggests stopping smoking decreases, not increases, the probability of relapse to alcohol/drug use.

Successful treatments for smoking cessation among alcohol/drug abusers have not been developed. In one study, we found that 12% of smokers reported a history of alcohol/drug problems. These smokers appeared more nicotine dependent in that they smoked more cigarettes, began smoking at an earlier age, smoke earlier upon arising, reported more difficulty refraining from smoking, and were more likely to smoke even when ill. In our trial with nicotine gum, smokers with a past history of problems did not have more withdrawal symptoms or craving nor use more nicotine gum or use it longer. However, in terms of initial cessation, smokers with a history of alcohol/drug problems benefitted

more by nicotine replacement (4 week quit rates - 45% with nicotine gum vs 23% with placebo gum) than smokers without this history (57% vs 55%). A similar trend occurred with long-term cessation rates (Hughes, in press).

Interest in providing smoking cessation therapy is increasing due to: (1) recent JCAH requirements for smoke-free medical facilities, (2) interest among patients and counselors, (3) recognition that smoking kills many successfully recovering alcohol/drug abusers. It is imperative that the research community respond by providing scientifically based data on which to tailor smoking cessation programs to the needs of alcohol/drug abusers (Bobo 1989; Sobell, et al. 1990).

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SYMPOSIUM INTRODUCTION: PHARMACOTHERAPY OF ADDICTIVE DISEASES

M. J. KREEK

The goals of pharmacotherapy for an addictive disease should include amelioration of the signs and symptoms of any significant drug withdrawal effects (i.e., abstinence syndrome), a significant decrease or elimination of craving for the specific drug of abuse and to the extent achievable, prevention of relapse to use of that drug of abuse, along with full restoration to or towards normalcy of physiological functions disrupted by chronic use of the drug of abuse. The rational basis for the development of any pharmacotherapeutic agent would ideally include information concerning the specific sites and mechanisms of action of the drug of abuse, and the cascade of events which results from such use. Considerable laboratory and basic clinical research have led to increased information concerning the site of action, to a limited extent, the mechanism of action, and many of the cascade of effects of short-acting opiate drugs such as heroin, which is one of our leading drugs of abuse. Increasing laboratory and basic clinical research is now also underway concerning both cocaine and alcohol dependency and their effects. Heroin addiction now afflicts between 500,000 and 1,000,000 persons in the United States. and increasing numbers worldwide. Increasing numbers of those who have begun their drug abuse history by using primarily cocaine are now turning to heroin use. Both basic clinical research and laboratory research from our group, as well as some evidence from many other laboratories, suggest that cocaine abuse may involve disruption of the endogenous opioid system, just as our group and others have shown that heroin addiction involves disruption of this system. Also, based again on both evidence from the laboratory of a variety of groups, as well as some basic and applied clinical research studies, there is recent evidence that the endogenous opioid system may also be involved in the addiction of alcoholism.

SYMPOSIUM SPEAKERS

"Opioid Agonists: Use in Treatment of Opiate Dependency"
Mary Jeanne Kreek, M.D., The Rockefeller University, New York, NY

"Opioid Antagonists and Mixed Agonist-Antagonists: Use in Treatment of Opiate Dependency and Alcoholism"
Charles O'Brien, University of Pennsylvania, Philadelphia, PA

"Diverse Pharmacological Agents for Possible Treatment of Cocaine Dependency"
Thomas Kosten, Yale University, New Haven, CT

"Pharmacotherapy for Alcohol Abuse and Dependency"
Jack Mendelson, McLean Hospital/Harvard Medical School, Belmont, MA

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OPIOID AGONISTS: USE IN TREATMENT OF OPIATE DEPENDENCY

M. J. KREEK

Currently, there is one major pharmacotberapeutic agent proven safe and effective for chronic treatment of heroin addiction: methadone. The racemic (dl) methadone has a very long plasma half-life in humans (but not in most sub-human species) of around 24 hours. As shown by use of stable isotope tracer techniques using specific deuterium-labeled separate enantiomers of methadone, the half-life of the active enantiomer is around 48 hours. This long plasma half-life is coupled with long lasting effects, including prevention of withdrawal symptoms and prevention of "drug hunger." By virtue of developing a high level of tolerance and cross tolerance, our group and others have shown that methadone also prevents any euphorogenic or other narcotic-like effects when heroin or any other short-acting narcotic is superimposed. The mechanism of action of methadone involves steady state perfusion of endogenous opioid receptors. During steady moderate to high dose (60-100 mg/d) methadone treatment, in very good programs in which counseling, rehabilitation efforts, and access to primary health care, including psychiatric care, is available, retention in treatment may reach 70-80% with successful return to job, school, and an otherwise normal lifestyle. Also, in such programs, the continued abuse of heroin drops to less than 15% of all patients who have been in treatment for 6 months or more. Of great public health importance, in 1984, we showed that whereas over 50% of all IV drug users on the streets of New York were at that time infected with the AIDS virus (anti-HIV-I positive), less than 10% of those who had entered effective methadone maintenance treatment prior to the epidemic entering the drug abuse population in 1978, were positive for the HIV-I virus. Our laboratory, complemented by work from others, has shown that normalization of many physiological functions, disrupted by heroin abuse, occurs during chronic long-term methadone maintenance treatment. Normalization of neuroendocrine function, including the extremely important hypothalamic-pituitary-adrenal stress responsive axis occurs, along with normalization- of the hypothalamic-pituitary-gonadal axis. Our group has hypothesized that addiction may in part be due to an atypical responsivity to stress. Thus, normalization of neuroendocrine function may be directly related to the reduction and cessation of drug-seeking behaviors along with normalization of mood. We have also shown that immunological function normalizes during chronic methadone treatment.

Other agents which are being used successfully or may in the future be used for treating heroin addiction include the l-enantiomer of methadone, and also the acetylated congener of methadone, l-alpha-acetylmetbadol (LAAM), both of which have a longer half life than methadone. LAAM has been under study since 1969. It is similar to methadone in its actions and is effective. It is expected that LAAM will be approved by the U.S. Food and Drug Administration in 1993. Some very provocative studies, primarily from laboratory research, as well as a few on-going clinical studies suggest that the kappa opioid receptor-preferring endogenous peptide ligand dynorphin A and its derivative peptides, may have a beneficial effect in amplifying the action of primarily mu opioid receptor preferring ligands such as methadone and also the short-acting drugs heroin and morphine. Future research may show that very selective kappa ligands may be effective in management of some aspects of the pharmacotherapy of opiate and possibly also cocaine addiction.

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BEHAVIORAL AND PHARMACOLOGICAL TREATMENTS FOR COCAINE DEPENDENCE

T. R. Kosten

The treatment of cocaine dependence has utilized both behavioral and pharmacological approaches. Behavioral approaches include 12 Step Programs based on the A.A. model, as well as cognitive and conditioning (extinction) therapies to cope with cocaine related cues in the environment. Conditioning therapies can reduce the craving, withdrawal and high associated with cocaine related cuts and thereby decrease relapse to cocaine abuse. Another promising behavioral approach is the use of Day Hospitalization to initiate and sustain more effectively than routine outpatient treatment. Pharmacotherapies are based on the premise of neuroadaptation, as evidenced by elevations in prolactin, reductions in dopamine brain receptor binding, neuropsychological deficits and abnormalities in brain imaging. Treatment agents include antidepressants, dopamine agonists and novel agents such as buprenorphine. Controlled studies with the antidepressants desipramine, fluoxetine and bupropion have shown some promise with abstinence rates as high as 65%. While controlled studies of fluoxetine, gepirone, and other serotonergic agents have shown no greater efficacy than placebo, preliminary studies with bupropion have shown abstinence rates of 70%. Dopamine agonists such as amantadine and bromocriptine have shown efficacy in controlled studies, although side effects have been a limitation of bromocriptine. Recent pilot work has suggested the efficacy of buprenorphine for the treatment of cocaine abusing opioid addicts. Combinations of medications with behavioral therapies have shown promise particularly relapse prevention therapy and antidepressants in combination with these therapies.

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PHARMACOTHERAPY OF ADDICTIVE DISEASES: PHARMACOTHERAPY OF ALCOHOLISM

J. H. MENDELSON

The development of safe and effective drug treatment for alcoholism has been impeded by skepticisms about the use of any medications for the treatment of alcoholism. Jaffe et al. (1992) have noted "in the United States and some other countries as well, clergy, non medical health professionals, and recovering alcoholic laymen all play prominent roles in the treatment and rehabilitation of the alcoholic patient. In general, they believe that the alcoholic's central problem is the use of the drug (alcohol) to manage feelings. Furthermore, they believe that learning to cope with life while abstaining from alcohol and other drugs is both the essence of treatment and its only acceptable goal." In contrast to ambivalence about treatment of alcoholism with medications, there has been general professional and popular acceptance of the use of drugs for the treatment of alcohol withdrawal syndromes. There are currently seven generic benzodiazepines which are widely used for treatment of moderate to severe alcohol withdrawal (Kranzler and Orrok 1989). Appropriate use of these drugs in concert with management of intercurrent illness, nutritional supplementation and correction of water and electrolyte imbalance has resulted in a significant decrease in both mortality and mobidity associated with moderate and severe alcohol withdrawal. Use of benzodiazepines in outpatient therapy of alcohol withdrawal has resulted in a striking decrement in the prevalence of alcoholic hallucinosis, delirium tremens and alcohol-related seizure disorders. Although alcohol sensitizing agents such as disulfirum (antibuse) and calcium carbimide have been widely used in medical practice for the treatment of alcoholism the effectiveness of these pharmacotherapies for preventing recrudescence of alcohol abuse following abstinence has been limited. In general, patient compliance has been poor for self-administration of alcohol sensitizing agents. Basic and clinical research endeavors continue for developing drugs for the treatment of acute alcohol intoxication. However, the imidazobenzodiazepine which binds at Gaba-BZ receptors (Suzdak et al. 1986) cannot be successfully used in humans because of the drug's anxiogenic and proconvulsant properties (Kolata 1986). Basic research findings which demonstrated a role of serotonergic neurotransmitter systems in the development of both functional and innate alcohol tolerance (Tabakoff and Hoffman 1989) has prompted clinical investigation of serotonin uptake inhibitors for the treatment of alcoholism (Naranjo et al., 1987, 1989, 1990). Although these drugs have been shown to induce some reduction in alcohol inlake, the ultimate efficacy of these compounds for the treatment of alcoholism remains to be determined. Clinical investigations are also assessing the effects of drugs for the treatment of psychiatric co-morbidity associated with alcohol abuse and dependence. Such studies involve assessments of tricyclic antidepressants, monoamine oxidase inhibitors, anxiolytics, dopaminergic blockers, dopaminergic agonists and lithium. When used judiciously these compounds may facilitate treatment of persons with alcohol abuse who also have concurrent affective or anxiety disorders. There are recent reports that naluexone, an opioid antagonist, may be highly effective in sustaining remission from alcohol abuse (Volpicelli et al., 1990; O'Malley 1992). Although the mechanisms of naltrexone's action for reduction of alcohol consummatory behavior are unknown, one factor may involve effects of naltrexone on neuroendocrine function involving the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axis (Mendelson et al., 1986).

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ACKNOWLEDGEMENTS: This research was supported in part by grants AA06252 from the National Institute on Alcohol Abuse and Alcoholism and DA00064 from the National Institute on Drug Abuse.

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PROBING THE MEANING OF RACIAL/-ETHNIC GROUP COMPARISONS IN CRACK-COCAINE SMOKING

M. LILLIE-BLANTON, J. C. ANTHONY AND C. R. SCHUSTER

Racial and ethnic group comparisons retain a central place in summaries of national data on the prevalence of illicit drug use. In some cases, these comparisons provide useful descriptive information on patterns of drug use specific for a racial/ethnic population group. Nonetheless, in other cases, these basic comparisons by race/ethnicity can be misleading because they do not account for differences in the age structure of the population groups or in the community environments they experience. As a result, these basic comparisons sometimes reinforce racial prejudices and draw public attention away from factors that may better explain patterns of drug use.

In this study, we probe the meaning of a prior analysis of the 1988 National Household Survey on Drug Abuse (NHSDA) which reported that crack-cocaine smoking is more common among African Americans and Hispanic Americans than White Americans. To examine this issue, we undertook a re-analysis of the original data from the 1988 national drug survey to assess whether crack-cocaine smoking is associated with factors specific to race/ethnicity. We hypothesized that the reported racial/ethnic group differences might be an artifact of macro-social environmental risk factors or determinants of prevalence.

The 1988 NHSDA interviewed 8,814 individuals residing within households in the coterminous United States. Subjects were selected using a multi-stage area probability sampling of all residents aged 12 and older. In the original NHSDA reports and in this re-analysis, crack use was operationally defined as self-reported use of cocaine in rock or chunk form one or more times ever in an individual's lifetime. To hold constant social and environmental risk factors that might potentially confound racial comparisons, we used an epidemiologic strategy that involves post-stratification of respondents into neighborhood risk sets. A conditional logistic regression model was used to estimate the relative odds of crack use by race/ethnicity.

Once respondents were grouped into neighborhood clusters, the relative odds of crack use did not differ significantly for African Americans (RO=1.03, 95% CI=O.46-2.09) or for Hispanic Americans (RO=0.92, 95% CI=O.50-1.71) when compared to White Americans. This analysis provides evidence that, given similar social and environmental conditions, crack use does not strongly depend on race-specific personal factors (e.g., biologic or cultural). Future research should seek to identify which characteristics of the neighborhood social environment are important and potentially modifiable determinants of drug use. Although the study finding does not refute the prior analysis, it gives evidence that crude prevalence estimates may provide misleading information about the role of race and ethnicity in the epidemiology of crack use. (Supported by NIDA grant DA04392)

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DRUG PREVENTION WITH HIGH-RISK ADOLESCENTS: SOME LIMITATIONS OF PROBLEM BEHAVIOR THERAPY

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Substance use before age 15 is a clear risk factor for adult substance abuse (Anthony & Petronis in press; Robins & Pryzabeck, 1985). Antisocial behavior is prognostic of early adolescent substance use; both with the variety of substances used by age 15-16 as well as the frequency with which they are used (Dishion, Capaldi, & Ray, in press; Smith & Fogg, 1978). Problem behavior theory (Jessor, 1975; Jessor & Jessor, 1976) suggests that substance use, sexual activity, and other health compromising behaviors are part of one underlying general deviance syndrome, and all are caused by similar underlying conditions. An alternate point of view is that early antisocial behavior is a risk factor for adolescent substance use, yet the determinants for antisocial behavior and substance use are quite different (Dishion, Capaldi, & Ray, in press). This report describes an intervention, the Adolescent Transitions Program (ATP), with two components that target family management and peer influence to reduce problem behavior in at-risk families of young adolescents (middle school). The two intervention components are delivered in a group format: one, to parents (Parent Focus); and two, to teenagers (Teen Focus). Study families had an 11- to 14-year-old boy or girl (50%) deemed as at-risk for substance abuse by their parents. One hundred and twenty families were randomly assigned to one of four versions of the Adolescent Transitions Program. The four conditions were Parent Focus Only, Teen Focus Only, Parent and Teen Focus, and Self-Directed. In addition, 23 families with at-risk adolescents were recruited (same as above) as a quasi-experimental control group.

Outcome analyses revealed improvement (associated with the ATP intervention) in observed negative family interaction patterns. For antisocial behavior, there was a statistically marginal trend for the Parent Focus intervention to stop the escalation of antisocial behavior, according to teacher ratings. A path analysis revealed a reduction in parent-child negative engagement associated with improvements in the youth's antisocial behavior at school. However, no changes in the youth's tendency to use substances, as a function of exposure to ATP, was found on either parent of youth reports. The detection of an intervention effect on early adolescent antisocial behavior that does not translate from initiations to substance use questions the assumption that both are aspects of a problem-behavior syndrome.

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REINFORCING EFFECTS OF EXTENDED INHALATION OF NITROUS OXIDE IN HUMANS

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Nitrous oxide is an inhaled general anesthetic that is abused in humans (Layzer, 1985). The reinforcing or rewarding effects of N_2O at different concentrations have been demonstrated in animals (Wood et al., 1977). but to our knowledge, not in humans. The subjective and reinforcing effects of nitrous oxide at subanesthetic doses (30% and 40% in oxygen) were determined in two experiments with 12 healthy volunteers each (six males and females). Each choice experiment consisted of seven sessions. The first four sessions of each experiment were *sampling sessions.* On two of these sampling sessions, subjects were exposed for 30 min to a given concentration of nitrous oxide (35% in Experiment 1; 40% in Experiment 2) and on the other two sessions were exposed for 30 min to 100% oxygen. For each subject, the two substances were associated with distinctive colors for identification. Subjects were blind to the agent being administered. Mood (as assessed by the Addiction Research Center Inventory, a Visual Analog Scale, and a Drug Effects/Liking Questionnaire) and psychomotor effects (as assessed by an eye-hand coordination test and the Digit Symbol Substitution Test) were measured before, during and after a 30-min inhalation period. The last three sessions were *choice sessions.* At the beginning of each choice session, subjects chose which of the two agents they wished to inhale by color. The number of times the active agent was chosen over placebo (drug choice) was taken as the primary indicator of the agent's reinforcing efficacy. Thirty percent nitrous oxide was chosen no more often than oxygen (41.6% choice rate), indicating that, for most of the subjects tested, extended inhalation of this nitrous oxide concentration did not function as a positive reinforcer. Forty percent nitrous oxide was chosen significantly less often than oxygen (22% choice rate), indicating that, for most of the subjects tested, extended inhalation of this nitrous oxide concentration was actively avoided. Nitrous oxide produced robust subjective effects (e.g., increased rating of 'high', 'tingling', and 'dizzy'). Subjects who chose nitrous oxide at 2-3 times reported experiencing pleasant subjective effects (e.g., increased ratings of 'happy') and liked it during sampling sessions. In comparison, those who always chose placebo reported experiencing mom unpleasant subjective effects from nitrous oxide (e.g., increased dysphoria) and they disliked it during sampling sessions. Both concentrations of nitrous oxide impaired psychomotor performance. The lack of reinforcing effects noted in the present study is paradoxical, given nitrous oxide's known abuse potential. Further research is needed using the same preparation with larger sample sizes or different subpopulations to determine what the predictors are (e.g., demographic, personality, drug use history) of nitrous oxide performance.

ACKNOWLEDGEMENTS: This research was supported by NIDA Grants DA 07103 and DA 02812.

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Effects of Intranasal Cocaine on Human Aggressive and Escape Responding

D. R. Cherek, R. H. Bennett and D. L. Creson

The effects of intranasal administration of 4mg (placebo) and 24, 48 and 96 mg of cocaine HCl on operant responding were studied in male subjects with recent histories of cocaine use. Twenty-five min sessions were conducted 1 hr before and 0.0, 0.5, 1.5 and 2.5 hrs after cocaine adminstration. Subjects received each active dose twice with intervening placebo doses. Subjects were not given an active dose until urine levels were free of all drugs. Subjects were given three operant response options. Responding on lever A was maintained by a fixed-ratio (FR) 100 schedule of point presentation (1 pt = 10 cents). Aggressive and escape responding was engendered by subtracting points from the subject's counter. Following point subtractions, completion of an FR 10 on either lever B, aggressive responses, or lever C, escape responses, initiated a 125 or 250 sec interval free of further point subtractions. Subjects were instructed that: (1) their points were subtracted by another person, (2) lever B responses subtracted a point from the other person, and (3) lever C responses protected the subject's counter for some period of time. Initial results indicate that aggressive responding was increased at the 48 and/or 96 mg dose in 3 of 4 subjects. Escape responding was increased at the 24mg dose, while point-maintained responding was clearly increased in only one subject. There was a small elevation of aggressive responding on days following administration of a cocaine dose.

Supported by NIDA Grant DA-03166

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SUBJECTIVE AND REINFORCING EFFECTS OF DIPHENHYDRAMINE AND LORAZEPAM

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The present study was designed to 1) assess the relationship between the subjective and reinforcing effects of lorazepam and diphenhydramine; 2) assess the stability of the subjective effects of lorazepam and diphenhydramine with repeated exposures. Twelve healthy adult males with a history of recreational sedative abuse participated in a double-blind crossover study in which subjects received placebo, lorazepam (4 mg) and diphenhydramine (400 mg) in a block-random sequence four times each (i.e., 4 cycles of the three compounds) on a total of 12 separate days. Compounds were administered in color-coded capsules. The color-code for each compound remained the same throughout the study but different color-codes were assigned to each subject. Subject-related subjective effects and psychomotor and cognitive performance were assessed each day 30 min before and 0.5, 10, 2.0, 3.0, 4.0, 5.0 and 6.0 hours following drug administration. As previously demonstrated, lorazepam increased scores on subjects' liking of the drug, desire to take the drug again, and monetary value of the drug relative to placebo. Diphenhydramine, relative to placebo, produced comparable increases across these measures but also produced increased ratings on scales of bad (i.e., unpleasant) effects. There were no systemic changes in any of these measures across the four cycles. Reinforcing effects were assessed in a choice procedure at the end of each of the four cycles. When the choice was between drug and placebo, both drugs were chosen significantly more often than placebo (lorazepam 83%. diphenhydramine 75%). When the choice was between lorazepam and diphenhydramine, both drug were chosen an equal number of times. These data demonstrate a concordance between several subjective measures thought to predict drug reinforcement and actual drug reinforcement. In addition, the data indicate that the subjective effects and reinforcing effects were relatively stable over the course of the study.

ACKNOWLEDGEMENTS

This work was supported by USPHS grant DA01147.

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PENTOBARBITAL-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF PRESYNAPTIC GABA AGONISTS

D. M. Grech and R. L. Balster

There is increasing pharmaceutical interest in using drugs which activate GABAergic neurotransmission by acting at presynaptic sites. It is of interest to compare the behavioral effects of some of these compounds to those of post-synaptic $GABA_a$ agonists such as the barbiturates. Six male Sprague-Dawley rats were trained using a 2-lever operant procedure to discriminate 5.0 mg/kg pentobarbital (PB) from saline. Responding was maintained under a FR-32 schedule of food reinforcement. Substitution tests were completed with PB (1-20mg/kg), the GABA transaminase inhibitor, valproic acid (10-300 mg/kg). and the GABA uptake inhibitors, AOAA (amino-oxyacetic acid) (0.3-30 mg/kg) and CI-966 (0.3-30 mg/kg). PB (3-10 mg/kg) dose-dependently substituted for the training dose (5.0 mg/kg) without lowering rates of responding. Valproic acid completely substituted for PB, however only at doses which also decreased responding. Response rates following valproic acid administration were reduced by >50% of control values. AOAA and CI-966 produced only partial substitution for PB, yielding a maximum of 45% and 50% PB-lever responding, respectively, although both drugs substantially decreased rates of responding. The data provide evidence for differences in the behavioral effects of PB and a GABA transaminase inhibitor, which produced PB-lever responding only at behaviorally disruptive doses, and two GABA uptake inhibitors, which failed to produce PB-like effects (Research supported by NIDA grants DA01442 and DA07027).

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EFFECTS OF SEVERAL DOPAMINE ANTAGONISTS ON THE REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE IN RHESUS MONKEYS

K. E. Vanover and W. L. Woolverton

The present experiment was designed to evaluate the effects of several dopamine (DA) receptor antagonists on the reinforcing and discriminative stimulus effects of cocaine in rhesus monkeys. One group of monkeys (N = 6) was allowed to self-administer cocaine (0.03 or 0.1 mg/kg/inj, i.v., FR 10, 2 hours/day) while a second group (N = 5) was trained to discriminate cocaine (0.2 or 0.4 mg/kg, i.m., 10 min pre-session) from saline in a two lever, food-reinforced, drug discrimination paradigm. When behavior was stable, chlorpromazine (CPZ), clozapine (CLZ) or (+)-AJ76 (AJ) were administered i.m., 15 or 30 min pre-session. CPZ and CLZ are antipsychotics with DA antagonist actions while AJ is a putative DA autoreceptor antagonist. All three compounds increased cocaine self-administration in a manner that was consistent with blockade of the reinforcing effects of cocaine (0.3 - 3.0 mg/kg CPZ; 0.3 - 1.0 mg/kg CLZ; 1.0 - 3.0 mg/kg AJ). Analysis of the distribution of responding over the session showed no effect on pattern of responding, suggesting that the blockade was partial. In only one monkey at one dose each for CPZ and CLZ was a pattern of responding similar to that seen when saline was available for self-administration (extinction). In combination with cocaine in the discrimination experiment, CPZ (0.1 - 3.2 mg/kg) decreased cocaine-appropriate responding from >80% to <20% and cocaine reversed the rate-decreasing effects of CPZ in 2 of 3 monkeys. In contrast, CLZ (up to 3.2 mg/kg) and AJ (up to 6.4 mg/kg) had little or no effect at doses that did not completely suppress lever pressing. These results suggest that CPZ, CLZ and AJ partially blocked the reinforcing effects of cocaine. Alternatively, it is possible that the increase in cocaine self-administration was due to attenuation of the rate-decreasing effects of cocaine. Blockade of the discriminative stimulus effects of cocaine was only apparent with CPZ. Although enhanced DA neurotransmission is involved in both of these behavioral effects of cocaine, the present results suggest that there may be some pharmacological distinctions between them. (Supported by NIDA DA-00250, DA-00161).

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BUPRENORPHINE ATTENUATES COCAINE'S REINFORCING PROPERTIES IN RHESUS MONKEYS

J. M. DRIEZE, N. K. MELLO, S. E. LUKAS AND J. H. MENDELSON

Chronic buprenorphine treatment (0.237-0.70 mg/kg/day) significantly reduced cocaine self-administration by rhesus monkeys for 15 to 120 days (Mello et al., 1989, 1990, 1992). Buprenorphine treatment also reduces cocaine abuse by heroin and cocaine abusers in outpatient clinical trials (Kosten et al. 1989; Gastfriend et al. 1991). There is a controversy over whether buprenorphine reduces cocaine self-administration by enhancing or by attenuating cocaine's reinforcing effects. We examined the effects of daily treatment with saline or buprenorphine (0.1 and 0.3 mg/kg/day) on cocaine's reinforcing properties over a wide dose range (0.001-0.3 mg/kg/inj). Cocaine doses and saline were studied in an irregular order for at least 5 days or until cocaine/saline self-administration was stable for 3 days (±20 percent). Cocaine and saline self-administration were maintained on an FR4 (VR 16:S) schedule of reinforcement. During treatment with 0.1 mg/kg of buprenorphine, the peak of the cocaine dose-response curve shifted one-half log unit to the right in 4 monkeys but the maximum number of injections were equivalent (76 to 80 inj/day). The effects of the higher dose of buprenorphine (0.3 mg/kg/day) were less consistent than the lower dose (0.1 mg/kg/day). In one monkey, the peak of the dose response curve remained at 0.01 mg/kg/inj but the number of injections was decreased by 41 percent during daily treatment with 0.3 mg/kg of buprenorphine. In another monkey, the higher dose of buprenorphine (0.3 mg/kg) did not change the cocaine self-administration dose-response curve. Peak response rates were equivalent or decreased by 34 to 55 percent from the saline treatment base-line. We conclude that buprenorphine decreased the reinforcing potency of cocaine in cocaine-experienced rhesus monkeys.

ACKNOWLEDGEMENT8

Supported in part by Grants DA02519, DA04059, DA00101, DA00064 and DA00115 from the National Institute on Drug Abuse.

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THE ABILITY OF A D1 AND D2 ANTAGONISTS COMBINATION TO ANTAGONIZE THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE

B. GETER AND A. L. RILEY

Although cocaine blocks the reuptake of dopamine, norepinepherine and serotonin, only dopamine reuptake inhibitors have been shown consistently to substitute for the discriminative stimulus properties of cocaine (Kleven et al., 1990), suggesting a dopaminergic mediation of this effect. Despite this finding, neither selective D1 nor D2 antagonists invariably block (Barrett and Appel, 1989) the cocaine cue. The present study further evaluated the ability of the D1 antagonist, Schering-23390 (SCH), and the D2 antagonist, haloperidol (HAL), to antagonize the discriminative stimulus properties of cocaine within the conditioned taste aversion baseline. Given that dopamine reuptake inhibitors substitute for the cocaine cue, while D1 and D2 agonists fail consistently to do so (Colpaert et al., 1979), it is possible that both D1 and D2 receptors must be activated to produce the cocaine cue and that both receptors must be blocked to antagonize the effect. The following study tested this hypothesis by assessing the ability of SCH and HAL given both alone and in combination to block cocaine's discriminative stimulus properties. Following the establishment of drug discrimination learning with cocaine (7.5 mg/kg), female Long-Evans rats were given varying doses of SCH or HAL prior to cocaine during probe sessions. As has been reported by others, most animals displayed at least partial antagonism of the cocaine cue. However, when SCH/HAL combinations were given prior to cocaine, complete antagonism of the cocaine cue did not occur. In fact, the antagonism demonstrated with the D1/D2 combination did not exceed that produced by either antagonist alone. These data do not support the hypothesis that both D1 and D2 receptors must be activated to produce the cocaine cue. The mechanism underlying the discriminative stimulus properties of cocaine remains unknown.

REFERENCES: Available upon request from the first author.

ACKNOWLEDGEMENTS: This research was funded by a National Research Service award from the National Institute on Drug Abuse (1 F31 DA04577-01).

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DYNORPHIN (1-13) IMPAIRS MEMORY FORMATION FOR BOTH AVERSIVELY AND APPETITIVELY MOTIVATED LEARNING IN CHICKS

P. J. COLOMBO, K. R. THOMPSON, J. L. MARTINEZ, JR., E. L. BENNETT AND M. R. ROSENZWEIG

Each of the three main families of endogenous opioid peptides, which include erdorphins, enkephalins, and dynorphins, are known to affect memory formation, however the dynorphins have been characterized least. The majority of experiments that examined the effects of dynorphin on memory formation used aversively motivated learning paradigms. The current study examined whether effects of dynorphin on memory formation are general to both aversively and appetitively motivated learning.

Two- or four-day-old White Leghorn cockerels were injected bilaterally with dynorphin$_{(1-13)}$ into the intermediate medial hyperstriatum ventrale - a brain region important for memory formation in the chick - and trained on either a one-trial peck-avoidance (PA) task, or an appetitive visual discrimination (AVD) task; retention was tested at 24 h.

In two-day-old chicks, administration of 0.01, 0.03, or 0.1 mM dynorphin caused significantly fewer chicks in each drug group to avoid pecking a dry bead at 24 h test compared to saline injected chicks. However, two-day-old chicks injected with these doses of dynorphin also took longer to initiate pecks than saline injected chicks during training, which suggests a possible performance deficit during acquisition of the task. In contrast, only the highest dose of 0.1 mM dynorphin impaired memory formation for peck-avoidance training in four-day-old chicks. There were no differences among treatment conditions on either the latency to peck or number of pecks during training in four-day-old chicks. Administration of 0.03 mM dynorphin significantly impaired memory formation for appetitive visual discrimination training in four-day-old chicks. There were no differences among treatment conditions on latency to peck during training or the total time to complete the training trial. Chicks in each condition showed significant improvement during training, which indicates that dynorphin impairs memory formation for appetitive visual discrimination, but does not impair acquisition of this task.

The results of this study are twofold: (1) Similar doses of dynorphin impaired memory formation for both an aversively and an appetitively motivated task in four-day-old chicks. (2) lower doses of dynorphin impaired test performance in two-day-old chicks than were effective in four&y-old chicks. The first finding suggests that dynorphin plays a general role in memoly formation that is not task specific. The second result suggests a possible difference in opioid receptor development of two- and four-day-old chicks.

ACKNOWLEDGEMENTS

Supported by NIDA DA05492 (PJC), DA04795 (MRR & JLM) and DA04195 (JLM).

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OUTCOMES OF SOCIALLY REHABILITATED METHADONE MAINTENANCE PATIENTS IN MEDICAL MAINTENANCE: FOLLOW-UP AT 33-102 MONTHS

D. M. NOVICK; H. JOSEPH; E. A. SALSITZ; M. F. KALIN; J. B. KEEFE; E. L. MILLER AND B. L. RICHMAN

Medical maintenance, the treatment of socially rehabilitated methadone maintenance patients in physicians' offices, was begun in 1983 to determine if such patients can be treated within the context of general medical practice (Novick and Joseph 1991). Using strict eligibility requiremcnts, the first 100 patients were admitted to medical maintenance during 1983-89. The following outcomes ensued: 77 remain in good standing, 13 had unfavorable discharges (nine for cocaine abuse, three for misuse of medication, and one for administrative problems), six detoxified, three died, and 1 voluntarily returned to a conventional methadone clinic. The cumulative proportion remaining in medical maintenance at 90 mo. (life table analysis) is .66 ± .08. The median (with range) time from entry to discharge was 25 (10-45) months for the nine cocaine abusers and 38 (24-93) months for the six detoxitied patients ($p < 0.05$). We found no differences in demographic features or heroin addiction histories between the 77 patients who remained in good standing and the 13 who had unfavorable discharges. Patients with unfavorable discharges returned to conventional methadone clinics. The six detoxified patients had been in methadone maintenance treatment, including medical maintenance, for 17.5 (11-24.4) years. We conclude that the high retention rate in medical maintenance supports the feasibility of this form of treatment for socially rehabilitated, methadone-maintenance former heroin addicts.

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HUMAN DISPOSITION OF INTRAVENOUS, ORAL AND SUBLINGUAL [^{3}H]BUPRENORPHINE

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Young-adult, male, paid volunteers each received a single 0.63 μg/kg body weight dose of [^{3}H]buprenorphine (B) (6 iv, 6 sublingual, 4 po) containing <150 μCi of ^{3}H. This dose, ca. 16% of the effective analgesic dose, when administered iv produced distinctive subjective effects and persistent reduction in pupillary diameter. Cardiovascular changes were minimal. Plasma concentration of B and metabolites were measured by high performance liquid radiochromatography. After iv administration plasma B averaged 359 ± 164 (SD pg/ml at 6 min after administration. At 30 min. B still accounted for ca. 80% of total plasma ^{3}H. An averaged 0.0308 ± 0.0085 (SEM) h^{-1}. The half-life was therefore longer than has been previously reported. Peak norbuprenorphine (NB) concentrations were ca. 8 pg/mL and occurred 0.2-3h after dosing. Peak B-glucuronide (BG) and NB-glucuronide (NBG) concentrations were 8 pg/mL (6-15 min after dosing) and 10 pg/mL (1-2 h after dosing), respectively. Average peak plasma concentrations of B after sublingual administration was ca. 60 pg/mL while much lower peak concentrations (average of 7 pg/mL) occurred after oral administration. Peak concentrations of NG, BG and NBG were similar in both cases to those found following i.v. administration. Excretion of ^{3}H was predominantly in feces. Urinary excretion, accounting for 11% of the oral dose and 14-15% of the sublingual and iv doses, had essentially ceased by 96 h. Fecal excretion accounted for 72% of the oral dose, 59% of the sublingual dose and 47% of the iv dose over 96 h, but was still not complete at that time. Oral bioavailability was <15%. Sublingual bioavailability was >50%. Persistence of small amounts of buprenorphine in plasma over extended time periods limits the precision of these values.

ACKNOWLEDGEMENT

Supported by Contract No. 27 1-87-8 126, National Institute on Drug Abuse

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AN OUTPATIENT TRIAL OF METHADONE VERSUS BUPRENORPHINE IN THE TREATMENT OF OPIOID DEPENDENCE

E. C. STRAIN, M. L. STITZER, L. A. LIEBSON AND G. E. BIGELOW

Buprenorphine is an opioid mixed agonist-antagonist that may be useful in the treatment of opioid drug abuse. This double-blind, double-dummy clinical trial compared buprenorphine to methadone in the outpatient treatment of opioid dependence. Participants were randomly assigned to buprenorphine or methadone, and underwent a rapid induction in the first week of treatment with stabilization on either 8 mg of buprenorphine or 50 mg of methadone. A flexible dosing procedure was employed during treatment weeks 3-16, and dose increases in units of 10 mg of methadone or 2 mg of buprenorphine were given based upon patient requests and continued illicit opioid use. Participants were then detoxified over the last 10 weeks of treatment.

There were no differences between the methadone (n=80) and buprenorphine (n=84) groups on demographic features, including rates of pre-admission cocaine use. The study population had a mean age of 32 years, 49% were white, 71% were male, and 72% of patients had a pre-admission cocaine positive urine. 32 patients from each condition received dose increases, and the mean dose of methadone was 54.1 mg, and of buprenorphine was 8.9 mg, during the stable dosing period.

There was no significant difference between groups for retention in treatment (Lee-Desu = 0.136, d.f. = 1, $p = 0.71$); mean days in treatment were 104 for the methadone group and 105 for the buprenorphine group. There was also no significant difference in the percent days attended for medication (83% for methadone and 91% for buprenorphine; $p = 0.32$). Summarizing urine results in 2 week blocks for those who remained in treatment through week 16 ($n = 45$ for methadone, $n = 47$ for buprenorphine), the rate of opioid-positive urines significantly decreased over time ($p < 0.001$), but there was no significant difference between conditions. The overall rate of opioid-positive urines (through week 16) was 41% for the methadone group and 38% for the buprenorphine group. Cocaine-positive urines for the same population of patients did not significantly decrease over time, but there was a significant difference between conditions ($p < 0.05$). The overall rate of cocaine-positive urines (through week 16) was 46% for the methadone group and 61% for the buprenorphine group. For the population of patients who remained in treatment through the detoxification ($n = 19$ for methadone, $n = 22$ for buprenorphine), differences between conditions in the rates of cocaine-positive urines were lost by the end of the detoxification phase of treatment.

These results suggest buprenorphine is equally effective as methadone in retaining opioid-dependent patients in treatment and decreasing illicit opioid use. They also suggest methadone may exert some beneficial effect on cocaine use in this population. These findings are consistent with other studies that support the potential utility of buprenorphine in the treatment of opioid dependence.

ACKNOWLEDGEMENTS: This work was supported by NIDA grants DA06165, DA00166, DA06120, and DA00050.

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SIX MONTH TRIAL OF BUPRENORPHINE VERSUS METHADONE FOR OPIOID USE

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Buprenorphine (BUP) at 2 mg and 6 mg daily was compared to methadone (M) at 35 mg and 65 mg during 24 weeks maintenance among 125 opioid dependent patients. Treatment retention was significantly better on M (20 vs 16 weeks), and M patients had significantly more opiate free urines (51% vs 26%). Abstinence for at least 3 weeks was also more common on M than B (65% vs 27%). The M patients also attained substantially more opiate. free urines faster, reaching 70% by week 5 on M and reaching only 40% by week 8 on BUP. Self reported illicit opiate use declined substantially in all groups, but by month 3 significantly more heroin abuse was reported at 2 mg than 6 mg BUP or M. From an initial average of $1860/month, month 3 usage dropped to $41 (M 65 mg). $73 (M 35 mg), $118 (BUP 6 mg) and $351/mo (BUP 2 mg). Days of use also dropped from 29 days to 1.7 (M 65 mg), 2.8 (M 35 mg)), 4.0 (BUP 6 mg) and 6.6 days/mo (BUP 2 mg). During the trial the ratio of money spent on heroin for 2 mg/6 mg BUP ratio rose from 0.9 ($1709/$1899) (base) to 4.8 ($261/$54) (mo. 5) and the 2m/6mg ratio of days using heroin rose from 1.0 (30/29 days) (base) to 5.1 (7.2/1.4 days) (mo. 6) indicating substantially superior efficacy for 6 mg than 2 mg BUP. This low efficacy for 2 mg BUP was associated with significantly greater and persistent opiate withdrawal symptoms. Thus, M clearly superior to these two BUP doses, and higher BUP dosage appeared better than lower BUP dosage in facilitating opioid abstinence.

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ACUTE EFFECTS OF COCAINE ON PLASMA ACTH, LUTEINIZING HORMONE AND PROLACTIN LEVELS IN COCAINE-DEPENDENT MEN

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Experimental animal studies have shown that cocaine administration may adversely effect the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axis. In order to assess the acute effects of cocaine on endocrine function in humans we measured plasma ACTH, LH and prolactin levels in 18 men with a current history of concurrent history of opioid and cocaine dependence following i.v. administration of cocaine (30 mg) or placebo. Each subject served as his own control for the i.v. placebo and cocaine administration studies. Peak plasma cocaine levels averaged 260 ng/ml within five minutes following the i.v. injection. Plasma ACTH levels were significantly increased above baseline levels at 5, 15, 30 ($P<0.01$) and 45 minutes ($P<0.05$) after i.v. cocaine. Plasma LH levels were significantly increased above baseline levels at 5 ($P<0.05$) and at 15 minutes ($P<0.01$) following i.v. cocaine. No changes in plasma ACTH levels were found following i.v. placebo injection. Plasma prolactin levels decreased significantly at 30, 45, 60, 90, 120 minutes ($P<0.01$) following both i.v. cocaine and placebo administration. Because close parallelism between peak plasma cocaine and plasma ACTH levels were found in this study, we postulate that cocaine stimulates an increase in plasma ACTH levels as a consequence of a dose effect related action on dopaminergic systems which modulate CRF release in brain. Cocaine-induced stimulation of CRF release in brain may represent one mechanism underlying the reinforcing properties of the drug. Cocaine-induced changes in LH secretion may be associated with reports of heightened sexual arousal in men following acute cocaine.

ACKNOWLEDGMENT

This research was supported in part by grants DA 00064, DA 00101, DA 04059 and DA 06116 from NIDA.

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DOUBLE-BLIND FLUOXETINE TREATMENT OF COCAINE DEPENDENCE IN METHADONE MAINTENANCE TREATMENT(MMT) PATIENTS--INTERIM ANALYSIS

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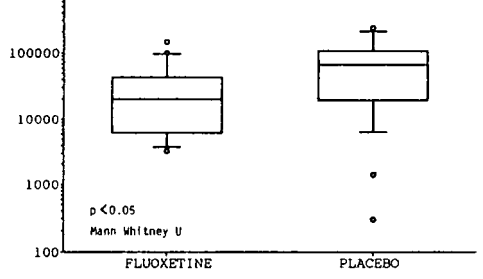
Cocaine-dependent MMT patients are currently being treated in a randomized, double-blind, placebo-controlled, 12 week trial of fluoxetine in conjunction with standard methadone treatment and weekly cocaine group therapy. All subjects meet DSM-III-R criteria for both opioid and cocaine dependence. Forty-one cocainedependent MTT patients have been enrolled into the study. Thirty-two (78%) are HIV-infected. Twenty-one (51%) are African-American and 2 1 (51%) are female. Comparison analysis between fluoxetine (FLX) and placebo (PLA) groups was performed for differences in outcome variables from preliminary data on the first 41 subjects of an eventual 60. Outcome measures were averaged across weeks 1 through 12 to provide summary measures for each subject. Cocaine craving self-reports were significantly less for the FLX group. The mean craving scores were 6.0 (FLX) and 9.0 (PLA) (range 0-24 (t test $p < 0.05$). Urine benzoylecgonine (BE) adjusted, ng BE/mg creatinine) concentrations were significantly lower for the FLX group (FLX median = 20,320.6 ng/mg; PLA median = 65532.9 ng/mg, Mann-Whitney U $p < 0.05$) (Figure 1).

Figure 1
MEAN URINE BENZOYLECGONINE CONCENTRATIONS FOR ENTIRE STUDY (BE ng/mg creatinine)



Adverse effects were relatively minor. In summary, fluoxetine continues to show promise as an adjunctive treatment approach for cocaine abusing MMT patients. Of particular interest is the low rate of adverse effects in this exceptionally ill population.

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ACKNOWLEDGMENT

NIDA Grants, principally, No. DA 01696 and in part, No. R18 DA 06097

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ABUSE POTENTIAL OF ORAL TRAMADOL

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The opioid analgesic tramadol (50 or 100 mg doses) is widely used in Germany since 1977 without a significant incidence of abuse. The drug remains unscheduled. A previous study of tramadol indicates that a 300 mg dose IM produced minimal subjective effects. These effects were not clearly opioid-like. The present studies were conducted with orally given tramadol to determine if the non-opioid actions and prodrug character of tramadol account for this lack of abuse. Single oral doses of tramadol 175, 350, 700, oxycodone (20 and 40 mg) and Placebo were compared in 12 volunteer opiate abusers. Doses were given double-blind every other day according to two 6 x 6 latin squares. Tramadol and oxycodone produced opiate-like subjective effects with the maximum response for tramadol 700 and oxycodone 40 being similar. The maximum effect for tramadol occurred 1 hour later than for oxycodone and persisted longer. The miotic responses were less for tramadol suggesting non-opioid actions. In contrast, tramadol raised blood pressure earlier and to a greater extent than did oxycodone suggesting non-opioid actions reside in the parent compound. By extrapolation, tramadol orally is 1/40 as Potent as parenteral morphine on a mg for mg basis. These data suggest that the prodrug character and non-opioid actions account for low incidence of abuse of tramadol.

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IDENTIFICATION OF DRUGS OF ABUSE THAT INHIBIT HEPATIC CYTOCHROME P450 2D6

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While the genetic variation of debrisoquine/sparteine/dextromethorphan oxidation in humans (also called CYPD6 polymorphism) is one of the most extensively investigated polymorphisms in the field of pharmacogenetics, no studies have been conducted of its importance in drug abuse despite the fact that some drugs of abuse have been shown to be either substrates (dextromethorphan, codeine) or inhibitors of this hepatic enzyme. Cytochrome P450 2D6 activity is genetically variable and is absent in about 7% of Caucasians.

Human liver microsomes were prepared and incubated with dextromethorphan added to final concentrations of 0.5 μM, and 5.0 μM. At each level of the substrate, metabolite production (dextrophan) was monitored in the absence and in the presence of different concentrations of each test drug. The effect of 21 psychotropic drugs on the kinetics of dextromethorphan O-demethylation by human liver microsomes was examined. The Km and V_{max} values were estimated from Eadie-Hofstee plots.

Only nicotine was without effect; the others were competitive inhibitors with the following Ki values: thebaine (2 M), oxycodone (70 M), codeine (80 M), methadone (3 M), naloxone (40 M), (-)-pentazocine (0.4 M), (+)-cocaine (90 M), (-)-cocaine (0.15 M), phencyclidine (2.4 M), methylphenidate (95 M), mescaline (575 M) and 9 amphetamine analogues (Ki values ranging from 12 M to 240 M). The clinical importance of methadone inhibition was confirmed by demonstrating a significant increase of the dextromethorphan/dextrophan ratio in urine after a single oral dose of dextromethorphan in 42 methadone patients compared to 210 normal Caucasian controls. 4-Methoxyamphetamine was found to be a substrate of P450 2D6 in human liver micorsomes (Km = 85 66 M, V_{max} = 22 14 mol/mg protein/min, N = 6 livers). O-Demethylation of this drug was stereoselectively inhibited by the qunidine/quinine isomer pair and was not detected in incubations using microsomes of a liver with no P450 2D6 activity.

These data predict that the 7% poor metabolizer group will have increased toxicity of para-methoxyamphetaminc and a reduced abuse liability to oxycodone and codeine. In addition, a number of drugs of abuse can be expected to cause clinically important interactions with psychoactive and other drugs which are substrates for CYP2D6. We have recently reported that monkey "CYP2D6" is catalytically very similar to the human hence it should be possible to produce an animal model phenocopy of the human poor metabolizer (Otton et al., 1992). CYP2D6 activity may be an important determinant of the abuse liability and toxicity of drugs. Supported in part by NIDA Grant R01 DA06889.

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RESOLUTION OF MULTIPLE [^{3}H]GBR-12935 AND [^{3}H]BTCP BINDING SITES IN RAT STRIATAL MEMBRANES

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The present study addressed the hypothesis that there exist multiple sites/states associated with the dopamine (DA) transporter. We used [^{3}H]GBR12935 AND [^{3}H]BTCP to label the DA transporter present in striatal membranes, and conducted the assays under identical assay conditions: 18-24 hr incubations at 4° C in 55.2 mM sodium phosphate buffer, pH 7.4, with a protease inhibitor cocktail. In order to obtain data suitable for quantitative curve fitting, it was necessary to periodically repurify the [^{3}H]ligands by HPLC. Under these conditions, we observed greater than 90% specific binding. The method of binding surface analysis was used to characterize the interaction of GBRI 2935, BTCP, mazindol, and CFT with binding sites labeled by the [^{3}H]ligands. Fitting of the data to one and two site binding models, using MLAB-PC, demonstrated that for both [^{3}H]ligands, the two site model fit the data far better than did the one site model. The results indicated that both [^{3}H]BTCP [^{3}H]GBR12935 label two binding sites (see Table), and that [^{3}H]BTCP may be resolving two components of [^{3}H]GBR12935 site 1.

	[^{3}H]GBR12935		[^{3}H]BTCP	
DRUG	SITE 1	SITE 2	SITE 1	SITE 2
Bmax	11700±801	8140±1960	3228±1174	11740±1174
GBR12935	1.35±0.14	7.97±2.18	8.9±2.6	0.98±0.10
Mazindol	55.7±5.5	7752±2486	613±203	40±4.4
CFT	44.4±4.7	44230±21135	777±317	36±4.3
BTCP	5.84±0.79	1394±481	9.3±2.4	6.3±0.5

Bmax units are fmol/mg protein±SD. Ki/Kd values are nM±SD.

Viewed collectively with other reports and our previous studies, these data support the hypothesis of multiple binding sites/states associated with the DA transporter. Identification of selective agents for these sites should be valuable tools for identifying sites which might modulate the effects of cocaine. AFFILIATION: CPS, NIDA Addiction Research Center, Baltimore, MD and LMC, NIDDK, NIH, Bethesda, MD

NICOTINE REDUCES CEREBRAL GLUCOSE UTILIZATION IN HUMANS

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Studies in our laboratory and others have indicated that drugs of abuse, including morphine and cocaine, produce widespread reductions in cerebral glucose utilization. Nicotine is a legal drug which has substantial abuse liability, but does not cause severe impairment in psychosocial functioning. We are investigating the effects of acute intravenous nicotine on cerebral glucose utilization and other measures of brain function. The study asks several questions such as the following: (1) What brain areas contribute to the effects of nicotine on mood and other measures? (2) Is this pattern of functional brain activity similar to the effects of other euphoriants? (3) Does chronic nicotine alter baseline metabolic activity? (4) Do the patterns of metabolic response to the drug differ in regular users compared to drug-naive subjects?

Glucose utilization is measured by positron emission tomography (PET), using the [18-F] fluorodeoxyglucose (FDG) technique. Each subject receives two PET scans, one with nicotine (1.5 mg iv) and the other with a saline placebo, in randomized counterbalanced order. Subjects are normal nonresidential volunteers, 21-40 years of age, who do not abuse illicit drugs. Half are cigarette smokers, and half are nonsmokers. Preliminary data indicate that smokers show a globally higher metabolic rate than nonsmokers under placebo conditions, and both groups show a widespread decrease in cerebral metabolic rate of about 10% in response to nicotine. These data suggest that nicotine is fundamentally similar to other abused drugs in its effects on cerebral glucose utilization.

ACKNOWLEDGEMENTS

Merrily Smith, R.N. and Robin L. Stauffer, R.N. provided nursing services. W. Robert Lange, M.D. and Carlo Contoreggi, M.D. provided medical coverage. Beverly Beall, P.A. assisted in preadmission medical screening. Diane Frankenfield provided pharmacy services. David Clough and William Boitnott provided nuclear medicine technologist services. Valerie O'Brien, Jennifer Schmidt, Tracy Folio, Catherine Chen, Loretta Spurgeon and Stephen Gilson, Ph.D. assisted in data collection. Supported in part by a grant from the Council for Tobacco Research.

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IN VIVO DISTRIBUTION OF [^{3}H] (-)-COCAINE IN PRIMATE BRAIN: COMPARISON WITH [^{3}H] MAZINDOL DISTRIBUTION

B. K. Madras and M. J. Kaufman

The objectives of this study are to map the distribution of cocaine in brain following i.v. administration. This approach may be effective, a) for determining the principal targets of cocaine in brain; b) for comparing targets of cocaine with those of mazindol, a more potent dopamine transport inhibitor than cocaine that produces dysphoria in humans (Chait et al., Pharmacol. Biochem. Behav., 1986, J. Pharmacol. Exp. Ther., 1987); and c) for establishing neuroanatomical criteria to be used in the development of novel high affinity probes for cocaine recognition sites. The *in vivo* brain distribution of behaviorally relevant doses of cocaine was determined by *ex vivo* autoradiography using techniques previously used for higher affinity probes (Kaufman and Madras, Synapse, 1992, in press). A high specific activity form of [^{3}H]cocaine (spec. act. 86.8 Ci/mmol) was prepared for this study*. Squirrel monkeys *(Saimiri sciureus)* were injected i.v. with [^{3}H](-)- cocaine diluted with unlabeled (-)-cocaine HCl to yield a dose of 0.1 or 0.3 mg/kg. The most prominent targets for [^{3}H](-)-cocaine were regions rich in dopamine and D1/D2 dopamine receptors. High levels of radioactivity were detected in the caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, substantia nigra, and locus coerules. Within the caudate nucleus to a medial-to-lateral gradient of distribution was observed. Moderately high levels were found especially in the hippocampus, and in the amygdala, several thalamic nuclei, and hypothalamus. Using similar techniques, the *in vivo* distribution of low doses of [^{3}H]mazindol was determined. The highest levels of radioactivity were detected in norepinephrine-rich brain regions and included the pineal gland, discrete regions of the hypothalamus (e.g. supraoptic nucleus) and the locus coeruleus. Moderately high levels were detected in the caudate-putamen and nucleus accumbens. These studies a) indicate that brain dopamine systems are principal but not exclusive targets of behaviorally relevant doses of cocaine; b) may provide a neuroanatomical basis for the different spectrum of effects of cocaine and mazindol and, c) may furnish a neuroanatomical guide needed to develop and evaluate higher affinity probes for cocaine recognition sites in brain.

ACKNOWLEDGEMENTS: Supported USPHS grants DA00499, DA06303, MH14275, RR001688, *We thank Dr. S. Hurt of Dupont-NEN who prepared high specific activity [^{3}H](-)-cocaine (86.8 Ci/mmol; N-methyl[^{3}H]).

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REPEATED COCAINE ADMINISTRATION IN MICE: SENSITIZATION TO THE CONVULSIVE EFFECTS INVOLVES UP-REGULATION OF THE NMDA RECEPTOR

Y. ITZHAK AND I. STEIN

Cocaine-induced seizures and cerebellar infarction are frequently identified in humans exposed to the drug. Repeated exposure of animals to cocaine results in sensitization to many actions of the drug and pharmacological kindling that is typified by an increased sensitivity to the convulsive responsiveness over time. It is thought that repeated use of cocaine by man might lead to the development of lethal seizures after the intake of a dose that had previously been tolerated. In order to elucidate the neurochemical mechanisms underlying cocaine-induced neurotoxicities, the involvement of the N-methyl-D-aspartate (NMDA) type of glutamate receptors in cocaine-induced convulsions and death was investigated.

Repeated administration of cocaine (45 mg/kg/day; i.p.; for 7 days) to Swiss Webster mice produced a progressive increase in the convulsive responsiveness to the drug (e.g., convulsions on day 1: 20±5%; on day 7: 100%). This phenomenon was accompanied by an increase in lethality rate after the 5th day of treatment (e.g., survival on day 1-3: 100%; on day 7: 50±5%. Pretreatment of animals with the noncompetitive NMDA receptor antagonist, MK-801 (0.35 mg/kg/day; s.c.; for 7 days), abolished completely the development of sensitization to cocaine-induced convulsions and lethality. MK-801 also partially reduced the lethal effects following the acute administration of cocaine. To further investigate the involvement of the NMDA receptor in the sensitization to the neurotoxic effects of cocaine, potential alterations in the NMDA receptor complex were assessed. *In-vitro* receptor binding experiments, utilizing the competitive NMDA receptor antagonist [^{3}H]CGP 39653, were performed in cortical membrane preparations from saline-, cocaine-, MK-801- and MK-801/cocaine-treated mice. Saturation binding assays indicated a significant increase (140±5% of control saline) in the number of NMDA receptor sites in the cortex of cocaine-treated mice. However, binding of [^{3}H]CGP 39653 in cortical membranes of MK-801/cocaine-treated mice indicated a small reduction (80% of control) in the number of NMDA receptor sites. In agreement with these findings, [^{3}H]MK-801 binding in the cortex of mice from the four groups expressed differential sensitivity to the stimulatory effect of glutamate. Thus, binding of [^{3}H]CGP 39653 to the NMDA receptor and [^{3}H]MK-801 to the PCP receptor - located in the ionophore of the NMDA receptor complex - conveyed evidence for NMDA receptor sensitization.

The development of sensitization to the convulsive and lethal effects of cocaine, *in-vivo,* parallel to supersensitivity of the NMDA receptor observed *in-vitro,* and the ability of MK-801 to block these effects strongly support the involvement of the NMDA receptor in the sensitization to the neurotoxic effects of cocaine. Supported by BRSG SO7 RR-05363 (NIH) and DA07589 (NIDA).

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DOPAMINE RELEASE IN THE MESOLIMBIC SYSTEM IS MODULATED BY OPPOSING ENDOGENOUS OPIOID SYSTEMS

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There is evidence that the administration of opioids can influence the activity of mesolimbic dopaminergic A10 neurons, and it has been postulated that such actions underlie the motivational properties of these agents, as well as the development of various aspects of opiate dependence (Di Chiara and Imperato 1988; Herz and Shippenberg 1989). Depending on their receptor selectivity, opioids elicit different motivational behaviors: μ-opioid receptor agonists serve as positive reinforcers, whereas κ-receptor agonists are aversive (Mucha and Herz, 1985). Opposing effects of μ- and κ-agonists are also observed in the mesolimbic system: p-agonists increase, whereas κ-agonists decrease, dopamine (DA) release within this system (Di Chiara and Imperato 1988). However, the site of action of exogenous opioid agonists and the role of endogenous opioid systems in the modulation of mesolimbic dopaminergic activity are unknown. These issues were examined by the use of in viva microdialysis in the anesthetized rat to determine DA release in the nucleus accumbens (NAC), the major terminal projection site of A10 neurons, following treatment with μ and κ ligands.

The opioid ligands were infused into the NAC through a liquid switch connected to the microdialysis probe, or microinjected into the ventral tegmental area (VTA) from which the A10 neurons originate (for further methodological details, see Spanagel et al. 1992).

Mu-opioid ligands exerted marked effects on DA release in the NAC following their intra-VTA administration: DAMGO (u-agonists) increased DA-release, whereas CTOP (p-antagonist) produced a significant decrease in basal DA release. In contrast, infusion of either ligand into the NAC was without effect. κ-opioid ligands failed to modify DA release following their intra-VTA injection. However, infusion of U69593 (κ-agonist) into the NAC caused a decrease in DA release; the opposite occurred after infusion with the κ-antagonist norbinaltorphimine.

These results demonstrate opposing and anatomically distinct effects of opioids on DA release in the mesolimbic system. Furthermore, they provide evidence that tonic activation of μ-receptors in the VTA and presynaptic κ-receptors in the NAC contribute to the maintenance of basal DA release in the NAC of the drug-naive animal.

REFERENCES: Available upon request.

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OPIOID EFFECTS IN THE VTA, MD AND PPN: MEDIATION BY MESOLIMBIC GABA

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A variety of evidence lends support to a circuit posited to be comprised of the VTA, nucleus accumbens and ventral pallidum (VP). Increased dopaminergic transmission within this circuit results in an increase in locomotor activity. In the first experiment the effects of morphine administration on extracellular levels of GABA were assessed using *in vivo* microdialysis in the VTA. In the second experiment the regulation by GABA in the VTA of the motor activity elicited by DAMGO in the mediodorsal nucleus of the thalamus (MD) or pepunculopontine nucleus (PPN) was examined. Adult male Sprague-Dawley rats (300±20g; N=5-14/group) were prepared with bilateral guide cannula 3mm dorsal to the VTA (for dialysis) or with bilateral guide cannula 1 mm dorsal to both the VTA and MD or PPN. Testing for both experiments began after 8 days of recovery. For dialysis, a removable dialysis probe was inserted into the guide cannula 24 hrs prior to the experiment. Samples of dialysate were collected every 20 min and levels of GABA were measured by HPLC/EC. For microinjection experiments animals were adapted to a photocell cage for 1 hr then received an injection of baclofen (0.15 nmoles/side) into the VTA and DAMGO (0.1 nmoles/side) into either the PPN or MD. Locomotor activity was then measured for 2 hrs. Data from each experiment were analyzed with a repeated measures ANOVA. In the first experiment it was found that morphine administration through the dialysis probe into the VTA produced a significant decrease in extracellular levels of GABA. This is in agreement with the results of other studies suggesting that within the VTA an indirect action by morphine via GABAergic afferents on dopamine neurons, or disinhibition, is the mechanism involved in the increased dopaminergic activity in the terminal fields and the resultant hyperactivity. In the second experiment, picrotoxin or DAMGO injections into the MD or PPN elicited a dose-dependent increase in locomotor activity which was blocked by peripheral haloperidol (2 mg/kg). Whereas administration of baclofen into the VTA had no effect on DAMGO-induced locomotion elicited from the MD, it did attenuate the activity produced by DAMGO injections into the PPN. These results suggest that while opioid-induced locomotor activity from the MD and PPN is dopamine-dependent, only the effect elicited from the PPN and not the MD is mediated through the VTA.

(Supported by DA-03906, DA-00158, MH-40817 (PWK) and DA-05391 (MAK)

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OPIOID RECEPTORS IN PHEOCHROMOCYTOMA CELLS: RECEPTOR SELECTIVITY

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PC12 rat pheochromocytoma cells are useful as a model system for neuronal development. They are derived from a rat adrenal chromaffin tumor. Upon exposure to nerve growth factor (NGF), their morphology changes from that of a chromaffin-like dividing cell to a neuronal phenotype with dendrite-like processes extending from the cell bodies; the cells flatten, become electrically excitable and stop dividing. In one subclone of PC12 cells, PC12h, low levels of opioid binding sites markedly increase in response to (NGF) (Inoue and Hatanaka 1981). We are currently investigating the properties of the opioid receptors in PC12h cells. After 10 days of treatment with NGF, the number of opioid receptors (as measured by 3H-diprenorphine binding) increases from a B_{max} of 40 to 220 fmols/mg protein, with concentrations up to 10 nM. ^{3}H-diprenorphine was used as a ligand so that binding to μ, δ and κ sites could be assessed. Competition binding studies were performed with the selective μ,δ and κ agonists [D-Pen^{2,5}]. Enkephalin (DPDPE), [D-Ala^{2},N-Me-Phe^{4},Gly-ol^{5}]-Enkephalin (DAMGO) and U50,488, respectively. The order of displacement was DPDPE > U50,488H > DAMGO with calculated Ki 's of 1.72 nM for DPDPE, 167 nM for U50 and 1.17 μM for DAMGO. The primary opioid binding site on these cells thus appears to be the δ-subtype. The NGF and non-NGF treated cells showed similar displacement characteristics. In order to estimate whether the binding sites on these cells were functional opioid receptors, we took advantage of a known property of δ receptors in cell lines, down-regulation in response to opioid agonists. After exposure to 10 nM etorphine for 48 hours, the number of binding sites on the cell surface decreased on the average of 30% in the NGF-treated cells. The Kd for diprenorphine was not significantly changed. These results indicate that the receptors on NGF-treated PC12h cells are capable of responding to opioid agonists. Total RNA was prepared from the etorphine treated cells, and the message levels of G proteins in these cells were assessed. Compared to the control cells, a 30% increase in $G\alpha_s$ mRNA was observed. The levels of $G\alpha_{i1}$, $G\alpha_{i2}$, $G\alpha_{i3}$ and $G\alpha_o$ were unchanged. These data are consistent with the hypothesis that cellular tolerance to opioids may be conferred by modulation of the cAMP system, originally proposed by Sharma et al. (1975). In this hypothesis, opioids initially decrease the levels of cAMP, but with continual exposure to opioid agonists, cAMP levels return to normal, and upon addition of naloxone, rise to levels higher than normal. An increase in $G\alpha_s$ could be responsible for the increase in cAMP. Future experiments in PC12h cells will examine this hypothesis. In conclusion, the PC12h pheochromocytoma cells appear to be a useful model system for investigating the cellular action of opioids.

REFERENCES: Senior author will furnish on request.

ACKNOWLEDGEMENT: This work was supported by DA-06867.

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The Influence of Pregnancy Upon Trough Plasma Levels of Methadone and Its' Opioid Effects

P. M. Gazaway, G. E. Bigelow and R. K. Brooner

The physiologic changes associated with pregnancy alter the pharmacokinetic behavior of many drugs. The influence of pregnancy upon methadone's therapeutic efficacy has been characterized only in a small number of patients. Previous investigators have reported decreased half life (Kreck 1979) and increased withdrawal symptoms (Pond 1985) as pregnancy progresses.

PURPOSE: The aim of this study was to examine the effects of pregnancy on: 1) trough plasma methadone concentration, 2) objective and subjective measures of opioid agonist effects, and 3) withdrawal symptoms.

METHODS: Pregnant methadone maintenance patients were enrolled after twenty weeks estimated gestation and having had no dose changes for at least two weeks. Non-pregnant controls were recruited from the general female population of the methadone clinic with no dose changes for two weeks. At each study session, an opioid withdrawal symptom scale was completed, a pupillary photograph was taken, and blood was drawn for though total plasma methadone concentration. The subject then received her usual daily methadone dose. Opioid agonist adjective ratings and pupillary photographs were obtained at 30, 60, and 90 minutes post-dose. The mean values of the first two (mean EGA 26 weeks) and last two (mean EGA 37 weeks) sessions were analyzed with ANOVA and Tukcy's post hoc tests.

RESULTS: Plasma methadone concentrations were significantly lower in pregnant than non-pregnant women in the first two ($p<0.01$) and last two sessions ($p<0.05$). Withdrawal scores overall were very low in both groups and no significant difference was present between groups or across time. Both groups had a significant pupillary constriction after the methadone challenge at early and late sessions ($p<0.01$). Despite greater trough plasma methadone levels, the pupils of non pregnant women were larger than those of pregnant women at all time points in early and late sessions ($p<0.01$). No significant difference in either group's pupil size was noted across weeks. Finally, non pregnant women reported significantly greater opioid agonist effect at 30 and 90 minutes post dose ($p<0.01$).

DISCUSSION: As expected, trough plasma methadone levels were lower in pregnant than non-pregnant women. Lower plasma levels were not associated with increased withdrawal scores in either second or third trimesters, though this may be due to low level of withdrawal symptoms reported by both groups. Pregnant women did not report less agonist effect after receiving their daily methadone dose in both early and late sessions. This may be related to delayed gastric emptying during pregnancy which may delay the systemic absorption of methadone. The greater miosis seen in the pregnant women despite lower plasma methadone levels was unexpected. Pupillary measures, however, may reflect increased autonomic nervous system tone associated with pregnancy rather than central opioid tone. Our results confirm the previously reported decrease in trough plasma methadone levels during pregnancy, however unlike previous studies, signs and symptoms of withdrawal did not increase with advancing pregnancy.

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BASAL PROLACTIN, BUT NOT GROWTH HORMONE, IS ELEVATED IN ADULT MALE RATS GIVEN COCAINE PRENATALLY

N. S. Pilotte and E. P. Kornak

The endocrine responses to apomorphine and the behavioral responses to cocaine were examined in adult rats given cocaine prenatally. The mothers were injected twice daily sc with 15 mg/kg of cocaine or 1 ml/kg saline throughout pregnancy. When the offspring were 120 days old, we measured the concentrations of prolactin (PRL) and growth hormone (GH) in serum before and after an acute administration of the dopamine agonist apomorphine. The preinjection levels of PRL in rats given cocaine in utero were 60% higher than those of rats given saline. Apomorphine inhibited PRL more profoundly in cocaine-treated rats, at doses lower than those required for behavioral activation. In contrast to PRL, the pre- and post-injection levels of GH did not differ between the two groups. In separate groups of adult male rats treated with cocaine or saline in utero, we found that the development of behavioral sensitization to one or three subsequent injections of cocaine occurred to the same extent and with the same time course as in rats given saline prenatally. These data suggest that the administration of cocaine in utero affects the regulation of prolactin secretion, a hormone regulated primarily by dopamine, and that these effects can persist into adulthood.

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CHARACTERISTICS OF PREGNANT COCAINE ABUSERS

K. T. Brady; D. E. Grice; L. Dustan; R. Malcolm and T. Killeen

Substance abuse during pregnancy is a health care issue with far reaching implications. Because of the serious consequences of drug use during pregnancy it is important to determine those at risk and specifically tailor treatment for this population. To this end eighteen pregnant women who were mandated to inpatient substance abuse treatment as a result of positive screening for cocaine use were compared with 18 age- and sex-matched controls. All subiects met DSM-III-R criteria for cocaine dependence. Subjects were administered the Structured Clinical Interview for DSM-III-R (SCID I and II) and a standardized interview about sexual and physical assault histories. There were no significant differences between the two groups in education or socioeconomic variables, but there were more African-Americans in the pregnant group. This likely reflects the racial distribution of the referring clinic. The pregnant cocaine abusing group (PC) were more likely to have a history of victimization ($p \leq .05$, $x^2=4.34$). There was a trend towards more childhood victimization in the PC group ($p \leq 0.1$, $x^2=2.92$). In both groups, there was a high prevalence of Axis I disorders. There was a trend towards more severe character pathology, as defined by ≥ 2 Axis II disorders in the PC group ($p \leq 0.1$, $x^2=3.13$). This group also had significantly more antisocial personality disorders ≤ 0.05, $x^2=4.8$). One-third (6.18) of the PC group were aftercare treatment compilers (attended at least one-half of aftercare sessions). Of the treatment compilers, none had severe character pathology ($\geq$ Axis II) and none had antisocial personality disorder. It appears that a history of victimization, particularly childhood victimization, may be a risk factor for substance abuse in pregnancy. This is consistent with the theory that inadequate parenting and nurturing creates parents who continue the cycle of child abuse, even in utero. Severe character pathology and antisocial personality disorder are more common in PC women and appear to predict non-compliance with aftercare. Such patients should be targeted for early and aggressive intervention.

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PRENATAL COCAINE EXPOSURE ALTERS CEREBRAL FUNCTION IN THE PERIWEANLING RAT

D. L. DOW-EDWARDS; L. M. DONOHUE; L. A. FREED; H. E. HUGHES AND E. A. GROSE

Previous studies from this laboratory have demonstrated that prenatal cocaine exposure produces long-term alternations in brain function (Dev. Brain Res. 57:263, 1990). Whether these changes were quantitatively and qualitatively constant throughout the maturational period, however, was not known. For the present study, female Sprague-Dawley rats were intubated daily with either 30 or 60 mg/kg cocaine HCl during the last two weeks of gestation. A pair-fed, pair-watered, vehicle intubated control group and a non-treated control group were also maintained. On the day of birth, all pups were fostered. Cocaine produced only subtle changes in gestational indices (litter size, birth weights, etc.) However, in male pups at 21 days of age, several brain regions showed decreased rates of glucose metabolism as measured by the Deoxyglucose method including the caudate nucleus, accumbens, lateral septum, vertical limb of diagonal band, lateral hypothalamus, DM hypothalamus, VM hypothalamus, medial preoptic area, and anterior amydgala (ANOVA). T-lest comparisons showed that rates of metabolism in 19/44 structures in the males receiving 60 mg/kg and 17/44 structures in the males receiving 30 mg/kg were significantly different from the pair-fed males. The CAI region of hippocampus, lateral habenula, central amygdala, and globus pallidus showed decreased rates of glucose metabolism (T test) in both the 30 and 60 mg/kg cocaine treated males. The female rats receiving cocaine generally showed similar rates of brain metabolism compared to the pair-fed females.

These data can be compared to behavioral data collected on littermates during the periweanling period using the Omnitech activity chamher. Here, females receiving both doses of cocaine were less active than pair-fed females in the baseline condition and responded less to 0.25 mg/kg amphetamine challenge. There were no differences in baseline activity levels in the male groups and there were no responses to amphetamine at the doses tested. Therefore, higher doses of amphetamine are currently being examined.

The brain metabolism data in the present study correlate to a high degree with the findings we previously reported for adult male rats exposed to cocaine prenatally. In both studies, the hypothalamus, caudate, accumbens, hippocampus, lateral septum and amygdala were significantly metabolically depressed. The major differences in the data was that there were no consistent changes in metabolism in the cortex of the 21 day old rats while both the primary motor and primary somatosensory cortex were metabolically depressed in the adult males. Therefore, changes in brain metabolism produced by prenatal cocaine exposure appear to be constant at the two ages examined. Adult females exposed to cocaine prenatally arc currently being examined to determine whether the lack of significant changes in metabolism at 21 days of age persists into adulthood.

Supported by NlDA grant DA04118
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EFFECTS OF PRENATAL EXPOSURE TO COCAINE ON DISCRIMINATION LEARNING IN ADULT RATS

C. J. HEYSER, N. E. SPEAR AND L. P. SPEAR

Previous work from our laboratory has shown that offspring exposed gestationally to cocaine exhibited deficits in first-order conditioning and sensory preconditioning early in life (Spear et al. 1989; Heyser et al. 1990). In an effort to determine if such conditioning deficits persist into adulthood, adult male offspring prenatally exposed to cocaine and control offspring were trained on an instrumental conditioning task for assessment of the acquisition and reversal of an appetitive conditional discrimination based on olfactory cues. Offspring were derived from Sprague-Dawley dams that received subcutaneous injection of 40 mg/kg/3cc cocaine hydrochloride (C40) daily on gestational days 8-20, pair-fed (PF) dams injected with saline, nutritional control dams (NC) receiving saline, and nontreated control dams (LC). Although C40 and PF dams gained significantly less weight than LC dams, offspring body weights did not differ at birth or when tested in adulthood among the four prenatal treatment groups. There were no differences among the prenatal treatment groups in acquisition of the bar press response or response rate throughout all phases of training. Likewise, all prenatal treatment groups required approximately the same number of sessions to criterion on the initial odor discrimination. In contrast, adult C40 offspring required more sessions to acquire the reversal of the conditional discrimination than animals from the other treatment groups (PF, NC, and LC). In addition, even after reaching the defined criterion for acquisition of the reversal, C40 animals exhibited lower accuracy in the first 10 responses and made significantly more errors prior to the first reward. Taken together with previous results, these findings suggest that gestational cocaine exposure results in long-lasting alterations in performance on conditioning tasks that are evident early in life and which persist into adulthood.

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ACKNOWLEDGEMENT: Supported by NIDA Grants R01 DA04478, KO2 DA00140, F31 DA05511, and NIMH Grant R01 MH35219

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COGNITIVE BRAIN POTENTIALS IN BOYS EXPOSED TO OPIATES IN UTERO

X. Guo, J. SPENCER, P. SUESS, J. HICKEY, W. BETTER AND R. HERNING

Cognitive event related potentials (N=14) (ERPs) were studied in 7 to 12-year-old body who were exposed to opiates in utero (N=13). Boys (N=14) who lived with drug abusing mothers but who were not exposed to opiates in utero served as controls for genetic and drug environment effects. Another control group included boys (N=l3) with similar social economic status and mothers who had never abused drugs. The drug abusing mothers had no history of barbiturate and cocaine use. Each group of boys were matched with age and race. Cognitive event related potentials (Fz, Cz and Pz) and task performances (% correct and reaction time) were obtained in the auditory rare event monitoring task and the Sternberg Memory Task with two memory set sizes (2 and 4). P200 amplitude ERP and behavioral performance was significantly impaired both in reduced auditory rate event task and Sternberg memory task in boys exposed to opiates in utero and boys having heroin-using mothers, but not exposed in utero. However, boys exposed to heroin in utero were more impaired on neurophysiological measures. These changes in cognitive ERPs arc similar to attention deficit disordered children, in which P200 is reduced and are reversed by methylphenidate (Halliday et al. 1976). The reduction in P200 suggests that these boys habituate more rapidly to task relevant stimuli and consequently may have learning problems in school.

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INTRAUTERINE COCAINE/POLYDRUG EXPOSURE: 3 YEAR OUTCOME

I. J. CHASNOFF, D. R. GRIFFITH AND S. AZUMA

The present study discusses the cognitive and behavioral development of two groups of drug exposed infants and a group of non-exposed infants through three years of age. Group 1 consisted of 81 children whose mothers' drug of abuse was cocaine plus tobacco, alcohol, and/or marijuana. Group 2 were infants were exposed to tobacco, alcohol, marijuana, but not cocaine. Group 3 consisted of infants whose mothers were drug free. All groups were similar with regard to maternal age and racial distribution. Weights, lengths, and head circumferences were collected during the pediatric evaluation. The Stanford-Binet Intelligence Scale (4th Edition) and a brief rating scale concerning each childs' test-taking behaviors were completed by the developmental psychologists. The mothers completed the Achenbach Child Behavior Checklist (CBCL). Results by group on the Stanford-Binet are summarized in the table.

	Group I (N=81)	Group II (N=21)	Grout III (N=17)
Test SAS	94.5	94.9	99.5
Verb Rsng SAS	89.6*	91.3	96.8
Abstract Rsng	93.1*	90.8*	99.1

*Significant difference from Group III, ANOVA ($P < .05$)

One way analysis of variance procedures (ANOVA) indicated significant differences on both Verbal Reasoning SAS, and Abstract Reasoning SAS. Post-hoc analysis on these subtests indicated that Group 1 children scored significantly lower than Group 3 children on both the Verbal and Abstract SAS. Group 2 children scored significantly lower than Group 3 children on the Abstract Reasoning SAS ($p < .05$). Analysis of the examiner rating scales indicated that children in Group 3 were more likely to display age appropriate persistence at tasks and tolerance for difficult tasks. CBCL scores showed that the mothers of Group 1 children were more likely to perceive their children as displaying problem behaviors in the areas of social withdrawal, somatic concerns, and destructive behavior. Analysis of the growth parameters indicated that the three groups did not differ in mean weight or length. Significant differences were noted, however, for head circumference (HC). Post-hoc analysis indicated that both drug-exposed groups had significantly smaller HC when compared with the drug-free children. Across the drug exposed groups, children with head circumference below the fifth percentile were found to have decreased intellectual performance on the Stanford-Binet. The results of this study indicate that drug exposed children perform in the average range on the overall measure of intelligence on the Stanford-Binet (Test SAS). However, the results also indicated that Group 1 children were more likely to have smaller head circumferences, to display behavioral problems, and to score lower on verbal and abstract/visual reasoning tasks when compared to non-exposed children. Group 2 were more likely than non-exposed children to score lower on abstract/visual erasoning tasks. It is likely that other biological and environmental risk factors to which these children are often exposed are factors in the eventual developmental outcome of this population.

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CASE-CONTROL COMPARISON OF PSYCHOLOGICAL FUNCTIONS AND HIV STATUS IN DRUG ABUSERS

I.D. MONTOYA; K. D. LEE; J. M. HESS AND D. A. GORELICK

PURPOSE Neuropsychiatric manifestations of HIV infection may be due to complications of AIDS. direct infection of the brain by the virus. or psychosocial factors' associated with the infection. Studies. of asymptomatic HIV + drug abusing individuals are scanty and controversial. This study compares the psychological and cognitive status of HIV + and HIV - drug abusers who were either seeking treatment or participating in drug abuse research studies.

METHODS This is a retrospective case-control analysis of admission psychological and cognitive test data on 762 research volunteers with reported history of drug abuse who had HIV test results at the National Institute on Drug Abuse - Addiction Research Center in Baltimore. Tests to evaluate the psychological state (Symptom Check List-90-Revised, SCL-90R) and cognitive functioning level (Shipley-Institute of Living Scale, SILS) were administered at the time of initial blood sampling and medical screening.

RESULTS Of the 762 subjects, 65 asymptomatic HIV + cases (8.2%) were matched with 65 HIV - controls by: 1) drug of choice; 2) age (± 6 years); 3) gender; 4) ethnic group; and 5) psychological testing period (± 3 months). Subjects' mean age was 32.6 ± 5.2 years, 88% were male, 91% black, 9% white, 73.8% were treatment-seeking, and 26.2% were non-treatment-seeking. Drugs of choice were: cocaine (57%), opiates (32%), marijuana (9.2%), or benzodiazepines (1.5%). Comparisons between the two groups were made using ANOVA and Kruskal-Wallis test. For the SCL-90R, there were no significant differences for somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, paranoid ideation, psychoticism, global severity index, positive symptom distress index, or positive symptom total scores. The only significant finding ($p<0.05$) was higher scores for phobic anxiety in the HIV + group. Analysis by drug of choice (cocaine or opiates) and/or treatment-seeking status between HIV + and HIV - did not show differences. However, treatment-seeking subjects had all scores significantly higher than non-treatment-seeking subjects, regardless of their HIV status. These differences were present more in cocaine abusers than in opiate abusers, For the SILS, there were no significant differences between the two groups for vocabulary, abstraction, and total scores, conceptual and abstraction quotients, and estimated WAIS-R full scale IQ. Analysis by drug of choice and/or treatment-seeking between HIV + and HIV - subjects did not show any differences.

CONCLUSIONS HIV seropositivity per se does not significantly influence overall intellectual ability or psychological symptoms in asymptomatic HIV + drug abusers. Drug abuse treatment-seeking status may be a confounding factor for studies comparing psychological functions.

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INJECTION DRUG USE AND HIV INFECTION: RISK FACTORS AND CURRENT TRENDS

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Introduction: Seroprevalence studies have demonstrated high rates of HIV infection in injection drug users (IDUs) and have identified risk factors such as needle sharing. Alcohol has also been identified as a possible risk factor for HIV infection. The goals of this study (Study III) include: 1) To determine the HIV seroprevalence for IDUs in New Haven, CT entering drug treatment (9/90-9/91); 2) To examine trends in HIV seroprevalence over time by comparing these results with two previous New Haven cohorts: 1982-83 (Study I) and 1986-87 (Study II) and; 3) to explore risk factors for HIV infection, particularly alcohol.

Methods: This blinded HIV seroprevalence study was performed in the Central Medical Unit, a primary care clinic for IDUs. Eligible subjects included all patients entering drug treatment. HIV results were linked only to non-identifying patient data.

Results: Serum was collected from 227 IDUs entering drug treatment. Overall, 35% of the cohort was female, 20% African-American, 17% Hispanic, and 61% Caucasian. Sixty-two percent of patients were enrolled in methadone maintenance, 30% in outpatient opiate detoxification, 3% in cocaine treatment, and 5% in other programs. In Study III, 28% (63/227) of IDUs were HIV+. Although the rise in seroprevalence from 8% (24/283) in Study I to 24% (43/181) in Study II was statistically significant ($p<.0001$), the subsequenl increase in Study III to 28% was not significant vs Study II ($p=.36$). Interestingly, while 74% of patients reported needle sharing in the Study II cohort, 58% reported sharing in Study III (<.01). Demographic factors associated with HIV in Study III included ethnic minority: 48% (40.84) vs 14% (20/138) for nonminority ($p<.0001$), and age <40: 46% (18/39) vs 24% (45/188) for 5 ($p<.001$). Clinical features associaled with HIV included needle sharing: 36% (45/124) vs 19% (17/91) for nonshares ($p<.01$). and primary cocaine IDU: 53% (19/36) vs 23% (44/191) for nonusers ($p<.01$). All patients were administered a CAGE questionnaire: of those who were CAGE+ 34% (30/88) were HIV+ as compared to 24% (33/139) for those who were CAGE- ($p=.09$).

Conclusions: The HIV seroprevalence for IDUs entering drug treatment in New Haven between 9/90 and 9/91 was 28%, a rate higher but not significantly different than that seen four years earlier. Decreasing high risk behavior such as needle sharing may partly explain why HIV seroprevalence has not increased more dramatically. Finally, alcohol use may place IDUs at additional risk for HIV infection.

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VALIDITY OF DRUG ABUSERS' REPORTED HIV-1 RISK BEHAVIOR CHANGE

L. GREENFIELD, G. E. BIGELOW AND R. K. BROONER

The validity of self reported drug injection behavior and behavior change in IVDUs was assessed. Relying on self report, studies of HIV risk behavior have found significant reductions over time in both high risk sexual and drug injection behaviors. Urinalysis testing permits assessing the validity of self reported changes in drug use behavior.

METHOD. N=281 IVDUs were assessed with respect to intravenous drug injection behaviors at intake and successive followups by means of both self report and urinalysis. Ss were provided with information concerning HIV-l and tested for HIV infection. A urine sample was taken at each interview. Of the 281 IVDUs, 146 were receiving methadone treatment at intake and 135 were not receiving treatment (Community). Ss were interviewed at intake and followup months, 2, 4, and 6. Ss reported the number of times they injected cocaine and opiates and shared needles during the past 7 days, past month, and in each of the 6 months prior to intake. At intake and the 6-month followup, Ss were asked about other routes besides injection. With 57% retention, the smallest cell size was N=74. The data were analyzed both with all Ss and only those responding in each period.

RESULTS. Treated IVDUs reported fewer injections and needle shares and more frequently denied use of cocaine and opiates than untreated ($p<.01$). Urinalysis confirmed these group differences. Smaller percentages of Treated Ss tested positive for opiates and cocaine than Community ($p<.01$). Overt time, IVDUs reported fewer injections ($p<.02$) and less needle sharing ($p<.03$). No differences were found over time in the percentages who tested positive through urinalysis. In further analysts of IVDUs who completed intake and the 6-month followup (N=160), self reports of drug injection abstinence during the 7-days prior to each assessment were compared to urinalysis. Reported abstinence increased from 36.2% at intake to 51.2% at followup. Reported abstinence was disconfirmed at a rate of 5.2% (N=58) at intake in comparison to 17.1% (N=82) at followup. Almost half (45.8%) of the reported increase in abstinence was disconfirmed through urinalysis.

CONCLUSION: These data raise serious questions about the validity of seolf reported changes in IVDUs' HIV risk behavior.

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SELF-HELP INTERVENTION AND AIDS IN A METHADONE MAINTENANCE SETTING

D. N. NURCO, B. J. PRIMM, M. B. BALTER, M. LERNER, P. STEPHENSON, L. S. BROWN AND D. AJULUCHUKWU

This report evaluates some outcomes of AIDS-related treatment interventions in a methadone maintenance program in New York City. The interventions were: standard treatment, i.e., methadone maintenance plus individual counseling, considered as the control group (Sub-Group C, 13 members); standard treatment plus a clinically guided self-help regimen (Sub-Group A, 15 members, the primary experimental group); and standard treatment plus a series of lectures on AIDS (Sub-Group B, 10 members). The outcomes, based on self-reports, were: knowledge of the etiology of and the high-risk behaviors associated with drug use and AIDS, attitudes regarding internal and external locus of control over behavior related to drug use, and recent participation in high-risk drug behavior (needle-sharing) and sex behavior (multiple partners). Interview schedules were administered at intake into the program and at 3-month intervals, but analysis was limited to baseline and last follow-up. The knowledge questions consisted of 39 items, each rated by a panel of judges on its importance to the prevention of HIV infection. Attitudinal orientation was measured by 15 "locus of control" questions, 11 focusing on the "past", i.e., the external forces causing addiction, and four on the "future" i.e., what could or should be done about it. Attitude questions were focussed on drug abuse in general rather than on the specific respondent's problem. Two questions were analyzed for high-risk behavior by each respondent in the recent past. Results revealed that for the total group (N=38), the number of correct responses to the knowledge questions increased significantly at follow-up ($p<.001$). This was true also for responses weighted by importance ($p<.001$). Each study group alike recorded a significant increase in average number of correct responses. The number of external responses by the total group to past locus of control questions decreased from baseline to last follow-up, but not significantly. However, this decrease was statistically significant for Sub-Group A, which became significantly more internally oriented on past locus-of-control questions. On future locus-of-control questions, each sub-group was strongly internally oriented, both at baseline and follow-up. The majority of respondents denied engaging in the two high-risk behaviors, either at baseline or follow-up. Respondents reported decreased involvement at follow-up, but the numbers were too small for statistical significance. Educational interventions in settings of this type increase knowledge about high-risk behaviors, but it may be impossible to prevent contamination across subjects, since knowledge items are likely to be discussed among experimental and control groups. However, attitudinal orientations to locus of control questions about past behaviors are not subject to contamination, and in this study external orientations to past locus of control questions on drug abuse decreased in the primary experimental group, a change in the desired direction. A serendipitous fringe benefit of this study was the involvement of Group A in community activities, where they presumably learned much about everyday living, while enhancing their self-esteem and general sense of self-worth.

D. N. Nurco, University of Maryland; B. J. Primm, ADAMHA & Addiction Research and Treatment Corporation; M. B. Balter and M. Lemer, The Johns Hopkins University; P. Stephenson, Friends Medical Science Research Center, Inc.; L. S. Brown and D. Ajuluchukwu, Addiction Research and Treatment Corp. This study is funded by NIDA Grant No. R01 DA04346.

TEMPORAL CHANGES IN AIDS RELATED RISK BEHAVIORS IN A SAMPLE OF CRACK ADDICTS

K. A. MILLER; M. E. KHALSA; M. R. KOWALEWSKI AND D. ANGLIN

As part of a prospective treatment evaluation, we examined AIDS-related risk behaviors and cocaine and other drug use in a sample of male crack cocaine users (n=261) at two points in time: At contact during 1990 and one year later. We assessed cocaine use and AIDS risk behaviors during the year prior to initial contact (period 1) and during the following year (period 2). We divided our sample into 4 groups according to changes in their cocaine use between period 1 and period 2; Group 1: those who did not use cocaine during periods 1 and 2; Group 2: those who used cocaine severely during both periods 1 and 2; Group 3: those whose cocaine use increased during period 2 as compared to period 1; and Group 4: those whose cocaine use decreased during period 2 as compared to period 1. Thirty-seven subjects were not included because their cocaine use changes were too atypical to categorize.

Respondents reported a high level of knowledge concerning AIDS-related issues and HIV transmission. AIDS knowledge level was not related to cocaine use patterns. Across the four groups, nearly half were worried about spreading HIV, believed they had done things which could have exposed them to HIV, and believed they could spread HIV to others it they were not careful about AIDS-related behaviors. Fewer respondents, however, believed condom use was easy for them and fewer still reported using condoms on a regular basis. Furthermore, many respondents reported more than one sex partner. These behaviors remain relatively consistent between both periods. Comparisons between groups support the view that cocaine use is relatively to a higher number of sex partners. Moreover, severe cocaine users were more likely to believe they were at risk for AIDS than non-users. They were also more likely to believe they would get AIDS. These findings reveal that despite knowledge about AIDS risks, these subjects have not managed to change their behaviors. Respondents may have a low self-efficacy that inhibits change in response to AIDS concerns. Moreover, severe cocaine users are more likely to feel resigned to contracting AIDS. Thus, severe cocaine use may be an attitudinal barrier to AIDS risk reduction and may impede users' commitment to change behaviors. Further analysis will explore the links between AIDS-related behavioral change and perceived susceptibility to AIDS.

AFFILIATION: UCLA Drug Abuse Research Center, Neuropsychiatric Institute, Los Angeles and Xavier University, New Orleans, Louisiana

HIV SEROCONVERSION AMONG STREET-RECRUITED DRUG INJECTORS: A PRELIMINARY ANALYSIS

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Objectives: To assess rates of, and risk factors for, HIV seroconversion among drug injectors.

Methods: 4,644 seronegative IDUs in 14 cities were HIV antibody tested 2+ times (ELISA; Western blot). Subjects were 74% male; 44% Black, 26% White, 28% Latino. Mean age 35.2. All had injected drugs within 6 months prior to intake interview. Cox regression (backward elimination) started with risk factors significant in bivariate analysis ($p<.05$). Mean duration between first and last tests = 8.7 months. Date of seroconversion = midpoint between last negative and first positive test. 10 cities had low seroprevalence rates (<12%) and 4 had high rates (<20%).

Results: 56 (1.21%) seroconverted (1.83/100 person years at risk). In Cox regression, significant predictors were city seroprevalence (risk ratio = 1.06; C.I. 1.12, 1.29); no prior drug abuse treatment (RR=2.03, C.I. 1.19, 3.46); and renting or borrowing used syringes (RR=2.16; C.I .1.08, 4.33). **Significant predictors in subsets: 1.** In four high seroprevalence cities (seroprevalence > 20%). 5.5% (32/581) seroconverted (7.89/100 person-years at risk); renting used syringes (RR=2.15; CI 1.50, 3.07) and cocaine injections/day (RR=1.20; C.I. 1.01, 1.43) were independent predictors. 2. In the 10 lower seroprevalence cities (seroprevalence < 12%). 0.6% (24/4063) seroconverted (0.90/100 person-years at risk), with city seroprevalence (RR=1.27 for 1% increase; C.I. 1.10, 1.46) no prior drug abuse treatment (RR=2.94; CI 1.16, 7.43) and Black (RR=2.77; CI 1.08, 7.09) and Puerto Rican ethnicity (RR=13.17; C.I. 1.58, 110.02) significant. The reference group for race/ethnicity is composed of White, Mexican-origin, and other subjects. In low seroprevalence cities, Blacks and Puerto Rican IDUs are significantly more likely to be seropositive at intake than are IDUs of other eithnicity. 3. Among males, all these variables and lack of AIDS information. 4. Among females, 0.8% (10/1269) seroconverted (1.21/100 person-years at risk). Significant predictors were sex with women (RR=5.42; C.I. 1.40, 20.99) and city seroprevalence (RR=1.04 for 1% increase; C.I. 1.01, 1.08) were significant predictors of seroconversion. To explore why women who had sex with women are at higher risk, cross tabulation identified variables (not remaining in the stepwise equation) on which women who had sex with women and other female IDUs differ ($p<.05$). Women who had sex with women were more likely to: use amphetamines or poppers; be homeless; inject only with illicit syringes, rent used syringes, inject at drug dealers' houses, share syringes with more people; and have sex for drugs, or for money. All 3 seroconverters among women had sex with women had had both sex with men and sex for money in the prior 6 months.

Conclusions: The total seroconversion rate is low due to the rates in low seroprevalance cities. Determinants of seroconversion seem to differ by city seroprevalance. In the early stages of a city's epidemic, HIV may spread most rapidly within pockets of infection -- such as ethnic networks, so targeted interventions may then be particularly appropriate; expansion of drug abuse treatment should also be valuable. If city seroprevalance **reaches** 20%. renting syringes in shooting galleries or dealers' houses may facilitate HIV spread across networks, and cocaine injection frequency is associated with seroconversion.

Lesbian and bisexual female IDUs seem to be at greater risk than other women who inject drugs. They accounted for 30% of seroconversions among women -- perhaps an underestimate if sex with women is underreported. Possible explanations include differences in drug behaviors or prostitution; also, they may be more likely to shoot up with gay male drug injectors. Research with larger N's and targeted risk reduction campaigns should be conducted.

AFFILIATION: *National Development and Research Institutes, Inc.; **Beth Israel Medical Center; ***NIDA National AIDS Demonstration Research/AIDS Targeted Outreach Model projects.

SMALL GROUP AIDS EDUCATION WITH INJECTION DRUG USERS IN OUTPATIENT TREATMENT: 12-MONTH FOLLOW-UP

J. L. SORENSEN; J. LONDON; C. HEITZMAN; D. GIBSON; E. MORALES; R. DUMONTET AND M. ACREE

Among injecting drug users HIV infection continues to spread, and it is imperative to develop AIDS prevention activities for them. However, relapse to unsafe sex has been a significant problem in some AIDS risk groups, and there is reason to believe that even if interventions have a temporary effect, relapse to unsafe drug use will be a problem for the injection drug-using community. Thus there is a need to develop long-lasting approaches to changing the risky behavior of injecting drug users.

SMALL GROUP APPROACH: One approach has been to develop small-group interventions to skills training. The approach is compatible with drug treatment programs, which have a rich history of conducting small-group psychoeducational interventions. Several research groups have been working in this area (see Sorensen, 1991). Some interventions have demonstrated short-term efficacy, but their longer-term effects are not known. In this random assignment study, twelve-month follow-ups demonstrate the limitations of an AIDS education program. In a trial of a small-group AIDS prevention approach 50 methadone maintenance patients and 98 heroin addicts in outpatient detoxification were randomly assigned to experimental or comparison conditions. Experimental-condition subjects received a 6-hour small-group intervention that aimed at improving their knowledge and attitudes about AIDS, increasing their skills at syringe sterilization and condom use, and lowering their high-risk needle use and sexual behaviors. Comparison subjects received a set of written materials about AIDS.

RESULTS AND CONCLUSIONS: Twelve-month follow-ups revealed that, relative to comparison subjects, experimental subjects in maintenance, became more knowledgeable about risk reduction practices, and experimental subjects in detoxification were more concerned about their susceptibility to HIV infection. Subjects in both study conditions increased their skills in demonstrations of syringe sterilization. The parallel changes may indicate that small-group interventions are vulnerable to diffusion effects or that community norms were changing. These results do not indicate changes in behaviors that transmit HIV, and they are less robust than previously-reported follow-ups three months after the intervention. The study's follow-up results indicate that more potent, sustained interventions need to be developed to slow the spread of HIV among injection drug users.

REFERENCE: Sorensen, J.L. Preventing HIV transmission in drug treatment programs: What works? J Addictive Diseases 10:67-69, 1991.

Supported by NIDA grants 1R18DA06097 and 1R0lDA04340

AFFILIATION: University of California, San Francisco

EFFECTS OF LYMPHOCYTIC CHORIO-MENINGITIS VIRUS (LCMV) INFECTION ON LEARNING IN MICE

L. H. GOLD; G. F. KOOB; I. POLIS; R. SCHROEDER; F. E. BLOOM AND M. B. A. OLDSTONE

LCMV is a nonlytic murine virus that forms a model system for studying the behavioral correlates of CNS virus infection. Newborn or immuno-deprived mice infected with LCMV develop a persistent infection characterized by continuous viral production. Virus can be found in various body organs including lung, liver, kidney and brain. In brain, the greatest number of persistently infected neurons are found in the cerebral cortex, hippocampus and other limbic structures and part of the hypothalamus. The purpose of these experiments was to evaluate the behavioral consequences of persistent viral infection, in particular the effects on learning.

Mice from the DBA/2J strain were infected with LCMV virus within 24 hours of birth (1000 plaque-forming units) and tested behaviorally 8-10 weeks later. Plaque assays were performed to determine viral titers. Mice were tested for their ability to learn a Y-maze spatial avoidance discrimination. The mice were required to learn to run from the start box to the safe arm (opposite to the initial preference) of the maze within 10 set to avoid the onset of a mild footshock (0.43mA). If the shock was not avoided, footshock was turned on until the mouse entered the safe arm, with a maximum footshock duration of 30 sec. The number of correct avoidance responses made during training was taken as a measure of acquisition performance. The virus infected mice showed a deficit in acquisition of the Y-maze discrimination compared to sham-injected (injected with the vehicle suspension at birth) and non-injected controls. The infected mice also failed to reach the near-perfect performance that is characteristic of this mouse strain. Following additional training to reach control levels of performance, the infected mice and the controls were injected with the cholinergic antagonist scopolamine. Scopolamine disrupted the performance of the infected mice significantly more than control performance suggesting that a cholinergic dysfunction may account for some of the learning deficit. Virus-infected and sham-injected mice were retested 7 months after the initial evaluation. Again, the virus-infected mice exhibited a reduced ability to acquire the discriminated avoidance.

Results from the present studies suggest that viral infection can have pronounced behavioral effects in the absence of overt disease and suggest a novel means by which environmental insult could alter behavioral responses to drugs.

This work was supported by a National Institute of Mental Health grant MH 47680 and NS 12428.

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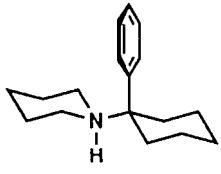
COMPUTER-ASSISTED MOLECULAR MODELING OF THE PCP BINDING SITE BASED ON ALKYL- SUBSTITUTED PCP DERIVATIVES

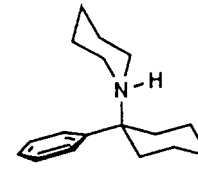
J. T. M. LINDERS, M. V. MATTSON AND A. E. JACOBSON

Phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP), a major drug of abuse, shows a broad spectrum of biological activities which are related to its interactions with various neurotransmitter (regulatory) systems, most notably the dopamine reuptake complex and the NMDA-receptor ionophore complex. Overactivation of the NMDA receptor which can be the result of traumatic injury, leads to increased intracellular Ca^{2+} concentrations, which can ultimately result in neuronal damage and cell death. PCP and other compounds such as MK-801 and dexoxadrol block the influx of cations by binding to a site within the ion channel, acting as an anticonvulsant and neuroprotective agent.

PCP can occur in conformations with the phenyl ring either in the axial **(Phax)** or in equatorial position **(Pheq).** Based on structure-activity and conformational studies it can be concluded that **Phax** is the preferred conformation under most conditions, and probably also the receptor-bound conformation.



Phax



Pheq

Introduction of methyl groups in the three rings of PCP affords a series of compounds whose affinity for the PCP binding site (labeled by [^{3}H]TCP) ranges from 11 to 6800 nM (PCP 65 nM, MK-801 10 nM). Using computer-assisted molecular modeling, we have studied the theoretical conformations of the methyl analogs and compared them with the preferred conformation of PCP. The methyl analogs can be divided into two groups, based on the stability of the Phax conformation relative to PCP. Using the "active analog approach", derivatives, for which the **Phax** was stabilized relative to PCP but which showed lower affinity for the PCP binding site than PCP, were used to describe the receptor-essential volume of the PCP binding site. Similarly, data on a series monomethyl derivatives of the conformationally rigid MK-801 (P. D. Leeson et al., 1990) were used. The resulting receptor-essential volumes partly overlap and are complementary to each other. Dexoxadrol and etoxadrol both show some interaction with the receptor-essential volume which may explain their lower affinity compared to PCP.

REFERENCES: Available upon request.

AFFILIATION: Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD 20892

SYNTHESIS AND EVALUATION OF NOVEL AFFINITY LIGANDS FOR FURTHER CHARACTERISTICS OF SIGMA RECEPTORS

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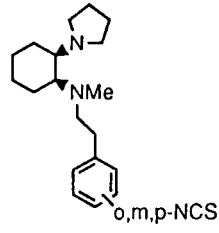
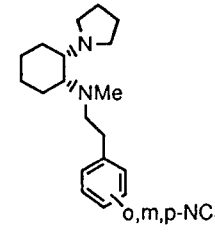
M. J. WALKER;[2] M. HEMSTREET[3] AND B. DE COSTA[1]

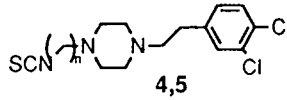
Sigma receptors are a unique class of non-dopaminergic, non-opioid CNS binding sties that have been implicated in numerous pharmacological and biochemical effects which include movement disorders, psychoses, and cerebroprotection. In order to further delineate the structure and function of sigma receptors, we developed novel electrophilic and photoaffinity ligands from three different classes of high affinity sigma receptor ligands.



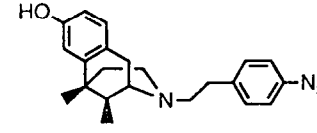
(-)-**1,2,3**



(+)-**1,2,3**



4,5



6

Compounds (+)- and (-)-**1,2** and **3** are representative of the first or cis cyclohexanediamine class. Piperazines **4,5** and (+)-azidophenazocine **6** constitute the second and third classes. Affinity ligands (+) and (-)-**1,2** and **3** were synthesized from enantiomeric (+) and (-)-cis-N-(1-methyl)-2(1-pyrrolidinyl) cyclohexylamines. The isothiocyanate moiety was generated via treatment of the corresponding aromatic aniline precursors with thiophosgene in the presence of aqueous $NaHCO_3$. Compound **4** (n=2) was synthesized via a DCC coupling of 1-(3,4-dichlorophenethyl) piperazine with N-BOC-glycine. Ligand **5** (n=3) was obtained via a Michael addition of 1-(3,4-dichlorphenylacetyl)piperazine to acrylonitrile. Irreversible ligand **6** was synthesized by alkylation of (+)-normetazocine with 4-azidophenethyl tosylate. The p-derivatives (+) and (-)-3 exhibited irreversible sigma binding properties and (+)-**3** seemed to antagonize (+)-pentazocine induced circling behavior in rats. Further studies are currently under way to investigate these phenomena.

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STRUCTURAL MODIFICATIONS OF COCAINE: INCREASED SELECTIVITY FOR THE DOPAMINE TRANSPORTER

J. W. BOJA; F. I. CARROLL; A. H. LEWIN; P. ABRAHAM; K. PARHAM; T. KOPAJTIC; M. MILBERGER; R. M. MCNEILL AND M. J. KUHAR

Previous work by this laboratory has demonstrated that certain modifications of the cocaine molecule has profound effects upon its potency at the dopamine transporter. For example, modifications at the C-3 position such as elimination of the ester linkage between the tropane and phenyl rings of cocaine increases potency to inhibit binding of [^{3}H]WIN 35,428 to the dopamine transporter. Further increases in potency are achieved by halogen substitutions on the phenyl ring. These increases in potency at the dopamine transporter were mirrored by increases in potency at the norepinephrine and serotonin transporters as well. In contrast, modifications to the C-2 ester linked methyl group of cocaine did not result in significant potency changes in potency at the dopamine transporter. However, these modification did result in profound reduction in the ability of these compounds to displace both [^{3}H]paroxetine from the serotonin transporter and [^{3}H]mazindol from the norepinephrine transporter. Replacement of the C-2 methyl group by ethyl, propyl, isopropyl or phenyl groups resulted in, at most, a 2 fold reduction of potency at the dopamine transporter. In contrast, the potency at the serotonin transporter was reduced up to 50 fold in the case of the phenyl substituted analog with a concurrent 30 fold reduction in potency at the norepinephrine transporter. Elimination of the methyl ester group at the C-2 position reduced potency at all monoamine transporters. The increased selectivity of these compounds was apparent not only in inhibiting binding of the various uptake blockers to the monoamine transporters, but was significant in the inhibition of uptake as well. Substitution of a phenyl group for the C-2 methyl group of cocaine resulted in less than a 2 fold reduction in potency to inhibit [^{3}H]dopamine uptake. However, there was a 54 fold reduction in ability to inhibit [^{3}H]norepinephrine uptake and a 41 fold reduction in potency to inhibit [^{3}H]serotonin uptake.

Cocaine has been shown to be a relatively non-selective uptake inhibitor of monoamine transport. It is potent not only at the dopamine transporter, but also at the serotonin and norepinephrine transporters as well. These data indicate C-2 modifications produce a cocaine analog that is a selective dopamine uptake inhibitor. This will be useful in elucidating the dopaminergic component of cocaine's action.

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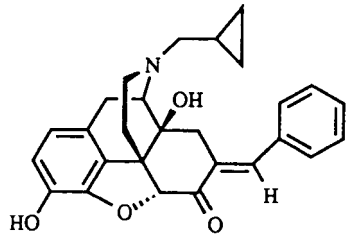
7-BENZYLIDENENALTREXONE (BNTX), A HIGHLY SELECTIVE δ1 ANTAGONIST, THE FIRST CLEAR EVIDENCE FOR δ RECEPTOR SUBTYPES BASED ON BINDING

M. SULTANA, A. E. TAKEMORI AND P. S. PORTOGHESE

Recent reports (Sofuoglu et al. 1991; Jiang et al. 1991) have presented in vivo evidence for two δ opioid receptor subtypes: DPDPE and DADLE are selective for δ_1 while DSLET and deltorphin II are selective for δ_2. These studies have employed DALCE as a δ_1 antagonist and naltriben (NTB) and 5'-naltrindole-isothiocyanate (NTII) as δ_2 antagonist to distinguish between the antinociceptive effects mediated by these δ receptor subtypes. We now report on 7-benzylidenenaltrexone (BNTX) which is the first highly selective antagonist for δ_1 receptors that exhibits selectivity in binding and antinociceptive assays.



BNTX

BNTX and its congers were synthesized in an effort to examine the role of the phenyl group in mimicking a putative δ address component. In this context, the phenyl group of BNTX is non-planar with respect to the C-ring of the morphinan structure. This is in contrast to the δ_2 antagonist, NTB, where the benzene moiety of benzofuran is coplanar with ring C.

Opioid receptor binding experiments have shown that BNTX has 100-fold greater affinity (K_i = 0.1 nM) for [^{3}H]DPDPE binding sites as compared to those of [^{3}H]DSLET. Also, in the tail-flick assay BNTX (6.3 pmol/mouse) effectively antagonized DPDPE (ED_{50} ratio 7.2) but did not significantly change the ED_{50} value of DSLET, morphine or U50488H. Thus, both the binding and in vivo data are consistent with δ1-selectivity for BNTX. Molecular modeling studies show that the phenyl group of BNTX assumes an out-of-plane conformation with respect to the C-ring, while in NTB this ring is coplanar. The preferred conformation of the phenyl group of BNTX may facilitate binding to a δ1 address subsite.

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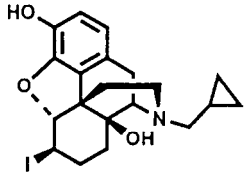
IODOMORPHINANS AS A NOVEL CLASS OF POTENTIAL SPECT IMAGING AGENTS FOR OPIOID RECEPTORS IN THE CNS

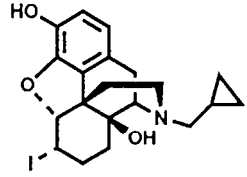
B. R. DE COSTA; M. J. IADAROLA; R. B. ROTHMAN; K. F. GEORGE; A. H. NEWMAN; A. MAHBOUBI AND K. C. RICE

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are related non-invasive imaging techniques which in the last ten years have provided a breakthrough in the visualization and quantitation of drug-receptor distribution in living subjects.

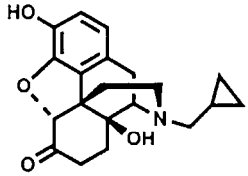
The opioid receptor-endorphin system consists of numerous endogenous peptides which interact with three well defined μ, δ, and κ-opioid receptor subtypes which effect several physiological processes including the perception of pain, pleasure and mood. As part of our program to further-



1 (Ioxy)



2 (Epiioxy)



3 (naltrexone)

investigate the role of this system, we synthesized (from naltrexone 3), ioxy 1 and its 6α-epimer 2 as potential agents for opioid SPECT. In the rat paw withdrawal latency test, i.v. administration (5 mg/kg) of 1, 2, their 3-O-acetyl derivatives, or 3 produced a complete and persistent (>40 min) reversal of the effects of morphine (10 mg/kg, s.c.). These results indicate that 1 and 2 (a) penetrate the blood brain barrier and (b) are antagonists, both of which are desirable for brain imaging. The persistence of the in vivo antagonist effects of 1 and 2 suggests that they remain in the brain long enough to perform receptor imaging studies. In vitro binding of 1-3 in rat and guinea pig (Table) revealed 1 to be more μ/κ selective and potent than 2 and 3.

Compd	Receptor Subtype Affinity K_i (nanomolar)			
	μ (Rat) [^{3}H]DAGO	κ1 (G. P.) [^{3}H]U69.593	κ2 (G. P.) [^{3}H]BREM	δ (Rat) [^{3}H]DADLE
1 (Ioxy)	0.80	0.42	2.73	11.7
2 (Epiioxy)	2.09	1.49	8.46	46.2
3 (Naltrexone)	1.18	2.81	16.8	101

In the halogen series, I>Br>F for opioid receptor affinity. The 6-F derivative (cyclofoxy) was developed in our laboratory in 1984 as the first successful agent for opioid PET in primates. Based on both the in vivo, in vitro data, and structural similarity of 1 to cyclofoxy, we synthesized and evaluated [^{125}I]1 in rats using a gamma camera and ex-vivo autoradiography. The result indicated robust uptake into rat brain with characteristic opioid receptor localization thus identifying [^{123}I]1 to be suitable for opioid receptor SPECT.

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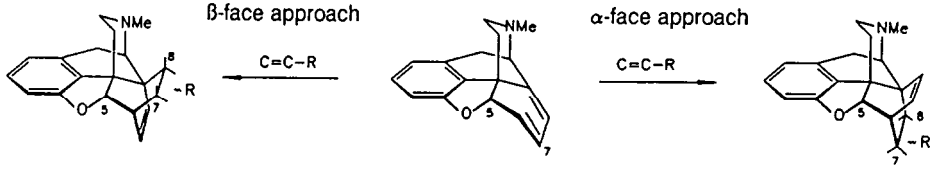
ANOMALOUS DIELS-ALDER REACTIONS OF THEBAINE DERIVATIVES

R. H. WOUDENBERG AND L. MAAT

A rationale behind the search for more selective analgesics is the construction of rigid moieties in the morphine molecule. The C-ring bridged 6α,14α-ethenoisomorphinans fulfill this request and are the basis of several highly potent analgesics, such as etorphine and buprenorphine. The synthesis of the 6α,14α-ethenoisomorphinans is accomplished by Diels-Alder reaction of thebaine with an appropriate dienophile.



6α,14α-ethenoisomorphinan

6ß,14ß-ethenomorphinan

During our study directed to the synthesis of Diels-Alder adducts with the substituent in a position other than the 7α-position, we found that introduction of a 5β-methyl group in 6-demethoxythebaine gives after Diels-Alder reaction both the 6α,14α-ethenoisomorphinan and the 6β,14β-ethenomorphinan in a ratio of about 1:1. To force the cycloaddition electronically to the 8-substituted adducts, we prepared two 7-chloro-6-demethoxythebaines. Reaction of 7-chloro-6-demethoxythebaine with ethyl acrylate yields four adducts. The main adduct was identified as the 7α-substituted ethenoisomorhinan (55%), formed together with the 8α-substituted analogue (25%) and the 8β-substituted ethenomorphinan (15%). Striking differences were found with 5β-methyl-7-chloro-6-demetoxythebaine. Now the 8β-substituted ethenomorphinan was found as main adduct (75%), besides some 7α-substituted (20%) and 8α-substituted (5%) ethenoisomorphinan. The adducts were converted into the 3-hydroxy analogues by demethylation with boron tribromide. Reaction of the ester groups at 7 or 8 with methylmagnesium bromide yielded the corresponding alcohols.

An approach for the synthesis of adducts with the substituent in the 7β-position proved to be an intramolecular Diels-Alder reaction. Cycloaddition of both the acrylate and the methacrylate of thebaine-5β-methanol gives the ethenoisomorphinan with an additional 6β-7β-bridge over the C-ring. Further modification yields compounds, which are in biological tests very selective for the u-receptor.

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National Survey of Drug Abuse Treatment Services: Implications for Treatment Referrals

B. A. Rouse and C. E. Steigerwald

A nationally representative sample of 1,183 drug treatment facilities was drawn to study clients in treatment, available services, capacity, costs, and quality of care for drug abusers in the U.S. Excluding criminal justice facilities and alcohol-only facilities, this Drug Services Research Survey estimated the number of clients in drug treatment facilities on 3/30/90 to be 743,134. A subsample of facilities stratified by treatment modality and drawn to collect data on discharged clients was analyzed to determine referral sources and correlates of treatment success. The modality strata were: Hospital Inpatient, Residential, Outpatient Drug-Free, and Outpatient Detox/Drug Maintenance. In the subsample of 118 facilities (82% response rate), data were abstracted from a representative sample of 2,182 records of clients discharged between 9/1/89 and 8/31/90. As part of the quality control, a sample of 9% of the client records was independently reviewed for abstracting accuracy.

The primary referral sources into drug treatment for the study period were: self-referrals (27%). criminal justice system (26%), health care providers (14%), other substance abuse treatment programs (11%), family/friends (9%). social agencies (6%), and EAP/employer (4%). Clients under age 18 were usually referred by a social agency while those older were more likely to be self-referred or referred by an EAP/employer. Less than half (48%) of the clients completed treatment as planned, with the rates differing significantly by treatment modality and by referral source. Reasons for not completing treatment included: client choice (30%). administration choice (9%), referred to another program (5%). and other reasons which included incarceration and death (8%). Significantly more clients referred by an EAP/employer (64%) or the criminal justice system (58%) completed their planned treatment than those referred by other health programs (44%) or by family/friends (45%).

Discriminant analysis was used to determine significant differences between clients who completed their planned treatment and those who did not. Data were weighted based on the sampling ratios and adjusted for nonresponse. A stepwise procedure was used to select the variables for each discriminant analysis model. Characteristics of the client, facilities and treatment services were analyzed. Clinical variables (e.g., prior treatment, chronic medical conditions, history of psychological disorders and HIV/AIDS status) and history of prior arrests were also included in the discriminant analysis.

Discriminant analysis models were developed for the total sample and each of the 6 treatment types. The error rate for misclassifying treatment completers ranged from 0% for drug+alcohol treatment to 24% for hospital inpatient treatment. While the relative rank of variables differed for each treatment type, some general factors emerged as significantly associated with completion of planned treatment The type and quantity of services by clients while in treatment clearly influenced treatment discharge outcomes across most of the developed models. On the other hand, the unavailability of certain treatment services, polydrug abuse, multiple previous episodes of drug treatment and lower education levels tended to be detrimental to treatment completion. Completion of planned treatment, in most cases, was not affected by client race, age, or gender. The type of facility where treatment took place, i.e., whether it was private or public; or for-profit or non-profit, had little effect on completion of planned treatment. While the client's clinical condition is important, these results suggest that referrals based on the facility's availability of specific treatment services and ability to motivate the client to complete those are the best predictors of treatment success. AFFILIATIONS: Beatrice Rouse: NIDA and Charles Steigerwald: Washington Consulting Group, Inc.

HETEROGENEITY OF APD DRUG ABUSERS ON DIMENSIONAL MEASURES OF PERSONALITY AND PSYCHIATRIC DISTRESS

R. K. BROONER; J. G. JOHNSON; L. J. FELCH AND G. E. BIGELOW

The diagnosis of APD in intravenous drug abusers has been associated with increased risk of HIV infection and with a poor treatment prognosis compared to non-antisocial drug abusers (Brooner et al., in press). These findings have stimulated new interest in the diagnosis of APD and possible subtypes of the syndrome. For example, Alterman and Cacciola (1991) hypothesized that APD drug abusers with another personality diagnosis would obtain higher levels of emotional distress and instability compared to those with APD only. This issue was examined in the present study with 199 opioid drug abusers admitted to an outpatient drug treatment program incorporating methadone hydrochloride as one component of care.

Diagnoses of personality disorder were made using the Structured Clinical Interview for DSM-IIIR. Personality trait dimensions were assessed using the NEO Personality Inventory (NEO-PI) and psychiatric distress was measured using the SCL-90-R. Of the 199 patients 74% (148) did not receive an Axis II diagnosis (i.e., Non-Axis II group), 33% (N=33) were classified as APD only (i.e., Pure APD group), and 35% (18) were classified as APD plus other personality diagnosis (i.e., Mixed APD), represented primarily by Passive-Aggressive (39%), Borderline (33%), and Avoidant (22%) disorders. On the NBO-PI, the Mixed APD group had a higher Neuroticism domain score compared to both the Pure APD and the Non-Axis II groups ($p<.01$). The Mixed APD group also had significantly higher scores of 5 of the 6 facets of Neuroticism compared to both the Pure APD and the Non-Axis II groups; these difference included higher levels of Anxiety, Hostility, Depression, Self-Consciousness, and Vulnerability. Finally, the Mixed group had higher levels of interpersonal antagonism ($p<.01$) compared to the Pure APD and the Non-Axis II groups. In addition to these differences in personality traits, the Mixed ADS group also reported significantly higher state levels of psychiatric distress on each of the SCL-90 subscales compared to the Pure APD and the Non-Axis II groups. These data confirm the hypothesis by Alterman and Cacciola (1991); Axis II comorbidity among APD drug abusers was associated with high levels of emotional distress and instability.

These differences are particularly interesting since APD patients are generally viewed as poor treatment responders. It has been argued that APD patients may do poorly in treatment because they lack the capacity to experience the sustained dysphoria and distress that motivates others to enter and remain in treatment. If this is true, the marked vulnerability and emotional distress reported by Mixed APD patients may contribute to improved retention in treatment and better clinical outcomes. This is clearly an important area for further research, particularly in light of data linking APD to higher risk of HIV transmission compared to drug abusers without the personality disorder. At present, we are examining this issue by comparing the Mixed vs. Pure APD drug abusers on several indices of treatment outcome. Preliminary data on treatment retention appears promising. For example, only 10% of Mixed APD patients left treatment prior to six months compared to 40% of the Pure APD and 24% of drug abusers with no Axis II disorder. **AFFILIATION:** The Johns Hopkins University School of Medicine, Baltimore, MD.

DRUG USE PATTERNS AND TREATMENT RETENTION AS A FUNCTION OF MCMI PERSONALITY DISORDER SUBTYPE AMONG OPIATE ADDICTS IN METHADONE MAINTENANCE

D. A. CALSYN, C. FLEMING, E. A. WELLS AND A. J. SAXON

Researchers have been interested in identifying personal characteristics predictive of response to drug abuse treatment in order to design better treatment options. The Millon Clinical Multiaxial Inventory (MCMI), which measure personality and psychiatric disorders, was administered to 193 males and 113 females within one month of entering methadone maintenance treatment. The racial composition of the sample was 59.8% white, 36.9% black, 3.3% other. The mean age was 38.0 (sd = 7.5) years. Most had completed high school or obtained a GED (71.6%). 30.7% were employed and 12.7% were married. MCMI profiles were classified separately by gender into four Axis I and six Axis II subtypes. Sorting rules were based on cluster analysis and authors' previous research with MCMI subtypes. Subtypes were compared on demographics, high risk HIV transmission behaviors, drug use and treatment retention. The distribution of Axis I subtypes for males was: no elevations (18.7%) drug and alcohol abuse only (31.6%). affective disorders (27.5%) psychotic features (15.0%). For females the distribution was: no elevation (19.5%). drug and alcohol abuse only (14.2%) affective disorders (38.9%) psychotic features (20.4%). On Axis II subtypes the distribution for males was: no elevations (13.0%), narcissistic/anti-social (40.9%). dependent (14.0%). withdrawn/negative (15.0%) histrionic (5.7%). severe disorder (6.2%). For females the distribution was: no elevations (7.1%). narcissistic/anti-social (28.3%). dependent (19.5%), withdrawn/negative (13.3%) histrionic (13.3%). severe disorder (9.7%). Compared to whites, more non-white males were classified in the narcissistic (61.3%). severe (9.3%) and psychotic features (26.4%) subtypes, with fewer being in the affective disorder (15.3%). Axis II no elevations (8.0%) and histrionic (0%) subtypes. More non-white females were classified into the severe (34.3%) subtype. Male subtypes differed on ASI psychiatric severity in the expected direction with lower mean composite scores for Axis I no elevations (.10), Axis II no elevations (.10), and narcissistic (.11) subtypes, while higher scores were obtained for withdrawn (.26), histrionic (.21), and affective (.24) subtypes. Fewer male Axis I no elevation (8.3%) subjects engaged in high risk drug injection behaviors during the 6 months prior to admission than affective disorder (26.8%) or drug/alcohol only (32.8%) subjects. During the first 12 months of treatment male Axis I no elevation (29.1%) and affective disorder (34.1%) subtypes provided fewer urines positive for cocaine than drug/alcohol only (48.6%) or psychotic (48.6%) subtypes. Narcissistic (47.8%) dependent (44.8%) and Axis II severe (47.9%) subtypes provided more cocaine positive urines than other Axis II subtypes. Eighteen month treatment retention curves were calculated for the total sample utilizing survival analysis. The cumulative proportion retained at 18 months was larger for withdrawn (.48) and histrionic (.34) than other Axis II subtypes (range = .20 to .12, Lee-Desu = 14.8, p = .01). Results demonstrating significant relationships between MCMI subtypes and treatment outcome measures emphasize the need for providing psychiatric services and individualizing drug abuse treatment. Supported by NIDA grant RI 8 DA05281

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LATE VERSUS EARLY ONSET ANTISOCIAL BEHAVIORS AMONG WOMEN: DIFFERENCES AND SIMILARITIES IN DRUG USE PATTERNS

L. B. COTTLER, R. K. PRICE, W. M. COMPTON, A. M. SHILLINGTON AND D. E. MAGER

A literature is accumulating on gender differences and history of antisocial personality disorder (ASPD) among substance users. Our work and that of others' suggest that the ASPD criteria need to be further evaluated for nosological differences related to number of symptoms and age of onset. As the DSM-IV Task Force evaluates their newly proposed criteria, studies evaluating similarities and differences among women in particular need to be reported.

This asks a) are female substance users who meet full criteria for ASPD different from those who meet the adult criteria but do not meet the childhood conduct criteria (Late ASPD) with regard to a number of substance use characteristics such as age of onset of substance use, IV drug use and patterns of drug use; b) are women with ASPD more likely to be physiologically dependent than those with Late ASPD?; c) are there differences in the ages of onset of psychiatric symptoms among the two groups?; d) does family history of disorders differ between the groups?; e) does high risk behavior differ between the two groups?

The sample pool for these analyses are the 243 women interviewed for the Substance Abuse and Risk for AIDS study (SARA) who are St. Louis substance abusers aged 18-45 newly admitted to treatment. Of these, 55 (22% of the sample) met all of the criteria for DSM-III-R ASPD; however, 92 (37% of the sample) had Late ASPD. ASPDs were not more likely than Late ASPDs to report such childhood conduct symptoms as setting fires or stealing. All other conduct problems were more likely to be reported more by ASPDs than Late ASPDs. ASPDs were more likely than Late ASPDs to report adult aggressive behavior. Regarding drug use patterns, ASPDs were also more likely to use substances such as cannabis, amphetamines, barbiturates, and cocaine and use earlier and drink more than Late ASPDs; however, the two groups were similar regarding experiencing problems from such use. The groups did not differ on psychiatric history except for phobic disorder and tobacco dependence which were more prevalent among women with ASPD. Neither did the groups differ with regard to family history of substance abuse and ASP behavior. Using conditional logistic regression, an association was found between four or more adult antisocial behaviors and being black, having an earlier onset of drug use and having one or more childhood conduct symptom.

These data demonstrate a significant lack of differences between women who experience early versus late onset of antisocial personality symptoms, furnishing evidence to support further evaluation of the antisocial personality disorder criteria among this population.

ACKNOWLEDGEMENTS
This work was in part supported by DA05619, DA06163 and DA05585.

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PATTERNS OF REGULAR SUBSTANCE USE IN 61 CONDUCT DISORDERED BOYS

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General Population studies have shown that the majority of polysubstance abusers have conduct disorder in their youth. 61 boys aged 14-20 years with clinical diagnosis of conduct disorder and dependence in a residential treatment program were evaluated with the Comprehensive Addiction Severity Index for Adolescents (CASI-A); 48 of these with the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM); and 41 of these with the Diagnostic Interview Schedule for Children-Revised (DISC). Conduct Disorder and Dependence: 41/41 boys had their diagnoses of DSM-III-R conduct disorder confirmed by the DISC. CIDI-SAM data for 48 boys resulted in prevalence of dependence diagnoses ranging from 76% for marijuana and alcohol, 60% tobacco, 42% hallucinogens to 18%, 16%, 12% for inhalants, cocaine and amphetamines, respectively. CASI-A data: 26% of boys used >5 categories of drugs regularly (1+/month). Across drugs, regular use was strongly associated with dependence diagnoses ($r = .97$; $p < .01$) Regular use: ranged from 95%, 93%, and 79% of boys for marijuana, alcohol, and tobacco to 21%, 10%, and 5% for inhalants, sedatives, and opiates, respectively. Initial use progressed to regular use in 7 of 10 drug categories in over 50% of cases. Daily use: 72%, 64%, and 26% of boys reported daily use of tobacco, marijuana, and alcohol as their typical pattern. Route: 100% of the boys reported regular use by transpulmonary route, 97% oral, and 26% intranasal; only 7% of boys had tried injecting drugs and 0% used this route regularly. Circumstance: 97% of boys used drugs with peers and 41% (26% tobacco excluded) used alone; less than 8% of boys reported using in other circumstances regularly. Problems: high numbers of problems were associated with regular use across drug categories. Conclusions: patterns of substance use in boys with conduct disorder are characterized by polysubstance use, dependence, and rapid progression to regular use which is intense and associated with morbidity. This may be determined more by the youths' impulsive, rebellious behaviors than by the pharmacologic reinforcing properties of the drugs.

REFERENCES: Available upon request.

ACKNOWLEDGEMENTS: Supported by grant DA06941 from National Institute on Drug Abuse

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TRAUMATIC EVENTS AND POST-TRAUMATIC STRESS DISORDER IN TREATED COCAINE USERS

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Studies have shown that persons with post-traumatic stress disorder (PTSD) are at higher risk for drug and alcohol use than persons with no PTSD and that substance users, relative to nonusers, report elevated rates of PTSD. These findings are important since the co-occurrence of psychiatric and substance use disorders has etiologic and treatment implications. Data are presented on traumatic events and PTSD in 389 cocaine users in treatment. Ss were from a multi-site study of the efficacy of inpatient and outpatient treatments for cocaine dependence conducted at six private, hospital-based chemical-dependence programs. As part of the study baseline assessment, Ss completed the NIMH Diagnostic Interview Schedule (DIS-III-R). All Ss reported on here met DSM-III-R criteria for cocaine dependence in the 6 months before treatment entry. Ss were 78.1% male; 56.3% Caucasian, 35.7% African-American, and 8.0% other race/ethnicity; and predominately crack smokers (66.3%). Almost two-thirds of Ss (66.1%) reported having been exposed to at least one traumatic event in their lifetime. One quarter of the sample, 25.7%, met lifetime criteria for PTSD, and 13.9% met criteria and also experienced at least one PTSD symptom in the last 6 months.

Important gender differences concerning PTSD were obtained. The most common precipitating events for PTSD in women were rape and physical assault (33.8% and 32.3% of reported events, respectively). For men, seeing someone seriously hurt or killed and physical assault were the most prevalent (25.3% and 20.3%). Women and men were equally likely to have been exposed to trauma. Women, however, were more likely than men to meet criteria for lifetime (odds ratio =4.4) and current (OR =4.3) PTSD. Race was not associated with PTSD prevalence. Adjusting for gender differences, Ss who were severely dependent on cocaine were more likely than moderately dependent Ss to meet lifetime criteria for PTSD (OR = 3.7). PTSD also was more prevalent in Ss with a history of major depression (OR = 3.01, antisocial personality disorder (2.71, and cannabis dependence (OR = 2.01, but not alcohol dependence (OR = 1 .0). This pattern of results is consistent with findings from recent, large-sample investigations of PTSD in substance users and in young urban adults. The rate of PTSD, however, was predictably higher in this treatment sample. The obtained prevalence of traumatic events and PTSD argue for thorough assessment of trauma history in cocaine users presenting for treatment, as PTSD symptoms may affect patients' ability to respond optimally to treatment interventions.

Supported by NIDA Grant #DA05582.
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STANDARD INDICES AS PREDICTORS OF COCAINE USE AND CRAVING

J. BROWN. M. E. KHALSA AND F. H. GAWIN

Clinical experience shows that craving for cocaine contributes to relapse. Reducing craving for cocaine is hypothesized to reduce use. Finding general predictors of craving or use would enable clinicians to more precisely define these entities and to focus interventions.

In an earlier pilot study with 21 cocaine addicts medicated with desipramine we found that self-reports of craving on an analogue scale were most clearly related to both the use of cocaine and to dysphoria indices from scales largely developed for depressive disorders (Beck Inventory, Hamilton-depression scale, and SCL90), but not to other standard indices.

Attempting to understand what the dysphoria indices explain we have expanded the study of the relationship between cocaine craving, use, withdrawal symptoms and psychological measures of stress, depression and anxiety.

Our present study includes 42 subjects meeting DSM-III-R criteria for cocaine dependence and receiving desipramine (n = 14), flupenthixol (n = 14). or placebo (n = 14) for six weeks in a double-blind design. The SCL90, Beck, Hamilton-D and Hamilton-A, Subjective Stress, craving scales, the Quantitative Cocaine Inventory (to assess level and pattern or cocaine use with detail) and the Withdrawal Index for cocaine are being collected at admission and weekly.

We have focused on the utility of standard measures of psychological states in making simple prognosis of craving and use. Our pharmacological hypotheses are the patients on placebo will present greater withdrawal symptoms and greater cravings than those on desipramine or flupenthixol. We also hypothesize that flupenthixol may differentially improve anxiety and anergia and that it will work more rapidly.

Our preliminary results show that standard measures of dysthymia like the Beck and the SCL-90 predict cocaine craving well: $r = .49$ for SCL-90 and craving ($p < .001$) and $r = .48$ for Beck and craving ($p < .0001$). These standards indices do not predict cocaine use as strongly: $r = .30$ for SCL-90 and use, and $r = .24$ for Beck and use.

Further assessments will inspect the dimensions tapped by these instruments as outcome indicators in the pharmacological treatment experiments.

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DIFFERENCES IN SUBJECTIVE REPORTS OF WITHDRAWAL AMONG COCAINE USERS WITH AND WITHOUT OPIATE USE

L. B. COTTLER, A. M. SHILLINGTON, W. M. COMPTON AND D. MAGER

The proposed DSM-IV criteria for substance use disorders have included as an option a subtyping for physiologic dependence, characterized by either tolerance or withdrawal. This weighting scheme justifies wider surveillance of these symptoms, especially for the more newly described cocaine dependence disorder. Wider surveillance of withdrawal (W/D) is possible with the CIDI Substance Abuse Module (SAM), a WHO/ADAMHA diagnostic interview which covers criteria of substance use disorders according to the DSM-III, III-R, proposed ICD-10 and DSM-IV systems.

A master list of all symptoms in the DSM manuals related to W/D from any substance was compiled for the SAM to assess W/D symptoms from all substances (n= 17). We hypothesized that the persons who used opiates with cocaine might misattribute W/D symptoms to cocaine; thus, we compared the responses of persons who used cocaine and opiates (C+O) with the responses of persons who used cocaine without opiates (C w/o 0). Data from two St. Louis studies were combined for these analyses-- users not in treatment or newly enrolled to drug-free or methadone treatment from a NIDA Demonstration project; and users selected for the DSM-IV Field Trial. Of the 196 persons included from the Field Trial, 80% used cocaine; 91% of the 412 persons from the Demonstration project used cocaine.

The symptoms mentioned in the diagnostic manuals were among the most frequently endorsed by both cocaine use groups. However, other symptoms not included in the manual were reported with equal or higher frequency to those in the manual-- regardless of opiate use. “Feeling anxious or irritable” and “having trouble concentrating” were symptoms endorsed by about 40% and 35% of the sample respectively. No significant difference between the C+O group and the C w/o O group was found, lending strength to the conclusion that these might be cocaine W/D symptoms. Also, these two symptoms were not found to be frequently attributed to withdrawal from any other substance. Controlling for the effects of age, gender, onset of cocaine use and opiate use, we found that these two symptoms were predicted by an earlier age of onset of cocaine use. Additionally, 14% of cocaine users with either “anxiety” or “trouble concentrating” did not meet the criterion for DSM cocaine withdrawal. Although more epidemiologic and clinical work along these lines is needed in this area, our recommendation is that these two symptoms be considered for the DSM-IV Cocaine Withdrawal Syndrome.

ACKNOWLEDGEMENTS
This work was in part supported by DA05619, DA06163 and DA05585.

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CHRONIC COCAINE ABUSE IN METHADONE MAINTENANCE PATIENTS IS ASSOCIATED WITH ABERRANT METHADONE METABOLISM

F. TENNANT AND J. SHANNON

Cocaine abuse in methadone maintenance patients has emerged as a major clinical problem, particularly since intravenous cocaine use is now recognized as a risk factor for AIDS. To develop effective treatment strategies to eliminate chronic cocaine abuse in methadone patients, 74 subjects maintained on daily methadone dosages between 30 and 80mg and who were determined to chronically abuse cocaine, were studied by a standard protocol. These 74 subjects were identified between July and December 1991 from approximately 300 patients enrolled in four methadone maintenance treatment programs in Southern California. All had been heroin addicts from 4 to 30 years. There were 38 (51.4%) males and 36 (48.6%) females and ages ranged from 29 to 71 years.

Once identified as a cocaine abuser by repeated urine tests and self-report, subjects were urine-tested twice per week for cocaine metabolites by Fluorescence Polarized Immunoassay (FPIA) at a 95% sensitivity of 30ng/ml. Daily methadone dosage was raised 5 to 15mg each week until cocaine use ceased or a daily dose of 160mg was given. Seven (9.5%) subjects ceased cocaine abuse when their daily maintenance dosage was raised to between 80 to 100mg a day. The 67 (90.5%) subjects who did not cease cocaine use at a daily methadone dosage of 100mg had a methadone plasma concentration determined by FPIA 24 hours after a dose of 100mg. All 67 of these subjects were given sequentially higher dosages of methadone until they were given a maximum dosage of 160mg a day. Only 8 of the 67 (11.9%) had an adequate methadone plasma concentration over 200ng/ml while taking a daily methadone dose of 100mg. While taking a daily dose of 160mg, all 67 were treated with a variety of dopamine agonists, antidepressants, and calcium channel blockers to stop cocaine abuse, and 14 (20.9%) ceased cocaine abuse.

Twenty (20) subjects who had a low, inadequate methadone plasma concentration below 200ng/ml at a daily methadone dose of 100mg were retested at 160mg and only 3 (15%) showed an increase to an adequate level above 200ng/ml. It was possible to repeat the methadone plasma concentration in 4 of the 8 (50%) subjects who demonstrated an adequate (>200ng/ml) plasma methadone concentration at a daily methadone dose of 100mg a day. These four subjects continued to abuse cocaine and showed a lower plasma methadone concentration under 100ng/ml despite a higher daily methadone dose of 160mg.

This study indicates that the majority of methadone maintenance patients who abuse cocaine do not demonstrate an adequate plasma concentration of methadone above 200ng/ml at 24 hours after a 100mg methadone dose. Cocaine appears to sometimes be used as a response to inadequate methadone plasma concentrations, since some subjects ceased cocaine use with a higher daily methadone dose. Cocaine abuse may, however, interfere with methadone metabolism and prevent the attainment of adequate plasma concentrations, perhaps by accelerating methadone elimination. Methadone maintenance patients patients who chronically abuse cocaine are initially best treated by administration of a higher methadone dosage, but other treatment methods must be identified when this strategy fails.

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CHRONIC COCAINE ADMINISTRATION INCREASES MRNA LEVELS FOR DYNORPHININ THE CAUDATE PUTAMEN OF RATS

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The level of dynorphin (DYN) peptides and mRNA is increased in the striatum of rat brains after treatment with indirect dopamine agonists such as apomorphine and amphetamines, and the indirect dopamine agonist cocaine increases DYN peptide levels in the striatum. Using a quantitative solution hybridization assay, we determined DYN mRNA levels in selected regions of the rat brain following a binge protocol of cocaine treatment. A significant increase in DYN mRNA in the caudate putamen of cocaine-treated rats was observed.

Methods: Male Fischer rats were injected intraperitoneally at 9:30, 10:30, and 11:30 AM with either 3.3, 10, or 15 mg/kg cocaine HCl, or with saline, for 14 days. Thirty min after the final injection, brain regions were homogenized in guanidine isothiocyanate, phenol extracted, ethanol precipitated, and hybridized to SP6-generated riboprobes labelled with ^{32}P. After digestion by RNase T1 and RNase A, double-stranded hybrids were precipitated with TCA and radiolabel quantified by liquid scintillation. Unlabelled SP6-generated DYN sense cRNA of known concentration was used to establish a standard curve for assigning picogram values. Each extract was assayed for total RNA with a probe for 18s rRNA; thus, results are expressed as pg mRNA/ug total RNA.

Results: DYN levels (pg mRNA/ug total RNA, +/- SEM, n=12) found in pituitary, hypothalamus, frontal cortex, nucleus accumbens, caudate putamen, hippocampus, central grey, and cerebellum are shown in the table below.

PIT	HVP	FCX	ACB	CPU	HIP	CG	CER
.43 .05	2.6 .27	.15 .06	5.3 .64	4.7 .31	.70 .07	< 1 pg in 11 ug	< 1 pg in 125 ug

Levels of DYN mRNA were significantly higher ($p<.05$) in caudate putamen of rats treated with 10, 30, and 45 mg/kg/day of cocaine (n=6, 9, 12, respectively). All three doses led to an approximately 20% increase in DYN mRNA in the CPU. There was no significant differences between the levels of DYN mRNA at the three doses. A marginally significant ($p=.067$) increase in DYN mRNA was detected in the hippocampus with 45 mg/kg/day cocaine - the only concentration tested. No change was detected in the pituitary, hypothalamus, or nucleus accumbens. Support: NIDA Center Grant DA05130; Aaron Diamond Foundation. AFFILIATION: The Rockefeller University, New York, NY 10021

COCAINE SELF-ADMINISTRATION CAUSES AN INCREASE IN PREPRODYNORPHIN, BUT NOT C-*FOS*, MRNA IN RAT STRIATUM

J. F. MCGINTY, J. B. DAUNAIS AND D. C. S. ROBERTS*

Wistar rats were implanted with a jugular cannula and trained to self administer cocaine (~0.6 mg/injection, i.v.) on fixed ratio (FR1) schedule for 5 hr/day. The rats were then placed on a progressive ratio (PR) schedule for 5-15 days followed by FR1 5 hr/day fro the last 7 days. In a separate study, a single 10, 20, or 30 mg/kg. i.p. cocaine injection was administered. One hour after the last drug injection, the rats were anesthetized and decapitated. Brains were removed and frozen until 12 µm sections cut on a cryostat, adhered to coated slides, and fixed in 4% buffered paraformaldehyde. The sections were defatted, pretreated, and hybridized with a 48mer oligonuclcotide probe to preprodynorphin (PPD) or 40mer oligonucleotidc probes *c-fos* or *zif*/268 at 37°C for 20 hr. After stringent washing, the slides were dried and apposed to Kodak X-OMAT film for 2 wk (PPD) or 1 wk (*c-fos, zif*) along with ^{35}S-labeled brain paste standards. Film autoradiograms were analyzed using the IMAGE program (Wayne Rasband, NIMH) with transmission values converted into dpm/mg. Rats with a mean daily cocaine intake above 45 mg/kg during the last 7 days on FRI demonstrated a significant increase in PPD hybridization signal restricted to striatal patches as compared to saline controls ($p < .03$, "nested" ANOVA followed by Least Squares Means test). No significant difference in PPD mRNA levels in the nucleus accumbens was found between cocaine and control groups. No induction in *c-fos* mRNA, and a reduction in zif/238 mRNA (vs. control levels), was evident in the cocaine self-administering rats. In contrast, striatal *c-fos* and *zif*/268, but not PPD, mRNA levels were induced in a dose-dependent manner acute i.p. administration of cocaine. These data indicate that the expression of preprodynorphin, but not *c-fos* or *zif* /268, is upregulated as a consequence of cocaine self administration. The i.v. route of administration, the process of self administration, and/or repeated cocaine exposure may have contributed to the downregulation of these immediate early genes. Finally, these data suggest that the regulation of PPD gene expression is dissociable from that of the nuclear transcription factors, *c-fos* and *zif*/268.

Supported by DA 03982. Affiliations: Dept. of Anatomy & Cell Biology East Carolina University School of Medicine, Greenville, NC and *Dept. of Psychology, Carleton University, Ottawa, Canada

CARIOVASCULAR EFFECTS OF COCAINE IN CONSCIOUS RATS: RELATIVE SIGNIFICANCE OF CENTRAL SYMPATHETIC STIMULATION AND PERIPHERAL AMINE UPTAKE AND RELEASE MECHANISMS

S. R. TELLA; C. W. SCHINDLER AND S. R. GOLDBERG

Cocaine's cardiovascular toxicity has been thought to be due in large part to its strong sympathomimetic properties. One possible mechanism considered important in determining cocaine's cardiovascular actions is its inhibitory effect on uptake of endogenous norepinephrine by peripheral sympathetic nerve endings and subsequent enhancement in levels and function of this neurotransmitter (e.g., MacMillan, *Br. J. Pharmacol. Chemother.* 14:385, 1959). However, these earlier investigations were performed in anesthetized or spinal animals. As cocaine does not consistently produce increases in blood pressure (BP) and heart rate (HR) in anesthetized animals *(e.g.,* Moore, *J. Pharmacol. Exp. Ther.* 153:218, 1966) as it does in conscious human subjects (Fischman et al., *Arch. Gen Psychiatry,* 33:983, 1976) or in conscious animals (e.g., Gonzalez and Byrd, *Life Sci.* 21: 14 17, 1977), the influence of uptake mechanisms in conscious animals is unclear. Another possible mechanism for cocaine's cardiovascular actions is central stimulation of the sympathetic nervous system. However, results of studies addressing this issue have been inconclusive. (e.g., Wilkerson, *J. Pharmacol. Exp. Ther.* 246:466, 1988; Tella et al., *J Pharmacol. Exp. Ther.* 252:491, 1990; Raczkowski et al., *J. Pharmacol. Exp. Ther.* 257:5 11, 1991). A third possible mechanism for cocaine's cardiovascular actions is release of norepinephrine from sympathetic nerve terminals (e.g., Teeters et al., *Life Sci.* 7:509, 1963), which also could result in an excitatory influence on the cardiovascular system.

The relative involvements of the above mentioned different neural actions of cocaine in mediating its cardiovascular effects were studied in conscious Sprague-Dawley rats. Cocaine (0.03-3 mg/kg i.v.) produced a dose-dependent increase in BP and HR. Pretreatment with the competitive ganglionic blockers pentolinium or hexamethonium attenuated cocaine's pressor effect, while noncompetitive (chlorisondamine) or mixed (mecamylamine) type blockers not only abolished but also reversed it to a depressor effect. Cocaine's tachycardiac effect was attenuated by all four ganglionic blockers. The relative effectiveness of the four ganglionic blockers in antagonizing cocaine-induced cardiovascular effects was similar to that of antagonism of phenylephrine-induced centrally mediated reflex bradycardia. Despite these differences in antagonistic efficacies, all four ganglionic blockers produced similar reductions in base-line BP. The pressor responses to norepinephrine (0.2 μg/kg) were potentiated, while those to tyramine (0.3 mg/kg) were inhibited by cocaine (0.3-3 mg/kg); the former effect was not dose-dependent (bell-shaped dose-response curve), while the latter effect was. The amine uptake inhibitory potency (ED_{50}: 0.85 mg/kg) of cocaine is about 10 times less than its potency to produce pressor (ED_{50}: 0.075 mg/kg) and tachycardiac (ED_{50}: 0.083 mg/kg) effects. Chlorisondamine did not antagonize the pressor effects of the indirect sympathomimetic agent, tyramine. These results suggest that the cardiovascular effects of cocaine in conscious rats are mainly of central nervous system origin. Cocaine's peripheral actions, namely release of norepinephrine from sympathetic nerve terminals and inhibition of sympathetic neuronal uptake of norepinephrine, are not critical for its cardiovascular effects.

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SYNTHESIS AND EVALUATION OF (+)-3-SUBSTITUTED-17-METHYLMORPHINANS AS NOVEL ANTICONVULSANT AGENTS

A. H. NEWMAN; K. BEVAN; N. BOWERY AND F. TORTELLA

Dextromethorphan (DM, (+)-3-methoxy-17-methylmorphinan) demonstrates anticonvulsant activity the rat maximal electroshock (MES) test, as well as other models of convulsive action. The mechanism of this anticonvulsant action is not understood although it has been suggested that it may involve DM binding to high affinity DM sites or DM acting as a noncompetitive antagonist at the excitatory amino acid NMDA/PCP receptor. Additionally, since DM is rapidly converted to its phenolic metabolite dextrorphan (DX), which is a more potent anticonvulsant and binds with higher affinity at NMDA/PCP sites, the anticonvulsant actions demonstrated by DM may be due to its more active metabolite. Since DX causes undesirable PCP-like behavior, in animals, we prepared a series of (+)-3-substituted-17-methylmorphinans which either would not be expected to metabolize to DX or would do so at a much slower rate than DM. Evaluation in the rat MES test revealed three active anticonvulsants, all of which were more potent and efficacious than DM. *In vitro* displacement studies using the radioligands [^{3}H]DM, [^{3}H]TCP and [^{3}H]glycine, in guinea pig and rat brain demonstrated unique binding profiles for these agents which suggest a possible role of DM sites in their anticonvulsant action.

Table 1: Anticonvulsant Activity and Binding Affinities of DM analogs

Compd	3-R	MES ED_{50} (mg/kg)	[^{3}H]DM (rat) (IC_{50}, μM)	[^{3}H]TCP (rat) (IC_{50}, μM)
DM	OCH_3	3 8	0.59	2.0
DX	OH	5	2.5	1.2
AHN 649	NH_2	2 5	>10	7.8
AHN 1036	OEt	6	0.42	>10
AHN 1037	O-i-Pr	4	0.88	>10

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NOVEL ANALOGS OF DEXTROMETHORPHAN: IN VIVO EVALUATION IN RAT SEIZURE MODELS

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Dextromethorphan (DM) has been shown to be an effective anticonvulsant in a number of experimental seizure models. DM is metabolized to dextrorphan (DX) which is also anticonvulsant and therefore could account for DM's seizure protective actions. Although the PCP-like properties of DX have been established, DM, while purported to have psychotomimetic-like subjective effects in humans, exhibits behavioral effects in animals which can be distinguished from DX or PCP. In the present study we have evaluated the anticonvulsant and neurologic side-effects of a series of novel 3-substituted analogs of DM which would not be expected to be metabolized to DM, or might do so only at a reduced rate.

Of the several active analogs synthesized at least three were determined to be more potent than DM against maximal electroshock (MES) convulsions in rats; namely the aniline (AHN649), the o-ethylether (AHN1036) and the o-isopropyl ether (AHN1037) derivatives. The respective anticonvulsant ED_{50}s (mg/kg) were 38 (DM), 21 (AHN649), 6 (AHN1036), 4 (DX) and 4 (AHN1037). Of these compounds only DM exhibited limited efficacy as an anticonvulsant. Interestingly, in a seizure threshold model (the rat flurothyl test) the three analogs were found to be ineffective while DX raised and DM lowered convulsive thresholds. This proconvulsant effect of DM probably accounts for it's limited anticonvulsant efficacy seen in other seizure models.

Assessment of neurologic impairment using rotorod performance in rats further distinguished these compounds. In preliminary experiments DM and the analogs were devoid of behavioral effects in doses up to 100 mg/kg. In contrast, for DX the ED_{50} was 23 mg/kg yielding a protective index (PI, ratio of the $rotoED_{50}/mesED_{50}$) of 4.6. The calculated PIs for the other compounds were: >2.6 (DM), >4 (AHN649), >17.8 (AHN1036) and >25.6 (AHN1037).

These results further distinguish DM from DX as anticonvulsants and support other *in vivo* and binding studies suggesting separate receptor mechanisms of action. Critically, both the o-ethylether and o-isopropyl analogs of DM display exceptional selectivity as anticonvulsants with PIs far in excess of those established for standard anticonvulsants (i.e. no greater than 4) in similar testing paradigms. Therefore, their potential for psychotomimetic activity would appear negligible.

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NALBUPHINE N-OXIDE PRODRUG: ANALGESIA AND NALBUPHINE SERUM LEVELS FOLLOWING ADMINISTRATION OF DUP 769 IN RATS AND DOGS

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The nalbuphine prodrug program was designed to develop metabolically stabilized forms of nalbuphine with enhanced oral potency. Oral nalbuphinc has approximately 17% absolute bioavailability in man (M.-W. Lo et al., J. Clin. Pharmacol. 27: 866, 1987). Nalbuphine N-oxide (DuP 769) was prepared under the hypothesis that changing the hydration and electronic environment around the basic nitrogen might enhance nalbuphinc absorption and prevent nalbuphinc recognition by drug metabolizing enzymes. Literature reports have shown that many N-oxides can be reduced back to parent amines in vivo (M. H. Bickel, Pharmacol. Rev. 21: 325, 1969). Pharmacokinetic and tooth-pulp analgesia studies in the dog indicate that nalbuphinc N-oxide produces a 2.9x increase in nalbuphine bioavailability and a 4.9x increase in analgesic potency. Studies in rats show a not-significant 1.7x increase in apparent bioavailability and no increase in analgesic potency compared to nalbuphinc. The data suggest that DuP 769 protects against phenolic conjugation which is the major (100%) metabolic pathway in the dog but a minor pathway in rats (9%). DuP 769 did not appear to protect against ring oxidation or N-dealkylation which are primary metabolic pathways in the rat (25% and 21%, respectively). Studies are planned to evaluate nalbuphine N-oxide effects in man.

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NOR-BINALTORPHIMINE PRETREATMENT SPECIFICALLY INHIBITS Δ^9-THC INDUCED ANTINOCICEPTION IN MICE WITHOUT ALTERING THE BEHAVIORAL EFFECTS

P. B. Smith, B. R. Martin, and S. P. Welch

The antinociceptive and behavioral effects of Δ^9-THC following i.t. administration have been well documented. Recent data indicates that nor-binaltorphimine (nor-BM), a highly selective kappa opioid receptor antagonist, modulates the antinociception produced by cannabinoids. In order to determine if nor-BM could alter other Δ^9-THC-induced effects, both drugs were administered it in mice. Groups of animals were pretreated with either 2 µg *nor*-BNI, 10 µg *nor*-BNI, or vehicle. Animals in each of these groups were then given either 50 µg Δ^9-THC or vehicle by a second intrathecal injection. The vehicle/Δ^9-THC group demonstrated profound antinociception (85% MPE) while those pretreated with *nor*-BNI were significantly less in both the 2 µg nor-BM/Δ^9-THC (17% MPE) and 10 µg *nor* BNI/Δ^9-THC (30% MPE) groups. Several other cannabinoid-induced effects including hypothermia, decreases in spontaneous activity, and catelepsy were not significantly blocked by either dose of nor-BNI. These studies demonstrate that pretreatment with nor-BNI selectively modulates Δ^9-THC-induced antinociception while not significantly affecting other commonly observed cannabinoid actions including hypothermia, hypoactivity, and catelepsy. Chronic administration studies were performed to determine if cross tolerance could be established between Δ^9-THC and U-50,488, a highly specific kappa opioid receptor agonist. The chronic Δ^9-THC treated groups were significantly tolerant to i.t. Δ^9-THC-induced antinociception and also demonstrated an attenuation of the tail-flick response following i.t. U-50,488 when compared to those treated chronically with vehicle. Animals treated chronically with U-50,488 were significantly tolerant to i.t. U-50,488-induced antinociception and also demonstrated an attenuation of the tail-flick response following it. Δ^9-THC when compared to vehicle. This study indicates a possible interaction of i.t. administered cannabinoid compounds with the kappa opiate receptor.

Supported by grants DA-03672, DA-05274, and DE-00151.

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IN VIVO pA_2 AS A TOOL FOR CHARACTERIZING OPIOID ANTINOCICEPTIVE AGENTS AND ANTAGONISTS

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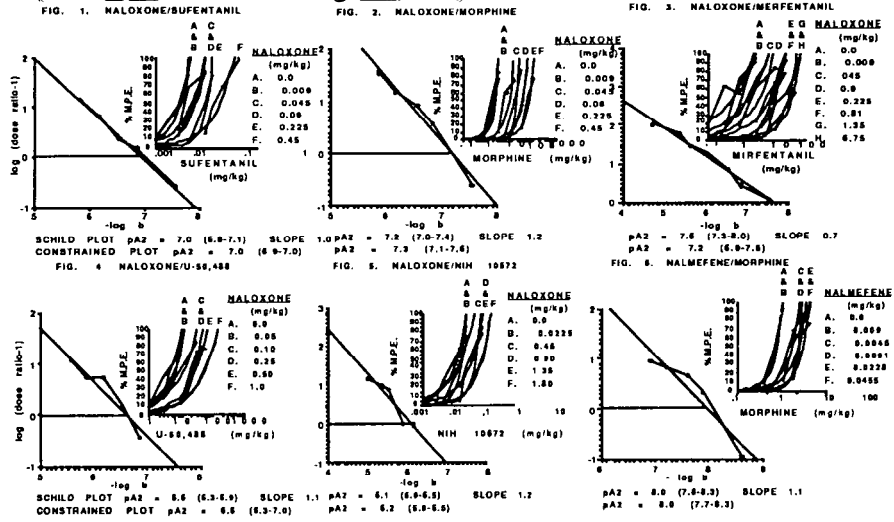
pA_2s are useful as tools for classifying drugs and receptors (e.g. Schild, Br. J. Pharmacol. 2, 1947 and Tallarida et al. Life Sci. 25, 1979). To better characterize opioids with antinociceptive properties and selective opioid antagonists, we utilized the mouse tail-flick test (Aceto et al., NIDA Res. Monog. 105, 1990). The data are illustrated below.



TREATMENT	SCHILD PLOT		CONSTRAINED PLOT
Antagonist/Agonist	pA_2 (95 % C.L.)	Slope	pA_2 (95 % CL)
Naloxone/Sufentanil	7.0 (6.9-7.1)	1.0	7.0 (6.9-7.0)
Naloxone/Morphine	7.2 (7.0-7.4)	1.2	7.3 (7.1-7.6)
Naloxone/Mirfentanil	7.6 (7.3-8.0)	0.7	7.2 (6.9-7.5)
Naloxone/U-50,488*	6.6 (6.3-6.9)	1.1	6.6 (6.3-7.0)
Naloxone/NIH 10672**	6.1 (5.6-6.6)	1.2	6.2 (5.9-6.5)
Nalmefene/Morphine	8.0 (7.6-8.3)	1.1	8.0 (7.7-8.3)

*(±)-trans-N-Methyl-N-(2-pyrryolidinylcyclohexyl)-2-(3,4-dichlorophenyl)acetamide HCl
**[(-)-5R-(5a,7a,b)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-4-benzofuranacetamide HCl.

The predominantly mu opioid agonists, morphine and sufentanil, share similar naloxone pA_2s. On the other hand, the naloxone pA_2s calculated using the relatively selective kappa agonists, U-50,488 and NIH 10672, contrast clearly with those calculated for the mu agonists. The naloxone/mirfentanil pA_2 does not fall into either category when calculated using the Schild plot. However, a constrained plot gives a pA_2 not unlike that of the mu agonists. Other inherent pharmacological actions, such as opioid antagonist properties and/or possible motor deficits, may account for this difference. Nalmefene's pA_2 suggests much greater affinity for the mu receptor compared with naloxone. (Supported by NIDA Contract #271-90-7200).

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THREE DIAGNOSTIC SYSTEMS FOR SUBSTANCE USE DISORDERS DSM-III-R, ICD-10 AND DSM-IV

K. J. Bryant, B. R. Rounsaville and T. Babor

Diagnoses derived from the proposed research criteria for DSM-IV and ICD-10 for Substance Use Disorders were contrasted with diagnoses derived from DSM-III-R. The sample under analysis was composed of substance users, psychiatric patients, and a general community sample (N=521). Four sets of analyses were carried out to compare 1) rates of diagnostic overlap for DSM-IV when compared with DSM-III-R and ICD-10, 2) impact of changes in diagnostic rules for abuse and dependence with the requirement of withdrawal within DSM-IV, 3) effect of varying the number of criteria requited and 4) identification of criteria with poor internal consistency within each diagnostic system.

A high degree of overlap for diagnoses of dependence was found for all systems (DSM-III-R, DSM-IV, and ICD-10). However, there was substantial disagreement over the diagnosis of abuse. Requiring the criterion of withdrawal within DSM-IV lead to differential agreement across drugs with the poorest agreement for drugs without clear cut withdrawal syndromes (Marijuana and Cocaine). Finally, several criteria within each system were found to have low internal consistency with other criteria. It is suggested that these criteria either be modified or dropped (e.g. narrowing of drug use repertoire within ICD-10).

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RELIABILITY OF DUAL DIAGNOSIS: SUBSTANCE ABUSE AND PSYCHIATRIC DISORDERS

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The Structured Clinical Interview for DSM-III-R (SCID) was used to examine the effects of the co-occurrence of psychiatric and substance dependence disorders on diagnostic reliability. The test-retest reliability over a one-week period was studied in groups of: 1) individuals with current substance abuse diagnoses (N=97), 2) individuals with past (but not current) drug histories (N=146), and 3) individuals without substance abuse diagnoses (n=356; primarily psychiatric patients). A measurement of reliability (Kappa coefficients) is estimated for four general psychiatric categories (Psychotic, Mood, Anxiety, Eating disorders) along with specific most frequent diagnoses in each category (Schizophrenia, Major Depression, Panic Disorders, Bulimia Nervosa, respectively). Past and Non-drug using groups were similar in their generally reliable reporting of current and past psychiatric disorders. Although current substance users received reliable diagnoses, current Mood. and Psychotic disorders were less reliably diagnosed in this group than in past or non-substance use groups. Current and Lifetime Mood Disorders were more likely to be diagnosed with the initial interview than at the subsequent interview.

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VALIDITY OF THE "DUAL DIAGNOSIS" IN DETERMINING ELIGIBILITY FOR MICA TREATMENT PROGRAM II

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The most prevalent approach for defining the Mentally Ill Chemical Abusing or MICA population uses the criterion of dual diagnosis. This preliminary investigation compares the DSM-III-R diagnosis assigned by community service providers with the diagnosis determined as the result of administering the Structured Clinical Interview for DSM-III-R (SCID). As part of a NIDA funded project to evaluate residential treatment options for the MICA population, 40 male subjects accepted into treatment have been evaluated using the SCID-P and SCID-II in order to obtain a "valid and reliable" diagnosis. Subjects are only evaluated after they have been in a controlled environment for at least two months in order to minimize the toxic effects of psychoactive substances. Reported symptoms that appear to be induced by substances are distinguished from those that are not in an attempt to separate out those subjects who may not have a major psychiatric disorder. This was done using a standard set of decision rules. SCID coding was modified to indicate whether a client ever had psychotic, mood or anxiety related symptoms and whether these symptoms were induced by substance use or were due to a mental disorder independent of substance abuse.

Comparisons were made between the diagnostic approach typical of community service providers and the SCID. This investigation also explored the issue of whether a MICA client's history of symptom presentation is useful in distinguishing between those who's psychiatric problems are substance induced and those who have "true" mental disorders. Results show that the SCID diagnosis assigns less psychotic disorders, reports more substance abuse and personality disorders, and is better at differentiating between "true" psychiatric symptoms and those that are substance induced when compared to the community diagnosis. The differences found in the rate of reporting may be attributed to several factors. One is that the exhaustive nature of the SCID develops a more complete picture of a client's history of psychiatric symptoms than would otherwise be found. Another may be the practice of many community providers who have been trained to find the one diagnosis that accounts for all problems. Practitioners may also neglect personality disorders and substance abuse disorders given the work involved in establishing presence of each distinct disorder. A final factor may be a lack of awareness of the impact of personality disorders and substance abuse among the persistently mentally ill.

Supported by a research demonstration award from NIDA DA06968-02

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THE IMPACT OF DRUG ABUSE ON PSYCHOPATHOLOGY AND MOVEMENT DISORDERS IN CHRONIC PSYCHOTIC OUTPATIENTS

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This study of 398 chronic psychotic outpatients on neuroleptics compared the rate of movement disorder symptoms (parkinsonism and dyskinesias) and psychiatric negative symptoms of schizophrenia by three illicit drug use categories (no-drug use, drug use, drug abuse / dependence). Using the SADS-L with lifetime RDC, 75% of the patients met criteria for schizophrenia or schizoaffective disorder and 14% for illicit drug abuse / dependence (primarily marijuana and stimulants). Another 9% had a history of illicit drug use but did not meet criteria for a disorder. The rates of other substance use disorders were 73% for nicotine and 24% for alcohol dependence.

Compared to non-drug users, drug abusers were significantly younger (31 versus 45 years), more frequently male (70% versus 41%), had higher neuroleptic dosages (average chlorpromazine equivalents of 586mg vs 410mg). and took neuroleptics for a shorter period (5.2 vs 8.8 years). Of note, drug users were very similar to drug abusers.

The severity of psychiatric "negative symptoms" using the SANS was significantly lower in drug abusers than non-drug users (19 vs 27). and age was not a significant variable. Drug abusers had lower scores in each of the 5 areas of negative symptoms, with significantly lower scores in affective flattening (6 of 8 items), alogia (3 of 5 items), avolition / apathy (1 of 3 items), anhedonia / asociality (4 of 5 items), and attention (1 of 2 items). Drug users were similar to drug abusers. Heavy nicotine dependence (>25 cigarettes/day) was associated with significantly lower severity of negative symptoms and higher rates of drug abuse (25%). An alcohol use disorder was not associated with severity of negative symptoms.

Compared to nonusers, significantly more drug users / abusers reported previous dyskinesia and parkinsonism symptoms, including dystonia (30% vs 13%, $p<0.0001$), tremor (38% vs 18%, $p<0.008$), drooling (25% vs 12%. $p<0.001$), stiffness (48% vs 11%, $p<0.0001$), and akathesia (48% vs 18%, $p<0.0001$). However, this finding contrasted with our Webster's parkinsonism exam in which drug users / abusers had significantly lower rates of current parkinsonism symptoms of bradykinesia (4% vs 22%, $p<0.001$), rigidity (12% vs 31%, $p<0.001$), reduced upper arm swing (2% vs 14%. $p<0.004$), and masked facies (3% vs 22%, $p<0.0001$). We did not find significant differences between the drug use categories in the severity of tardive dyskinesia using the AIMS rating scale. This result was expected since all patients admitted into our study could not have tardive dyskinesia (an AIMS score greater than 3). Because of age differences, we examined those under 50 years old, and all associations remained significant.

These results suggest that psychiatric patients with a history of a drug use disorder have significant differences in severity of psychopathology and movement disorder symptoms compared to those without drug abuse. Prospective studies in this area should occur.

Supported by NIMH MH39665, NIDA P50-DA04060 and NIDA R18-DA06190.

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MULTI-SYSTEM SCREENING IN SELECTING NORMAL Ss FOR DRUG ABUSE RESEARCH: HOW NORMAL IS NORMAL?

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Although of critical importance, the throughness with which Ss are assessed for exclusion criteria varies widely. Studies using self-report assessments may not recognize Ss with covert exclusion criteria and may be compromised. We compared three screening procedures for rates of exclusion criteria detection. Exclusion criteria, not counting age, included (1) present or past medical illness or injury with possible CNS sequelae, (2) open or closed head injury regardless of when it occurred, (3) current and/or past DSM-III R Axis I psychiatric diagnosis, (4) any past psychiatric treatment, (5) all prescription medication, (6) past use of neuroleptics, antidepressants, lithium carbonate, or anticonvulsants, (7) seizure patterns or focal slowing on EEG, (8) mental retardation, and (9) abuse of non-THC drugs (tobacco and social alcohol excepted) or THC use in controls.

STAGE 1 SCREENING (self-report data) consisted of telephone interviews during which Ss were asked about all exclusion criteria. Phone screening identified exclusion criteria in 218 Ss (53.6% of study applicants) or 71.5% of the 305 Ss found to have exclusion characteristics. Nonetheless, stage 1 screening failed to identify 87 Ss with exclusion characteristics. STAGE 2 SCREENING (also self-report) consisted of an in-depth in person interview focused on all exclusion criteria and a complete longitudional drug use history. In stage 2 an additional 49 Ss were identified with exclusion criteria (previously unrecognized) involving drug use variables and psychiatric or medical exclusions. Ss remaining underwent STAGE 3 DIRECT EXAMINATION SCREENING consisting of a medical/psychiatric examination, EEG, 8 weeks of twice/week urine drug screens and neuropsychological testing. Of Ss passing the first two screening stages, 34.9% (an additional 38 Ss) had verifiable exclusion criteria on direct examination screening. Of all three screening stages, stage 3 direct examination screening was necessary to identify 88.2% of all psychiatric exclusions, 33.3% of all non-THC abuse drug exclusions and 66.7% of all medical or CNS disorder exclusions. Reliance on self-report assessments would have compromised our study by including many Ss with exclusion characteristics. It is suggested that exclusion criteria similar to ours may be incompletely detected in studies where subject assessment relies exclusively on self-report data.

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SPANISH VERSION OF THE ARCI (49, ITEM SHORT FORM): STUDY UNDER SIMULATED CONDITIONS IN OPIOID ADDICTS

J. Cami, X. Lamas and M. Farre

The Addiction Research Center Inventory (ARCI) has demonstrated to be an useful tool for evaluating subjective effects induced by psychotropic drugs. This instrument is commonly used in drug abuse liability studies conducted in drug abusers population.

The objective of this study was to assess if a Spanish translation of the 49-item form of the Addiction Research Center Inventory is sensitive to and specific for the simulated effects of different classes of drugs of abuse in opioid addicts, as a previous step to its use in drug studies in Spanish-speaking population.

METHODS: Forty-five adult opioid addict individuals, with with previous experience with the use of stimulants, alcohol and hallucinogens, participated while residing in a general hospital. They were not taking drugs with CNS action other than benzodiazepines and opioids for detoxification or maintenance. Subjects completed a 49-item form of the ARCI (containing 5 subscales: MBG, PCAG, LSD, BG and A scale) on four occasions describing the feeling they usually experienced under the effects of four classes of drugs (conditions) in their normal environment. Conditions were: mu-agonist opioids (heroin), alcohol, stimulants (cocaine) and hallucinogens. The order of administration of the questionnaires was randomized. A discriminant analysis of the data was carried out to identify the subscales that were relevant for distinguishing among the four studied conditions and to predict group membership for the answered questionnaires.

RESULTS: A characteristic pattern was obtained for each condition. Simulation of heroin effects produced increases on MBG, alcohol on PCAG and LSD, cocaine on MBG and BG, and hallucinogens increased scores on MBG, BG and LSD. In the discriminant analysis, four subscales (PCAG, LSD, BG, MBG) correctly discriminated between drug conditions. A total of 60.56% of the answered questionnaires were correctly classilied by the discriminant functions.

CONCLUSIONS: These findings indicate that the Spanish version of the 49-item ARCI can be a useful tool in evaluating subjective effects produced by drugs in Spanish-speaking populations.

Supported by a CTRAN grant. Gloria Perez assisted in statistical analysis.

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THE PREDICTIVE VALIDITY OF THE PSYCHOPATHY CHECKLIST-REVISED IN TREATED OPIATE ADDICTS

M. J. RUTHERFORD, J. S. CACCIOLA AND A. I. ALTERMAN

Antisocial Personality Disorder (APD) appears to be a heterogeneous diagnosis and more specificity is warranted to improve its predictive validity. The DSM-III and DSM-III-R APD is based largely on the expression of antisocial behaviors in childhood and adulthood rather than on personality characteristics. It maybe that APD addicts who respond positively to treatment manifest antisocial behaviors but do not have a core psychopathic personality. Conversely, those APD addicts with a psychopathic personality may respond poorly to treatment.

Psychopathy as measured by the Psychopathy Checklist-Revised (PCL-R), developed by Hare (1990). is an alternative conceptualization of APD. The PCL-R may prove to be a superior predictor of treatment outcome as it assesses personality and behavioral traits. The predictive validity of the PCL-R and APD diagnosis over six months are compared on 130 male methadone maintained opiate addicts.

No significant differences were found in the proportion of change in substance use, illegal involvement, interpersonal problems, and employment status between APD and non-APD subjects or between high and low scoring PCL-R subjects over six months. The PCL-R, a more comprehensive measure of personality and behavior did, however, identify a more severe group of SAs at baseline and follow up compared to an APD diagnosis. Subjects scoring above 25 on the PCL-R not only reported more problems with employment and drug/alcohol use, but were also more likely than subjects with low PCL-R scores to engage in illegal activity, have left treatment within six months and have urines positive for cocaine, benzodiazepines, or barbiturates. No such differences were found between APD and non-APD subjects.

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THE NEUROBEHAVIORAL COGNITIVE STATUS EXAMINATION FOR BRIEF SCREENING OF NEUROCOGNITIVE DEFICITS IN METHADONE TREATMENT

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We report the preliminary analysis of 19 male subjects who have completed a battery of brief neuropsychological screening tests to assess for neurocognitive deficits. Special attention is paid to the utility of the Neurobehavioral Cognitive Status Examination (NCSE), a brief, easily administered, neurocognitive test that detects and quantifies gross cognitive impairment. Testing was done during the first week of methadone treatment (T1) and repeated after two months of dosing (T2). Subjects were either in methadone maintenance or in six-month detoxification; they tended to be black (42%), white (42%), or Hispanic (16%); their average age was 45 years (range 34-66); they had 12.9 years of education (range 9-16); they were unemployed (63%); they used alcohol in the month prior to testing (58% at T1 and 47% at T2); they tended to be on 45 mg of methadone at T1 (range 35-60) and 57 mg at T2 (range 30-90). They were administered the NCSE, the Trail Making Tests A & B, the Shipley Institute of Living Scale (SILS), the Short Booklet Category Test (SBCT), and several other tests not addressed here.

At T1, 42% of subjects showed at least mild impairment on one or more NCSE scales; the scales most likely to show impairment reflect attention, comprehension, memory, abstract reasoning, and judgment. The failure rate on Trails A was 37% and on Trails B was 58% at T1. The SILS yielded at T1 an estimated WAIS-R IQ score of 95.9, an average Conceptual Quotient (CQ) of 80.4, an average Abstraction Quotient (AQ) of 94.2. Scores on the SBCT, which reflect the number of errors made on the test, yielded a percentile ranking of 61.3. The finding of impairment on the NCSE was associated with poor performance on Trails A ($p < .0511$) and significantly associated with poor performance on Trails B ($p < .0004$) at T1, but not T2.

At T2, on tests of association, a larger number of subjects passed Trails B than at T1 ($p<.066$); the SILLS CQ showed a significant improvement ($p=0.0458$), as did the SILS AQ ($p=0.0101$); the SBCT showed significant reduction in the percentile ranking of errors ($p=.0496$).

These preliminary data suggest that there may be neurocognitive impairments in patients who present for methadone treatment. These data also suggest persistence of the impairment in a number of subjects at the two-month time point. If subsequent data support these preliminary findings, then assessing neurocognitive functioning may be useful in the early phases of methadone treatment. Thus, a test such as the NCSE could be of clinical importance, as it does not require a trained psychologist to administer, but can be administered by a trained substance abuse counselor. Previous experience by the authors on administering the NCSE in an inpatient polysubstance abuse treatment setting supports this conclusion.

ACKNOWLEDGEMENTS: This research was primarily supported by a VA HSR&D Far West Grant, and, in part, by NIDA grant 1R1SDA06097.

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SCREENING FOR MOOD DISORDERS AMONG ADDICTS USING THE GENERAL BEHAVIOR INVENTORY

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Individuals suffering from psychoactive substance dependence also exhibit a high prevalence of mood disorders. Oftentimes, the effects of substance use confound the clinical diagnosis of mood disorders in this population. An efficient method of screening for mood disorders among drug dependent patients would help direct focused attention to those most likely to have this additional problem. One potential instrument, the 73 item self-report General Behavior Inventory (GBI), exists though it has not received systematic a application in drug dependent subjects. This study used the GBI to screen for mood disorders in a series of addicted patients admitted to outpatient treatment (n = 190). All subjects provided urine specimens for toxicology analysis at least once per week. GBI cutting scores previously determined on non-addict samples defined unipolar, bipolar, and no mood disorder subjects in the current sample. Overall, 21 (11.1%) subjects demonstrated GBI unipolar depression, 26 (13.7%) scored as GBI bipolar, and 143 (74.9%) had no GBI mood diagnosis. The 3 mood groups did not differ in demographic variables or treatment retention. Among primary opiate users (n = 100) 11 (11%) scored as unipolar and 19 (19%) as bipolar cormpared to 7 (12.5%) and 3 (5.4%) among primary cocaine users (n =56) and 3 (8.8%) and 4 (11.8%) among primary users of other substances (n=34). Concordance rates between GBI and clinical mood diagnoses performed by a psychiatrist blind to GBI results using DSM-III-R criteria were 77.4% for subjects with no GBI mood diagnosis, 70% for those with GBI unipolar diagnosis, but only 20% for those with GBI bipolar diagnosis. Addiction Severity Index psychiatric severity ratings of GBI bipolars (mean=6.2, SD=2.1) but not of unipolars (5.5, 2.4) were higher than those of no diagnosis subjects (4.5, 2.1; F [2,157] = 7.27, p = .001). On the Minnesota Multiphasic Personality Inventory-168 and the Millon Clinical Multiaxial Inventory GBI unipolars and bipolars compared to the GBI no diagnosis group endorse significantly more psychophatology in general and experience more emotional distress, somatic complaints, dependency, social withdrawal, and interpersonal isolation. The no diagnosis group displays higher ego strength, social conformity, and defensiveness. The GBI bipolars demonstrate more hypomania and suspiciousness than do the other 2 groups. GBI bipolars reported more lifetime months of cocaine use (mean = 125.8, SD =97.4, median= 125.0) than did subjects with no GBI diagnosis (70.2, 108.7, 36.0) or unipolars (76.3, 75.1, 39.0:, Kruskal-Wallis $\chi^2 = 10.0$, $p < .007$). The 3 groups did not differ in months of lifetime use of other substances. Among subjects remaining in treatment more than 6 months (n = 116), GBI bipolars (n = 17) gave more cocaine positive urine specimens per month (mean = 0.62, median = 0.25) than did GBI unipolars (n = 13, 0.24, 0.12) or no GBI diagnosis subjects (n = 142, 0.30, 0.0; Kruskal-Wallis $\chi^2 = 9.89$, $p < .008$). These results suggest that opiate addicts have a higher prevalence of bipolar disorders than previously believed, that bipolar disorders in addicts may escape clinical detection, and that cocaine use poses a greater problem for GBI bipolars than for those without GBI mood disorders.

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MOOD STATES AND PSYCHOPATHOLOGY AMONG COCAINE USING METHADONE PATIENTS

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Introduction: This study presents baseline data on cocaine-using methadone patients who were randomly assigned either to intensive out-patient cocaine treatment or a low-intensity treatment control group. The experimental treatment is based on Rawson's neurobehavioral relapse prevention model for cocaine use.

Method: Subjects were administered structured questionnaires as well as the Structured Clinical Interview Schedule for DSM-III-R (Axis I and the Anti-Social Personality Disorder). Subjects with psychotic disorders were not admitted to the study; all subjects had to meet the DSM-III-R criteria for cocaine dependence.

Results: Our current sample represents the first 65 patients who entered the study and completed the baseline instruments: men (49%) women (51%); Hispanic (66%), Black (26%), White (8%); mean age = 36 years; mean number of days of cocaine use past 30 = 21 days. The subjects showed elevations in psychopathology as measured by the Brief Symptom Inventory (BSI). Significant associations ($p < .05$) were found, between two craving measures (mean craving intensity in the past week and cocaine use in response to craving) and negative affect scales from the POMS and the Global Severity Index on the BSI as well as 4 BSI symptom scales: Somatization, Obsessive-compulsive, Anxiety and Phobic anxiety. There were no significant correlations between any of the POMS scales or the BSI symptom scales with frequency of cocaine cravings or with frequency of cocaine use (number of days used in the past 30). Cocaine craving frequency and cocaine use in response to craving were associated ($p < .05$) with cocaine use but craving intensity was not related to cocaine use. Sixty-five percent had at least one additional AXIS I diagnosis (other than cocaine dependence); 28% had an additional substance abuse disorder, 51% had a non-substance abuse AXIS I disorder.

Conclusions: The lack of a relationship between cocaine craving intensity and cocaine use frequency is consistent with the emerging scientific evidence that there is not a simple correspondence between craving and cocaine use. The data suggest that negative affect regulates the intensity of cocaine craving but that craving alone does not determine frequency of cocaine use.

ACKNOWLEDGMENTS: Supported by NIDA Grant No. R18 DA06959

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GENDER AND ETHNIC DIFFERENCES IN PSYCHOPATHOLOGY IN A METHADONE POPULATION

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As part of the research program of the NIDA-funded Comprehensive Vocational Enhancement Program (CVEP), data on different aspects of psychopathology were collected from 390 methadone treatment clients.

Measures of psychopathology are: DSM-III Axis I and Axis II diagnoses; The Psychopathology Checklist: Clinical Version; Psychiatric Severity Score (ASI), Psychic Status Score, and self-report of psychological functioning along a number of dimensions. Our objectives were: to determine levels of psychopathology; to test the hypothesis that drug abusers resemble normal populations with respect to gender differences in psychopathology; and to test the hypothesis that there are no ethnic differences in psychopathology among drug abusers.

Depressive disorders are the most frequently diagnosed non-drug Axis I disorders. The level of depressive disorders diagnosed -- 14% for major depression and dysthymitidepressive disorder NOS -- is lower than that reported in many other studies. Antisocial personality disorder is the most frequently reported Axis II disorder, with 40% of the sample so diagnosed. The hypothesis regarding gender differences is supported by the data: Women have higher rates of depression as well as higher rates of self-reported distress, and men have higher rates of antisocial personality as well as higher scores on the Psychopathy Checklist: Clinical Version. The null hypothesis regarding ethnic differences is not supported. Blacks have higher rates of DSM-III antisocial personality, although there are no ethnic differences in scores on The Psychopathy Checklist: Clinical Version. There are no ethnic differences in Axis I diagnoses of depression, although whites have higher rates of self-reported depressive mood, serious thoughts of suicide, and serious anxious mood or tension.

The ethnic discrepancy between DSM-III diagnoses and other measures requires further investigation, especially since congruence between DSM-III and other measures is found for gender differences.

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THE PSYCHOPATHY CHECKLIST IN METHADONE MAINTENANCE PATIENTS WITH ANTISOCIAL PERSONALITY DISORDER

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The Psychopathy Checklist (PCL; Ham, 1980) was developed to provide a reliable measure of Cleckley's (1941) definition of psychopathic/antisocial personality. In contrast to the strong behavioral emphasis used by the DSM-III in diagnosing antisocial personality disorder (APD), the PCL offers a more comprehensive assessment of the personality traits that appear to be associated with the disorder. While the PCL has been shown to have good reliability in studies of prison inmates, less is known about the instrument's psychometric properties in other populations.

The present study examines the validity of the PCL in 84 opioid abusers admitted to outpatient treatment incorporating methadone hydrochloride as one component of care. The population had a mean age of 34.7 years (s.d. = 4.9), 54% were white, and 46% were unemployed. This population provides a good opportunity to examine the validity of the PCL since many opioid abusers are diagnosed with APD. Specifically, the validity of the PCL was examined in two ways: 1) concurrent validity was determined by comparing mean PCL total scores, and scores for Factor 1 (i.e.. psychopathic personality traits) and Factor 2 (i.e., antisocial lifestyle) for drug abusers categorized by the DSM-III-R with antisocial personality disorder versus drug abusers with no personality diagnosis and; 2) discriminant validity was determined by comparing mean PCL total scores, and scores for Factor 1 and Factor 2 for drug abusers categorized with antisocial personality versus drug abusers with other personality diagnoses. Finally, the distribution of PCL scores among outpatient opioid drug abusers was examined to provide a comparison with the cutoff score established in Hare's population of prison inmates.

Psychiatric diagnoses were ascertained using the Structured Clinical Interview for DSM-III-R. Study measures, including the SCID and the PCL-R were administered by master's level clinical research interviews who received intensive reliability training. PCL scores for subjects who received a diagnosis of APD (APD; N=28) were compared to those who had no Axis II diagnosis (non Axis II; N=45) and to those who met criteria for one or more non-APD Axis II diagnosis (other PD; N=11). Group differences were assessed using a one factor ANOVA with Tukey's poshoc tests. Chi-square tests with Yates Continuity Corrections and ANOVA's were used to examine demographic variables.

Striking differences in the means of the API) and non-Axis II groups were found. These differences were apparent for the total score (18.1 vs. 7.7, respectively, $p<.001$), for both of the factor scores and for twelve of the twenty PCL item scores. There were also significant differences between the APD and Other PD groups on the total score (18.1 vs. 8.4, $p<.001$), the two factor scores, and two of the PCL item scores, demonstrating the discriminant validity of the PCL.

Hare (1991) established a PCL cutoff score of 30+ to classify prison inmates as psychopathic. Using this criterion, only 14% of the APD group in the present study would be classified as psychopathic. This finding suggests that a score of 30+ may result in a high rate of false negatives among outpatient drug abusers. Alternatively, the distribution of PCL scores obtained by the APD drug abusers suggest heterogeneity on this measure of psychopathy. Further research is necessary to address this issue.

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THE IMPORTANCE OF ADULT AND CHILDHOOD CRITERIA FOR DIAGNOSIS OF ANTISOCIAL PERSONALITY DISORDER

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This study examines whether substance abuse patients satisfying adult, but not childhood antisocial personality disorder (APD) criteria, are more similar to patients with an APD diagnosis, or to patients with fewer than the required number of adult APD symptoms. Subjects were 269 male veterans, newly admitted to substance abuse treatment with an alcohol or cocaine problem. The Addiction Severity Index (ASI) was used to determine problem severity and the NIMH Diagnostic Interview Schedule (DIS) to obtain substance use and APD diagnoses. The sample was divided into three groups: APD group (n=92); adult APD group (n=87), subjects meeting the adult criterion only; and nonAPD group (n=90). The APD group reported the most current family/social and legal problems and the nonAPD group the least. Recent drug use, however, was most severe for the adult APD group. Regarding lifetime variables, problem severity was most serious for the APD group, particularly for drug use and legal status, followed by the adult APD group, and the nonAPD group with the least problems. There was a positive correlation between the number of childhood and adult APD behaviors so that the APD group had most adult APD symptoms. Analyses revealed that the number of adult APD behaviors appeared to account for the differences in problem severity among the three groups.

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SUBSTANCE ABUSE IN LIVER TRANSPLANT CANDIDATES

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Alcohol induced cirrhosis is the most common cause of end-stage liver disease. While alcohol is responsible for more than 50% of cases, less than 10% of liver transplants are performed on alcoholics. The controversy about whether alcoholics should compete equally for organs is related to the "self-induced" nature of their problems as well as to issues of survival and recidivism. This pilot study was designed to characterize the liver transplant population in terms of addictive and psychiatric problems and to identify factors likely related to outcome. Transplant candidates were administered the ASI, the SCID, the MMPI-2, and various cognitive measures (WAIS-R, Trails A & B, WMS). A urine drug screen was also collected at the time of transplant evaluation. Patients in this sample had a mean age of 45.3 years: were 54% female, 46% male; were 73% White, 18% Black, 9% Hispanic; had a mean full scale IQ of 102; 64% had at least some college education.

We present the following preliminary findings: There was agreement between clinical ratings of poor transplant candidates and ASI psychopathology scores. Cognitive impairment was most pronounced in patients diagnosed with lifetime alcohol abuse or dependence. Four of 10 patients had SCID ETOH diagnosis (3 dependent, 1 abuse). Only 1 of 11 patients had an alcohol related medical diagnosis. One of 10 patients had other substance abuse diagnoses (cocaine, marijuana). One of 10 patients had a non-substance abuse Axis I disorder (bipolar); this patient also had a substance abuse disorder. Four of 12 patients had positive urine toxicology screens, 2 benzodiazepines, 2 opiates, all acknowledged by the patient. MMPI profiles are consistent with those of other medically ill patients and different from typical addiction profiles. This is true even for those diagnosed with alcohol problems.

The trend toward convergent validity of PACT final rating and ASI psychopathology score should be further investigated. The discrepancy between medical and SCID alcohol related diagnoses is of interest. This may represent under-recognition of alcohol problems in this population. The relative lack of self-reported problems in ASI medical area may represent significant denial. Alcoholic patients look remarkably similar to other patients in terms of personality.

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ACQUISITION RATES OF TEN DRUG CLASSES: CONDUCT DISORDERED BOYS

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Prevention and early intervention should occur before or during initiation of drug use. We assessed with the Comprehensive Addiction Severity Index-Adolescents (Meyers et al. 1991--unpublished) initiation and first regular (minimum of once monthly) use of ten drug classes in a group of adolescent boys (ages 14-20) with Substance Use and Conduct Disorders. A comparison of this group with published general population samples show a much younger onset of drug use, and a different order of use. Drug acquisition curves which compare ages of initial (any) and regular use show three general patterns. The first group of drugs (tobacco, alcohol, marijuana) has high prevalence of "any" use (80-100%) and of regular use (79-95%), sigmoidal acquisition curves with the steepest acquisition rates at ages 8-14, and a lag of 1-2 years between initial and regular use. The second group (cocaine, hallucinogens, amphetamines) shows a lower prevalence of "any" use (64-74%) and of regular use (28-41%), as well as sigmoidal acquisition curves with the steepest acquisition rates at ages 12-16. The third group (inhalants, sedatives, opioids, recreational OTC's) has the lowest prevalence of "any" use (11-41%) and of regular use (5-21%); the curves are more linear, and the lag between initial use and regular use is much larger than in the other clusters. Early and high acquisition rates among these severely disordered youths suggest a need for very early prevention and intervention.
Supported by NIDA grant DA06941.

REFERENCES: Available upon request.

ACKNOWLEDGEMENTS: Supported by grant DA06941 from National Institute on Drug Abuse

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SUBSTANCE ABUSING FEMALE ADOLESCENT: IMPACT OF ATTENTION DEFICIT WITH HYPERACTIVITY AND CONDUCT DISORDER

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The purpose of this investigation was to elucidate the impact of attention deficit disorder with hyperactivity (ADDH) and conduct disorder (CD) on the pattern of substance abuse and psychosocial severity in female adolescents with abuse or dependence (SA). Three groups of SA female adolescents were recruited from clinical facilities. The SA group was composed of 9 subjects, the CD/SA group included 20 subjects, and the ADD/CD/SA group was comprised of 11 subjects. The three groups had an average age between 15.9 and 16.2 years, a ninth grade education, and similar ethnic composition and socioeconomic status. An expanded K-SADS-E was administered to the subjects to obtain DSM-III-R lifetime diagnosis of SA, CD, and ADDH and onset and duration of substance use and abuse. The Drug Use Screening Inventory (DUSI), a self report, was also administered to each subject to evaluate the severity of problems in ten areas: substance use, behavior adjustment, psychiatric disorder, physical health, peer relations, family functioning, social skill, school adjustment, work, leisure, and recreation. The age of onset of use and abuse of substances in the three group of SA females was similar, although the duration of alcohol use was higher in the CD/SA females than in the other two groups of SA females ($p<.05$). The three SA groups had a similar distribution of cannabis, hallucinogen, and nicotine abuse. However, the SA group had a lower lifetime experimentation of substances ($p<.001$) and prevalence of alcohol abuse than the CD/SA and ADDH/CD/SA groups. Also, the SA group, in contrast to the CD/SA and ADDH/CD/SA individuals, was associated with less severe problems in family functioning ($p<.001$), behavior adjustment ($p<.05$), work adjustment ($p<.05$). and recreation ($p<.05$) as well as less psychopathology ($p<.01$). This study emphasizes the effect of CD on lifetime experimentation of number of substances, prevalence of alcohol abuse, and psychiatric and psychosocial severity in substance abusing female adolescents.

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Menstrual Cycle and Drug Use Behavior in Opiate or Cocaine-Dependent Patients in Treatment for Drug Abuse

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The purpose of this study was to investigate whether drug use patterns are influenced by menstrual cycle phase and premenstrual dysphoria. Seven normally cycling women in treatment for substance abuse (4 with a primary diagnosis of opiate dependence and a secondary diagnosis of cocaine dependence, and 3 with primary cocaine dependence) were followed over several menstrual cycles. Drug use was monitored twice weekly. Qualitative and semi-quantitative (for cocaine and THC) urinanalyses were conducted. Physical and affective distress symptoms were measured weekly using the Daily Rating Scale version of the Premenstrual Assessment Form. Patients were questioned twice weekly about onset and end of menstruation. Menstrual cycle was divided into three phases: premenstrual (7 days prior to onset of bleeding), menstrual (first to last day of bleeding), and other. Group data were analyzed using subject-by-phase repeated measures ANOVA, individual data were analyzed for differences across phase using one-way ANOVA, and Pearson correlations were used to assess the associations between symptomatology and drug use. The subject-by-phase analysis revealed no effect of phase on the percent of drug-positive samples (for cocaine, opiates, THC, benzodiazepines and phenothiazine), quantitity of cocaine and THC. In 6 subjects there were no statistically significant differences in terms of quantity of cocaine and THC. (One subject had increase in quantity of cocaine at the menstrual phase [p=0.035]). No reliable differences between phases were found for any of the physical and affective symptoms. There were no statistically significant correlations between drug use and physical and affective symptoms. These results suggest that in this sample, drug use patterns are not related to menstrual cycle phase or premenstrual dysphoria. Studies supported in part by a treatment grant from NIDA, DA 06143.

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DRUG EXPECTANCIES: GENERAL OR SPECIFIC?

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Drug expectancies arc potent determinants of the subjective effects of a drug, and their strength relates to drug abuse and treatment outcome. To test the degree to which drug expectations are specific to a drug and/or generalizable across drug classes, a drug expectancy questionnaire (DEQ), composed of items from the Alcohol- and Cocaine Expectancy Questionnaires (Brown, et al., 1987, Jafee and Kilbey, 1989) and the NIMH-DIS for substance abuse disorders were given to 986 young adults. Four factor scales were identified: Factor 1 - positive expectations for alcohol, Factor 2 - positive expectations for cocaine, Factor 3 - positive expectations for both drugs, and Factor 4 - negative expectations for both drugs. Factor scores were compared for 4 groups: (1) lifetime cocaine dependence only (n=11), (2) lifetime alcohol dependence only (n=188), (3) both disorders (n=23), and (4) all others (n=764).

Significant differences were found among the groups on mean scores for the factors (F=6.84, df=3,982). Individual comparisons with group 4 indicated that expectancies were higher for Factor 1 (positive alcohol expectancies) for both groups 2 and 3 (Item mean = 3.63 and 3.79 respectively vs. 3.37 for group 4, where 1 = strongly disagree and 5 = strongly agree). Group 2 also had higher expectancy scores than Group 4 for Factor 2 (positive cocaine expectancy, Item mean = 3.41 vs. 3.11). This finding is consistent with a generalized drug expectancy hypothesis. Factor scores for persons meeting criteria for significant levels of use: (1) only cocaine, (2) only alcohol, (3) both, (4) neither; were compared also. Compared to group 4, groups 2 (n=407) and 3 (n=104) had significantly increased expectancy scores for both Factor 1 (positive alcohol expectancies, Item mean = 3.25 vs. 3.55 and 3.67, respectively) and 2 (positive cocaine expectancies, Item mean = 3.04 vs. 3.25 and 3.41, respectively). Thus, both measures indicate that increased expectancy many be characteristic of cognitions about drugs beyond the drug on which one is dependent and/or using. Further exploration of the relationship between expectations across drug classes by patterns of use may reveal how expectations shape and arc shaped by drug use history.

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ACKNOWLEDGEMENT: This research was funded in part by a grant from Kingswood Hospital and a NIMH Research Scientist Development Award K02 MH-00380 to Naomi Breslau which supported an epidemiological study whose respondents were interviewed to collect the cxpectancy data. Funding was also provided by a WSU Graduate School grant to M. Kilbey. In addition, the cooperation of Health Alliance Plan of Southcastern Michigan is gratefully acknowledged.

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DESCRIPTIVE ANALYSIS OF COCAINE USE IN METHADONE PATIENTS

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Although the increasing prevalence of cocaine use among opiate-dependent participants in methadone treatment has been documented, there is little information about the quantity-frequency aspects of use. This study examined in detail the cocaine use of methadone maintenance patients to determine amounts and patterns of use as well as use in combination with other drugs. Forty-five cocaine using methadone maintenance patients reported their drug use for each day over the past seven days. Patients were informed of their most recent urinalysis results to enhance the validity of responses. Number of cocaine-postive urine tests in the interview week (N=1, 2, or 3) was significantly correlated with both self-report gm/wk (r= .38, p < .001) and self-report days of cocaine use/wk (r= .50, p < .001). Seventy-eight percent of the target patients reported intravenous cocaine use during the interview week; 13% reported intranasal use, 9% used by smoking. On average, patients reported using .22 grams of cocaine per day on 3.4 days per week. Fifty-three percent of patients reported using less than .5 gm/wk of cocaine, while only seven percent reported using over 2 gm/wk. The sample could be divided into four independent groups regarding their pattern of polydrug use: 1) cocaine only (38%), 2) cocaine + alcohol (27%), 3) cocaine + heroin (24%), and 4) cocaine + alcohol and/or heroin (11%). Patients who used cocaine with other drugs on the same day (groups 2,3, & 4 above) reported more cocaine use (M=1.02 gm/week; SD=.84) than patients who used cocaine alone (group 1 above; M=.50 gm/wk; SD=.45; t (43)=.01). The mean time between heroin and cocaine use was 19 minutes (75% of patients used cocaine and heroin "speedball") and the mean time between alcohol and cocaine use was approximately two hours (53% of patients used cocaine and alcohol within one hour of each other). The results suggest that methadone maintenance patients typically engage in low dose IV cocaine use, not high dose binge use that is typical of non-opiate dependent persons presenting for cocaine treatment. The study further suggests that patients had clear preferences for drug use combinations within the time frame of the assessment, and that patients who use cocaine in combination with other drugs engage in more cocaine use than patients who use cocaine alone.

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CHARACTERISTICS OF COCAINE USE IN SUBJECTS IN METHADONE AND NON-PHARMACOLOGIC DRUG TREATMENT PROGRAMS

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As part of ongoing NIDA demonstration projects, seven sites in New England, New York City, Dayton, Ohio, St. Louis, Missouri and Los Angeles, California with a total of 2,949 subjects have begun a collaboration to examine patterns of cocaine use. The sites include both methadone and non-pharmacologic treatment programs. Enrollment in the programs varied among the different sites; data collection instruments also varied significantly. Because of these differences, data were not pooled for analysis; rather, comparison (and summation) were made of odds ratios for suspected predictors at each of the sites.

In total, 1,504 respondents acknowledged having used cocaine recently. Recent cocaine use was more common in the non-pharmacologic programs (62%-79%) compared to the methadone programs (41%-67%). Injection cocaine use ranged from 3% to 52% and was more common among persons with a history of having been arrested. At the non-pharmacologic programs, injection of cocaine seemed to be more common in the older cohorts compared with the younger. No such trend was apparent for the methadone programs.

Marijuana was generally the first illicit substance used (the "gateway drug") and mean age of first drug use ranged from 14.7 to 16.7 years at the seven sites. Age of first cocaine use ranged from 20.3 to 25.3 years. Examining age of onset of any drug use and age of onset of cocaine use among progressively older age cohorts indicated a fairly stable age of onset of drug use overall but a latter age of onset of cocaine use among older age groups. This is consistent with an "epidemic" in cocaine use with the main exposure five to ten years ago.

Among the recent cocaine users, African-Americans had lower rates of polydrug use; men had higher rates of marijuana use; and African-American women had lower rates of marijuana use and polydrug use. Race and gender were not predictive of recency of cocaine use (among those who had ever used cocaine), heavy/problem alcohol use, or cocaine injection. Also, no significant association was found between education (whether or not a high school graduate) and recency of cocaine use, recent polydrug use, recent cocaine injection or recent heavy/problem alcohol use. In general, these preliminary findings are consistent with clinical practice. They indicate that cocaine continues to be a predominant drug of abuse at treatment programs throughout the USA. In addition to confirming several expected associations, the lower rates of polydrug use among African-Americans, and especially among African-American women, was noteworthy. This will be explored in follow-up.

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DEMOGRAPHIC CHARACTERISTICS, DRUG USE, AND HIV RISK BEHAVIORS IN DRUG USERS AND THEIR PARTNERS

S. K. KEATING; J. E. WORKS; W. M. COMPTON, III; D. E. MAGER AND L. B. COTTLER

For analysis of a NIDA-funded study of HIV and drug use among substance users and their partners, 91 subjects (index) were matched to their partners. Indexes and partners were compared with respect to demographic and relationship characteristics, drug use and HIV risk behaviors.

The mean age was 31 for index subjects and 32 for partners. Sixty-seven percent index and 64% partners were black, 21% index and 24% partners were white; and 10% index and 4% partners were other racial or ethnic groups. Seventy-five percent index and 27% partners were male. Fifty-three percent index and 48% partners had never been married. Of those never married, 56% had lived with someone as though married. Thirty-eight percent index and 59% partners were employed at the time of the interview. Mean years of education was 11.5 years for indexes and 12 for partners.

The mean duration of the index/partner relationship was 7 years, and mean difference in ages of each matched pair was 5 years. Fourteen percent were interracial pairs; 2% (2) were same sex pairs, both male/male. In 58% of the pairs, the index lived with the partner.

In general, rates of lifetime drug use were higher among index subjects, but significantly higher statistically for sedatives, opioids, heroin and hallucinogens. Index/partner concordance was highest for lifetime use of amphetamines (26%) and hallucinogens (52%); concordance was <14% for the other drug categories and 0% for PCP. The categories in which DSM-III-R psychoactive substance dependence diagnosis was most prevalent were marijuana (I 31%, P 13%), cocaine (I 57%, P 15%), heroin (I 34%, P 13%) and opioids (I 18%, P 2%).

HIV rates in both indexes and partners were low (1% in each group). Although knowledge of HIV risk was good as measured by a NIDA AIDS knowledge questionaire (81% correct) and perceived risk of HIV infection was high among IVDUs in the sample, HIV risk behaviors were common in both groups. Twenty-eight percent indexes and 19% partners had >1 sexual partner in the prior 6 months. Among those, 54% indexes and 53% partners never used condoms, and only 8% indexes and 12% partners always did. Forty percent indexes and 16% partners had ever injected; of these, 55% indexes and 47% partners had injected in the last 6 months. Of the recent injectors, 43% indexes and 40% partners had shared needles in the past months. In 13% of the pairs, both indexes and partners reported lifetime injection use. In 36% of the pairs, one member of the pair reported lifetime injection use and the other did not, a finding which suggests high potential for spread of HIV from IVDU to non-IVDU using partners. Although rates of high risk behaviors were higher in the index group, the rate of those behaviors among partners was also significant.

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COCAINE-RELATED PROBLEMS AS INFLUENCES IN PATTERNS OF COCAINE USE

K. MILLER, E. KHALSA AND D. ANGLIN

Data were collected from a sample of 294 male cocaine addicts admitted voluntarily to a drug treatment program at the Brentwood VA Medical Center. At admission, subjects were asked if they had experienced any of 32 possibly cocaine-related problems during their cocaine use career. The mean number of problems reported by subjects was 16. A factor analysis was performed on the 32 variables (problems) using the SAS procedure with a varimax rotation. Four problem group dimensions were identified: psychological/physical, social relations/work, financial, and extreme physical. Forty percent of the variance was explained by the four factor solution. The majority of patients reported past problems for psychological/physical and financial Fewer problems were reported in the social relations/work and extreme physical categories. These derived dimensions were not significantly correlated, and were not observed to occur in consistent combinations.

Most symptoms appeared for most subjects (36% to 66%) in the later stages of their cocaine career (averaging more than 11 years after first cocaine use). Preliminary analyses were conducted to study whether conditions such as alcohol use, marijuana use preceding cocaine use, antisocial behavior, and individual characteristics such as age and race were predictors of types of cocaine related problems, either of the factors or of other more specific problems. Younger subjects (<=20 years) reported more psychological/physical and social relations/work problems. White subjects reported having generally more psychological/physical problems, then African-American or Hispanic subjects. They also had higher levels of drug dealing, other arrests, and other physical violence. Subjects who drank in excess of 4 oz. of pure alcohol daily before first cocaine use were more likely to overdose on cocaine and to have more cocaine possession arrests than subjects who drank more moderately or did not drink at all.

Three groups of subjects were selected to represent the most common symptom patterns, including a group with few symptoms. Preliminary results a statistically significant difference between the two high-rate problem groups and the length of the cocaine career (longer for those with more problems) and grams of cocaine used (higher amounts). The authors are planning further analyses to determine if the different sets of cocaine-related problems are factors that might influence relapse and treatment outcome.

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PREDICTORS OF COCAINE RELAPSE FOLLOWING TREATMENT

R. N. EHRMAN; S. J. ROBBINS, A. R. CHILDRESS; M. A. CARTER AND C. P. O'BRIEN

In several treatment-outcome studies, we have assessed the physiological and subjective impact of cocaine-related cues on cocaine abusing subjects. These cues include audiotapes of "drug talk," videotapes of scenes of drug use, and drug paraphernalia which the patient is asked to handle in the usual way. Physiological measures included heart rate, skin resistance and skin temperature; subjective measures included self-reports of feelings of high, craving, and withdrawal. Assessments were performed at the beginning of treatment. Additional information on psychological problems, family/social problems, and drug-use history was collected through administration of the Addiction Severity Index (ASI). Effectiveness of different therapeutic interventions was assessed through weekly urine monitoring. The present analysis examines whether a combination of information from the ASI and from cue exposure sessions could be used to predict treatment success. A sample of 85 male subjects undergoing treatment for cocaine abuse at either the Philadelphia VA Medical Center or the Treatment Research Unit at the University of Pennsylvania were divided into two groups on the basis of urine results over an 8-week period. Missing urines were considered dirty for the purposes of this analysis. Group 1 consisted of subjects with 75% or more dirty urines; group 2 consisted of subjects with fewer than 75% dirty urines. Preliminary results from a discriminant analysis indicated that a combination of 16 variables drawn from the ASI and cue session distinguished between those subjects who relapsed soon after treatment from those who remained abstinent longer with 84% accuracy. This level of predictiveness was greater than that achieved using either ASI or cue variables alone.

ACKNOWLEDGMENTS

This work was supported by the VA Medical Research Service and USPHS grant DA 03008.

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PLASMA PSEUDOCHOLINESTERASE ACTIVITY IN COCAINE-DEPENDENT HUMANS

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The major pathway for cocaine metabolism in humans is hydrolysis by the plasma enzyme psuedocholinesterase (also called butyrylcholinesterase, BChE). In normal populations, BChE activity varies with genotype, sex, age, and body weight. Little is known about BChE activity or stability in human cocaine addicts. BChE activity may also vary in cocaine users, possibly resulting in differences in response to cocaine.

We studied BChE activity (method of Ellman, et. al.,) in 27 cocaine-dependent (DSM-IIIR criteria) volunteers with no other current drug dependence (except nicotine) housed on a closed research ward. Pairs of samples (collected 72 hours apart) were drawn after admission (at least 4 days from last drug use) and again 5-9 weeks later (at least 3 days from last opportunity to self-administer cocaine). During the interim, subjects also received IV cocaine (0.6-0.9 g) and oral carbamazepine and/or diphenhydramine as part of another study.

All BChE values were within the range of published norms. BChE activity was stable over 3 days, but increased significantly after 5-9 weeks. Baseline BChE activity was greater in subjects with a lifetime history of alcohol abuse/dependence, with a trend towards higher activity in subjects with mildly elevated serum liver transaminase levels. There were no significant differences in BChE activity associated with age, weight, body mass index, height, cigarette smoking, or current or life-time self-reported use of cocaine.

These findings suggest that cocaine addicts have normal plasma BChE activity, and that such activity may change with exposure to alcohol or medications or changes in cocaine exposure.

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REGIONAL CEREBRAL BLOOD FLOW IMPROVES WITH TREATMENT IN CHRONIC COCAINE POLYDRUG USERS

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The cocaine abuse epidemic continues both in the general population and among heroin-dependent persons including those in methadone treatment programs. Buprenorphine is a partial opiate agonist-antagonist which is currently being evaluated for treatment of concurrent cocaine and heroin abuse. Cocaine abuse is associated with neurovascular complications. We have previously reported that brain perfusion defects occur with high frequency in polydrug abusers who are chronic cocaine users (Holman et al., 1991). In this study, we employed high resolution ^{99m}Tc-HMPAO SPECT to assess regional cerebral blood flow in 10 men with concurrent cocaine and heroin dependence (DSM-III-R) under controlled clinical research ward conditions during early (2nd or 3rd day), sustained (7th or 8th day) and protracted (17th to 29th day) drug abstinence. These men also received 4 to 8 mg of sublingual buprenorphine daily during the 10th through 29th day of the inpatient clinical research study. Imaging began 10-15 minutes after injection of ^{99m}Tc-HMPAO (20mCi) using an annular gamma camera system. MRI was performed during hospitalization using a 1.5 Tesla system. SPECT and MRI were merged and 5 transaxial slices centered at the level of the basal ganglia were selected for analysis. Regions were defmed manually over abnormal and normal cortical areas as determined visually from the first SPECT study. Activity ratios were derived for cortical regions relative to cerebellar activity and were corrected for linearity with regional cerebral blood flow. The cortical regions were classified as abnormal (activity ratio <.6). borderline (.6 - .72) and normal (>.72) based on the results of the first SPECT study. In abnormal zones, regional cerebral blood flow increased 11.0 ± 9.0% at 7 to 8 days and 23.8 ± 9.4% at 17 to 29 days after treatment. The increase in cerebral blood flow was smaller in borderline regions and was not significantly changed in normal zones. In conclusion, the perfusion defects observed in chronic cocaine polydrug users are partially reversible with short-term abstinence and buprenorphine treatment.

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ACKNOWLEDGEMENT

This research was supported in part by grants DA 00064, DA 00101, DA 04059 and DA 06116 from NIDA.

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CHARACTERISTICS OF SMOKED DRUG USE AMONG CHRONIC COCAINE SMOKERS

D. A. GORELICK; D. P. TASHKIN; M. S. SIMMONS AND N. J. CARRIERO

Smoking the alkaloidal form ("crack," rock") is an increasingly popular route of administration for cocaine, yet there is relatively little systematically collected data on the characteristics of cocaine smoking or its relationship with 2 other popular smoked drugs, tobacco and marijuana. We collected such data by structured interview from a convenience sample of 228 chronic cocaine smokers ($\geq$1 g/week for $\geq$9 months) recruited 2/88-9/90 from cocaine addiction treatment programs (85%) and newspaper ads (15%) in LA, CA. Subjects were part of a study on pulmonary effects of cocaine smoking (Tashkin et al., 1992), so were excluded if they had a history of lung disease, chestsurgery, occupational exposure to lung toxins, lifetime IV drug use $\geq$ 6 times, or smoked drug use > 20 times, except for tobacco (17%), marijuana (18%), or both (61%). Mean age was 35 years (range 22-60); 83% were black, 9.6% white, 6.1% Hispanic; 95.2% were men. The mean age at first regular smoking was cigarettes -17.4 years, marijuana (97% as joints) - 17.7 years, and cocaine - 31 years. Within the past year, 17% had also sniffed or snorted cocaine and 2% had taken it orally; none had used it IV. 38% smoked their cocaine mixed with another drug, chiefly marijuana (64%,), tobacco (21%), or both (11%). The commonest smoking device was a glass pipe (used a mean of 88% of the time), lit with a butane lighter (62% of the time). When a dipstick was used, the favorite lighting fluids were 151 proof rum (73%) and rubbing alcohol (24%). Non-smokers of tobacco and marijuana reported a shorter duration of cocaine smoking, were more likely to use a glass pipe, less likely to smoke cocaine mixed with other drugs, and had more education and less income than the other groups. There were no other significant sociodemographic or cocaine use differences among the groups.

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COGNITIVE FUNCTIONING OF PCP AND COCAINE ABUSERS SEEKING TREATMENT

J. M. HESS, L. COVI AND N. A. KREITER

Consecutively admitted white applicants for treatment of either phencyclidine (PCP) (n=45) or cocaine dependence (n=72) were administered a battery of psychological instruments as part of an initial screening on their first visit to an outpatient treatment research facility. One-way analyses of variance (PCP vs. cocaine) were performed both for all subjects and for only those subjects who had used their problem drug in the past 48 hours on the following measures: Shipley Institute of Living Scale (SILS), Symptom Checklist-90 Revised (SCL-90-R), and selected components of the Mini Mental State Examination (MMSE). There were no differences between the drug groups in the analyses using all subjects. However, when subjects who had used drugs in the previous 48 hours were compared PCP subjects did significantly worse than cocaine subjects in some cognitive areas of each measure. PCP subjects scored lower on the Attention and Calculation item in the MMSE, the Abstraction score of the SILS, and higher in the Obsessive-compulsive factor of the SCL-90-R which includes several cognitive items. These items accounted for the difference between the groups.

Two-way (drug X gender) analyses of variance using all subjects were also performed on the above measures to evaluate the role of gender. A significant interaction between gender and drug of choice was found on the Paranoid Ideation scale of the SCL-90-R.

In general, PCP and cocaine applicants for treatment were significantly more symptomatic an all subscales of the SCL-90-R than the non-patient normal population and more closely resembled psychiatric outpatients. These study results demonstrate several significant differences in cognitive functions between cocaine and PCP abusers as an effect of the use of drug in the previous 48 hours.

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TIME DISTORTION AS A PERSISTENT SEQUELAE OF CHRONIC THC USE

P. WEBB; F. STRUVE; J. LEAVIIT; G. NORRIS; M. FITZ-GERALD; F. NIXON AND J. STRAUMANIS

Acute exposure studies suggest that Ss given THC experience time passing faster than it actually does causing them to underproduce a specified time interval or overestimate the duration of a stimulus. However, the effect of chronic THC use on time estimation measured when Ss are not "high" is unknown. Following 24 hours of abstinence, we measured time production error in 28 daily THC users (>7 "joints"/week for >3 years) and 32 controls with all Ss screened to exclude present or past psychiatric or medical disease or non-THC drug use. Ss estimated 2 minute intervals on 8 trials. Trials 1-4 were without feedback. In trials 5-8 the S's preceeding trial accuracy was given prior to each new trial. For each trial the S's score was the difference (in seconds) between the target interval and the S's produced interval.

A repeated measures ANOVA indicated that time production accuracy significantly improved ($p<.001$) across trials. Although THC users showed the greatest time underproduction, the group main effect and groups X trials interaction were not significant. Similarly, feedback significantly ($p<.001$) increased time production accuracy. However, the condition by group interaction was not significant suggesting that both groups respond similarly to feedback. Because of large intragroup and intertrial variability we averaged each S's scores across no feedback and feedback trials. A trend ($p=.07$) for THC users to show greater time underproduction on non-feedback trials was found. During feedback trials, THC Ss showed significantly greater ($p=.01$) time underproduction as compared with controls. Feedback appears to reduce intersubject variability and allow THC effects to be detected. We examined feedback produced increase in time production accuracy by comparing each S's average score on no-feedback and feedback trials. Ultra long duration THC users (>15 years daily use) are less able to improve performance with feedback than moderate duration THC users (3-7 years daily use) or controls. Only 44% of ultra long duration THC users are able to focus in to a average feedback trial score within 10 seconds of the target interval but 71.8% of the controls and 70% of moderation duration THC users are able to do so. Chronic THC use may be associated with persistent time underproduction errors, especially among very long duration users.

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ALTERED QUANTITATIVE EEG TOPOGRAPHY AS SEQUELAE OF CHRONIC THC EXPOSURE: A REPLICATION USING SCREENED NORMAL SS

F. STRUVE; J. STRAUMANIS; G. PATRICK; G. NORRIS; F. NIXON; M. FITZ-GERALD; J. MANNO; J. LEAVITT AND P. WEBB

In two pilot studies using psychiatric inpatients with no access to THC, prior daily THC use (>1 year) was associated with distinct topographic quantitative EEG features. As contrasted with both normal and patient non-user controls THC users showed significant elevations of (1) Absolute Power, (2) Relative Power, and (3) Interhemispheric Coherence of Alpha over frontal cortex ("HYPERFRONTALITY OF ALPHA"), (4) significant generalized voltage increases for all frequencies ("GENERALIZED POWER ENHANCEMENT"), (5) significant decreases in Relative Power of Beta and Delta, and (6) Significant elevations of Frontal Interhemispheric Coherence of Delta. Because psychiatric diagnoses and psychotropic medication were uncontrolled, we attempted to replicate the findings using normal subjects.

Using identical quantitative EEG methods, 18 daily THC users were contrasted with 35 non-user controls. All Ss were screened by direct examination and 8 weeks of twice/week urine drug testing and were free of medical disease, past disease or injury with possible CNS seguelae, DSM III-R Axis I Psychiatric Dx, any past psychiatric treatment, all prescription medication, and any recent non-THC drug use (Tobacco and social alcohol excepted). All EEGs were recorded and quantified blind to S's group identity. Findings 1 to 3 regarding increased frontal Alpha received robust confirmation ($p<.001$, all comparisons). Findings 4-5 regarding generalized power enhancement and decreased Relative Power of Beta and Delta were also strongly confirmed ($p<.05$ to $p<.001$, all comparisons). Both Delta and Theta coherence (finding 6) were significantly elevated over frontal areas for THC users ($p<.001$ to $p<.008$, all comparisons). In addition the replication study using normals led to new findings. Daily THC use was associated with significant decreases of mean Alpha frequency at all electrode locations, significant increases in mean Theta frequency at all electrode locations, and significant increases in Delta mean frequency at all central, parietal and occipital locations.

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PERFORMANCE OF CHRONIC DAILY MARIJUANA USERS ON NEUROPSYCHOLOGICAL TESTS

J. LEAVITT; P. WEBB; G. NORRIS; F. STRUVE;J. STRAUMANIS; M. FITZ-GERALD; F. NIXON; G. PATRICK AND J. MANNO

We report preliminary findings regarding the neuropsychological performance of long term THC users (N = 11, mean use = 19.5 years), short term THC users (N = 14, mean use = 4.9 years) and nonusers (N = 39). Subjects were normals screened with medical, psychiatric, clinical EEG, and 8 weeks of twice weekly drug screens. Psychological tests included reaction time (Sternberg's procedure), divided attention (PASAT), learning/memory (WMS-R, CVLT), and "higher mental abilities" (WAIS-R, CLAT, Category, WCST) as well as several other tests. Age/education effects were addressed using a multiple *regression* procedure that removed "expected values" (computed using *only* age and education) from all outcome variables. Only the nonuser group was used to estimate the appropriate weights and these were jackknifed. Outcomes were then submitted to conventional multivariate analyses followed by univariate procedures when appropriate. Results suggested an association between duration of THC use and lowered test performance. Long term users performed more poorly than short term users and controls on several tasks including reaction time ($p < .0.01$), verbal learning and recall ($p < 0.01$), and complex logical/nonlogical reasoning tasks ($p < 0.01$). A tentative interpretation suggests that long term THC use may impair an individual's ability to respond adaptively to novel, complex tasks.

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BRAIN STEM AUDITORY EVOKED RESPONSE (BAER) IN POLYDRUG ABUSE SUBJECTS AND NON-POLYDRUG ABUSE COMPARISON GROUPS

G. PATRICK, F. STRUVE AND J. STRAUMANIS

We compared BAER data from PSYCHIATRIC POLYDRUG USERS (n=19) with PSYCHIATRIC THC USERS (N=10), PSYCHIATRIC NON-USERS (n=22), SCREENED NORMAL THC USERS (N=25), SCREENED NORMAL NON-USER CONTROLS (n=17). UNSCREENDED NORMAL NON-USER CONTROLS (n=l8), and ULTRA LONG TERM (>15 year use) THC USERS (n=21). Ss had no history of hearing impairment. Inpatient psychiatric Ss were primarily non-psychotic with minimal exposure to psychotropic medication. THC use was daily in THC user groups. BAERs were obtained with conventional recording methods. Using Mann-Whitney U Tests, Polydrug Ss, when compared with other groups, had significantly increased latencies for waves I, II, III and V as compared with screened and unscreened normal Ss, screened normal THC users, and normal ultra long term THC users. There were no significant latency differences between polydrug Ss and psychiatric THC users. When compared with psychiatric non-users, polydrug Ss show increased latency on waves I and II but not on waves III and V. This suggests that patient status rather than polydrug use is the discriminating factor. Since the largest intergroup differences involved wave I latencies, we did an ANOVA with wave I as a covariate. All between group latency differences were lost for waves II, III, and V when adjusted for wave I latency, suggesting that those differences were epiphenomena explainable by latency differences of wave I. Analyses of interpeak latency intervals supported the results of covariate analyses. Significant intergroup differences in BAER peak amplitudes or amplitude ratios were very infrequent.

In studying drug effects on BAERs comparison groups should have an absence of the drug studied but the presence of variables comorbid with drug use, Had we only compared polydrug Ss with normals, we would have falsely concluded that polydrug abuse was associated with prolonged BAER latencies. Secondly, in studies focusing on later BAER waves the modifying effects of earlier wave prolongations are not considered. Since BAER waves follow one another, it is plausible that Wave I latency delays would propagate down the line causing a forced delay in wave V. Thus wave V delay would not be due to disruption of wave V generation but would reflect processes responsible for the original delay at wave I.

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NICOTINE DEPENDENCE IN A POPULATION-BASED SAMPLE

K. L. HALE; J. R. HUGHES; A. H. OLIVETO; J. E. HELZER; S. T. HIGGINS; W. K. BICKEL AND L. B. COTTLER

As one of the DSM-IV field trial sites, we completed a random-digit-dial telephone survey of 201 residents of the greater Burlington, VT area. Women were over represented in the sample (62%) therefore, the following results were analyzed according to gender. One year prevalence rates among current tobacco users (n = 46) using DSM-III-R criteria for drug dependence were 24% (M = 24%, F = 25%) for severe dependence (7-9 criteria), 26% (M = 24%, F = 29%) for moderate dependence (5-6 criteria), 30% (M = 43%. F = 17%) for mild dependence (3-4 criteria), and 18% (M = 10%, F = 25%) for no dependence (0-2 criteria). The most common criteria endorsed were persistent desire to quit/unsuccessful attempts to control use 93% (M = 95%, F = 92%) and any withdrawal when stop or cut down 74% (M = 75%, F = 71%). Only 18% of males and 21% of females met Fagerstrom criteria for nicotine dependence. Our results should be considered estimates because how to apply DSM-III-R criteria to nicotine use is still unclear and because our sample size is small. Supported by grants MH-47200, RSDA DA-00109 (Dr. Hughes) and training grant DA-07242 (Ms. Hale and Dr. Oliveto).

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METHODS FOR THE ANALYSIS OF URINE TOXICOLOGY RESULTS IN THE PRESENCE OF MISSING DATA

K. L. DELUCCHI

Results of urinalysis toxicology screens (UA) are one of the major outcome measures in research into substance abuse treatment. An important, frequent, and unresolved problem among researchers in the field is deciding how to analyze and report outcome data when some of the UA results are missing. For the most common situation-comparing the proportions of positive UA results in a 2-group, randomized design in the presence of missing UA data-three standard approaches are available. First, use only the remaining data. This is a conservative method that lacks power and does not allow generalization to the original population. Second, assume the missing data would have produced a positive result for use (i.e., "missing=dirty"). Though common, the effects of this assumption vary with the patterns of missing data and the underlying assumption is not true in all cases. Third, assume the data is missing at random and use standard statistical imputation. This assumption is also not valid, and most of those techniques are not applicable to the type of data found in this case. A fourth, proposed solution, is based on the concept of "modeling our ignorance" by examining all possible outcomes, given a known number of missing results with a bivariate outcome, and then describing the distribution of those results. Given, for example, a non-significant difference from the available data with 2 missing subjects in one group and 3 in the other, a total of 12 additional 2 x 2 contingency tables are possible. If only 1 of those configurations produce a significant difference, one could argue it is unlikely that a Type II error was committed. To ignore the missing data and to assume that "missing=dirty" are just the two extreme cases of this approach. This method fills in the variety of possible outcomes in between. Researchers could report the distribution of all-possible p-values, group differences, and measures of variance to provide a context for reaching conclusions about the observed data. This procedure can be adapted to the one-group, two-time-point case directly. Extensions to cases with more than bivariate outcomes and more complex designs are briefly discussed.

ACKNOWLEDGEMENTS

This work was supported by the San Francisco Treatment Research Unit, funded by NIDA Grant 1R18DA06097. Andrew Therber wrote the computer program for the analysis.

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INTERPRETATION OF URINE SURVELLIANCE DATA IN METHADONE PATIENTS

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For Patients on the methadone maintenance program, it is required by the FDA to have randomized urine surveillance under supervision. This is also good for the quality of care in that intake of licit and illicit drugs by the methadone patients are closely monitored and evaluated. In the last seven years, we have noted a continuous increase in the presence of cocaine and benzodiazepine in the urine. One of us (RW) reported to CPDD in 1988 and 1991 how to manage such situations. In this report, we present another commonly encountered issue: that is, the meaning of negative methadone in the urine screening of methadone patients. We found out about 20% of our methadone patients had one or more episodes of negative methadone in their urine. Among the six patients who had more than three negative methadones in their urine in a two year period, we hospitalized two patients, one with 28 and one with 15 negative methadones. Patients were given the usual dose of methadone (40mg daily) at 8 AM in front of a nurse and urine was collected every time in separate containers from 12 midnight to 12 noon. The order of the samples was rearranged in order to establish unbiased information to the laboratory technician. Urines were screened by EMIT DAU which detects concentrations of methadone in the urine greater than 300 ng/ml. Below that cut off value, the urine was considered negative methadone. It was found that both patients had more than adequate amount of methadone in their urine in the multiple samples taken for two consecutive mornings in the hospital. On the other hand, such patients received the methadone daily in front of the pharmacist who carefully observed the patients. Urine drops were carried out in strict direct observation. It is concluded that negative methadone in the urine does not necessarily mean the patient did not take the methadone because the patient swallowed down the dose. Therefore, such patients should be excussed. We have since then doing quantitative determination of patient's urine for methadone of lower than 300 ng/ml by gas chromatography and CC mass spectrometer report the actual amount of methadone in the urine. Those with methadone in the urine between 100 and 300 ng/ml will be assessed by the clinical staff and those with 100 ng/ml or below will be consider unequivocally negative methadone urine.

We also noticed some of the patients on methadone maintenance are also taking diuretics. Such patients will have frequent urination at night. Similarly, diabetic patients not well controlled with insulin or oral hypoglycemic agents also have frequent nocturia resulting in dilute urine samples in the morning when such patients drop their urine samples in the clinic the following mornings. Such dilute urine may have lower amount of methadone (below 300 ng/ml). Also methadone patients receiving diphenhydramine (Dilantin) may have lower amount of methadone in the morning urine samples due to rapid methabolism of methadone. Affiliation: Zablocki VA Med. Ctr., Med. Col. of Wisconsin, Milwaukee, WI

ETIOLOGICAL CUES TO DUAL DIAGNOSIS: A REPORT FROM AN ONGOING EVALUATION RESEARCH PROJECT

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Despite high prevalence of the comorbidity of psychiatric and substance abuse disorders there is little known about its etiology. As part of a five year longitudinal study of homeless mentally ill chemical abuser (MICA) men, data were collected on 296 MICA clients aiming at identifying psycho-social characteristics in their background that may help to explain how and why the MICA syndrome develops.

The first part of this paper reports on socio-demographic and clinical characteristics of the 296 MICA men. Their mean age was 32; 60.7% were black and 24.8% Hispanic; 73% never married; 45% had 10 year of education or less; 90% did not have a driver's license and 98% did not have a car; 55.7% were diagnosed as schizophrenic and 21.6% as depressive disorder. The majority had current and/or past history of suicide ideation and/or attempts, delusions, hallucinations and depression. Crack was the main substance of abuse followed by alcohol and cocaine. 60.9% of the MICA clients' fathers had alcohol and/or drug and/or psychiatric problems themselves, and so had 38.6% of the clients' mothers and 57.1% of their brothers. The majority of clients were abused emotionally and/or physically in the past. For 28.7% of the clients parents had never been married. Of those parents who were married, 57.9% got divorced.

The second part of the paper describes a questionnaire, the Personal History Form (PHF) that was developed in order to identify family and early age background characteristics of MICA clients, using 5 different scales. Factor analyzing these scales yielded the following results: a) Feeling about Father scale with internal consistency reliability of .85; b) Feeling about Mother scale with reliability of .90; c) Relationship with Father scale, three factor solution: "Good Father," "Bad Father," and "Drug and Alcohol" with .72, .80 and .60 reliabilities respectively; d) Relationship with Mother scale, three factor solution: "Good Mother," "Addictive Mother," and "Bad Mother" with .83, .67 and .74 reliabilities, respectively; e) Relationship in Client's Family scale, two factor solution: "Positive Relationship" and "Negative Relationship" with .85 and .71 reliabilities.

The paper tentatively concludes that MICA clients have experienced grave socio-economic, psychological, and family deprivations. These deprivations may be risk factors, etiologically related to the MICA syndrome. The PHF may be a valid and reliable measure to tap some of these deprivations.

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PREDICTING HIGH RISK SEXUAL BEHAVIORS IN THE GENERAL POPULATION

A. M. SHILLINGTON AND L. B. COTTLER

In a previous report of the St. Louis Epidemiologic Catchment Area (ECA) study, a study of psychiatric disorders among the general population (Cottler, Helzer and Tipp, 1990) a strong association was found between lifetime substance use patterns and lifetime high risk sexual behaviors (St. Louis was the only site which asked about sexual behaviors). However, the data in that report were not controlled for risk factors other than gender. The new analyses presented here control for race, age, gender and the use of other substances, among the ECA sample of 18-44 year olds which was 45% black and 40% male.

High risk sexual behaviors include marital infidelity, 8% (having sex outside of marriage with 3+ different people), promiscuity, 13% (having 10+ different sexual partners in one year), prostitution, 5% (being paid for sex), homosexuality, 3% (having engaged in a homosexual act since age 18), and any of these high risk sexual behavior (AHRSB), 22%.

Each of the high risk behaviors was predicted with age, race, gender and substance use as independent variables, using conditional logistic regression. The substances included as independent variables in each model include heavy alcohol use (29%). lifetime marijuana use (35%), stimulant use (13%). sedative use (6%), tranquilizer use (5%). cocaine use (6%), opiate use (4%), and pcp use (5%).

We hypothesized that persons who were heavy users of alcohol or who have been users of illicit drugs would be more likely to be involved in high risk sexual behaviors compared to non-users. All substance use variables used in the analyses were found to be significantly related to each high risk behavior in the bivariate analyses at $p<.05$. Therefore, every substance was included in the multivariate analyses.

The model predicting AHRSB found males were more than three times as likely than females to be involved in high risk behaviors. Older age and being Black was also associated with high risk behaviors. Heavy alcohol use, marijuana use, and tranquilizer use were all associated with high risk behaviors. Cocaine use most strongly predicted involvement in high risk sexual behaviors, with users being over four times as likely compared to nonusers even after controlling for all other effects.

For the first time, data are available which allow for an association to be determined between substance use and high risk behaviors, controlling for other variables among the general population. These data are particularly useful because they do not only consider persons who have been in treatment but include persons randomly selected from the general population. Further follow-up of these subjects will help us understand the continuing associalions.

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PATTERNS OF DRUG ABUSE IN DETOXIFICATION PATIENTS

M. I. FINGERHOOD, J. T. SULLIVAN AND D. R. JASINSKU

The study of patterns of drug abuse in patients can identify new trends in drug abuse, provide indirect data on abuse liability and assist in prevention and treatment. Between November, 1990 and May, 1991, 860 consecutive patients admitted to the chemical Dependency Unit at Francis Scott Key Medical center were entered into a database. The patients were predominantly male (62%) and black (76%). Other than nicotine, the most frequently abused drugs by self-report were cocaine (74%), heroin (68%), alcohol (66%), marijuana (38%) and benzodiazepines (27%). Patterns of abuse were similar between the sexes, except that alcohol abuse was more common among men than women (74% vs 53%, p<.001). Cocaine and heroin use was, more frequent among blacks than whites (80% vs 55%, p<.001 and 75% vs 46%, p<.001, respectively). Whites were more likely than blacks to abuse benzocliazepines (38% vs 24%, p<.001). Age at presentation for treatment by drug revealed that alcoholics were older. Methadone maintenance patients comprised 23% of the population and had significantly higher rates of abuse of all drug categories, especially benzodiazepines (mostly alprazolam), 62% vs 17%, p<.001. The results reveal that there are significant differences in drug abuse when patients are stratified in groups.

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RELATIONSHIP BETWEEN METHADONE TREATMENT AND ARREST PATTERNS OF ADDICTS OVER TIME

S. B. GREBERMAN AND J. C. BALL

INTRODUCTION

In this study, the influence of methadone maintenance treatment on arrest patterns of heroin addicts was investigated. Data sources were official police records and the Addiction Severity Index. A total of 1002 arrests of 144 male methadone maintenance patients in Baltimore were analyzed. A time series regression model was developed revealing the effects of arrest patterns prior to entry into methadone treatment along with methadone treatment patterns themselves on arrest patterns during treatment.

RESULTS

For men addicted at least 10 years, a decrease in arrests following the initiation of methadone therapy has been identified for individuals remaining in treatment for at least 2 years. A similar decrease in arrests does not appear in patients who drop out of treatment.

Arrests before treatment produce a statistically significant decrease in future arrests in most of these men. The group that shows a statistically significant increase in future arrests as a result of past arrests is patients having >1 year of methadone treatment in 1985 who were not previously incarcerated. R^2 for the entire time series model achieves statistical significance for all groups of patients addicted at least 10 years before treatment.

A subsample of 13 patients addicted <10 years was analyzed separately. The effect of methadone treatment on arrests during treatment is to produce an immediate decrease in arrests during the first year. This decrease continues through the second year of treatment; the pattern reverses in the third year as methadone treatment begins to decrease. The R^2 is statistically significant; however, the results cannot be considered conclusive for this subsample because of the small sample size.

CONCLUSIONS

In heroin addicts addicted at least 10 years, a decrease in arrests occurs in either the first or second year of methadone treatment; this decrease disappears, becoming an increase in the subsequent time periods when treatment begins to decrease. Arrest patterns developed during the decade preceding entry into a methadone treatment program have a powerful influence on arrest patterns while in treatment. This means that any effect of methadone therapy can be overshadowed by the arrest history of the individual. These results suggest that initiating treatment earlier in an addiction career may result in a different response to therapy.

Analysis of a subsample of individuals addicted <10 years before entering treatment reveals a more rapid decrease in arrests in these individuals. These results are limited by the size of the subsample; however, the results do indicate an area for continuing research into addiction and criminal careers in methadone maintenance patients and in addicts receiving other types of treatment.

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STREET LEVEL CRACK DEALING AS INFORMAL SECTOR ACTIVITY: AN ETHNOGRAPHIC STUDY OF NEW YORK CITY CRACK DEALERS

A. MANWAR AND B. D. JOHNSON

Like all commodities, drugs (including crack, the dominant drug at present) are commodities that are produced, processed, packaged, distributed, and used by consumers. Crack and cocaine go through a long process of production, organization, distribution, and exchange markets. The organizational structure and operational activities of street-level crack dealers display features of an urban informal sector, but with important differences. The national economy may be divided into three broad sectors. The formal sector includes all industrial, service, and agricultural enterprises. The informal sector consists of small-scale legal and illegal enterprises operating outside state regulations and taxation. The criminal sector includes illegal operations outside and against the laws and regulations of the state. Street-level drug distribution displays the following features of the informal sector: ease of entry; reliance on indigenous resources; family or individual ownership; a small scale of operation; labor-intensive and adapted technology; skills acquired outside the formal school system; unregulated competitive market; and small capital required for starting an operation. Street-level crack dealing differs from the informal sector in two major ways: Fist, almost all dealers are also abusers. Second, their drug dependence makes them casualties (economic and physical) rather than successful entrepreneurs in the informal sector. While they have a high cash flow and income, they rarely accumulate any capital or move into the formal sector.

Street crack dealers are also structurally constrained by their socio- economic environment. Two main constraints are their household and labor market. Most street dealers come from poor, public-assistance-dependent, and drug abusing households. Parents rarely provide necessary financial, cultural, and emotional support to their children. Children are often placed with relatives, fictive kin, or in foster care. Before learning any employable skills, children drop-out of schools. They engage in petty crime, and become entangled in the web of the criminal justice system. Not acquiring necessary skills to be employed in the formal sector, youths from these dysfunctional households view street-level drug distribution as a money-making opportunity. Their street knowledge is useful and employable in this sector. They are also locked into dealing by reasoning that other alternatives are not available and a descent life is not possible. Their rationality lies outside the logic of standard economics, and is meaningful only within their immediate social context. Thus they calculate flow of cash as “profit,” and underestimate “risks” of addiction, HIV infection, physical injury and death. From their vantage point, they are making the best use of the limited resources and opportunities available to them.

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Funded by 1 RO1 DA05126-04 from National Institute on Drug Abuse.

COCAINE USE AND THE RISK OF OBSESSIVE-COMPULSIVE DISORDER: A NEW HYPOTHESIS TESTED WITH EPIDEMIOLOGIC DATA

R. M. CRUM AND J. C. ANTHONY

Hypothesis: Using prospectively gathered data, we sought to estimate the degree to which the risk of obsessive-compulsive disorder (OCD) might be elevated among adults actively using cocaine, with and without illicit use of marijuana or other controlled substances. Methods: Study subjects were selected in 1980-84 by taking probability samples of adult household residents at five sites of the NIMH Epidemiologic Catchment Area Program: New Haven, Connecticut; Baltimore, Maryland; St. Louis, Missouri; Durham-Piedmont, North Carolina; and Los Angeles, California. Soon after sampling at baseline, and approximately one year later, interviews were administered to identify incident cases among the 13,306 participants, 414 being active cocaine users. Both conditional and unconditional multiple logistic regression analyses were used to estimate OCD risk for the 414 active cocaine users versus the 12,892 participants not using cocaine. Results: Both of these epidemiologic strategies yielded consistent results: Subjects actively using cocaine and also marijuana were found to be at increased risk for OCD. Using the conditional model, the estimated relative risk was 7.2 ($p = 0.03$), while the value from unconditional regression was 4.1 ($p = 0.01$). Conclusions: Active users of cocaine almost always were active users of marijuana or some other controlled substance, so it was not possible to estimate a relative risk value for subjects using cocaine only. Nonetheless, if replicated, this epidemiologic test of the cocaine-OCD hypothesis warrants attention in laboratory and clinical research.

The work was supported by research grant DA03992 from the National Institute on Drug Abuse. Data gathering was supported by the Epidemiologic Catchment Area (ECA) Program of the National Institute of Mental Health Division of Biometry and Epidemiology. The PIs and grant award numbers during data gathering were Jerome K. Myers at Yale University (MH34224), Morton Kramer at the Johns Hopkins University (MH33870), Lee N. Robins at Washington University (MH33883), Dan Blazer and Linda George at Duke University (MH35386), Richard Hough and Marvin Karno at the University of California, Los Angeles (MH35865). At the NIMH, principal collaborators during data gathering were Darrel A. Regier, Ben Z. Locke, William W. Eaton, Carl A. Taube, and Jack D. Burke, Jr.

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TOBACCO USE AMONG COCAINE ABUSERS

A. J. STONE, M. E. KHALSA AND D. ANGLIN

Data on tobacco use by 300 male cocaine addicts were obtained at intake to treatment at a VA hospital.

Lifetime and current smoking prevalence was extremely high in this population: 92% reported that they had been regular smokers and only 10% of these were ex-smokers. Age of smoking initiation appears to have been fairly typical, by age eighteen 80% of this group had smoked their first cigarette.

Although some investigators have reported that the typical drug user is a heavy smoker, 44% of these cocaine addicts were relatively light smokers (the Surgeon General defines those who smoke less that three-fourths of a pack per day as light smokers); 31% of American smokers fall in this category. Conversely, only 13% smoked 1.5 or more packs per day compared to 27% of U.S. smokers. Nonetheless, they showed clear signs of nicotine addiction.

The brands commonly used by 74% are classified as high in nicotine, containing more than 0.9 mg of nicotine per cigarette. Also, 81% reported lighting up within 30 minutes after awakening (considered to be an indicator of nicotine dependence). Forty-seven percent reported waking up to smoke (another indication of nicotine dependence) once a week or more, and about 6% every night.

While unusual in dependent users, 68% reported having made at least one serious attempt to quit. Because we did not ask about cocaine use at the time of quitting, we do not know how many cessation attempts were made prior to initiation of cocaine use. However, at least 39% reported they made a serious cessation attempt during a time period in which they were using cocaine heavily. Data were also collected on cigarette craving, cocaine craving, triggers for cigarette smoking, and effects obtained from cigarettes during the first two weeks of cocaine abstinence. Overall, tobacco dependence and craving for tobacco were high and subjects reported craving and smoking more when feeling upset, angry and depressed.

In most cases, those who work with cocaine abusers have not placed a priority on smoking cessation. These data show the need for studies to explore the dynamic links between tobacco and cocaine use, how the two drugs are concurrently used, the interactive and reciprocal effects of cocaine use/abstinence on tobacco consumption/cessation.

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ICE: HOW ABUSERS LEARN OF A NEW STREET DRUG

S. E. MCNAGNY, R. C. GREEN AND R. M. PARKER

Ice, a smokable form of crystal d-methamphetamine, is emerging as a new drug of abuse. By 1990, methamphetamine had become the number one drug problem in Taiwan, Japan and Hawaii; it was gaining popularity in California, and was moving toward the East coast. We studied how users learn of this new drug.

As part of a larger study, 214 men at an indigent care Atlanta hospital were surveyed and gave urine samples. Testing for cocaine and methamphetamine metabolites was later performed anonymously using an immunoassay technique, and all positive methamphetamine assays were confirmed by gas chromatography/mass spectrometry (GC/MS). Of the 214 men who agreed to participate (refusal rate=19%), the average age was 29 years (range 18-39) 88% were black, 87% had no medical insurance, and 85% admitted to any prior illicit drug use. No subjects had GC/MS confirmed methamphetamine assays, but 25% tested positive for cocaine metabolites. 183 (86%) had heard of Ice, 6% reported seeing someone selling Ice, and 4% had seen someone using it. Although only 4 (2%) had been told about this substance by drug pushers, 182 (85%) reported having heard about Ice from television and radio. Ninety per cent could not name any of the medical dangers of methamphetamine. When asked what qualities would make Ice popular, 132 had no opinion; but of the remaining 82, 90% said that a good "high" was more important than price. There was no significant difference in the answers to questions about Ice between those who tested positive and those who tested negative for cocaine metabolites.

Individuals at high risk for drug abuse learned of Ice predominantly from the media, but did not appear to have absorbed information on the medical dangers of Ice. Media focus on new illicit drugs may inadvertantly increase interest and encourage the use of illegal and potentially harmful drugs.

ACKNOWLEDGEMENTS

The study was supported by grants from The Centers for Disease Control and The Emory Medical Care Foundation, Atlanta, Ga.

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COMPONENTS OF ANTISOCIAL PERSONALITY DISORDER AMONG WOMEN CONVICTED FOR DRUNKEN DRIVING

B. W. LEX; M. E. GOLDBERG; J. H. MENDELSON AND N. S. LAWLER

For women, the temporal relationship between Antisocial Personality Disorder (ASPD) and alcoholism is unclear. Driving while intoxicated is both a symptom of ASPD and the alcohol-related problem most typically reported by women. Accordingly, a period prevalence sample of 33 women incarcerated for drunk driving offenses were assessed with the SCID to identify other symptoms of ASPD. Excluding behaviors that only occurred while drinking, only one of the 33 women met DSM-III-R criteria for ASPD. When behaviors while drinking were included, 18.2% met criteria for ASPD by having both a history of childhood conduct disorder and characteristic ASPD behaviors as adults. However, 57.6% of the sample displayed the pattern of adult behavioral symptomology without a history of childhood conduct disorder. Women with a history of conduct disorder had a younger mean age of onset of alcohol dependence (17.9 **vs** 25.6 yrs) and a higher rate of concurrent borderline personality disorder (85.7% **vs** 42.1%) than the women who had only adult symptomology of ASPD (71.4% **vs** 72.2%), but the same rate of reported parental alcoholism. All but one woman exhibiting full ASPD with childhood conduct disorder in this sample were truant and ran away from home, but few acknowledged acts of violence, vandalism, or arson in childhood. Thus, behaviors diagnostic of ASPD were largely consequent to substance abuse, while childhood behaviors appeared limited predictors of ASPD. Relationships among gender, prodromal behaviors, and substance abuse appear more complex than anticipated, and indicate need to recognize adult onset ASPD associated with substance abuse as a legitimate diagnosis manifested differently by women and men.

ACKNOWLEDGEMENTS

This study was supported by Grant Nos. NIAAA 06252, 06794 and NIDA 00064 and 04870.

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SEXUAL AND REPRODUCTIVE BEHAVIOR AMONG A SAMPLE OF FEMALE DRUNK DRIVERS

M. E. GOLDBERG; B. W. LEX; J. H. MENDELSON AND N. S. LAWLER

Sexual and reproductive behaviors of female alcoholics can result in insult to the fetus, child abuse or neglect, or transmission of AIDS. This study examines reproductive, sexual, and parental behavior reported by 34 women incarcerated for drunk driving offenses, the most common drinking problem acknowledged by women. Mean age was 33.6 years and mean age of onset of alcohol dependence was 24 years, with 61.8% also meeting DSM-III-R criteria for substance abuse or dependence. Reproductive capacity may have been compromised since 61.8% of the total sample reported having unprotected intercourse for at least 6 months without becoming pregnant. About two-thirds (70.6%) had been pregnant and 52.9% had had live births, but only 23.5% gave birth after onset of alcohol dependence. Of women who had been pregnant, 43.4% reported drinking heavily during pregnancy, and an additional 17.4% reported drug use without heavy drinking during pregnancy. No one indicated that their children appeared to have been affected by to have been affected by alcohol or drug use during pregnancy. There were no reported birth defects or learning disabilities, but 66.7% of women who had children did not have their children resident with them for some or all of the children's minor years, a striking finding. The majority of these placements (64%) were private arrangements with family or friends without involvement of official child protective service agencies. AIDS risk was also less than anticipated. Although only 8.8% used condoms regularly, and a 23.5% had a history of STDs, current intercourse with multiple partners was uncommon. In the previous 6 months over two-thirds reported having no sexual partner or only one sexual partner, and of the remainder, no one had over 5 partners in that interval.

ACKNOWLEDGEMENTS

This study was supported by Grant Nos. NIAAA 06252 and 06794, and NIDA 00064 and 04870.

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INDICATIONS OF CAFFEINE DEPENDENCE IN A POPULATION-BASED SAMPLE

J. R. Hughes, A. H. Oliveto, J. E. Helzer, W. K. Bickel and S. T. Higgins

At the VT site of the DSM-IV field trials, a random-digit-dial telephone survey of 202 residents of greater Burlington, VT, applied the DSM-III-R generic criteria for drug dependence to current caffeine users (n = 166). One year prevalence rates were 3% for severe dependence (7-9 criteria), 14% for moderate dependence (5-6 criteria), 27% for mild dependence (3-4 criteria) and 58% for no dependence (0-2 criteria). The most common criteria endorsed was persistent desire or unsuccessful attempt to control use (51%). 12% met DSM-III-R criteria for caffeine intoxication. Among current users who had stopped for $\geq$ 24 hrs, 42% reported either withdrawal headaches, fatigue or drowsiness when they stopped. Clinical validation of these self-reports is underway. Our results should be considered preliminary estimates because this is the first attempt to apply DSM-III-R criteria to caffeine use. Supported by grants MH-47200, DA-04843, RSDA DA-00109 (Dr. Hughes) and training grant DA-07242 (Dr. Oliveto).

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SOLVENT USERS: CHARACTERISTICS AND PREDICTORS

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As part of a NIDA funded project on substance abuse and risk of AIDS, 605 persons recently admitted to treatment and their sexual partners/friends were interviewed concerning their drug use histories, demographic variables, and HIV risk behaviors. Among those who admitted using any drugs (total n = 548), solvent inhalation was reported by 10% (n = 56). The rate was higher among whites compared to blacks (19% vs. 4%, $p < .0001$) but was not significantly different between men and women (11% vs. 8%). Among the drug users in general, solvent users, compared to non-solvent-users, had higher rates of DSM-III-R Major Depression (38% vs. 21%, $p < .0003$), Alcohol Dependence (89% vs. 61%, $p < .0001$) and injection drug use (IDU) (86% vs. 48%, $p < 10^{-6}$). Solvent users had earlier age of first use of most specific substances than non-solvent-users and used a larger number of substances than non-solvent-users (6.7 substance vs. 3.9 substances, $p < .0001$). Regression modeling to predict IDU found significant prediction by history of solvent use, presence of Antisocial Personality, older age and white race. These results indicate the importance of solvent use as a predictor of severe drug abuse and IDU. They show that adolescent solvent users could be an important target for aggressive intervention.

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CASE MANAGEMENT/SELF-HELP GROUP FOR DRUG ABUSERS: SUBJECT CHARACTERISTICS

W. W. WEDDINGTON; J. A. LEVY; R. RAMAKRISHNAN AND W. W. WEIBEL

We describe intake characteristics of enrollees in a project which establishes and evaluates efficacy of a community-based service model (CBS) combining peer case management and self-help groups to promote drug-free living in a sample of active Chicago drug abusers. Indigenous outreach workers recruited 200 subjects from a northside, racially-mixed area and a southside, predominately black neighborhood. After evaluation subjects were randomly assigned to a control (existing treatment) (STD) or CBS-intervention group. Subjects will be evaluated at 4 points in Year 1 and at 6 month intervals in Years 2-4. Quantitative measures to examine outcomes are obtained by the Addiction Severity Index (ASI), Symptom Check List-90-Revised, and Social Support Instrument. Ethonography is utilized to examine social systems.

Our model of case management is designed to intervene with drug abusers by providing them with social support needed to adjust to demands and to counter the problems of living drug-free in the community. It draws heavily on the Chicago Model of community intervention which combines medical epidemiology with established capabilities of ethnography to offer insight into social systems of addicts. In the CBS model, a case manager meets formally on a regular basis to help a subject set realistic goals for recovery, offer counseling, link the individual to service providers, and provide education regarding drug-related problems, including HIV transmission.

Subjects are also encouraged to form and maintain membership in a professionally assisted self-help group which meets at project field stations. Such groups provide encouragement, a system of beliefs which reinforce positive attitudes, and behavior, and practical suggestions for bringing about change through advice and social support of individuals who find themselves in similar situations.

The peer support component of the CBS model draws conceptually on the community self-help movement which emerged during the late 1960s and early 1970s. Self-help groups have proven effective in helping people to cope with a variety of medical and social problems.

Compositions of subjects (N=2OO) is: Age range 18-64 y, mean (SD) 38.4 (11.0) y; 56.6% male, 43.4% female; 28% never-married, 10% legally married; 21.5% living with spouse, 6.5% widowed, 38% separated or divorced; 35.5% of participants are employed full-time, 5% are retired or disabled, 33.5% are unemployed; 46.5% have a major problem with one abused drug other than nicotine, 23% with alcohol and drugs, 26.5% with polydrug abuse. Means (SD) of ASI intake data are: Family 3.56 (2.13); Psychological 3.58 (2.38); Legal 2.54 (2.56); Drug 5.97 (2.01); Alcohol 3.35 (2.89); Medical 3.09 (2.70); Employment 3.83 (2.42). SCL-90-R data suggest moderately severe psychological symptoms, although tests/retests of a sub-sample demonstrate poor reliability with this instrument. There are no significant differences in characteristics between subjects randomized to STD or CBS groups.

(Supported by NIDA Grant # R18 DA 06994-01)

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THE ACCURACY OF ADDICT PATIENTS' REPORTS ABOUT THEIR LIFETIME ARRESTS

J. C. BALL AND S. B. GREBERMAN

Skepticism and doubt about addict patients' ability and willingness to recount their prior criminality have persisted over the years. Although there has been a certain consensus among knowledgeable researchers that addicts' will - under appropriate conditions - recount various aspects of their criminal behavior (e.g., frequency and type of common offenses in the past year), it is still questionable whether they can recount their entire criminal history accurately. This issue has far-reaching significance because addicts' reports of their prior illicit experiences is a principal source of data when obtaining life history information.

In order to investigate addicts' ability and willingness to recount life history events, 151 male methadone maintenance patients in Baltimore clinics were selected to study; These were part of a larger study of 617 patients in Baltimore, Philadelphia and New York City.

The 151 patients completed valid ASI interviews which included items pertaining to their prior arrests. A second confidential face-to-face ASI interview was conducted with these same patients one year later. Both of these sets of interviews were later compared with official arrest records.

It was found that the 151 patients recounted 1,241 lifetime arrests whereas 1,470 were documented in official records; this is an under-reporting of 16 percent. Deviation of each patient's report of his lifetime arrests from official records was measured (as to frequency and type) in order to determine the extent of accuracy of these patient reports. It was found that one-third (31.2 percent) of the patients recounted their lifetime arrest history with remarkable accuracy; one-third did so with average accuracy (35.1 percent); while somewhat less than one-third (27.8 percent) were marginal in this regard (in addition, 6.0 percent of the patients' reports were grossly inaccurate). Overall, these recapitulations were surprisingly accurate in that all but one of the patients were able to recall some, most, or all of their lifetime arrests.

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EVALUATING OUTPATIENT DRUG ABUSE TREATMENT PROGRAMS: SETTING EFFECTS

A. M. Horton, Jr., F. M. Tims, B. W. Fletcher

This paper reports the findings of a national survey of outpatient drug abuse treatment programs conducted in 1988. The purpose of the survey was to ascertain the extent to which drug abuse treatment programs in various settings (hospital based, mental health center, free standing facility) performed treatment evaluation activities. Information was obtained from treatment program directors regarding whether treatment evaluation activities were performed, the staff who collected evaluation information, the nature and types of data collected, whether performance comparisons were made, and whether program changes resulted from the evaluation activities.

The influence of treatment setting upon drug abuse treatment evaluation activities appears minor. While, there were differences in terms of the extent to which follow-up information was collected, how successful follow-up information collection was, kinds of information obtained and how the information was to be obtained, there were only trends in the data to suggest differences in the extent to which follow-up information was used to make comparisons and changes. Hospital-based programs, fairly consistently were more involved in evaluation-related tasks than free standing or mental health clinic based programs.

Interestingly, the small differences that were observed appeared to favor the hospital-based programs. Perhaps, hospital-based programs have access to more abundant financial resources and/or the multidisciplinary mix found in a hospital setting is more supportive of evaluation activities. It is possible that self-evaluation efforts in all treatment settings would be encouraged to a greater extent if specific resources were available to support evaluation tasks.

ACKNOWLEDGEMENTS:

Supported in part by NTDA Grant #501-DA03272 to the Institute of Social Research, University of Michigan, Ann Arbor, Michigan. Project staff included David Klingel. Thomas D'Aunno, Thomas Vaughn, and Richard Price who helped in the preparation of the data.

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EVALUATION OF DRUG ABUSE DAY TREATMENT: DESCRIPTIVE DATA

J. GUYDISH; T. NEMOTO; M. CHAN; A. ACAMPORA AND D. WERDEGAR

Walden House, Inc., is a drug abuse treatment provider located in San Francisco, California. In 1989, Walden House began a day treatment program to meet the changing needs of drug abusers. In the context of substance abuse, day treatment is non-specific in terms of drug of choice and addiction severity, addresses the needs of polydrug dependent clients, provides an alternative for those who cannot or will not participate in residential treatment, potentially increases access to, and decreases costs of drug abuse rehabilitation. The Walden House program is designed to emulate the atmosphere and activities of the adult residential therapeutic community.

This evaluation involves two phases. In the initial phase, a cohort of day treatment clients (N=91) was interviewed to establish various population characteristics. In the second phase, clients will be randomly assigned to residential or day treatment. Clients in both groups will be followed at six month intervals.

Initial data indicate that day treatment is attracting and serving a diverse population of drug abusing clients: 1) ethnicity (54% African-American, 33% White, 9% Hispanic, 4% Asian); 2) 25% female; 3) 75% high school completion; and 4) mean age of 33 years. Frequently reported drug use in the 30 days preceding interview included cocaine (39%), alcohol (37%), multiple drug (34%), marijuana (15%), and heroin (10%). For drug use of more than 1 year, cocaine was reported by 86% of the sample, second only to alcohol use (95%). The majority (79%) had a history of prior treatment, 33% were referred by the criminal justice system, and 45% had a history of outpatient psychiatric treatment. Early retention data indicate that 52% of the sample remained in treatment after 6 months; 38% had transferred to residential treatment. Attrition among day treatment only clients was 29% vs. 19% among those transferred to residential treatment, suggesting that day treatment, while more accessible, may have higher attrition rates than standard residential treatment.

This work was supported by NIDA (Grant R18 DA06979).

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A Test of Two Methods in Providing Adult Education Services in Methadone Maintenance

D. A. Zanis, D. S. Metzger and G. Moyer

Few methadone maintenance programs offer adult basic education services and to our knowledge, none have been scientifically evaluated for efficacy. We examined the practicality and feasibility of implementing two different forms of adult basic education for methadone patients without a high school diploma. These programs were evaluated on the basis of attendance, completion and achievement of a general high school equivalency diploma (GED). Two different methadone programs were used. In (Program A) a 20-week off-site, community-based education service was offered to 33 volunteers. In (Program B) the same curriculum was offered on-site to 20 subjects. Only one subject (3.3%) reported for the off-site services and this subject did not complete the program. In Program B, six subjects (30.0%) attended ten or more educational sessions, and three subjects completed the program. At the end of the 20-week course offered in Program B, an evaluation was conducted to examine several indicators of treatment outcome for Completers (N=3) versus non-Completers (N=16). We found Completers showed positive behavioral changes at the conclusion of the program as measured by ASI self-reports of decreased substance use, lesser severity of psychiatric symptoms and an increase in program attendance. A twelve-month follow-up evaluation was conducted with 16 of the 20 original participants referred to the on-site GED classes in Program B. At this evaluation point all three Completers and one additional subject who attended at least ten GED classes (N=4, 20%) were able to obtain a GED certificate. The data for this group was then examined to determine if the acquisition of a GED certificate yielded any significant results. There were no outcome differences as measured by employment, psychiatric symptoms, or substance use between clients who had obtained a GED and those who did not obtain a GED at the 12 month follow-up period. We conclude that adult education services can be an effective adjunctive treatment and should be incorporated in methadone programs. It is recommended traditional referral services should be further investigated for efficiency.

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SOCIAL NETWORKS AND METHADONE TREATMENT

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Objective: This study assessed the impact of social tics on substance abuse treatment outcome. Two models were evaluated: based on the self-medication model it was hypothesized that social support would aid in coping with painful affect and decrease the need for drugs: based on a social learning model it was hypothesized that drug use in the social network would threaten abstinence due to modeling and conditioning effects.

Method: 70 methadone maintenance patients were given baseline measures of mood, stress, social support and drug use in the network and followed prospectively for three months with weekly urine drug screens.

Results: Social support was correlated with positive affect ($r = 59$, $p<.001$), and stress with negative affect ($r = .46$, $p<.001$), but no measures of social support, affect or stress correlated with the proportion of drug positive urines. However, patients with at least one drug user among the closest significant others had 63± 38% positive urines versus 35 ± 36% positive among those without a drug using significant other ($T = 3.2$, $p<.002$).

Conclusions: Substance use in the social network had a substantial negative impact on treatment outcome. Consistent with the social learning model and the traditional "persons, places and things", this suggests interventions should get drug using significant others into treatment and teach patients coping skills to reduce their negative influence.

Correlation Matrix of Baseline Measures and Drug Use Outcome

	Functional Social support	Stress	Drug use in Network	Positive Affect	Negative Affect	Proportion Positive Urines
Functional Social Support		1.00				
Stress	-0.16					
Drug Use In Network	0.02	0.16	1.00			
Positive Affect	0.59***	-0.38**	0.14	1.00		
Negative Affect	-0.40***	0.46***	-0.01	-0.59***	1.00	
Proportion Positive Urines	0.05	0.19	0.36	0.11	0.02	1.00

2-tailed Significance: * = p <.05 ** = p < .01 *** p < .001

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ATTRITION FROM A RANDOMIZED TRIAL COMPARING PSYCHOSOCIAL TREATMENTS IN A 180-DAY METHADONE DETOXIFICATION CLINIC

K. L. SEES; K. L. DELUCCHI; P.M. REILLY; D. J. TUSEL; P. BANYS AND H. W. CLARK

This project deals with improving substance abuse treatment. They primary objective is to investigate whether high-intensity substance abuse treatment improves treatment outcome compared to a more typically low-intensity treatment during long-term (180 day) methadone detoxification in injection opioid abusers. This current report details the preliminary analysis of attrition in the first 107 subjects to enter this randomized trial. We focused on two hypotheses: 1) A greater proportion of subjects in high-intensity treatment will drop out of treatment during the stabilization phase (day 1-102), and 2) A greater proportion of subjects in low-intensity treatment will drop out of treatment during the taper phase (day 103-180).

Subjects tended to be living without a partner (81.3%). unemployed (69.2%), male (67%). white (51.4%), black (25.2%), or hispanic (16.8%), average age of 39.6 yrs (range 20-63), have 12 or less years of education (71.9%), abuse at least one other drug in addition to heroin and nicotine (91.6%), smoked cigarettes at the time of admission to the protocol (93.45%). and have another psychiatric diagnosis (41% with depression (41% with depression and/or ASPD). Forty-eight subjects (44.9%) have completed the stabilization phase of treatment (day 1-102), 45 (42%) have dropped out or been terminated before day 173, and 37 (34.6%) are currently in treatment. For the 70 subjects who have completed or dropped out of the study to date, the median length of treatment was 128.9 days.

A statistically significant relationship was found between attrition and several measures including: the ASI composite score for alcohol, the number of significant life events, the frequency of needle use, expectations of difficulty qutting, expectations of success in quitting, and desire to quit using all drugs. The best predictors of increased drop out were lower ASI alcohol composite scores, higher frequency of needle use, and higher expectations of difficulty quitting (Wilk's Lambda = .74, $F(3,66)=7.54$, $p=0.0002$). The attrition rate between the randomly assigned study groups did not differ substantially. Retention in the 180-day methadone detoxification program has been good. Most subjects have remained in treatment well into their taper phase and many have remained in treatment for nearly the full 180 days. The 180-day methadone detoxification modality holds promise as a treatment option for those injection opioid abusers who do not qualify for or are not interested in long term methadone maintenance.

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Assessment of Reinforcers for Clients in a Community-Based Methadone Treatment Program

G. Rowan-Szal

The focus of this study was to evaluate the effectiveness of a reinforcement system for clients in a community based methadone treatment program. The subjects consisted of 99 methadone maintained clients who were allowed to earn stars for performing specific behaviors, during the time the intervention was in effect (3 months). Behaviors included attending either individual or group sessions and providing clean urines. In addition to being able to earn stars for these behaviors, all clients were assigned to one of three reinforcement groups according to their primary treatment counselor. The 3 groups differed in terms of how many stars the clients had to earn before they could trade them for reinforcers. The groups consisted of the following: 8 stars earned a reinforcer, 4 stars earned a reinforcer or no reinforcer earned until the end of the intervention. Counselors at the treatment program chose the available reinforcers which consisted of items such as coupons for gasoline or food and bus tokens.

Analysis revealed a significant increase in attendance at group sessions during intervention months ($F(2,129) = 8.30$, $p < .001$). Individual session attendance showed a significant decrease following the preintervention months ($F(2,129) = 11.12$, $p < .001$). Total session attendance showed a significant decrease following the intervention months ($F(2.129) = 8.26$, $p < .001$). Reinforcement groups (0, 4 and 8 stars) did not differ with respect to the number of sessions the clients attended ($F(2.129) < 1.0$). Urinalysis results revealed a significant interaction between reinforcement group and time ($F(4,127)$ 3.11, $p < .05$). Clients in the 4 star reinforcement condition had fewer dirty urines than either the 0 or 8 star reinforcement groups through the postintervention period. These results suggest the compliance monitoring and recognition clients receive by earning stars may be sufficient to increase group session attendance. However, the ability to earn reinforcers in addition to stars may be required to influence drug use as detected by urinalysis.

ACKNOWLEDGMENTS:
This work was supported by NIDA Grant DA06162.

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FAMILY HISTORY OF SUBSTANCE ABUSE AS A RISK FACTOR IN PREDICTING CRACK SMOKERS' SUBSTANCE USE, RISK BEHAVIOR, AND PSYCHOPATHOLOGY

B. D. CAUDILL; J. A. HOFFMAN; R. L. HUBBARD; P. M. FLYNN AND J. W. LUCKEY

As part of a 5-year comparative treatment investigation with cocaine addicts in the inner-city Washington, D.C. area, an extensive intake assessment was conducted with 246 clients (94% of whom are African-Americans, and 96% of whom are primarily crack smokers). This assessment included measures of each client's family history of alcoholism or drug abuse, and an extensive series of current and historical measures of drug and alcohol use, psychiatric disorders, anti-social, and criminal behavior. 75% report a family history of alcoholism or drug abuse, while 36% report having fathers, and 19% mothers, who bad drug or alcohol problems. For the current paper, analyses were conducted to examine the impact of parental, and maternal, histories of drug or alcohol abuse on clients' prior and current levels of functioning.

For many current behaviors and historical variables examined, clients who were Parental History positive (PH+) were substantially different than were clients who had no parental history of alcoholism or drug abuse (PH-), as were clients who were Maternal History positive (MH+) different than those who presented with no maternal history of alcoholism or drug abuse (MH-). Having a history of parental, or maternal, alcoholism or drug abuse was associated with an increased risk for drug or alcohol use, abuse, and treatment in the past; was associated with prior and recent criminal behavior; was highly associated with a diagnosis of anti-social personality disorders (ASP), and with a series of related anti-social behaviors; and finally, other than its relationship to an ASP diagnosis, was not related to other measures of psychopathology. Findings were generally more dramatic when comparing MH+ clients with MH- ones, relative to PH+ with PH- ones, indicating alcohol or drug-abusing mothers have a substantial impact on a number of aspects of their childrens' subsequent lives. This latter finding is even more significant considering that 49 of the MH- families contained alcoholic fathers.

In general, the current findings clearly support a social learning or biopsycbosocial interpretation of the impact of a family history, and the dramatic impact of a maternal history, of drug or alcohol abuse on the children raised within that family -- a setting in which the addicted parent typically exhibits co-morbid disorders and family dysfunction, along with the modeling of substance-abusing behavior for the children. Exposure to these intluences would be expected to place these children at risk, which the current findings suggests has occurred with this sample of crack addicts. Future prevention and treatment efforts with similar drug addict populations also need to recognize the critical role that the family may play in this process. Affiliation: Ctr. for Drug Treatment & Res. The Koba Instit., Washington, DC and Res. Triangle Instit., RTP, NC

COCAINE ABUSE: PREDICTORS OF RELAPSE

C. BERNACCHI; M. E. KHALSA; J. LONG AND D. ANGLIN

Data were collected from 300 cocaine dependent male subjects seeking treatment at a VA hospital. The subjects were followed at one and two years after treatment entry. Eased on the total number of days of cocaine use during the first follow-up year, subjects were categorized into "abstinent" (0 days of use; (n=63), "slippers" (1 to 5 days of use; n=61), "bingers" (6 to 58 days; n=76), and "persistent users" (more than 59 days; n=68). Self report of recent cocaine use was validated with urine toxicologies, which revealed 10% under-reporting. To identify predictors of relapse among these four groups, several variables related to cocaine use patterns, alcohol consumption, other illegal drug use, treatment modality chosen, components of treatment programs and individual characteristics (demographics and background) were studied.

No statistically significant differences were found in demographic characteristics. Statistically significant differences were found between the groups for other variables. Subjects in the "abstinent" group reported having non-drug-or-alcohol using friends ($p<.000$) and confiding in their family, friends and self-help members ($p=.07$). When combined, those who stayed abstinent and those who used less than 5 days reported higher levels of support from the treatment staff ($p<.05$), from their non-drug friends ($p<.05$) and from their spouse or common law ($p<.05$) than those in the other groups.

In terms of the treatment received, those abstinent had higher rates of attendance to outpatient clinics and self-help groups after 21 days of inpatient treatment ($p<.001$), while most of those in the "persistent users" group had attended inpatient only, or had received episodes of residential treatment.

Helpfulness of inpatient treatment components were studied for two selected groups: inpatient only vs. inpatient followed by self-help groups. Statistically significant differences were found in that the inpatient with self-help group felt more satisfied with the inpatient treatment ($p<.01$), felt that the self-help groups during inpatient were helpful ($p<.03$), felt that drug education during inpatient was helpful ($p<.04$), and so were spiritual counseling ($p<.05$) and recreational activities ($p<.08$).

Analysis currently in progress will provide further findings that will aid clinicians in relapse prevention strategies.

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INTRAVENOUS COCAINE USE AND ACHIEVEMENT OF INITIAL ABSTINENCE

A. J. BUDNEY; S. T. HIGGINS; W. K. BICKEL AND J. R. HUGHES

This study assessed whether cocaine-dependent persons who administer cocaine intravenously (IV) versus intranasally (IN) differ in achievement of initial abstinence during outpatient treatment. It has been suggested that IV abusers need hospitalization so that impulsive use can be controlled and an initial period of abstinence obtained. Fifty-nine persons seeking outpatient treatment completed an intake interview and received behavioral treatment or standard drug counseling. IV users had less years of education, were employed in less skilled jobs, were less likely to be married, and reported more negative consequences from cocaine use. IV users reported using more cocaine per occasion and spent more money on cocaine per week. Overall, during the initial 6 weeks of treatment, IV and IN users achieved equivalent periods of continuous cocaine abstinence Number of consecutive weeks of cocaine-free urine specimens achieved during the first 6 weeks of treatment did not significantly differ between IV users ($\bar{x}$=3.2) and IN users ($\bar{x}$=3.2). A significant main effect for treatment ($p<.01$) indicated that the behavioral treatment produced more consecutive weeks of cocaine abstinence ($\bar{x}$=4.2) than standard drug counseling ($\bar{x}$=2.0). A nonsignificant trend towards an interaction (p=. 15) between type of treatment and route of administration was observed with the length of abstinence not differing between IV and IN users in the behavioral group ($\bar{x}$=4.2 versus $\bar{x}$=4.2), while in the standard group, IV users achieved fewer consecutive cocaine-free weeks than IN users ($\bar{x}$=0.9 versus $\bar{x}$=2.4). These results indicate that IV cocaine users may be able to achieve a substantial period of abstinence on an outpatient basis, although special types of treatment may be necessary to obtain a positive outcome.

Supported by Grants DA061 13 and DA07242 from the National Institute on Drug Abuse.

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THE INTERACTION OF ENHANCED CONTINUITY OF CARE AND DESIPRAMINE IN EARLY COCAINE TREATMENT

S. M. HALL; S. TUNIS; P. BANYS; D. TUSEL AND H. W. CLARK

The literature contains trials of pharmacological agents and of psychological treatments for cocaine abuse, but a definitive treatment has not emerged. This study focuses on increasing entrance into outpatient treatment after brief inpatient treatment for cocaine abuse, and enhancing retention, and therefore abstinence. In a random assignment, 2 X 2 design, we are comparing inpatient-initiated desipramine (200 mg.) versus placebo drug, and enhanced continuity of care versus standard treatment structure. Desipramine or placebo administration begins on the inpatient unit. Administration continues until Week 5 of outpatient treatment. In the enhanced continuity condition, subjects have the same counselor in inpatient and outpatient treatment, and begin attending groups on the outpatient unit while inpatient. In standard treatment structure, subjects have different counselors during inpatient and outpatient treatment and no contact with the outpatient clinic until the end of inpatient treatment, when they are referred to that clinic.

Primary hypotheses were that cocaine patients assigned to the combined desipramine-continuity condition will be more likely to (1) be abstinent from cocaine at all assessments; (2) be more likely to enter inpatient treatment and to remain in treatment for a longer time. We assessed subjects at baseline, Weeks 3, 8, 12, and 26 on drug use and psychosocial measures. N = 103. Here, we present data from the first 82 subjects to reach both the 3- and 8-week follow-up points.

At Week 3, preliminary results tend to support the first hypothesis. Cocaine abstinence rates (abstinent by both self-report and urine screen) indicate lower use rates in the combined condition that in the three other conditions. For desipramine-continuity, 87% of the subjects were abstinent; for desipramine-standard, 62%; for placebo continuity, 78%; for placebo-standard, 64%. Differences among conditions increased when Antisocial Personality (ASP) subjects were removed. With ASP-positive subjects removed, for desipramine-continuity, 90% of the subjects were abstinent; for desipramine-standard, 67%; for placebo continuity, 71%; for placebo-standard, 50%. Effects of the combined intervention may not endure to Week 8, however. At this time, including both ASP-positive and -negative subjects, for desipramine-continuity, 67% of the subjects were abstinent; for desipramine-standard, 64%; for placebo continuity, 71%; for placebo-standard, 56%. Differences in treatment entrance, or in days in treatment, did not emerge at either time point. Exploratory analyses indicated patient characteristics, particularly commitment to total abstinence, predicted cocaine abstinence.

[1]Funded by a Merit Review Grant and a Research Career Scientist Award to Dr. Hall, and by NIDA Grant #R18 DA06097. AFFILIATION: San Francisco Veterans Affairs Medical Center, University of California, San Francisco.

COGNITIVE-AFFECTIVE STATES IN COCAINE DEPENDENT INDIVIDUALS

S. K. Avants, A. Margolin and T. R. Kosten

Cognitive affective states are believed to be important factors in sustaining the addictive cycle. We conducted two studies based upon recent developments in cognitive psychology linking schematic self-structures to negative emotions via associative nodes in long-term memory. Specifically, we applied Higgins' self-discrepancy theory to cocaine dependence, using a modified version of Higgins' idiographic measure of self-representations. In Study 1, we compared the cognitive-affective states of cocaine users (n = 29) to those of methadone-maintained patients (n = 30) and non-drug users (n = 27). Cocaine users were found to have the most negative self-representations, to be discrepant with positive self-guides and congruent with their "addict" self-schema. They were also depressed, and reported being most vulnerable to cocaine use when feeling depressed. In Study 2, we assessed changes in these domains that occurred with initiation of abstinence. Eleven cocaine-dependent patients who successfully initiated abstinence subsequent to an 8-week psychopharmacological treatment demonstrated marked shifts in their cognitive-affective states. They became significantly less depressed, less discrepant with their "ideal" self-representation, more discrepant with their "addict" self, and used generally more positive attributes to describe themselves. We suspect that the shifts observed in these patients are extremely fragile and will need to be strengthened with continued treatment. Future research is recommended to examine fluctations in these shifts over time.

Higgins, E. T. (1987). Self-discrepancy: A theory relating self and affect. Psychological Review. 94, 319-340.

This research was supported in part by NIDA grants P50DA0460, K02DA0112 (TKR) and R18DA06190 to Yale University and by a grant to UC San Francisco School of Medicine from MacArthur Foundation.

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INPATIENT VERSUS OUTPATIENT TREATMENT FOR COCAINE DEPENDENCE: THREE-MONTH OUTCOMES FROM A CUT-OFF BASED RANDOMIZED CLINICAL TRIAL

B. E. HAVASSY, D.A. WASSERMAN AND C. J. SCHMIDT

Scientific, policy, and economic concerns about drug abuse treatments and their outcomes have led to increased scrutiny of existing treatments. We report the first results of a multi-site cut-off based randomized clinical trial of the relative efficacy of inpatient (IP) and outpatient (OP) treatments for cocaine dependence. The study was conducted at six, private, hospital-based 12-step oriented chemical dependency treatment programs. Each provided inpatient (IP) and intensive structured outpatient (OP) treatments for drug and alcohol use problems.

Cocaine users presenting for treatment who met DSM-III-R criteria for cocaine dependence and agreed to be research Ss were assigned to IP or OP treatment using a cut-off based randomized assignment procedure. Based on a measure of addiction severity developed for this study, Ss scoring within a preselected cutoff interval on the measure (i.e., moderately addicted) were randomly assigned to treatment. Ss scoring below this interval (less severely addicted) were assigned to OP and those scoring above the interval (more severely addicted) to IP. In some cases, the treatment assigned was not the treatment received. Ss received 12 assessments over 1 year and provided urine specimens at each assessment.

Tests were conducted of the main hypothesis that IP treatment, compared to OP, results in better outcomes for persons with more severe dependence. The outcome was continuous abstinence for 3 months after treatment entry. Ss were coded abstinent if all self-reports and urines specimens for the 3 months indicated no cocaine use. Excluding Ss who began day treatment, to date, 308 Ss completed at least the 3-month assessment. 68 additional Ss were lost to follow-up. The hypothesis was tested excluding lost Ss and also including them as not abstinent (n = 376).

Cocaine addiction severity scores, treatment modality, and their interaction were tested as predictors of abstinence in two logistic regressions. In both, severity interacted with treatment modality (χ^2 (1,376) = 11.72, p < .01; χ^2 (1,308) = 9.16, p < .01). In moderately addicted, randomly assigned Ss, there were no differences between IP and OP. Less severely addicted Ss receiving IP did better than those receiving OP. Results for severely addicted Ss are currently uninterpretable due to the small number receiving OP. Although these preliminary results do not support the hypothesis, they do indicate that consideration of efficacy of IP-OP treatment for persons dependent on cocaine should take severity of addiction into account.

Supported by NIDA Grant# DA 05582. UCSF Treatment Outcome Research, 5 Third Street, #320, San Francisco CA 94103.

TREATMENT EFFECTIVENESS FOR COCAINE ADDICTION: A FOLLOW-UP

D. ANGLIN; M. E. KHALSA; A. PAREDES; P. POTEPAN AND C. POTTER

Data were collected from 300 cocaine dependent male subjects seeking treatment at a VA hospital. The subjects have been followed at one and two years. A longitudinal retrospective natural history approach was used to break the lifetime drug career of the individual into segments pertaining to any significant life event, change in drug use, or a change in drug treatment. In addition, Treatment Evaluation and Treatment Summary forms were used to collect detailed information on the treatment career (sequence of treatment exposures since initial treatment), the characteristics of the treatment, and the subjectively reported effectiveness of each treatment experience. Time-series techniques have been applied to compare pre- and post-treatment behaviors, including the course of cocaine use, other drug use and associated behaviors, and to assess treatment effectiveness.

For the group as a whole, the 12 months pre- and post-initial treatment comparison showed: decreases in crack use, severe use of cocaine and use of other drugs. Work activities, engagement in stable relationships, and criminal activities did not show statistically significant differences. Dealing behaviors decreased however, and this change was statistically significant.

Most of the patients participated in other treatment modalities in addition to the initial treatment within the one year follow-up. Six categories defining combinations of treatment modalities were identified. The combination of inpatient and outpatient with self-help group attendance was the most commonly selected and was associated with more improvement. Patients who selected inpatient care followed by heavy involvement in outpatient with self-help groups care reported the longest periods of abstinence from cocaine. This group also was significantly less involved in criminal activities and drug dealing, although alcohol use did not show significant change. Patients who participated in multiple residential programs or those who received inpatient treatment only did not display better outcomes. Drug use decreased dramatically in these two groups but most dimensions of social behavior showed less striking changes, and deviant behaviors did not decrease significantly. Clinical outcome appeared to be more related to the treatment combination chosen than to patient characteristics.

Further research is needed to investigate the issue of treatment self selection and intensity of selected treatment, especially as influenced by motivation and other variables related to the emotional state of the individuals.

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CRAVING FOR COCAINE AND RETENTION OF CRACK ADDICTS IN COCAINE ABUSE TREATMENT

J. A. HOFFMAN, B. D. CAUDILL AND J. J. KOMAN, III

Initial results from a comparative treatment investigation with inner-city cocaine addicts in Washington, D.C. are presented that highlight the relative efficacy of comparative treatments for retaining cocaine abusers in treatment. For this investigation, data is examined for 169 cocaine addicts (93% of whom are African-Americans, and 96% of whom are primarily crack smokers) who have either completed 4 months of outpatient treatment, or who dropped out prior to completion. The relative efficacy of minimal and intensive forms of group therapy, alone and in combination with psychotherapy, and psychotherapy with family therapy, in retaining clients in treatment is being examined. Initial findings show that more intensive forms of treatment, such as group therapy five days a week versus two days a week, or adding psychotherapy and family therapy to either form of group therapy, are much more successful in retaining clients in treatment, and in encouraging active levels of client participation. Clients who receive group therapy five days a week, receive individual psychotherapy, and participate in family therapy sessions, are much more likely to remain in treatment and to actively participate in treatment than are clients from any other treatment condition. Initial findings suggest that providing cocaine addicts with more intensive forms of treatment than are typically available should contribute significantly towards enhancing cocaine abuse treatment. Adding family therapy to the treatment package had the greatest impact in enhancing these initial measures of treatment outcome (retention and participation rates).

In addition, prior to each group therapy session, clients are asked to complete a 7-item craving questionnaire. Questions ask clients: on how many of the last 7 days they have had cravings, how often they are, how intense they are, how long they typically last, how intense they are right now, how confident they are in coping with their cravings in the next week, and on how many days in the last week they have used cocaine. Internal reliability levels on these items were quite high, based on correlational analyses, as were test-retest analyses for the same clients. In addition, craving was significantly related to drug use during treatment - those with high cravings were more likely to relapse. Finally, an assessment of clients craving ratings over time in treatment also showed a reduction in average craving ratings as clients with more severe ratings relapsed in the initial stages of treatment. In general, clients ratings of cravings were predictive of risk for relapse.

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DESIRE TO DRINK OR NOT TO DRINK IN ALCOHOL-DEPENDENT PATIENTS IN TREATMENT

J. GREELEY, W. SWIFT AND N. HEATHER

A major dilemma facing problem drinkers in treatment is the ambivalence they experience between wanting to stop drinking and the continued desire to drink. It might be argued that, if treatment is to succeed, it must promote a shift toward an indifference for alcohol, if not a decided disinclination to drink. In the investigation of cue-reactivity, craving is typically measured by unidirectional rating scales in which the drinker's disinclination for alcohol is not explicitly considered. This study asks drinkers to confront the 'drink or not drink' dilemma and tell us where their preferences lie.

Thirty problem drinkers in inpatient treatment were asked to rate their desire to drink and their desire not to drink alcohol during exposure to alcohol and neutral beverage cues. A bi-directional scale was used on which the midpoint indicated indifference about drinking, while movement forward and backward indicated an increased desire to drink or an increased desire not to drink, respectively. Heart rate, blood pressure and stress and arousal levels were also measured.

Mean score on the Severity of Alcohol Dependence Questionnaire (**30.1** (±12.2)) was in the moderate range as was mean confidence in ability to resist drinking (Situational Confidence Questionnaire-39 was 72.3 (±22.0)). Overall, subjects reported being inclined not to drink under both cue conditions. In the alcohol cue condition, however, desire not to drink decreased ($F(1,24)=4.6$; $p<.05$). There were no cue-specific differences on the physiological measures.

Two distinct subgroups of drinkers were identified: One reported a positive desire for alcohol in the alcohol cue condition and the other reported a fairly strong disinclination to drink. A median split of the sample based on reported overall desire revealed that those reporting more positive desire for alcohol were younger ($F(1,27)=4.4$; $p<.05$), less confident about resisting drinking ($F(1,27)=10.7$; $p<.01$), more depressed ($F(1,27)=5.5$; $p<.05$) and reported greater stress in the presence of alcohol. They did not differ on dependence and consumption levels ($Fs<2.0$). Although self-reports of craving were highly variable, they were related to factors predictive of outcome from treatment (e.g., depressed affect and self-efficacy).

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EFFECT OF SMOKING STATUS ON ALCOHOL RECOVERY

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Despite high rates of smoking among alcohol abusers, research addressing these two disorders has progressed in relative isolation from each other. This study assessed the impact of smoking status on alcohol resolution in 3 samples of alcohol abusers; (i) untreated recovered (n = 120). (ii) treated outpatients (n = 155). (iii) participants in a nation-wide (n = 9916) survey of alcohol and smoking patterns. Untreated recovered alcohol abusers who had either continued smoking or had quit smoking and drinking simultaneously had a more severe alcohol problem than individuals who had never smoked or who had quit smoking prior to their alcohol resolution. Treated alcohol abusers were classified into: never smokers, ex-smokers, more nicotine dependent (< 10' to first cigarette of day), less nicotine dependent (≥ 10'). More nicotine dependent alcohol abusers had fewer days of abstinence than those less dependent but more abusive days (> 10 drinks), and fewer low (≤ 4 drinks) consumption days. All groups showed similar improvement by follow-up. Follow-up data showed smokers tend towards abstinence; the non-smokers tended towards non-abstinence. Surveyed subjects were classified into abstinent and non-abstinent alcohol recoveries. Of those who had ever smoked and had resolved their alcohol problem without treatment. 48.9% (79/162) of abstinent recoveries and 50% (90/180) of non-abstinent recoveries, had also quiz smoking. Clearly, alcohol and nicotine use are not independent of each other. Since those who abuse alcohol and nicotine appear to be a heterogeneous group, treatment decisions will likely need to be individualized.

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COUNSELING AND CONTINGENCY CONTRACTING IN METHADONE MAINTENANCE: A ONE YEAR FOLLOW-UP

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Although methadone maintenance has generally been found to be an effective treatment for opiate addiction, treatment effectiveness differs from clinic to clinic. This study seeks to vary the conditions of treatment and to determine which of six models are most effective in reducing drug use and HIV risk. In a 3x2 factorial design, new admissions to methadone maintenance are randomly assigned to one of three counseling; (1) "medication only" (MOMT), (2) "standard" counseling (STAND), and (3) "enhanced" services (ENHAN); and one of two contingency contracting conditions; (1) no contingencies (NC), and (2) contingency contracting (CC). Three hundred sixty subjects have been recruited. The sample is 65% male, 37% African American, 4% Hispanic, and 54% white, mean age, 38, 68% unemployed, and 51% with less than high school education. Results from 240 subjects who were 12 months beyond treatment admission are reported here. Contingency contracting includes discharge for continuous positive urines, and CC subjects were discharged at a greater rate than the NC group. However, CC subjects were more likely to be re-admitted. In the first six months of treatment groups did not differ with regard to urinalysis results. In months 6-12 a significant counseling level by contingency contracting interaction was found for opiate positives. NC subjects in MOMT and STAND groups had more positives than CC, and this was reversed in the ENHAN group. Also, in months 6-1, CC subjects had significantly fewer cocaine positives than did NC. Among 195 subjects with complete 6 and 12 month follow-up data, self reports of drug use showed mixed results. CC subjects reported a higher frequency of heroin use than NC in the 6 months prior to the 6 month interview, NC subjects reported more days of crack use. STAND and ENHAN subjects significantly reduced days using more than one substance per day and frequency of IV cocaine use. Changes in these variables in the MOMT group were not significant. Regarding HIV risk behavior, CC subjects reported more often sharing cookers and cotton in the 6 months preceding the 12 month interview than did NC subjects. At six months, MOMT subjects were more likely than STAND or ENHAN to share needles that were not cleaned, but by 12 months, they were less likely than STAND subjects to share, unclean needles. Regarding problems in other life areas, CC subjects had higher ASI Legal Severity scores at 12 months than did NC. CC subjects reduced their ASI Social Severity scores from initial to 12 months but social problems reported by NC subjects did not change. These results are preliminary. The impact of reduced or enhanced services and of contingency contracting will not be fully understood until longer term follow-up (12, 18 and 24 month) is completed with the full sample. Supported by NIDA grant #R18 DA 06104

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180 DAY METHADONE DETOXIFICATION TREATMENT: A SIX-MONTH FOLLOW-UP

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The San Francisco VA Medical Center, in association with the University of California San Francisco, opened a 180-day Methadone Transition Treatment (MTT) Clinic in June 1990. The two objectives of this clinic were to provide heroin addicts with ready access to six months of methadone treatment and to develop innovative pharmacological and psychosocial treatment strategies to slow the spread of AIDS. Thirty-eight heroin addicts enrolled in the first research protocol conducted in this clinic. The trial tested the difference between 40 mg and 80 mg of methadone in a long term detoxification program. The results of this trial have been previously reported. They were followed up six months after completion of the MTT. The first purpose of this six-month follow-up study was to determine whether any progress made during the 180-day methadone treatment was sustained. The second purpose was to determine whether the subjects followed through with the plan for enrollment in definitive, long-term substance abuse treatment. At the six-month follow-up date, two subjects had died; thirty-two (89%) of the remaining 36 subjects were located. All but one agreed to a follow-up interview. The one-third reduction in illicit drug use found during the 180-day treatment was sustained at the six-month follow-up date. In addition, the decrease in opiate craving, the amelioration in symptoms of anxiety (State-Trait Anxiety Inventory) and depressive symptoms (Beck Depression Inventory) were also sustained. Seventy-one percent of the subjects had entered into some form of substance abuse treatment during the six months between the MTT and follow-up, and 55% were in substance abuse treatment at the time of the six-month follow-up. Our conclusion is that 180-day methadone detoxification plays an important role in the comprehensive treatment of heroin addiction.

This study was funded by NIDA Grant 1R 18DA06097.

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METHADONE TRANSITION TREATMENT: A TREATMENT MODEL FOR 180-DAY METHADONE DETOXIFICATION

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In March 1989, federal guidelines were revised to permit 180-day methadone detoxification as a modality of treatment intermediate between 21-day methadone detoxification and long-term methadone maintenance. Methadone Transition Treatment (MTT), one model of the 180-day methadone detoxification modality, was created in June 1990 by the University of California, San Francisco (UCSF) Treatment Unit (TRU), and the San Francisco VA Medical Center (SFVAMC). The two-fold objective of the MTT is to facilitate a lasting transition from illicit drug use to either drug-free treatment or methadone maintenance, and to investigate a variety of pharmacological and psychosocial treatment strategies. The components of the MTT are described here, including the model's three phases (induction, stabilization, and taper), the high-intensity psychosocial treatment program, and the clinical indicators determining the specific type of long-term referral. Advantages of the MTT over 21-day methadone detoxification are also reported. Finally, research studies conducted to date using the MTT model are also referenced.

ACKNOWLEDGEMENTS

This work was supported by the San Francisco Treatment Research Unit, funded by NIDA Grant 1R18DA06097.

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LOW (40 MG) VERSUS HIGH (80 MG) DOSE METHADONE IN A 180-DAY HEROIN DETOXIFICATION PROGRAM

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Methadone Transition Treatment (MIT) is a treatment program for opioid addicts that takes advantage of a 1989 change in federal guidelines permitting the establishment of 180-day detoxification programs. Thirty-eight subjects were assigned to either high-dose (80 mg) or low-dose (40 mg) methadone in a double-blind design.

Both conditions showed initial decreases in illicit drug use and distress symptoms (opioid craving, withdrawal symptoms, and dysphoria). The high-dose condition showed a non-significant trend toward less frequent illicit drug use during the period of stable methadone dosing.

We speculate that intensive psychosocial treatment, including weekly individual counseling, and three-times a week group therapy, may have dampened outcome differences between high and low-dose methadone conditions. Attrition was low for both dosage conditions.

Supported in part by NIDA Grant #R18-DA06097

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METHADONE MAINTENANCE REHABILITATION. OUTCOME AT SIX YEAR FOLLOW-UP: TREATMENT CONTINUITY EFFECTS

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Methadone maintenance efficacy was examined for achieving objective rehabilitation criteria as a function of treatment continuity. A 1983 random sample of methadone maintenance patients (n=271) from three diverse populations, VAMC's at Philadelphia (n=111) and Sepulveda (n=100) and University of Alabama at Birmingham (n=60) were followed after six years by an independent research team. Examined were subjects' current treatment status and rehabilitation outcome as measured by a structured interview in which subjects were evaluated on five variables: 1) drug-free for six months or more evidenced by urinalysis (for subjects not in treatment (N=38) self-report was used); 2) living in the same place with the same people for 6 months or more; 3) engaged full-time in work, training, or education or combination work/education, including supervision of under-school-aged children; 4) 75% of friends do not use drugs other than marijuana or alcohol; and 5) sufficient non-drug-related recreational activities without reporting too much free time. The interviewed sample (n=102) was partitioned based on continuity in treatment. Inter-interviewer correlations for chart review and interview assessments ranged from .56 (recreational activity) to .97 (months on methadone) and averaged .77 indicating satisfactory reliability of measurement. Those continuously vs. discontinuously in treatment showed more subjects meeting each criterion (Chi Sq. = 14.35, d. f. = 5. p <.014) and more who met either four or five of the rehabilitation criteria reflecting highest levels of rehabilitation. Continuity group meeting four or five criteria was 63.9% vs. 36.1% (Chi Sq.=7.93, d.f.=1, p<.005). The continuity group also showed significantly more patients who met criteria for abstinence, 64% vs. 44%, (Chi Sq.=3.71, d.f.=1, p<.054) and stable productive activity, 78% vs. 56% (Chi Sq.=4.75, d.f.=1, p.=.029). Using ANOVA, consecutive months abstinence at follow-up was also compared. The duration of abstinence for the continuity group was 3.5 yr. and 2.5 times longer than the 1.4 yr. of the discontinuity group (F = 4.44, d.f. = 34, 66, p < .000). Results provide converging evidence for the efficacy of methadone maintenance and suggest continuity and time in treatment increases the likelihood of more positive treatment outcomes. Findings also suggest methadone programs could increase successfully completed detoxification by incorporating routine assessment and treatment for detoxification fear.

1. Research was supported by NIDA grant #1 RO1 DA5502-01A1.

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INPATIENT STABILIZATION OF METHADONE MAINTENANCE CLIENTS IN CRISIS

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Methadone maintenance clients intermittently have periods of relapse or escalating drug use which ultimately threaten their progression to a drug-free lifestyle. Clients receiving methadone maintenance at the Clinical Research and Treatment Institute (CRTI) of the Addiction Research Foundation (ARF) are given the option of, or may request, an admission to the medical unit for stabilization of a crisis in a protected environment. The objective of this retrospective analysis is to assess the outcome of inpatient stabilization of methadone maintenance clients in crisis as determined by duration of clean samples after discharge, change in percent of samples that were not clean before and after admission, and drugs used upon relapse.

Methadone maintenance at the CRTI is based on a multidisciplinary treatment model which has traditionally focused on counselling and social rehabilitation rather than methadone dose in order to meet the needs of a population using less heroin and more prescription opiates relative to other centres. Examination of the Bureau of Dangerous Drugs Report from January 1, 1990 to September 30, 1991 identified the methadone maintenance clients who were admitted to the unit in this time period. Charts were reviewed for demographic information and pharmacy prescription records determined the methadone doses surrounding the inpatient period. Laboratory records were analyzed to determine the duration of clean samples after discharge, the percent of samples not clean 4, 8 and 12 weeks before and after admission and the drugs used upon relapse.

There were 36 admissions to the medical unit from January 1, 1990 to September 30, 1991 involving 25 patients. Twenty of the patients were female and did not differ significantly from the males on any demographic measures: age 33 ± 7 years; education 11 ± 2 years. Mean length of admission was 5 ± 3 days. Patients were discharged on a methadone dose significantly higher than their most stable dose in the 12 weeks preceding admission (43 ± 12mg vs 39 ± 12mg, $p < .01$). In 26 (72%) of the 36 admissions, the patient relapsed to drug use in less than 1 week after discharge as determined by urine drug testing. At 4 and 8 weeks after discharge there was a significant decrease in the percent of urine samples which screened positive for drugs when compared to the corresponding 4 and 8 weeks prior to admission (57 ± 33% vs 69 ± 32% and 50 ± 33% vs 63 ± 33%, respectively; $p < .05$). However, at 12 weeks there was no difference. Categorizing change in dose into three groups (-5-0mg, 1-14mg and 15-30mg), outcome was better at 12 weeks for patients in the 15-30mg group compared to those with dose change of -5-0mg. The later group actually regressed to a positive change in the pre and post 12 week analysis while patients receiving increases of 15-30mg showed marked improvement in the change in percent of dirty samples (12 ± 22% vs -26 ± 41%, $p < .05$). Thirty-three (92%) of the patients used opiates upon relapse, 47% benzodiazepines and 39% cocaine. Cocaine use resulted in a significant increase in percent of dirty samples of 8 and 12 weeks after discharge compared to patients not using cocaine ($p < .05$).

We conclude that inpatient admission of methadone maintenance clients for stabilization of a drug-use crisis did intercept the crisis and significantly decrease drug use for up to 8 weeks after discharge and increasing the methadone dose 15-30mg during this inpatient period improves outcome at 12 weeks.

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MOOD STATE RESPONSE AND METHADONE PLASMA CONCENTRATION IN STABLE AND UNSTABLE METHADONE-MAINTAINED PATIENTS. PRELIMINARY DATA

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Methadone, an opiate agonist, is a more attractive medication for opiate addiction treatment than naltrexone, an antagonist. We hypothesized that chronic methadone administration induces mood changes that reinforce treatment compliance and are dependent upon the concentration of blood methadone. We also compared methadone mood state responses and blood methadone concentration in two groups of patients, stable or Responders (R) vs unstable or Non-responders (N). Responders were selected from patients having take home medication privileges and the Non responders were selected from patients having urines positive for opiates.

The subjects responded to an orally administered set of mood questionnaires (MBG (Morphine Benzedrine Group Scale), MOWS (Modified Opiate Withdrawal Scale) and MAACL Positive Affect Scale) and had a blood sample taken immediately prior to their usual methadone dose (T1 = trough), and again 1-1.5 hr after methadone (T2 = peak). Subjects also responded to the mood questionnaires at 6-8 hrs post methadone (mid).

The two groups R and N were similar for age, methadone dose, alcohol use and methadone treatment. There were no differences in the psychopharmacologic responses between R and N subjects although trends toward differences were observed. However, the methadone concentrations of N were significantly higher at the trough and exhibited a trend for higher concentrations at the peak. Comparisons of the mood questionnaire results for the trough, peak and mid confirmed that mood changes are induced by methadone. MBG scores, which measure positive mood states were significantly higher after methadone administration than at trough and at the midpoint. MOWS scores which measure opiate withdrawal were highest prior to methadone. The 6-8 hrs scores for both scales were between the trough and peak scores as predicted.

We found no evidence of differential psychopharmacological responses between treatment R and N groups. We found that the N who were also taking illicit drugs had higher methadone concentrations than R despite having the same dose of methadone. However, methadone does change mood in a positive direction after administration. We interpret these results as compatible with the hypothesis that methadone is more acceptable or useful because it induces mood changes which are not induced by a pure antagonist like naltrexone

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AVAILABILITY OF RELIABLE SERUM METHADONE DETERMINATION FOR MANAGEMENT OF SYMPTOMATIC PATIENTS

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Until recently, access to quality controlled, sensitive and specific determinations of serum methadone levels has been very limited. In this study, the concordance between three commerically available vendors of methadone serum levels using gas liquid chromatography was evaluated. The correlation between serum levels of methadone at 24 hours and symptoms of early abstinence was also examined. Twenty subjects in stable methadone maintenance treatment receiving daily methadone doses between 40-80 mg were studied; there were no other exclusion criteria. Using the modified Himmelsbach Opioid Withdrawal Rating Scale, ten patients with more than four symptoms of early abstinence were studied immediately before methadone dosing and compared with ten patients without abstinence symptoms. Methadone serum levels ranged from 0 to 500 ng/ml, and were highly correlated among the three laboratories (pairwise Pearson rs-.792, .881 and .929, $p<.01$). Dosage and Himmelsbach symptoms did not correlate with methadone serum levels. Three patients with both low serum methadone levels (<100 ng/ml) and more than four Himmelsbach symptoms, were found to be taking phenytoin. Dose adjusted serum methadone levels were lower but not significantly so in patients with symptoms ($t=1.54$. $p<.10$). The identification of abstinence symptoms is difficult in patients with other medical and psychiatric syndromes including HIV, alcoholism and depression. Commercially available tests for methadone serum levels are reliable and affordable and may be useful in symptomatic patients.

(Support: Department of Veterans Affairs; NIDA DA05130, DA00049)

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UNIT PRICING ANALYSIS OF BEHAVIOR MAINTAINED BY COCAINE UNDER A PROGRESSIVE-RATIO SCHEDULE IN RHESUS MONKEYS

M. S. KLEVEN, B. W. MASSEY AND W. L. WOOLVERTON

Behavioral economics predicts that drug consumption under fixed-ratio (FR) schedules is determined by unit price (responses/mg/kg) independent of the dose and response requirement that make up that unit price (Bickel et al., 1990). The purpose of the present study was to determine whether a progressive-ratio (PR) procedure could be used to examine relations between unit price and drug intake. Four rhesus monkeys were trained to press a lever in daily experimental sessions under a discrete-trials PR schedule of cocaine reinforcement in which the response requirement was increased every 5th trial. A total of 20 trials, with an inter-trial interval of 900 s and a limited hold of 720 s, were available in a session. Sessions were terminated following two consecutive incomplete trials. Following training, various doses of cocaine (0.01-0.20 mg/kg/inj) were made available with sequences of five, progressively increasing FRs during a session. The percentage of completed trials was an increasing function of cocaine dose, and, within each dose, increasing the response requirement caused a decrease in % completed trials. Total cocaine intake decreased as a linear function of unit price in all subjects ($r=0.85$-0.98; $P < .02$). These data support the hypothesis that drug intake under FR schedules is predicted by unit price, and that changes in either reinforcer magnitude or response requirement have functionally similar effects on intake. A PR schedule which allows drug intake to vary could be useful in studies of pharmacological mechanisms involved in reinforcing effects of drugs. (Supported by NIDA DA-00250, 00161).

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SOME EFFECTS OF REINFORCEMENT DELAY ON BEHAVIOR MAINTAINED BY COCAINE DELIVERY

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While the effects of reinforcement delay have been extensively studied with reinforcers such as food, the effects of this variable on behavior maintained by drug reinforcers has been little studied. In the present study, six male F-344 rats were fitted with chronic, indwelling jugular catheters and responded under a fixed-ratio 10 (FR 10) schedule of cocaine injections (0.33 mg/inj in 0.2 ml over 5.6 s). For three rats, the effects of an unsignalled, non-resetting delay were examined across experimental phases with each rat exposed to an ascending series of delay values beginning with 60 s. Responding was completely, or almost completely, suppressed at delay values between 60 s and 240 s. A return to a O-s delay resulted in a regeneration and subsequent maintenance of responding over the course of several sessions in two of the rats; with one rat, responding never recovered. The other three rats were exposed to a "progressive-delay" schedule in which, after the first injection at a 0-s delay, each subsequent injection was accompanied by a signaled delay. The duration of the delay began at 30 s and doubled with each succeeding injection until 30 min passed without a response, or until a total of 5 hr had passed. Under these conditions responding often was maintained at delay values of greater than 2 hrs, and the delay value reached was a monotonically-increasing function of cocaine dose for two of the rats. For the other rat, this function increased until the highest dose, where a decrease occurred. This progressive-delay schedule may possess advantages over other more common procedures for assessing the effects of manipulations designed to reduce the reinforcing effectiveness of abused drugs. (Supported in part by USPHS grants DA-06634 and DA-032628 and NIDA Contract #271-90-7402)

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COCAINE-FOOD CHOICE IN RHESUS MONKEYS UNDER SECOND-ORDER SCHEDULES OF COCAINE AVAILABILITY

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The intermittent presentation of stimuli that have been associated with drug injections can dramatically alter rates and patterns of drug-maintained behavior. The present experiment was designed to examine the effects of presentation of such stimuli on choice between cocaine and food in rhesus monkeys. Three rhesus monkeys, maintained at approximately 90% of their free-feeding body weights, were trained in a discrete-trials choice procedure to choose between intravenous cocaine (0.03-1.0 mg/kg/inj) and 4 food pellets (1 g/pellet; see Woolverton and Johanson, J. Exp. Anal. Behav. 41: 35-43, 1984 for details of method). One of the monkeys was experimentally naive while the other two had an extensive history with the present procedure. Initially, both reinforcers were available under a FR 30 schedule and an amber light was illuminated during injections (0.3 mg/kg/inj) for at least 30 consecutive sessions. When the dose-response function for cocaine was determined with the amber light paired with injections, the frequency of cocaine choice was an increasing function of dose. Subsequently, a dose of cocaine (0.3 mg/kg/inj) that resulted in $\geq$ 75% drug choice was made available in all sessions and the FR for cocaine delivery was increased to 480 while the FR for food delivery remained 30. The frequency of cocaine choice decreased to low levels (3 - 31% drug choice). Once choice was again stable, amber stimulus lights that had been paired with cocaine delivery were programmed to flash following every 30th response of the FR480 for cocaine [FR480(FR30:S)]. In the naive subject, presentation of the amber stimulus lights increased cocaine choice from 31% to 79%. At a lower dose (0.1 mg/kg/inj), presentation of the amber stimulus lights increased cocaine choice from 18% to 94% in this subject. In the two experienced subjects, presentation of the amber stimulus lights had no effect on cocaine choice. These results suggest that the intermittent presentation of stimuli that have been associated with cocaine injections can increase the probability of choice of a cocaine injection relative to a non-drug reinforcer. However, that effect can apparently be modified by behavioral history. (Supported by NIDA Grants DA-00250 and DA-00161).

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INVOLVEMENT OF STRESS IN COCAINE REINFORCEMENT

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Initial cocaine use is often reported by humans to produce profound subjective feelings of well-being and a decrease in anxiety. In addition, some people can use cocaine "recreationally" without escalating their patterns of use to levels which pose severe health threats, while other individuals are not able to control their drug intake. The following experiment was designed to examine the effects of controllable and uncontrollable electric footshock stress on the acquisition of intravenous cocaine self-administration in rats. Five groups of three rats were trained to respond on a discrete trial, fixed-ratio 10 schedule of food reinforcement. A 20 set limited hold was also included so that if a rat did not complete the ratio within 20 set, the food trial was terminated. A 30 set timeout period followed the termination of each trial so that each trial began simultaneously for all three rats in each group. A random ratio 15 schedule of shock presentation (0.6 mA) was also included for the first rat in each group. Therefore, this rat received a food pellet (45 mg) after pressing the response lever 10 times and also received response contingent (controllable stress) electric footshock after pressing the same lever an average of 15 times. The second rat in each group responded on the same schedule of food reinforcement with shock presentation yoked to food lever responding by the first rat. Therefore, whenever the first rat in each group received response contingent electric footshock (controllable stress), the second rat received an identical electric footshock whether he pressed his food response lever or not (uncontrollable stress). The third rat also responded under the same schedule of food reinforcement but was never shocked (no stress). The food component of the multiple schedule lasted for 100 trials (approximately 1 hr), and the first and second rats from each group typically received about 50 footshocks per session. Five minutes after the completion of the food component of the multiple schedule, the cocaine self-administration component began. Each response on a second lever located on the opposite wall of the experimental chamber resulted in an intravenous infusion of cocaine (0.2 ml delivered over 5.6 set). A 20 set timeout period followed each infusion. This component of the schedule also lasted 1 hr. The rats were initially tested with very low doses of cocaine (i.e., 0.031 mg/kg/infusion), and the concentration was doubled each week (e.g., 0.0625, 0.125, 0.25 and 0.5 mg/kg/infusion) and was followed by a saline substitution (extinction). The introduction of electric footshock initially decreased response rates for rats exposed to both response contingent as well as response independent electric footshock, although response rates gradually returned to near control levels. There were little or no differences between the number of food pellets obtained by all three rats in each group throughout the experiment. However, rats without control over footshock presentation (non-contingent shock) self-administered cocaine at a higher rate and at lower doses (e.g., 0.125 mg/kg infusion) than animals that received the same number of footshocks under different conditions (contingent shock) or that were never shocked. These data suggest that non-contingent electric footshock presentation increases sensitivity to cocaine, indicating that control over environmental stress influences vulnerability to self-administer cocaine. Control over environmental stress may be involved in why some individuals are able to control their cocaine use while others are not. If certain individuals are more sensitive to stress and find themselves in an environment where they do not have adequate control over this stress, then these individuals may be more likely to use cocaine and other drugs of abuse as well.

ACKNOWLEDGEMENT: Supported by USPHS Grant DA06013.

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A NONLINEAR PROCESS MAY UNDERLY COCAINE SELF-ADMINISTRATION DE-REGULATION IN RATS

M. P. PAULUS, A. MARKOU AND G. F. KOOB

Cocaine is a powerful reinforcing substance in both humans and animals. The assessment of the degree of dyscontrol in drug-administration behavior may lead to a quantitative measure of cocaine dependence. The transition from controlled to dyscontrolled use of the drug can be defined operationally as **progressive deregulation** of drug-administration patterns and implies that the rules (behavioral, cellular, or molecular) controlling drug-seeking behavior chance with repeated drug-administration. In animal self-administration (SA) paradigms, these behavioral rules may be inferred from the patterns of inter-response intervals (IRI or logarithmic IRIs, i.e. LIRI). The current SA experiments were designed to model the extended periods of cocaine use in humans described as "cocaine binges". Eight male albino Wistar rats (400-450 g) were prepared with intravenous jugular catheters and trained to self-administer cocaine hydrochloride (0.25 mg/injection) on a fixed-ratio 5 schedule of reinforcement. After SA patterns stabilized following a training phase of daily 3 hr SA sessions, animals were allowed to self-administer cocaine for 48 hr continuously. After the initial loading phase, all animals self-administered cocaine at very regular intervals with little variation in LIRIs during the first 200 LIRIs. However, during the latter part of the SA sessions, all animals exhibited a qualitatively different SA pattern characterized by increased variability in LIRIs due to increased frequencies of both short (30 set IRI) and long (300-400 set) LIRIs. The return plot analysis extracted three key features: 1. a fixed-point region for intermediate LIRIs; 2. long LIRIs are followed by short LIRIs and; 3. short LIRIs are followed by either short or long LIRIs. A simple discrete-time dynamical system was constructed that describes the nonlinear function between consecutive LIRIs based on the return plot results from the LIRI data. The control parameter associated with the "urge" to obtain the next cocaine infusion predicted the transition to deregulated behavior most sensitively. The psychopharmacological approach modeled human cocaine binges by extended SA sessions in animals. The nonlinear dynamical systems approach detected a nonlinear functional relationship between consecutive LIRIs using return plots, allowed the construction of a discrete-time dynamical system modelling the LIRI sequences. A simple dynamical and deterministic model accurately describes cocaine SA patterns of rats given unlimited access to cocaine for prolonged periods of time. This model yields a quantitative description of cocaine SA patterns and can define the "state" of the cocaine user. Moreover, the model has potential heuristic value in stimulating research to identify the dynamical parameters of the model with the specific neurophysiological and molecular mechanisms underlying these complex behavioral sequences.

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SELF-ADMINISTRATION OF COCAINE UNDER A PROGRESSIVE RATIO SCHEDULE IN THE RAT: ACQUISITION, STABILITY AND EFFECTS OF VARYING THE DOSE OF COCAINE ON PARAMETERS OF SELF-ADMINISTRATION

R. DEPOORTERE, D.-H. LI AND M. W. EMMETT-OGLESBY

Sixteen Fisher 344 rats were first shaped to self-administer cocaine (0.25 mg/100 ul) under a FR2 schedule and were then trained under a progressive ratio (PR) schedule, in which an increasingly greater number of presses was required for each subsequent cocaine infusion. Acquisition and stability of cocaine self-administration under the PR schedule was assessed by training these rats for over 50 daily sessions. They were then subjected to a parametric study of the effects of varying the dose of infused cocaine (saline, 0.028, 0.083 or 0.75 mg/100ul) on the number of reinforcers obtained, the highest ratio completed, the amount of cocaine taken per min and the inter-reinforcer time (IRT, in min). Stability in the 13 rats having completed the study was acquired within 10 sessions, and was strictly maintained throughout the rest of the 50 sessions (for the last 10 sessions: average breakpoint: 19.6, SD: 0.6). There was a direct relationship between the dose of infused cocaine (saline, 0.028, 0.083, 0.25 or 0.75 mg/100ul) and the breakpoint (respectively: 1.1, 8.4, 15.5, 19.5, 21.1), the highest ratio completed (respectively: 5, 51, 234, 599, 848), the amount of cocaine taken (respectively: N.A., 19.8, 36.8, 61.1, 63.2 ug/min) and the IRT (respectively: N.A., 1.57, 2.35, 4.65, 12.14 min). These results show that rats can readily acquire the task of self-administration of cocaine under a PR schedule and maintain a stable baseline for an extended period of time. They further suggest that the PR schedule would be suitable for the study of pharmacological treatments that affect cocaine self-administration. Supported by NIDA grant RO1 4137 and TX ATP grants 3718 and 9768031.

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SELF-ADMINISTRATION OF COCAINE UNDER A PROGRESSIVE RATIO SCHEDULE IN THE RAT: EFFECTS OF SCH 23390 AND ONDANSETRON

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The effects of the D1 antagonist SCH 23390 and the 5-HT_3 antagonist ondansetron were investigated in Fisher 344 rats trained to self-administer cocaine (0.25 mg/100ul) under a progressive ratio (PR) schedule of reinforcement. SCH 23390 (100 ug/kg) was tested either i.p. (100 ug/kg, 30 min pre-session, n = 11) or s.c. (10 ug/kg, 20 min pre-session, n=7) against four doses of cocaine (0.028, 0.083, 0.25 or 0.75 mg/100 ul). In addition, SCH 23390 (3.2, 10, 17.8 or 32 ug/kg, n = 10) was tested against the training dose of cocaine (0.25 mg/100 ul). Effects of i.p. pretreatment with ondansetron (0.001, 0.01, 0,1 or 1.0 mg/kg) was tested against the training dose of cocaine in 6 rats; ondansetron was also tested at a single dose i.p. (0.1 mg/kg) against 3 doses of cocaine (0.028, 0.083, 0.25 mg/100 ul) in 8 rats. The effects of each drug pretreatment were assessed on the number of reinforcers obtained and on the inter-reinforcer time (IRT, min). SCH 23390, given either i.p. or s.c., significantly reduced the breakpoint for all four doses of cocaine. In addition, s.c. SCH 23390 dose-dependently reduced the number of reinforcers against the training dose of cocaine. SCH 23390 showed a general tendency to shorten the IRT. Ondansetron, in all cases, failed to significantly affect either the number of reinforcers obtained or the IRT. The decrease in the number of reinforcer induced by SCH 23390 suggests that this D1 antagonist blocks the reinforcing properties of cocaine. In addition, the shorter IRT seen under SCH 23390 ruled out a motor-impairing effect as being responsible for the observed decrease in the number of reinforcers obtained. Failure of ondansetron to affect cocaine self-administration under a PR schedule is in accord with results published for low-value FR procedures. This set of data supports the hypothesis that the PR schedule is a sensitive tool for the screening of drugs which might act specifically on the reinforcing properties of cocaine. Supported by NIDA grant R01 4137 and TX ATP grants 3718 & 9768031.

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EFFECTS OF COCAINE AND SCH 23390 ON BEHAVIOR MAINTAINED BY TIMEOUT FROM AVOIDANCE

M. GALIZIO; M. LIBORIO; M. MILLER; S. CARPENTER AND T. WILSON

The effects of cocaine (3-40 mg/kg) were studied alone and in combination with the D1 receptor antagonist SCH 23390 (.03 - .003 mg/kg) on rat behavior maintained by negative reinforcement. Concurrent performances were studied under conditions where responses on one lever postponed shock on a Sidman avoidance schedule and responses on a second lever produced brief periods of signaled timeout from avoidance on either a variable-ratio 15 or a variable-interval 45-s schedule. Cocaine increased responding on both levers, but the effects on timeout responding were far more pronounced. These effects were observed regardless of whether responding was maintained at lower rates by variable-interval or at high rates by variable-ratio schedules. Thus, the selective enhancement by cocaine of responding maintained by timeout from avoidance did not appear to be due to schedule- or rate-dependency. These results were similar to those obtained in an earlier study with the timeout from avoidance procedure using amphetamine (Galizio & Allen, 1991). Higher doses of SCH 23390 (.01 or .03 mg/kg) reversed the effects of cocaine, but also decreased response rates when administered alone. However the ,003 mg/kg dose of SCH 23390 also attenuated the cocaine effects, but was without intrinsic action.

REFERENCE:

Galizio, M. and Allen, A. (1991). Variable-ratio schedules of timeout from avoidance: effects of d-amphetamine and morphine. Journal of the Experimental Analysis of Behavior. 56, 193-203.

ACKNOWLEDGMENT: This research was supported by National Institute on Drug Abuse Grant R01 DA07380 awarded to the first author.

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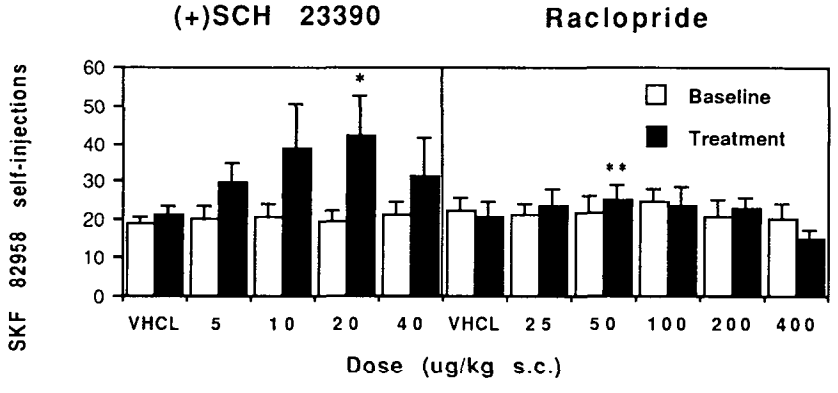
EFFECTS OF D_1 AND D_2-SELECTIVE ANTAGONISTS ON SELF-ADMINISTRATION OF THE D_1 AGONIST SKF 82958

D. W. SELF; D. M. LAM; S. R. KOSSUTH AND L. STEIN

The failure of the prototypical dopamine D_1 agonist SKF 38393 to act as a positive reinforcer constitutes the most important negative evidence against the hypothesis that D_1 receptor activation mediates reinforcement. However, SKF 38393 is a partial D_1 agonist and may have only a limited ability to penetrate the blood-brain barrier. In support of the D_1-reinforcement hypothesis, we recently reported that the full D_1 agonist SKF 82958 is avid1y self-administered by rats (Self & Stein in press). Given that SKF 82958 is somewhat less selective for D_1 over D_2 receptors than SKF 38393 in the rat, we tested whether the D_1-selective antagonist (+)SCH 23390 and/or the D_2-selective antagonist raclopride were capable of blocking the reinforcing effects of SKF 82958, as indicated by their ability to produce compensatory increases in SKF 82958 self-administration.

Six male, Sprague-Dawley rats were trained on a continuous reinforcement schedule of SKF 82958 reinforcement (10 ug/kg/injection i.v.; 10-s time-out) in daily 3-h test sessions. After self-administration baselines had stabilized (+ 10% of the mean of three consecutive sessions), the animals were pretreated with various doses of (+)SCH 23390 or raclopride (5 ml/kg vol. s.c.) 30 min prior to testing. Each pretreatment was separated by at least 2 stable baseline sessions, and the order of presentation of antagonist and dose was counterbalanced across the 6 animals.



Large, dose-related compensatory increases in self-administration were produced by D_1-antagonist pretreatment, but not by D_2 antagonist pretreatment (Figure). At the optimal 20 ug/kg SCH 23390 dose, the SKF 82958 self-administration rate more than doubled when compared to the previous test session (baseline vs. treatment, $p < .05$, paired t-test); a much smaller, but statistically significant increase also was produced by raclopride pretreatment at a single dose (50 ug/kg, $p < .01$). The results suggest that SKF 82958's reinforcing actions are mediated mainly at dopamine D_1 receptors.

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EFFECTS OF THE D_1 DOPAMINE RECEPTOR PARTIAL AGONIST, SKF 38393, ON COCAINE SELF ADMINISTRATION IN SQUIRREL MONKEYS

J. L. KATZ AND J. M. WITKIN

The effects of the dopamine receptor D_1 partial agonist, SKF 38393, on behavior maintained by cocaine reinforcement was assessed in squirrel monkeys *(Saimiri sciureus)*. One group of subjects was trained to press a key under a fixed-ratio 30-response schedule of cocaine injection. In the presence of green stimulus lamps each thirtieth response produced an injection (17 µg/kg) followed by a 1-min timeout period during which the lights were out and responses had no scheduled consequences. Another group of squirrel monkeys was trained under an identical schedule with food reinforcement. High rates of responding were maintained under the fixed-ratio component regardless of the reinforcing consequences, cocaine injection or food presentation, whereas low rates of responding were maintained during the timeout periods. SKF 38393 produced dose-related decreases in rates of responding maintained by either cocaine injection or food presentation. However, rates of responding maintained by cocaine were decreased to a greater extent than those maintained by food (Fig. 1A). The ED_{50} value for responding maintained by cocaine was 2.5 mg/kg (95% CL: 1.2-5.2), whereas that value was 15.6 mg/kg (95% CL: 2.8-86.3) for responding maintained by food. Rates of responding maintained by cocaine increased with dose/injection up to a maximum of 10 mg/kg/inj. Higher doses maintained lower rates of responding. Pretreatment with 3 mg/kg SKF 38393 shifted the ascending limb of the cocaine dose-effect curve to the right; the descending limb of the cocaine dose-effect curve was not appreciably altered (Fig. 1B). These findings suggest that D_1 dopamine receptor activation plays a role in the reinforcing effects of cocaine, and that drug acting at these receptors may show promise as therapeutic agents in the treatment of cocaine abuse.

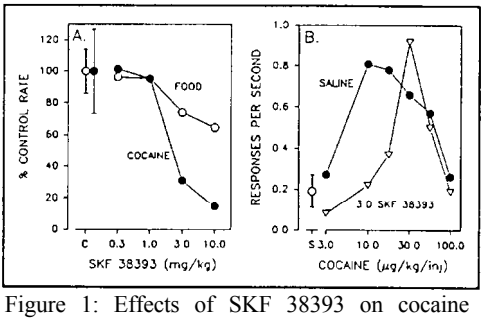

Figure 1: Effects of SKF 38393 on cocaine reinforced behavior.

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INTRAVENOUS SELF-ADMINISTRATION OF THREE DIFFERENT DOSES OF COCAINE DURING A SINGLE TEST SESSION IN RATS

R. L. PELTIER AND M. W. EMMETT-OGLESBY

The evaluation of intravenous (iv) self-administration of different doses of cocaine is typically done one dose at a time, over a period of many days. This experiment was designed to determine if different doses of cocaine could be assessed during a single test session. Male Fisher 344 rats were chronically implanted with an indwelling catheter in the right jugular. The rats were then allowed to lever respond under a schedule of 15 repetitions of a fixed ratio (FR) 2 schedule with each reinforcer followed by a 30 sec time out. A 100 microliter injection containing 0.25 mg of cocaine served as the reinforcer. When responding was stable, the rats were tested for self-administration of three doses of cocaine during a single test session. At the beginning of the test session, the rats received a priming injection of 0.5 mg of cocaine. After the priming injection, the test session consisted of 24 reinforcers, grouped in sets of eight, with sets of a high (0.5 mg/infusion), medium (0.25 mg/infusion) and then a low (0.125 mg/infusion) dose of cocaine. The average time between reinforcers for each dose of cocaine was determined by taking the mean time between reinforcement for the last seven reinforcers at each dose. There was a direct linear relationship between the dose of cocaine and the average time between each reinforcer, and results obtained with this multiple dose method did not differ significantly from those obtained with one dose of cocaine per session. Significant shifts to the right of the dose-effect curve during multiple dose testing were also observed when subjects were pretreated with either SCH 23390 (0.05 mg/kg, ip) or chronic cocaine. This method should allow for an increase in the rate of data acquisition for cocaine self-administration experiments. Supported by NIDA grant RO1 4137 and Texas ATP 3781 and Texas ATP 9768031. R. L. Peltier and M. W. Emmett-Oglesby. Department of Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, TX 76107-2699

ELECTROCONVULSIVE SHOCK PREVENTS COCAINE-INDUCED CONDITIONING

R. B. ROTHMAN[1] AND A. PERT[2]

We have previously shown that environmental stimuli associated with cocaine acquire the ability to induce behavioral activation and potentiate the effects of cocaine during subsequent administrations. The purpose of these studies was to determine if such context-dependent effects are mediated through associative processes. Four groups of rats were used. On day 1, animals in two of the groups (conditioned) were injected with 40 mg/kg cocaine in locomotor chambers, and with saline in their home cages. The other two groups (unconditioned) were injected with saline in the locomotor chambers, and with 40 mg/kg cocaine in their home cages. Immediately following removal from the locomotor test chamber, half of the conditioned and unconditioned rats were administered ECS (800 mA for 0.5 sec) while the other half received sham-ECS. On day 2, all of the rats were injected with 10 mg/kg of cocaine, and returned to the locomotor test chambers. The conditioned rats administered sham-ECS 1 hour before conditioning, immediately after conditioning, and 1 hour after conditioning, had locomotor activity levels nearly twice as high as the unconditioned rats on day #2. Only ECS administered immediately after the conditioning session attenuated expression of the conditioned response on day #2. Administration of ECS 1 hour prior to the test session (day #2) decreased cocaine-induced motoric activity in the unconditioned group, but not in the conditioned group, which resulted in an enhanced expression of the conditioned response. These findings indicate that expression of the conditioned response on day #2 requires memory of having received cocaine the day before, i.e. associative learning processes are required. The differential effect of ECS administered 1 hour prior to the test session, on the conditioned and unconditioned rats, suggests that the direct motoric effects of cocaine and the conditioned motoric effects of cocaine, may be mediated by somewhat different neurochemical mechanisms. AFFILIATION: [1]CPS, NIDA Addiction Research Center, Baltimore, MD 21224 and [2]BPB, NIMH, Bethesda, MD 20892

A SINGLE INJECTION OF EITHER FLUPENTHIXOL DECANOATE OR HALOPERIDOL DECANOATE CAUSES LONG-LASTING CHANGES IN COCAINE SELF-ADMINISTRATION IN RATS

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In a preliminary report, Gawin et al., (Arch. Gen. Psychiatry, 46:322-325, 1989) reported that flupenthixol decanoate might attenuate cocaine craving, reduce anhedonia and may increase the length of time crack addicts stay in treatment. Flupenthixol decanoate is a depot neuroleptic which is slowly absorbed and has a duration of action in humans 2-3 weeks following a single im injection. Very little data have been published on the behavioral pharmacology of depot neuroleptics in rodents. The present experiments were designed to assess the effect of two different depot neuroleptics on the reinforcing effects of cocaine in rats.

Each rat was implanted with a chronically indwelling jugular cannula and housed in a Plexiglas test chamber. The cannula was connected through a fluid swivel to a syringe pump, which when activated delivered an injection of cocaine (1.5 mg/kg). Rats were trained to self-administer cocaine on an FR 1 schedule of reinforcement during daily 5 hr test sessions. Once animals had demonstrated a stable and consistent pattern of cocaine intake, they were injected with haloperidol decanoate (2.5 mg, im, N = 8) flupenthixol decanoate (2.0 mg im, N = 9) or vehicle (N = 8). Treatment with either depot neuroleptic produced a significant increase in the rate of cocaine self-administration for 10-14 days. The pattern of drug intake within a session remained extremely regular.

Additional groups of rats were trained on a progressive ratio schedule in which the first response during the session produced an injection of cocaine, but the response requirements of subsequent injections escalated through the following series: 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219. The "breaking point" was defined as the last injection received prior to a one hour period of non-reward. Depot injections of either haloperidol (N = 5) or flupenthixol (N = 7) produced a long lasting decrease in the breaking points.

These data suggest that depot neuroleptics attenuate the reinforcing effects of cocaine. Whether increases or decreases in cocaine intake are observed depends on the behavioral "cost" and the availability of the drug.

Supported by NIDA contract #271-90-7401.

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MODIFICATION OF THE BEHAVIORAL EFFECTS OF COCAINE BY OPIOIDS IN SQUIRREL MONKEYS

J. BERGMAN, P. HESTERBERG AND R. D. SPEALMAN

INTRODUCTION: Considerable interest has focused on the modification of the behavioral effects of cocaine by buprenorphine and other opioids. For example, recent evidence indicates that the discriminative-stimulus effects of cocaine in monkeys may be accentuated by μ opioid agonist and attenuated by κ opioid agonists, perhaps reflecting dissimilar modulation of CNS dopaminc release by endogenous μ and κ mechanisms (Spealman and Bergman 1992). The present experiments were conducted to further investigate cocaine-opioid interactions in monkeys by determining how effects of cocaine on schedule-controlled behavior are acutely modified by the limited- and high-efficacy μ agonists buprenorphine and levorphanol or the κ agonist U50,488.

PROCEDURES: Squirrel monkeys responded under a 3-min fixed-interval (FI) schedule of stimulus-shock termination. Daily sessions consisted of 4 components, each comprising a 10-min timeout period followed by 5 cycles of the FI schedule. Cumulative dosing procedures were used to determine the effects of i.m. saline, cocaine (0.01-3.0 mg/kg), buprenorphine (0.0003-0.3 mg/kg), levorphanol (0.01-1.0 mg/kg), and U50,488 (0.01-1.0 mg/kg). Subsequently, the effects of cocaine were redetermined following the treatment with selected doses of each opioid.

RESULTS: Cocaine produced dose-related increases in responding up to a dose beyond which responding was increased less or decreased. Some doses of each opioid also increased rates of FI responding. After doses of buprenorphine or levorphanol that modestly elevated responding, previously ineffective doses of cocaine (0.01-0.1 mg/kg) increased response rates, whereas higher doses of cocaine (0.3 and 1.0 mg/kg) increased responding to a lesser extent than when administered alone. In the presence of U50.488, both ascending and descending limbs of the dose-effect function for cocaine shifted rightward, suggesting surmountable antagonism.

DISCUSSION: The results show that both μ and κ opioids increased rates of FI responding but modified the effects of cocaine in qualitatively different ways. The findings of apparently additive effects of buprenorphine or levorphanol and cocaine are consistent with the reported enhancement of cocaine's discriminative-stimulus effects by μ opioids in monkeys and suggests that comparable mechanisms may mediate the effects of the combined drugs in the two studies. The surmountable antagonism of cocaine's effects by U50,488 also is consistent with previous findings in cocaine-discrimination studies, and raises the possibility that κ receptor mechanisms might be exploited in designing novel therapeutics for cocaine dependence.

References available upon request to J. Bergman, NERPRC.

ACKNOWLEDGEMENTS:

Supported by Grants DA00499, DA03744, MH07658 and RR00168

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NALTREXONE ATTENUATES BUPRENORPHINE'S REDUCTION OF COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

N. K. MELLO; J. H. MENDELSON; S. E. LUKAS AND J. DRIEZE

An opioid mixed agonist-antagonist analgesic, buprenorphine, significantly reduced cocaine self-administration by rhesus monkeys (Mello et al. 1989, 1990, 1992), and polydrug abusers (Gastfriend et al. 1991; Kosten et al. 1989) but the mechanisms are unknown. This study examined the effects of concurrent treatment with naltrexone, (a long-acting mu opioid antagonist) and buprenorphine on cocaine self-administration.

Buprenorphine alone (0.40 mg/kg/day) and in combination with ascending doses of naltrexone (0.05, 0.10, 0.20 and 0.40 mg/kg/day) was compared with naltrexone alone (0.40 mg/kg/day) and saline control treatment. Each condition lasted 10 days. Buprenorphine alone reduced cocaine self-administration by an average of 53 percent ($P<.01$) in comparison to the saline treatment baseline (N=5). Ascending doses of naltrexone given *simultaneously* with buprenorphine significantly attenuated buprenorphine's suppressive effects on cocaine self-administration ($P<0.05$-0.01). Buprenorphine reduced cocaine self-administration by an average of 30, 30, 23 and 23 percent. Naltrexone alone did not reduce cocaine self-administration in any monkey.

When ascending doses of naltrexone (0.05-0.04 mg/kg/day) were administered *20 min before* buprenorphine, there was a significant naltrexone dose-dependent decrease in buprenorphine's effects on cocaine self-administration ($P<.05$-.0l). Cocaine self-administration was decreased by 42, 31, 19 and 8 percent after naltrexone 20 min before buprenorphine. Food self-administration did not differ significantly from the saline treatment base-line during treatment with buprenorphine or buprenorphine-naltrexone combinations.

These data suggest that naltrexone antagonized the mu agonist component of buprenorphine and that mu opioid receptor activity is an important factor in buprenorphine-cocaine interactions. These data are consistent with a recent report that naltrexone antagonized buprenorphine's reduction of cocaine-induced lethality in mice (Witkin et al. 1991). Yet, the opioid agonist, methadone, was significantly less effective than buprenorphine in reducing cocaine abuse by opiate-dependent men (Kosten et al. 1989). One practical implication of these findings is that the addition of an opioid antagonist such as naltrexone, to buprenorphine, to reduce the possibility of illicit diversion might also compromise the effectiveness of buprenorphine treatment.

ACKNOWLEDGEMENTS

Supported in part by Grants DA02519, DA04059, DA00101, DA00064 and DA00115 from NIDA.

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SELF-ADMINISTRATION OF HEROIN CAUSES ORAL STEREOTYPY

C. L. Duvauchelle, R. T. Livezey and C. Kometsky

In the course of an experiment involving heroin self-administration, we have observed oral stereotypy in all our test animals. Twelve male F-344 animals self-administering i.v. heroin on a CRT schedule (20 sec post-reinforcement delay) began showing pronounced oral behaviors (i.e., self-bitting, bar-bitting, cage bitting). In some instances, this oral stereotypy appeared after only one drug administration session. The heroin dose used in this study (0.07 mg/kg/inj; approx. 1.0 mg/kg/3 hr session) falls well within the typical dose range used in studies of heroin self-administration. Oral behaviors such as these have been typically observed in morphine treated animals after either very high doses or chronic exposure to low doses and are believed to be dopamine mediated. In the following study, the effect of D1 SCH 23390) and D2 (spiperone) antagonists on heroin-induced oral stereotypy was examined. Collection of scores on both oral stereotypy and general motor activity revealed that the D1 antagonist performed better than the D2 antagonist in attenuating oral stereotypy without significant diminishing motor behavior.

Supported in part by NIDA DA02326 and Research Scientist Award DA00099 to CK).

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SEDATIVE/MYORELAXANT AND PHYSICAL DEPENDENCE-PRODUCING EFFECTS OF ZOLPIDEM IN BABOONS

B. J. KAMINSKI[1], C. A. SANNERUD[3] AND R. R. GRIFFITH[1,2]

Zolpidem is a non-benzodiazepine hypnotic with selectivity for benzodiazepine receptor subtypes. Several studies have shown no physical dependence in rodents (Perrault et al. 1990; VonVoigtlander and Lewis 1991). Recently reported data Griffiths et al. 1991) suggest that the behavioral pharmacology profile of zolpidem in baboons is similar to that of the benzodiazepines. The present studies further characterize the sedative/myorelaxant and physical dependence-producing effects of zolpidem. In the first study, the behavior of 3 baboons was scored for 1 hr immediately following i.m. injections of zolpidem (0.01-10.0 mg/kg) and triazolam (0.001-3.2 mg/kg). A variety of behavioral effects were rated. Both drugs produced signs of sedation/myorelaxation in a dose-related manner. Sedation was first observed at and peaked at lower doses of triazolam than zolpidem. In another study, 3 baboons received i.v. injections of zolpidem (3.2 mg/kg/inj) at 3 hour intervals. Each day the baboon was observed for 1 hour. All 3 baboons initially showed signs of sedation/myorelaxation which tended to decrease with repeated administration. Food intake increased for 2 of 3 baboons. Injection of 5.0 mg/kg flumazenil on the 11th day of zolpidem decreased food intake for 2 or 3 baboons. Behavioral signs provided evidence of a weak precipitated withdrawal effect. Discontinuation of zolpidem after 15 days substantially decreased food intake in all baboons and several mild withdrawal signs were observed in 2 of 3 baboons. Taken together, the results indicate that zolpidem produces benzodiazepine-like sedation/myorelaxation and suggest the possibility that zolpidem may produce mild withdrawal in non-human primates. [Supported by NIDA Grant DA01 147-181.

REFERENCES furnished upon request.

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EFFECTS OF 5-HT$_3$ RECEPTOR ANTAGONISTS AGAINST SOMATIC AND MOTIVATIONAL ASPECTS OF OPIOID WITHDRAWAL

G. A. HIGGINS AND E. M. SELLERS

We have previously presented data suggesting that 5-HT$_3$ receptor antagonists (e.g. ondansetron, MDL72222) may modify certain behavioral aspects of a naloxone-precipitated withdrawal in morphine dependent rats (Higgins et al., 1991). The purpose of the present study was to extend these findings using the 5-HT$_3$ antagonist ICS205-930 and its quatemary derivative Q-ICS205-930 (Q-ICS). Experiments were focused on animal models presumably reflective of the motivational aspects of withdrawal as these seen particularly sensitive to 5-HT$_3$ antagonist (Higgins et al., 1991).

Male Wistar rats, following the acquisition of stable water consumption during a 20 min daily access period, were implanted with a 75 mg morphine base pellet. For the next three days, water access was followed by s.c. injection of saline vehicle. On the fourth day the rats were presented with a novel 0.1% w/v saccharin solution, followed by s.c. injection of naloxone (0.002-0.5 mg/kg) or vehicle. For the next two days the rats were presented with the saccharin solution. Naloxone (0.15-0.5 mg/kg) produced a significant conditioned taste aversion (CTA) in morphine pellet implanted but not placebo pellet implanted rats. In subsequent studies, a naloxone (0.15 mg/kg) induced CTA was non-significantly attenuated by ICS205-930 but not ondansetron (both 0.01-1 mg/kg) or MDL72222 (1 mg/kg).

Separate groups of male Wistar rats were trained in operant chambers to lever press for food (45 mg Noyes pellets) made available under an FRIS schedule during two daily 20 min sessions. At the end of the day each rat received a further food supplement (total 20 g/day). Following stable levels of responding, rats were implanted either with a 75 mg morphine base pellet ($n = 8$) or placebo ($n = 5$). By the third day, response rates had returned to pre-implantation levels. On the fourth and fifth days the rats were pre-treated with either saline or naloxone. (0.002, 0.01, 0.05 mg/kg s.c.) immediately prior to the operant session. Each rat received all treatments according to a randomized design. Naloxone at 0.05 mg/kg, and to a lesser extent 0.01 mg/kg, produced a marked disruption of food responding in morphine dependent rats only (vch = 73 ± 7 pellets, N 0.05 = 8 ± 1 pellets; $p < 0.01$). In separate studies ICS205-930 (0.01-1 mg/kg) failed to significantly effect the disruption of food responding produced by naloxone (0.05 mg/kg) in morphine dependent rats. However, ICS205-930 (0.1 mg/kg) but not Q-ICS (0.01-0.1 mg/kg), did attenuate the place aversion produced by this same dose of naloxone (see Higgins et al., 1991 for method).

Based on the studies carried out to date it seems that 5-HT$_3$ antagonists may only modify certain behaviors reflective of the motivational impact of opioid withdrawal.

REFERENCE: Higgins, G. A.; Nguyen, P.; Joharchi, N.; and Sellers, E. M. Effects of 5-HT$_3$ receptor antagonist on behavioral measures of naloxone-precipitated opioid withdrawal. Psychopharmacol, 105:322-328, 1991.

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EFFECTS OF SEROTONERGIC ANXIOLYTICS ON DIAZEPAM PHYSICAL DEPENDENCE

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It is known that benzodiazepine partial inverse agonists induce a convulsion in mice chronically treated with benzodiazepines, but not in naive mice. This procedure has been utilized for the evaluation of physical dependence on benzodiazepines. On the other hand, some serotoncrgic agents, e.g. buspirone. ondansetron, etc. have been recently developed as anxiolytics. Because anxiolytic effects of these drugs seem weaker than those of benzodiazepines, there is a possibility that these serotonergic agents may be used concurrently with benzodiazepines in clinical therapy. There are hitherto several reports in which effects of anxiolytic serotonergic agents on benzodiazepine withdrawal signs were studied. However, their effects on the development of physical dependence on benzodiazepines have not been examined. In the present study, the effects of serotonergic anxiolytics on development of physical dependence on diazepam were examined using this procedure. Male ICR mice were treated with diazepam (16 mg/kg, i.p.) and diazepam in combination with buspirone (5-HT1$_A$ agonist), mianserin (5-HT1$_C$ antagonist), ketanserin (5-HT$_2$) antagonist) or ondansetron (5-HT$_3$ antagonist) once a day for 7 days. Twenty-four hours after the last treatment, mice were treated with several doses of FG 7142, benzodiazepine partial inverse agonist, and observed chronic-tonic convulsions. Diazepam in combination with buspirone or ondansetron also potentiated the incidence of convulsion induced by FG 7142 as compared to diazepam alone. ED$_{50}$ values of FG 7142 for chronic-tonic convulsions were 36.95 mg/kg for diazepam alone group, 20.85 mg/kg for buspirone 3 mg/kg co-administration group, and 22.49 mg/kg for ondansctron 0.03 mg/kg co-administration group. Dose response lines of chronic-tonic convulsions induced by FG 7 142 were significantly shifted to left 1.77 fold by co-administration of buspirone 3 mg/kg and shifted to left 1.64 hold by co-administration of ondansetron 0.03 mg/kg. However, the incidence of chronic-tonic convulsions was not affected by co-administration of mianserin or ketanserin. It is thus suggested that co-administration of buspirone or ondansctron with diazepam may potentiate the development of physical dependence on diazepam, and that 5-HT$_{1A}$ and 5-HT$_2$ receptors may be involved in the development of physical dependence on diazepam.

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EFFECTS OF DRUGS AND VAPORS ON 1,1,1-TRICHLOROETHANE WITHDRAWAL REACTIONS IN MICE.

Eric B. Evans and Robert L. Balster

Mice were made physically dependent on the widely used and abused solvent 1,1,1-trichloroethane (TCE) by four days of continuous exposure to 2000 ppm. Subsequent to exposure the withdrawal reaction was assessed quantitatively by scoring the intensity of handling-induced convulsions. Once the withdrawal reaction was well underway the capacity of drugs and another abused solvent to modify the withdrawal was evaluated. Post-exposure administration of 1000 and 2000 ppm toluene vapor for 1 hr resulted in a concentration-dependent reversal of the peak withdrawal convulsions. Both pentobarbital (30 mg/kg) and midazolam (0.3-1.0 mg/kg) also suppressed the withdrawal reaction. No reversal was observed following administration of chlorpromazine (3 mg/kg) nor the anticonvulsant phenytoin (30 mg/kg). The suppression of TCE withdrawal convulsions by toluene and CNS depressant drugs suggests cross-dependence between these substances and TCE. (Research was supported by grants DA-03112 and ES-07087.)

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EFFECTS OF SETRALINE, A. SEROTONERGIC UPTAKE INHIBITOR, ON NICOTINE SELF-ADMINISTRATION IN SQUIRREL MONKEYS

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Nicotine (NIC) is the primary component of tobacco smoke responsible for persistent smoking behavior and for the withdrawal symptoms that appear upon smoking cessation in man. Previous research found that i.v. NIC serves as a reinforcer in animals under certain experimental conditions, thus, providing an animal model of NIC dependence. Recent reports suggest the involvement of serotonergic and dopaminergic mechanisms in NIC self-administration. The present study assessed the effects of sertraline, a selective serotonergic uptake inhibitor that is effective as an antidepressant, on the reinforcing effects of i.v. NIC in squirrel monkeys.

Three monkeys were maintained on NIC (30 µg/kg/inj) under an FR 30 schedule of i.v. reinforcement followed by a 5 min timeout. A NIC dose-response curve was generated by substituting a series of NIC doses (0, 10-100 µq/kg/inj) for 3 consecutive days. The effects of oral pretreatments of sertraline (3, 6, 12, 24 mg/kg, p.o.) on NIC self-administration were assessed.

Three monkeys were maintained under the identical FR 30 schedule of food reinforcement. A NIC dose-response curve was generated by giving i.m. injections of saline or NIC (0.1-1.0 mg/kg) for 3 consecutive days. The effects of oral pretreatments of sertraline (3, 6, 12, 24 mg/kg, p.o.) on the direct effects of NIC were assessed.

NIC served as a reinforcer in monkeys and produced an inverted U-shape distribution on FR rate. NIC maintained responding well above vehicle control with the highest rates of responding maintained by 30 µg/kg, i.v. NIC. NIC produced dose-dependent rate-decreasing effects on food-maintained responding.

Sertraline produced disrupted food-maintained responding at doses that did not disrupt nicotine self-administration. Sertraline did not affect self-administration maintained by 30 µg/kg, i.v. NIC. Sertraline appeared to potentiate the effects of 10 µg/kg NIC; however, this combination produced wide inter-animal variability that were not dose-dependent.

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TASTE AVERSION WITH LOW CONCENTRATIONS OF NICOTINE

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We previously reported that rats allowed to drink a low nicotine concentration (1 ug/ml) for several weeks showed an increased preference for that solution in two-bottle tests and showed a shift in their reactions to orally-infused nicotine toward more positive behavioral responses. The current experiments were designed to associate the consumption of nicotine with a taste stimulus that could then be presented separately from the nicotine. Unsweetened grape and lime Kool-Aid were chosen as the taste stimuli.

EXPERIMENT 1 employed mixtures of novel flavors (grape or lime) with either 1 or 5 ug/ml nicotine. Rats were allowed to drink for one hour from a bottle containing one of the flavors mixed with nicotine. On alternate days, the other flavor was presented without nicotine. Every 14 days the rats were given a two-bottle choice test using the two flavors alone. Rats exposed to 1 ug/ml showed no preference or aversion to the flavor paired with nicotine, whereas the rats exposed to 5 ug/ml showed an aversion to the flavor paired with nicotine.

EXPERIMENT 2 employed only 1 ug/ml nicotine, but added a location cue in that the flavor associated with nicotine was always presented at one end of the cage and the neutral flavor always at the other end. When a two-bottle test was conducted in a different type of cage with the bottles side by side no taste preference or aversion was seen. When two bottles both containing the unpaired flavor were presented at the two ends of the conditioning cage, no place preference or aversion was seen. When a test was conducted with both place and taste as cues, a significant aversion was demonstrated.

EXPERIMENT 3 provided rats with two bottles, one containing water and the other containing 10% sucrose solution. After 3 days, 2 ug/ml nicotine was added to the sucrose bottles. Every 4 days thereafter the nicotine concentration was doubled until 16 ug/ml was reached. The rats consumed an average of 139 ml per day of the 10% sucrose/8 ug/ml nicotine solution, resulting in a maximum intake of approximately 1.1 mg of nicotine per days, more than 10 times the maximum daily nicotine intake in the first two experiments. This implies that in the previous experiment rats were avoiding the nicotine solutions more because of their taste than because of adverse pharmacological consequences.

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CONTRASTING MOTIVATIONAL PROPERTIES OF NICOTINE DETECTED WITH A PLACE CONDITIONING PARADIGM

M. SHOAIB AND I. P. STOLERMAN

Nicotine is well known to serve as a reinforcing and as an aversive stimulus. However, little evidence exists to explain how different motivational effects of nicotine can be acquired by individuals. The place conditioning paradigm offers opportunities to assess both properties. The aim was to investigate conditions that would favour the acquisition of place preference (CPP) and aversions (CPA) with nicotine.

In counterbalanced designs, conditioning with nicotine (0.6 mg/kg SC administered **before** confinement in distinct environments), failed to elicit any significant preferences in subsequent extinction test. After pretreatment with nicotine (7 daily injections of 0.4 mg/kg SC prior to conditioning), nicotine (0.4-0.8 mg/kg SC) produced dose-related CPPs. In untreated rats, conditioning with nicotine (0.4-0.8 mg/kg SC) administered after confinement in distinct environments, resulted in dose-related CPAs. These results confirm that both motivational properties of nicotine are detectable in a place conditioning paradigm. The facilitating effect of nicotine pretreatment on CPP may be due partly to the attenuation of the initial aversive response.

ACKNOWLEDGEMENTS:

We thank MRC (United Kingdom) for their financial support.

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ASSESSMENT OF THE ABUSE POTENTIAL OF THE NOVEL CHOLINESTERASE INHIBITOR SDZ ENA 713 IN THE RHESUS MONKEY

P. H. KELLY, R. AMSTUTZ AND A. ENZ

The abuse potential of the novel cholinesterase inhibitor SDZ ENA 713 was examined in two experiments.

The possible intravenous self-administration of the compound by five rhesus monkeys was investigated. Doses of 5.6, 3.2 and 10 µg/kg/infusion were available on a continuous reinforcement schedule in successive 5-week experimental phases separated by phases when lever-pressing resulted in administration of saline vehicle. To stimulate the initial intake of a new solution each infusion during the first 20 minutes of the 23-hr daily session on each of the first four days of a new phase was accompanied by delivery of a sugar pellet into a receptacle in the cage. In four animals with typical low rates of initiating vehicle infusions, infusion rates for solutions of SDZ ENA 713 were clearly not increased compared to those for vehicle. In one animal which showed increasing rates of saline infusion throughout the study, infusion rate was decreased at the highest dose of SDZ ENA 713. Subsequently three of the four monkeys with low rates of saline infusion showed elevated infusion rates for morphine (0.1 mg/kg/infusion) whereas a decrease of infusion rate was observed in the animal with a high rate of saline infusion.

In a second experiment programmed intravenous application of SDZ ENA 713 every four hours was performed (2 weeks at 5.6 µg/kg/infusion, 2 weeks at 10 µg/kg/infusion and 4 weeks at 18 µg/kg/infusion), resulting in a 70-80% inhibition of plasma cholinesterase. Following the S-week period, saline was substituted for the SDZ ENA 713 solution in order to observe possible behavioral changes indicative of a withdrawal syndrome. There were no marked alterations of behavior. However when the application schedule was subsequently repeated in the same animals with morphine as a positive control (in successive doses of 1.0, 1.8 and 3.2 mg/kg/infusion), cessation of treatment elicited significant behavioral changes indicative of a withdrawal syndrome.

The results indicate that in doses which affect behavior SDZ ENA 713 has no reinforcing capacity and does not cause physical dependence.

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THE INTERACTIVE INFLUENCE OF ASSOCIATIVE AND NONASSOCIATIVE PROCESSES IN THE DEVELOPMENT OF MORPHINE TOLERANCE

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Classical conditioning or associative models posit that stimuli paired with drug administration become conditioned stimuli that elicit conditioned tolerance processes. There is controversy whether tolerance that develops with discrete drug administrations can be explained entirely by learning, or whether it may be a result of both learning and nonassociative influences. This study shows that both factors can lead to the development of tolerance, and that conditions conducive to the formation of nonassociative tolerance disrupt the acquisition of associative tolerance. Associative contingencies were manipulated by administering a series of morphine doses (8 injections of 20 mg/kg) either paired or unpaired with a distinctive context. Nonassociative tolerance processes were. manipulated by using either a short (6 hours) or long (96 hours) interdose interval (IDI). During conditioning, animals did not practice the test response, thereby reducing the potential confound of instrumental learning. Rats (n = 407) were tested in the distinctive context either immediately or 30 days after conditioning was completed. Tolerance was indexed as the shift to the right of the dose-response curve for analgesia on the tail-flick test.

Tolerance that developed at the long IDI was under strong associative control of the distinctive context. At the long IDI, there was a substantial shift in the dose-response curve to the right for animals that had received morphine explicitly paired with the test environment relative to those that had received the same amount of morphine unpaired with that environment. This effect was evident in animals tested immediately as well as those tested 30 days after the completion of conditioning. At the short IDI, tolerance appeared to be nonassociative; it was unaffected by contextual contingencies at the immediate test and showed no retention over the 30 day interval. The data indicated that conditions conducive to the acquisition of nonassociative tolerance completely eliminated associative tolerance. Models that invoke only learning or only pharmacological mechanisms to account for tolerance cannot explain these results.

ACKNOWLEDGEMENTS: Supported by NIDA grant DA04050.

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MORPHINE/NALORPHINE DISCRIMINATION LEARNING WITHIN A CONDITIONAL TWO-DRUG DISCRIMINATION PROCEDURE

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In unpublished work from our lab (Smurthwaite & Riley, 1992), animals trained to discriminate nalorphine from distilled water generalized this control to morphine, but not to naloxone or U50,488, suggesting that the stimulus properties of nalorphine utilized in the acquisition of the nalorphine discrimination are based on its agonist activity at the mu receptor. One possibility for these findings is that nalorphine's mu receptor activity is the most salient and thus the one that establishes control when the discrimination is based on a nalorphine vs. saline discrimination. Accordingly, if the mu antagonist and kappa agonist activity of nalorphine can support drug discrimination learning it should be possible to train an animal to discriminate between nalorphine and morphine, compounds with partial overlap in their mu agonist stimulus properties, based on the unique properties of nalorphine (i.e., mu antagonist and kappa agonist). In the present study, animals were trained to discriminate nalorphine from morphine in a two-drug discrimination procedure within the taste aversion baseline of drug discrimination learning (see Mastropaolo et al., 1986; 1989). Animals injected with morphine prior to a saccharin (Sacc)-LiCl pairing and nalorphine prior to Sacc alone acquired the simple two-drug discrimination, consuming less Sacc relative to controls following morphine than following nalorphine. Conversely, animals injected with nalorphine prior to a Sacc-LiCl pairing and morphine prior to Sacc alone consumed less Sacc relative to controls following nalorphine than following morphine. This discrimination is likely due to the differences in receptor activity between nalorphine and morphine (e.g., the mu antagonist and kappa agonist properties of nalorphine).

REFERENCES: Available upon request from the senior author.

ACKNOWLEDGEMENTS: This research was funded by a grant from the Mellon Foundation to Anthony L. Riley.

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THREE-CHOICE DRUG DISCRIMINATION IN RHESUS MONKEYS RECEIVING MORPHINE SUBCHRONICALLY

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Drug discrimination procedures have been applied to the study of drug dependence and withdrawal in humans (Preston et al., 1987) and other species France & Woods, 1989; Gellert & Holtzman, 1979; Valentino et al., 1983) in experiments where subjects treated chronically with an agonist have been trained to discriminate between vehicle and a pharmacological antagonist. Results of these studies are consistent with the view that in agonist-treated subjects antagonist discriminations might be related to withdrawal; however, there are other explanations that do not require postulating drug dependence (e.g., the antagonist training condition might represent the absence of agonist and, therefore, the discrimination might be between the presence and absence of agonist). The purpose of the present study was to see whether a three-choice discrimination could be established among morphine (MOR). saline (SAL). and a combination of MOR and naltrexone (NTX) in rhesus monkeys receiving MOR at a frequency that does not produce physical dependence (3.2 mg/kg/72 hrs). If the combination of MOR and NTX (at the same doses used in orevious studies[France & Woods, 1989]) represents the absence of MOR, then it should not be possible to establish a discrimination between SAL and the MOR + NTX combination. Conversely, if the MOR + NTX combination represents a small dose of MOR, then in the absence of NTX small doses of MOR should occasion responding on the MOR + NTX lever. Daily sessions were comprised of a 10-min time out, during which lever presses had no programmed consequence, and a response period, during which a schedule of stimulus shock termination was in effect. Subjects responded on levers under a fixed-ratio schedule of stimulus shock termination in daily sessions conducted 3 hrs after an injection of MOR or SAL. Stimulus control was established in three, adult female rhesus monkeys for all three conditions after an average of 285 training sessions. During test sessions there was a dose-related generalization to each of the training compounds: MOR + SAL to the MOR + SAL (center) lever; MOR + NTX to the MOR + NTX (left) lever. Subjects responded on the SAL (right) lever SAL + SAL. When subjects received MOR 3 hrs earlier they reliably responded on the MOR + SAL lever. With the administration of increasing doses of NTX subjects switched their response choice from the MOR + SAL lever to the MOR + NTX lever. With further increases in dose of NTX one subject continued to respond on the MOR + NTX lever while a second subject switched further to SAL+ SAL lever. When subjects had received SAL three hrs earlier they reliably responded on the SAL + SAL lever. Consistent with results obtained in the presence of MOR, one subject continued to respond on the SAL + SAL lever up to a dose of 3.2 mg/kg of NTX whereas the second subject switched from the SAL + SAL lever to the MOR + NTX lever. In fact, the dose NTX needed to occasion responding on the MOR + NTX lever in the second subject varied only three-fold between the MOR and SAL treatment conditions. Nalbuphine substituted for the MOR + SAL condition whereas ketamine did not substitute for any of the training conditions. Because monkeys discriminated reliably between no drug and a combination of MOR and NTX it appears unlikely that the discriminative stimulus effects of this dose combination in this and other studies is attributable simply to the absence of morphine. Moreover, there was no evidence that the MOR + NTX condition was discriminated as a small dose of MOR. Together with the lack of evidence for physical dependence under these dosing conditions, results from this study indicate drug discrimination results are not adequate for validating this procedure for the study of opioid dependence. Supported by USPHS Grant DA05018.

REFERENCES: Available upon request.

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KAPPA ANTAGONIST PROPERTIES OF MIXED MU/KAPPA AGONISTS IN THE PIGEON DRUG-DISCRIMINATION PROCEDURE

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In the present investigation, various mixed mu/kappa opioids were examined in separate groups of pigeons trained to discriminate the kappa agonist bremazocine (0.017 mg/kg) or the mu agonist fentanyl (0.056 mg/kg) from saline. All of the mixed mu/kappa opioids examined, including EKC, (-)-NANM, (-)-cyclazocine, levallorphan, buprenorphine, nalbuphine, butorphanol and nalorphine, substituted completely for the fentanyl but not the bremazocine stimulus. When administered in combination with the training dose of bremazocine in the bremazocine-trained pigeons, each of these opioids, as well as the opioid antagonist naloxone, produced a dose-related attenuation of the bremazocine stimulus. Naloxone, (-)-NANM, buprenorphine and levallorphan produced their kappa antagonist effects at doses considerably smaller than those that decreased response rates when these drugs were administered alone. In contrast, butorphanol, EKC, nalbuphine, nalorphine and (-)-cyclazocine produced their kappa antagonist effects at doses equal to or slightly smaller than those that decreased response rates. Unlike the mixed mu/kappa opioids evaluated, the mu agonist morphine failed to substitute for or antagonize the bremazocine stimulus. These data suggest that, in the pigeon, the mixed mu/kappa opioids evaluated have greater efficacy at the mu receptor than at the kappa receptor. In addition, the kappa antagonist effects of many of these opioids were limited by their rate-decreasing effects.

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PHARMACOLOGICAL ANALYSIS OF THE RATE-DECREASING EFFECTS OF MU AND KAPPA OPIOIDS IN PIGEONS

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Both mu and kappa opioid agonists decrease rates of schedule-controlled responding. The receptor mediation of this effect can be studied by comparing the potency of opioid antagonists in reversing the effects of representative mu and kappa agonists. In this study, pigeons were trained to key peck under a multiple Fixed Ratio 10 schedule of food presentation. Using a cumulative dosing procedure, dose-effect curves were obtained for the agonists morphine (MOR), l-methadone (l-METH), ethylketocyclazocine (EKC), bremazocine (BREM), U69,593 (U69) and U50,488 (U50) alone and in the presence of doses of naltrexone (NLTX) ranging from 0.01 to 10.0 mg/kg. In addition, dose-effect curves were obtained for l-METH, BREM, U69 and U50 alone and 2 hr, 24 hr and 6-7 days after the administration of 20.0 mg/kg of the mu-selective opioid antagonist, ß-funaltrexamine (ß-FNA). Also, dose-effect curves for l-METH, BREM and U50 were obtained before, during and after the chronic administration of U50. Naltrexone produced a comparable reversal of the rate-decreasing effects of morphine, l-methadone, ethylketocyclazocine, bremazocine and U69,593. In contrast, the rate-decreasing effects of U50,488 were not reversed by any dose of naltrexone tested. A 20 mg/kg dose fo ß-FNA shifted the l-METH dose-effect curve by ~ 1/2 log unit; the BREM dose-effect curve was shifted to a lesser degree and the U69 and U50 dose-effect curves were not shifted at all. Lastly, following chronic administration of U50,488, a small degree of tolerance (~ 1/4 log unit shift) developed to its rate-decreasing effects. Cross-tolerance to the rate-decreasing effects of bremazocine occurred (~ 2 log unit shift). No cross-tolerance to the rate-decreasing effects of l-methadone was observed. From these data it appears that the rate-decreasing effects of morphine, l-methadone and ethylketocyclazocine are mediated by a common mechanism, namely activity at the mu opioid receptor. The question of the receptor mediation of the rate-decreasing effects of bremazocine, U50,488 and U69,593 is complicated by the data obtained from these studies. The lack of antagonism by naltrexone of U50,488 versus the large degree of antagonism by naltrexone of bremazocine and U69,593 suggests different mechanism of action for these opioids. However, the tolerance/cross-tolerance data suggests a common mechanism of action for the rate-decreasing effects of U50,488 and bremazocine. Further research is needed to determine the receptor mediation of the rate-decreasing effects of these agonists.

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SEROTONERGIC MODULATION OF Mu- AND KAPPA- OPIOID DISCRIMINATIVE STIMULUS PROPERTIES IN RATS

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In order to determine the role of 5HT in the discriminative stimulus effects of opioids, the effects of 8-OH-DPAT, a 5HT-1A receptor agonist, NAN-190, a partial 5HT-1A receptor agonist and ketanserin, a 5HT-2 receptor antagonist, were evaluated in rats trained to discriminate the mu-opioid agonist, morphine (5.6 mg/kg) or the kappa-opioid agonist, U50-488 (5.6 mg/kg) from saline using a two lever, food-reinforced drug discrimination procedure. In rats trained to discriminate U50-488 from saline, U50-488 dose-dependently increased drug-lever responding. When administered alone, 8-OH-DPAT partially substituted for the U50-488 discriminative stimulus. NAN-190 produced a moderate amount of U50-488-appropriate lever responding, while ketanserin produced predominantly saline lever responding. The opioid receptor antagonist, naltrexone, failed to antagonize the dose of 8-OH-DPAT (10.0 mg/kg) that produced the maximal amount of substitution for the U50-488 discriminative stimulus, suggesting that 8-OH-DPAT's effects are not mediated by opiate receptors. When administered in combination with the training dose of U50-488, 8-OH-DPAT, but not ketanserin attenuated the discriminative stimulus effects of U50-488. In rats trained to discriminate morphine from saline, morphine dose-dependently increased drug-lever responding. 8-OH-DPAT, NAN-190 and ketanserin produced predominantly saline-lever responding up to doses that substantially decreased response rates. When administered in combination with the training dose of morphine, 8-OH-DPAT, but not ketanserin attenuated the discriminative stimulus effects of morphine. These results suggest that 5HT is involved in the expression of the discriminative stimulus effects of both mu- and kappa-opioids. This effect, however, does not appear to result from a direct action on opiate receptors.

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ATTENUATION OF THE INTEROCEPTIVE ("SUBJECTIVE") EFFECTS OF COCAINE BY THE NOVEL ANTIDEPRESSANT TRAZODONE: POSSIBLE THERAPEUTIC EFFICACY IN COCAINE ABUSE?

P.M. CALLAHAN AND K. A. CUNNINGHAM

Cocaine blocks the reuptake of dopamine (DA), norepinephrine (NE) and serotonin (5-HT). Drug discrimination procedures have been used as animal models to assess the "subjective" effects of cocaine in humans. Evidence from such studies suggests that DA systems are important in mediating the stimulus effects of cocaine, however, we have recently reported that the reuptake inhibitor for 5-HT (fluoxetine) and NE (desipramine) enhanced the cocaine state. In the present experiment, the ability of 5-HT and NE compounds to modulate the stimulus effects of cocaine was assessed further in rats trained to discriminate cocaine (5 or 10 mg/kg; N=8/group) from saline in a two-lever, water-reinforced task; our original finding with desipramine was also replicated. Administration of a low dose of fluoxetine or desipramine that resulted in <25% cocaine-lever responding when tested alone shifted the dose-response curve for the 5 and 10 mg/kg cocaine cues to the left. The 5-$HT_{1b/c}$ receptor agonist TFMPP also produced a leftward shift in the cocaine (5 and 10 mg/kg) dose-response curves. In contrast, the antidepressant trazodone (2.5-20 mg/kg) in combination with a dose of cocaine (5 mg/kg) which elicited >85% drug-lever responding when given alone significantly attenuated the cocaine (10 m&/k&) cue. Coadministration of the 5-HT_{1BC} receptor agonist and metabolite of trazodone m-CPP (1 m&/kg) or the 5-HT releaser fenfluramine (1 mg/kg) with cocaine (0.625-10 m&/kg) produced a rightward shift in the cocaine (10 mg/kg) dose-response curve. None of the antidepressants or 5-HT receptor agonists mimicked cocaine when given alone, although TFMPP engendered a persistent 30-45% drug-lever responding.

The present results confirm previous findings indicating that desipramine and fluoxetine *enhance* the "subjective" state induced by low doses of cocaine. These results are important since these antidepressants are currently being used in the clinical treatment of cocaine abusers. 5-HT innervation of the mesolimbic structures is thought to provide tonic inhibitory modulation of DA-mediated behaviors. As such, increases in 5-HT would be predicted to block DA-induced behaviors. In accordance with this hypothesis, increases in synaptic 5-HT in limbic regions may underlie the antagonist effects of trazodone, m-CPP and fenfluramine. On the other hand, a decrease in 5-HT function induced by reuptake inhibition at the 5-HT autoreceptor or terminal might be responsible for the enhancement observed with fluoxetine and TFMPP. Additionally, the actions of these compounds at NE, particularly alpha-adrenergic, receptors, must be considered. Nethertheless, these data support a modulatory role for 5-HT and NE in mediating the cocaine cue and suggest the possible therapeutic efficacy of trazodone in cocaine abuse. Supported by NIDA grants DA 05708 and DA 06511.

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DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE AND THE HIGH-EFFICACY D_1 AGONIST SKF 81297 IN SQUIRREL MONKEYS

S. ROSENWEIG-LIPSON AND J. BERGMAN

Previous studies in monkeys have demonstrated that high-efficacy D_1 agonists partially substitute for the discriminative-stimulus effects of cocaine or GBR 12909. In the present study, squirrel monkeys were trained to discriminate cocaine, methamphetamine, or the high-efficacy D_1 agonist SKF 81297 from saline in a two-lever drug discrimination procedure. Monkeys were trained under a lo-response fixed-ratio schedule of stimulus-shock termination to respond differentially on the left and right levers depending on whether drug or saline was injected. During test sessions, incremental doses of cocaine, methamphetamine, GBR 12909, or SKF 81297 were evaluated for their ability to substitute for the discriminative stimulus. In monkeys trained to discriminate i.m. cocaine (1-1.7 mg/kg) or methamphetamine (1 mg/kg) from saline, cocaine, methamphetamine, GBR 12909, and SKF 81297 produced dose-dependent increases in responding on the drug-appropriate lever, and full substitution was generally observed. In monkeys trained to discriminate i.v. SKF 81297 (0.3-1 mg/kg) from saline, SKF 81297 also produced dose-related increases in responding on the drug-appropriate lever. Full substitution was evident in all monkeys after doses comparable to or lower than the training dose of SKF 81297. In contrast, cocaine, methamphetamine, and GBR 12909 failed to substitute for SKF 81297 in these monkeys. However, in monkeys trained to discriminate SKF 81297 from saline following previous cocaine training experience, cocaine, methamphetamine, GBR 12909, and SKF 81297 produced dose-dependent increases in responding on the drug-appropriate lever. These results demonstrate that the high-efficacy D_1 agonist SKF 81297 can serve as a discriminative stimulus in monkeys. They also reveal an asymmetry in the discriminative-stimulus effects of cocaine and SKF 81297 in monkeys without previous cocaine training experience.

Supported by USPHS Grants DA03774, DA00499, MH07658, and RR00168.

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EFFECTS OF MAGNESIUM CHLORIDE IN RATS AND SQUIRREL MONKEYS TRAINED TO DISCRIMINATE DIFFERENT DOSES OF COCAINE

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Magnesium chloride ($MgCl_2$) has been shown to substitute for intravenously self-administered cocaine in rats (Kantak et al. 1991). Mouse aggression (Izenwasser et al. 1986; Kantak 1989) and conditioned place preference (Lawley and Kantak 1990a; 1990b) studies also have demonstrated that $MgCl_2$ has partial cocaine-like activity in rodents. When given as a pretreatment, however, $MgCl_2$ can decrease cocaine-maintained responding and cocaine intake in rats (Kantak et al. 1992). Collectively, these findings suggest that $MgCl_2$ has mixed actions as both a partial cocaine mimetic and a cocaine antagonist. The present study was undertaken to determine if $MgCl_2$ would substitute for the discriminative stimulus (DS) effects of cocaine as well as alter the DS effects of cocaine when given as a pretreatment to rats and squirrel monkeys trained to discriminate different doses of cocaine from saline.

In rats, as the magnitude of the cocaine training dose decreased, the cocaine generalization curve was displaced progressively to the left. In rats trained to discriminate a low (2 mg/kg) dose of cocaine, $MgCl_2$ (10-100 mg/kg, s.c.) partially reproduced the DS effects of cocaine. $MgCl_2$ did not reproduce the DS effects of cocaine in rats trained to discriminate an intermediate (5 mg/kg) or a high (10 mg/kg) dose of cocaine from saline. When given as a pretreatment, $MgCl_2$ (30 mg/kg) enhanced the DS effects of 1 mg/kg cocaine, and attenuated the DS effects of 5 and 10 mg/kg cocaine in rats trained to discriminate 5 mg/kg cocaine from saline. $MgCl_2$ (10-100 mg/kg, i.m.) did not reproduce the DS effects of cocaine in monkeys trained to discriminate intermediate to high doses of 0.3-1.0 mg/kg cocaine from saline. When given as a pretreatment, $MgCl_2$ (10 or 30 mg/kg) did not alter the DS effects of cocaine. These findings show that $MgCl_2$ can partially reproduce the DS effects of cocaine in rats and that the expression of cocaine-like DS activity of $MgCl_2$ depends upon the training dose of cocaine. Previous studies in rats have shown that the noncompetitive NMDA antagonist dizocilpine has partial cocaine-mimetic and cocaine antagonist effects in common with $MgCl_2$ (Koek et al. 1989; Spealman and Kantak 1992). As both compounds are known to bind to recognition sites within the ion channel associated with the NMDA complex (Johnson et al. 1988; Reynolds and Miller 1988) their similar effects in cocaine-trained rats may reflect common inhibition of NMDA-mediated neurotransmission. Additional studies in monkeys trained to discriminate lower doses of cocaine will be necessary to evaluate the species generality of the effects of $MgCl_2$ observed in rodents,

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WITHDRAWAL FROM CHRONIC HALOPERIDOL PRODUCES A PENTYLENETETRAZOL-LIKE DISCRIMINATIVE STIMULUS

M. E. BRONSON

The pentylenetetrazol (PTZ) drug discrimination procedure has been used extensively to study the anxiogenic component of withdrawal from drugs of abuse (Bronson and Roberts, 1992; see also review by Emmet-Oglesby, et al., 1990). The current study was conducted to determine whether there is an anxiogenic component to withdrawal from a therapeutic drug that is not abused, namely the antipsychotic, haloperidol (Hal). Rats were trained to discriminate the anxiogenic compound PTZ from water in a two lever, food reinforced, drug discrimination procedure. A dose effect curve was then determined for Hal (0.1 - 2 mg/kg). Hal did not substitute for PTZ at any dose, and Hal dose-dependently decreased responding, with 1 mg/kg Hal decreasing rates to approximately 15% of control values. Rats were then treated chronically with either 1 or 2 mg/kg/day Hal while training was suspended. All rats had previously had 2 weeks of chronic water injections while training was suspended, and were then tested with water, followed by PTZ, to insure that the discrimination had not been lost. After 5 days of chronic Hal, 4/6 animals in the 1 mg/kg/day group and 5/7 in the 2 mg/kg/day group chose the PTZ lever when tested 24-48 hours after the last injection. Hal, 1 or 2 mg/kg, did not reverse PTZ-lever responding, but it did reverse the rate-disrupting effects of Hal withdrawal. After 10 days of chronic Hal, 3/6 rats in the 1 mg/kg/day group and 5/7 rats in the 2 mg/kg/day group responded on the PTZ lever 24-48 hours after the last injection, and this was reversed with the anxiolytic, chlordiazepoxide. In psychotic patients, abrupt discontinuation of Hal results in various symptoms, including anxiety (Gardos, et al., 1978). The authors caution that separating withdrawal from relapse may be difficult. Our findings suggest that abrupt discontinuation of chronic treatment with non-abused, therapeutic agents, such as Hal, may result in behavioral disruption and anxiety that is withdrawal- rather than relapse-related.

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ACKNOWLEDGEMENTS: Supported by NIDA grant DA06637

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RANDOM REINFORCEMENT SELECTIVELY DETERIORATES DRUG DISCRIMINATIVE STIMULUS CONTROL IN RATS

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Rats were trained to discriminate between 3 and 15 mg/kg of chlordiazepoxide (CDP, injected i.p. 15 min prior to sessions) on a two lever, tandem VI40-FR10 schedule of food reinforcement task. Discrimination was considered established when the average of the group exceeded 80% of injection appropriate responding before the first reinforcement, in a row of 8 out of 10 consecutive training sessions. However, an average of no less than 80% correct responding was required during the last three training sessions of the row. Thereafter, two dose-equisensitive groups were formed (EXP and CONT); matched on the basis of dose-generalization test data (dose range: 2 to 20 mg/kg CDP, i.e., the groups exhibited similar ED50 values in dose generalization tests with CDP). EXP then had 30 sessions with random reinforcement training following daily i.p. saline administrations, i.e., which of the two levers would be associated with food varied, from trial to trial both within and between sessions. CONT received saline injections but had no training. Subsequent testing disclosed a selective, statistically significant ($p < 0.05$) decline in accuracy of responding for the low-dose CDP condition in the EXP group. Responding for high-dose CDP/EXP and both CONT drug stimuli conditions was intact ($p > 0.05$). Subsequent to these tests, additional training showed that the CONT group met the acquisition criterion in 9 sessions (8 sessions is the minimum), whereas the EXP group required 22 sessions to reach criterion. After reaquiring the discrimination, additional dose generalization tests revealed no differences either within or between groups. Then, the former CONT group had 30 random reinforcement sessions after pretreatments with 15 mg/kg CDP. This resulted in a statistically significant ($p < 0.05$) deterioration of responding associated with the high-dose CDP stimulus condition. Responding to low-dose CDP stimulus was intact. Subsequent training showed that the latter animals required 28 sessions to reach the criterion. After reaquisition, dose generalization test results were very similar to those seen prior to any random reinforcement training.

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OVERSHADOWING AND DISCRIMINATION OF A DRUG MIXTURE BY RATS

I. P. Stolerman and E. A. Mariathasan

Drug abuse may entail self-administration of mixtures (combinations) of two or more drugs and, therefore, the present experiments study the discriminative stimulus effects of a mixture of drugs (nicotine plus midazolam). The aim was to determine whether the midazolam stimulus could *overshadow* the nicotine stimulus, and thus weaken a behavioral effect of nicotine.

Rats were trained in a two-bar operant procedure with a tandem schedule of food reinforcement (n=8). All rats were trained to discriminate (-)-nicotine (0.32 mg/kg) from saline, but in two groups, midazolam (0.1 or 0.2 mg/kg) was co-administered with nicotine (Stolerman et al., 1991). Then, dose-response curves were determined separately for nicotine and midazolam in each group and, in rats trained with nicotine only, the direct effect of midazolam (0.1 or 0.2 mg/kg) on the response to nicotine was determined. In rats trained with nicotine only, there was a steep dose-response curve for the discriminative stimulus effect of nicotine. The smaller dose of benzodiazepine in the training stimulus attenuated, and the larger dose abolished, appearance of the discriminative effect of nicotine ($F_{2,21}$=27.6, P<0.001); these data were obtained during tests carried out in the absence of midazolam so the effect seen may be attributed to *previous* exposure of the rats to midazolam during discrimination training. In contrast, the effect on responses to midazolam was quite different; rats trained with the mixture containing 0.2 mg/kg of midazolam showed greater (82%) generalization to 0.2 mg/kg of midazolam than rats trained with either nicotine only or nicotine plus 0.1 mg/kg of midazolam (43% and 50% respectively). In rats previously trained with nicotine alone, midazolam administered before tests had no effect on the established discriminative response to the nicotine.

The presence of a second drug during training can suppress the appearance of discriminative responses to a co-administered agent *(overshadowing)*. This effect is not just pharmacological antagonism because it occurs as a function of *previous co-*administration of drugs, and not in conventional tests for antagonism. Thus, behavioral mechanisms can determine interactions between abused drugs (supported by NIDA grant DA-05543).

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GENETIC DIFFERENCES IN COCAINE EFFECTS: LEWIS vs. FISCHER 344 RATS

T. A. KOSTEN, M. J. D. MISERENDINO AND E.J. NESTLER

Current research suggests there are genetic differences in susceptibility to drug abuse. We studied behavioral effects of cocaine (COC; 7.5, 15, 30, mg/kg, i.p.) in two strains (Lewis and Fischer 344) of rats, previously shown to differ in drug preference. First, we examined locomotor activity. Both strains showed increased activity to the initial COC exposure. The F344 rats showed the greatest percent increase over baseline at the 15 mg dose, while the Lewis rats showed no dose effect. Activity increased from the first to the fifth COC exposure (behavioral sensitization) in both strains with the F344 showing progressively greater sensitization with increasing doses. Sensitization was not due to a conditioned response to the chamber as unpaired groups showed similar sensitization when the COC (15 mg/kg) was not paired with the chambers until Day 5. Second, we examined strain effects on COC conditioned taste aversion (CTA) using a 2-bottle test. Both groups showed a mild aversion to the training solution at the highest dose with no strain differences observed in CTA. Third, we assessed strain differences in COC reinforcement using self-administration (SA) and conditioned place preference (CPP). The F344 rats failed to acquire COC SA (FR1; 1 mg/kg/20 sec infusion) over a 10-day period, unlike the Lewis rats which acquired COC SA by Day 4. For CPP, we found no strain differences at the lowest doses; however, the Lewis rats showed the greatest CPP at 30 mg/kg dose, a dose the F344 rats found aversive. We tested CPP with 60 mg/kg in the Lewis rats and they developed a degree of conditioned place aversion similar to that seen for 30 mg/kg dose for the F344 rats. The effects of chronic COC (0, 15, 30 mg/kg) exposure (five days on; five days off) on COC CPP (training dose 15 mg/kg) lead to increased CPP for the Lewis rats and an aversion for the F344 rats at the highest chronic dose. Finally, we found strain effects in novelty responses. During the first exposure to the activity chamber, the Lewis rats showed greater locomotor activity that decreased with subsequent exposures, whereas the F344 rats showed less activity on day 1 that subsequently increased. Furthermore, the Lewis rats showed a classic avoidance of novel taste solutions (neophobia) upon first exposure to the CTA solutions, whereas the F344 rats were not neophobic. These data suggest F344 rats are more sensitive to the toxic effects of COC and show less reinforcing effects, particularly after repeated exposure. Yet, although the strains differ in novelty responses, they do not differ in conditioning ability to COC in general. Support: NIDA Center Grant P50-DA04060.

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THE ROLE OF MU- AND KAPPA-OPIOID RECEPTORS IN COCAINE-INDUCED CONDITIONED PLACE PREFERENCE

T. SUZUKI; Y. SHIOZAKI; Y. MASUKAWA; M. MISAWA AND H. NAGASE

Recently, Mello et al., (1990) reported that buprenorphine suppresses cocaine self-administration in rhesus monkeys. Based on this finding, it was suggested that buprenorphine might be useful for the pharmacotherapies of not only cocaine abuse but also cocaine-heroin combination abuse. Moreover, recent clinical reports have suggested some efficacy of buprenorphine for the treatment of cocaine abusers. In the present study, effects of buprenorphine, U-50,488H, naltrexone and lithium chloride on cocaine conditioned place preference were examined. Male Sprague-Dawley rats, weighing 160-190g. were used. Conditioning was conducted using the unbiased procedure for 6 days. On day 7, the time spent in each compartment during a 15-min session was measured. Cocaine (0.5 - 4.0 mg/kg) and saline were injected i.p. on alternate days. The rats were confined to each compartment after the injection. Buprenorphine (0.02 - 0.5 mg/kg) and saline were injected i.p. at 30 min before the training on alternate days. Naltrexone (3 mg/kg) was injected i.p. or s.c. at 10 min before the cocaine (4 mg/kg) and saline treatments. U-50,488H (1-10 mg/kg) and cocaine (4 mg/kg) or saline were injected i.p. simultaneously. Lithium chloride (40 mg/kg, s.c.) and cocaine (4 mg/kg, i.p.) were injected simultaneously. Cocaine induced a place preference in a dose-dependent manner. Buprenorphine (0.5 mg/kg, i.p.), a mixed opioid agonist-antagonist, induced a slight place preference. However, buprenorphine blocked the cocaine (4 mg/kg)-induced place preference. Furthermore, the kappa-receptor agonist U-50,488H and the mu-receptor antagonist naltrexone both antagonized the cocaine preference. U-50,488H or naltrexone alone induced a place aversion in a dose-dependent manner. However, the cocaine-induced conditioned place preference was not blocked by lithium chloride, although the latter induced a conditioned place aversion, indicating that the antagonism of cocaine-induced place preference by U-50,488H or naltrexone does not result from a functional antagonism. These results suggest that mu- and kappa-opioid receptors may be involved in cocaine-induced conditioned place preference.

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THE INVOLVEMENT OF THE MESOCORTICOLIMBIC DOPAMINE SYSTEM IN THE CONDITIONED EFFECTS OF COCAINE

D. N. THOMAS;. D. J. FONTANA; R. M. POST; S. R. B. WEISS AND A. PERT

Stimuli associated with cocaine acquire the ability to elicit behavioral effects to those produced by the drug itself. Although classical conditioning using drugs as the unconditioned stimuli has been found readily in both laboratory animals and humans, few efforts have been made to elucidate the neurochemical and neuroanatomical substrates involved. The purpose of this series of studies was to evaluate the participation of specific brain amine systems in cocaine-induced conditioned increases in locomotor activity and to determine whether stimuli associated with cocaine are able to induce the increases in mesolimbic dopamine.

In our present study we have used a one-day conditioning paradigm in which one group of animals (PAIRED) receive cocaine in a novel test cage on DAY 1, followed by saline in the home cage. Another group of animals (UNPAIRED) receive saline in the test cage and cocaine in the home cage. On DAY 2 both groups receive a cocaine in the test cage.

Selective DA lesions of the amygdala and nucleus accumbens prevent cocaine-induced increases in locomotor activity. Striatal and frontal cortex lesions did not affect locomotor activity but the striatal lesions attenuated the conditioned increases in stereotypy. Noradrenergic lesions of the locus coeruleus and serotonergic lesions of the dorsal raphe were unable to prevent the cocaine induced increases in locomotor activity. These findings suggest the primary involvement of the mesolimbic dopamine pathways in cocaine-induced conditioning.

The ability of environmental stimuli associated with cocaine to increase dopamine overflow in the mesolimbic dopamine system was evaluated using in vivo microdialysis. One group of rats were conditioned to cocaine (DAY 1) in the locomotor activity chamber while the others received cocaine in the home cage. On DAY 2, microdialysis probes were introduced via guide cannulae into the n. accumbens and all the animals were then tested in the locomotor chambers with low doses of cocaine. The conditioned rats exhibited significantly higher locomotor activity and increased dopamine overflow relative to the controls. These findings indicate that conditioned stimuli are capable of increasing dopamine release in the mesolimbic dopamine system and may provide a neurochemical basis for understanding incentive-motivational properties of stimuli associated with cocaine.

It has been found that 'priming' with cocaine will reinstate self-administration in rats following extinction. Likewise, it is possible that cocaine-related stimuli reinstate or precipitate drug-seeking behavior in cocaine addicts even after prolonged abstinence by producing a conditioned neurochemical state that is similar to that produced by the drug itself. Elucidation of the biochemical and neural substrates underlying the conditioned component of cocaine sensitization may thus provide novel targets for the therapeutic intervention in cocaine abuse disorders. **ACKNOWLEDGEMENTS:** This work has been partially supported by post-doctoral training fellowship from MacArthur Foundation Mental Health Research Network I (Psychobiology of Depression) for Dr. D. N. Thomas at the NIMH, Bethesda, MD 20892.

COCAINE-INDUCED BEHAVIORAL SENSITIZATION: EFFECTS ON OPEN FIELD BEHAVIOR AND AVOIDANCE ACQUISITION IN RATS

P. H. JANAK; R. V. HERNANDEZ; R. R. RULE; E. J. BAREA AND J. L. MARTINEZ. JR.

Behavioral sensitization is an increase in the behavioral response to repeated administration of a drug. We investigated the time course of appearance of cocaine-induced behavioral sensitization of locomotor activity in rats during the 8 days following a repeated cocaine treatment of 15 mg/kg per day for three days. Sprague Dawley rats received 3 daily IP injections of saline or 15 mg/kg cocaine. All rats were tested for sensitization in an open field following an injection of 15 mg/kg cocaine. After repeated cocaine (15 mg/kg) injection, movement in both the vertical and horizontal plane was increased in cocaine-treated rats 2, but not 5 or 8, days after treatment as compared to saline-treated subjects. Repeated cocaine treatment did not produce any abnormalities in the EEG.

It is possible that the cocaine-produced neuronal changes that underlie the phenomenon of behavioral sensitization are capable of affecting later behavior of animals in a drug-free state. In order to investigate this possibility, the subjects that participated in the behavioral sensitization study were tested for their ability to acquire a jump-up active avoidance response. Two weeks after the third cocaine treatment, the rats were given 8 trials in an automated shelf-jump task in which a house light preceded by 10 sec the onset of a 290 μA footshock. Rats escaped or avoided shock delivery by jumping on a raised shelf. Prior cocaine treatment facilitated jump-up responding as compared to saline-treated rats. While 100% of cocaine-treated rats avoided the footshock by Trial 8 of the training session, only 50% of saline-treated rats avoided the footshock by Trial 8. Importantly, the rats were tested in a drug-free state. Thus, exposure to cocaine may influence an animal's ability to learn new responses many days following the cessation of cocaine treatment.

Cocaine treatment, therefore, produces long-lasting effects on later behavior revealed both under the influence of a cocaine challenge (behavioral sensitization) and in a drug-free state (avoidance acquisition). These results indicate that a relatively brief exposure to cocaine my influence cognitive functioning.

ACKNOWLEDGEMENTS

Support by DA05375 to PHJ and DA06192 to JIM, both from NIDA.

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BEHAVIORAL SENSITIZATION FOLLOWING CHRONIC AMPHETAMINE TREATMENT IN RATS AND ASSOCIATED ALTERATIONS IN DOPAMINE

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Repeated administration of amphetamine to experimental animals has been shown to result in an increased abnormal behavioral response to a challenge dose of the drug. The exact mechanism underlying the development of this "behavioral sensitization" phenomenon is unknown, although Robinson et al. 1988 demonstrated that the hyperbehavioral response to amphetamine following an aggressive chronic regimen was accompanied by significantly elevated dopamine (DA) release in the ventral striatum.

Using in vivo microdialysis, we have examined and compared the effect of various doses of amphetamine, applied both to terminal regions and systemically on DA overflow in rats chronically treated with a moderate amphetamine regimen (7 days at 3 mg/kg/day) and compared responses to those in saline treated animals. Additionally, some behavioral aspects of the response to this same amphetamine regimen were investigated.

Animals treated with this chronic amphetamine regimen displayed behavioral sensitization to both the locomotor and stereotypic effects of a 1 mg/kg amphetamine challenge.

In acute microdialysis experiments, systemic amphetamine elicited dose-related increases in DA overflow in both the striatum and nucleus accumbens of anesthetized rats. The striatum appeared to be significantly more sensitive than the nucleus accumbens to this effect. Chronic amphetamine treated animals showed no apparent difference in their peak DA response to either 0.25 or 1 mg/kg challenge dose of amphetamine, as compared to saline treated rats. However there was an apparent difference in the overall response of the amphetamine pretreated rats in response to the low dose of amphetamine (0.25 mg/kg) only. It is therefore possible that this sensitization effect may be masked in the presence of large amounts of DA in the synaptic cleft, as induced by higher doses of amphetamine.

Amphetamine applied focally to the terminal region of the corpus striatum elicited dose-related increases in DA overflow. Chronic amphetamine treated animals were similar to saline animals in response to a focal challenge of amphetamine.

In conclusion, our data suggest that the DA system appears to be at least partially involved in the sensitization mechanism although there is an apparent dissociation between the behavioral and DA changes elicited by an amphetamine challenge. We suggest that other neurotransmitter systems may also mediate part of the amphetamine sensitization response, as also suggested by Segal and Kuczenski 1992. Furthermore, our results from the focal amphetamine experiments indicate that changes at a presynaptic level are unlikely to account for increased responsiveness in the DA system. One other possible explanation could be a dispositional change following chronic amphetamine treatment, as has been proposed to account for at least some of the apparent sensitization following cocaine.

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INTERACTION BETWEEN MU/DELTA AND KAPPA RECEPTORS IN THE LOCOMOTOR ENHANCEMENT AND DOPAMINE METABOLISM ELEVATIONS INDUCED BY INTRACEREBROVENTRICULAR INJECTION OF MORPHINE

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Mu and delta opioid receptor agonists are known to have similar effects in several pharmacological actions, whereas both mu and kappa agonists are known to have opposite and/or different effects with each other. Interestingly, it is possible that kappa agonists may suppress the side-effects of mu and/or delta agonists which is derived from the central dopaminergic systems. In the present study, we therefore investigated the effects of U-50,488H. kappa agonist, on the morphine-induced locomotor enhancing action and dopaminc (DA) metabolism elevations. Male ddY mice were used. The locomotor activity of mice was measured by an ambulometer using a tilting-type round activity cage. Morphine (i.c.v.) enhanced locomotor activity in mice. The locomotor enhancing action induced by i.c.v. morphine was completely suppressed by pretreatment with a mu-delta opioid receptor complex antagonist beta-FNA or 6-OHDA in combination with desipramine. U-50, 488H, a selective kappa agonist, dose-dependently reduced the locomotor enhancing action induced by morphine, but not apomorphine, a DA agonist. Nor-BNI, a selective kappa antagonist, significantly potentiated the morphine-induced enhanced locomotion. Additionally, the locomotion by i.c.v. morphine was significantly potentiated by chronic pretreatment with U-50,488H. Furthermore, the effects of U-50,488H on the DA turnover enhancement of i.c.v. morphine was investigated using the HPLC-ECD system. As a result, i.c.v. U-50,4888 dose-dependently antagonized the i.c.v. morphine-induced DA metabolism elevations in the whole brain without changing the DA steady-state levels. These results provide further evidence that activation of kappa receptors may suppress the CNS-excitation induced by activation of mu/delta receptors (mainly mu-delta complex sites) through inhibiting DA release. In addition, the i.c.v. morphine-induced locomotor enhancing action was potentiated by blockade or subsensitivity of kappa receptors. We therefore conclude that an adequate coactivation of mu and kappa receptors would be very useful for the clinical setting.

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COCAINE BASE SELF-ADMINISTRATION IN HUMANS

T. Thompson[1], D. Hatsukami,[1], P. Pentel[2]

GOAL: To examine and develop a laboratory model for the self-administration of smoked cocaine-base by varying the dose (within subjects) and cost per delivery of cocaine (between subjects).

METHODS: Male (n = 9) cocaine subjects attended four experimental sessions while hospitalized on a research unit During each experimental session, 10 tokens were given to a subject which could be exchanged for a delivery of smoked cocaine-base or money. The monetary value of the tokens varied between subjects ($2, $3, or $5) but remained consistent within subjects (n = 3 for each token value). One of three doses (5 mg, 0.2 mg/kg or 0.4 mg/kg) of smoked cocaine was given each session in a random-order, double-blind manner, with one dose size randomly repeated; doses varied between but not within sessions. Subjects received a free sample of smoked cocaine of that day's dose prior to the experimental session. Visual analog scales (VAS) were obtained before and after each dose.

RESULTS: All six subjects in the $3 and $5 conditions took 8-10 deliveries of 0.4 mg/kg dose of cocaine-base while none self-administered more than 4 inhalations of the 5 mg dose. In the $2 condition, results were more ambiguous as 2 or 3 subjects self-administration more than 8 deliveries of all doses. A significant mean correlation was obtained between the level of "high" reported on the VAS on the sample dose and the number of cocaine inhalations taken.

CONCLUSIONS: (1) Cost of cocaine can change the dose response curve; (2) A dose response curve was obtained when each dose cost $3 and $5 but not with a cost of $2; (3) The degree of subjective high measured at the sample dose correlates with the number of cocaine deliveries taken during that session.

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FACTORS INFLUENCING THE REINFORCING AND SUBJECTIVE EFFECTS OF D-AMPHETAMINE IN HUMANS

L. D. CHAIT

The reinforcing and subjective effects of oral d-amphetamine (AMP) were studied in a group of non-drug-abusing adults (16 males, 13 females). A discrete-trial choice procedure was used to assess the reinforcing effects of a single dose (which varied across subjects-mean, 16 mg; range, 7.5-20 mg) selected to produce a clear subjective response in each subject. After sampling color-coded capsules containing either AMP or placebo, subjects were allowed to choose between self-administration of either capsule or no capsule. Subjective effects were assessed with standard rating scales (POMS, ARCI, visual analog scales). A number of variables were examined in an attempt to explain both within- and between-subject variability in response to AMP. These variables included subject characteristics (gender, current and past drug use, personality); motor activity; and baseline autonomic and CNS arousal, mood and platelet alpha-2-adrenergic activity. Of the 29 subjects, 11 chose AMP on either 2 or 3 out of a possible 3 occasions. The mean number of AMP choices was 1.1 (38%). Tobacco smokers reported stronger aversive responses to AMP and chose the drug significantly less often than nonsmokers (0.6 vs. 1.4 choices). Subjects with a history of recreational stimulant use reported less subjective response to AMP than subjects without such history. Within-subject variability in AMP choice was related to variability in subjective response to the drug across choice trials, as well as to variability in baseline mood: AMP was more likely to be chosen on those occasions when subjects were in a more "positive" mood at the time of making the choice. These results provide new information regarding factors that may be relevant in determining individual differences in vulnerability to abuse of psychomotor stimulants.

ACKNOWLEDGEMENT

This research was supported by NTDA grant DA-00250.

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REACTIVITY TO SMOKING AND NON-SMOKING CUES IN SMOKERS AND NON-SMOKERS

A. DROUNGAS; A. R. CHILDRESS; R. ERHMAN; M. SEMANS AND C. P. O'BRIEN

Over the last two decades much effort has been devoted to the idea that Pavlovian conditioning mechanisms underlie the maintenance of substance abuse and relapse (Robbins and Ehrman, 1992). Within the Pavlovian framework, research has demonstrated that cocaine and opiate users display differentiable physiological reactivity and report craving for their drug of choice in response to cues which are related to their drug of use (Ehrman et al., in press). We have been interested in examining whether smokers (a) display differentiable physiological reactivity, (b) crave cigarettes, (c) perform differentially in a simple cognitive task, and (d) smoke faster in response to smoking and nonsmoking cues, compared to nonsmokers.

Heavy smokers (12) and nonsmokers (13) viewed a video (14 min), engaged in a task (5 min) and read scripts (14) during 2 cue-exposure sessions. In the smoking session the video showed people smoking while engaging in various activities, for the task subjects handled cigarettes and the scripts made explicit reference to smoking. In the nonsmoking session the video showed the same scenes except people were not smoking, for the task subjects blew bubbles and the scripts made no reference to smoking. In both sessions (a) heart rate, skin temperature and skin resistance were monitored during the video, (b) subjective ratings for desire and intention to smoke, nicotine high and withdrawal were assessed after the video, the task and at the end of the session, (c) performance in the Stroop task was assessed after subjects had read the scripts, and (d) the latency to smoke was assessed at the end of each session while subjects were waiting in the reception area where they were unobtrusively observed.

Statistical analyses showed (a) a reliable decrease in heart rate to the smoking video, a reliable decrease in skin temperature and a reliable increase in skin resistance to the nonsmoking video in smokers only, (b) a reliable increase in desire and intention to smoke after the smoking session in smokers, (c) a reliable disruption in performance on the Stroop task after the smoking session in smokers only, and (d) for 5 of the 8 smokers the latency to smoke was shorter after the smoking session.

REFERENCES

The reference list will be made available from the senior author upon request.

ACKNOWLEDGEMENTS

This research was funded by VA Medical Research Service and USPHS grant DA 03008

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NICOTINE PRE-LOAD ATTENUATES SMOKING BEHAVIOR

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A primary determinant of smoking desire and behavior is blood nicotine level, and smokers tend to regulate their smoking over time to maintain consistent nicotine levels. However, although nicotine replacement may suppress ad lib smoking, the decrease in tobacco consumption appears to be less than would be expected if the only determinant of smoking was nicotine regulation. In addition, females may be more sensitive than males to nicotine, and little is known of possible gender differences in smoking behavior to regulate nicotine. We examined effects of acute nicotine replacement via measured dose nasal spray on suppressing self-reported desire to smoke (Study I) and ad lib smoking behavior (Study II) in male and female smokers who had abstained overnight from smoking but were not trying to stop smoking permanently.

In Study I, 10 male and 10 female smokers received 0, 7.5, 15, and 30 ug/kg nicotine @ 30 mins for 2 hrs via measured-dose nasal spray, with each dose on a separate day. Desire to smoke tobacco was measured by the "Craving" scale of the Shiffman-Jarvik Withdrawal Questionnaire and was assessed 3 mins after each dosing. Self-reported desire to smoke was significantly suppressed 16-22% by the nicotine doses relative to placebo, but there were no differences among nicotine doses nor between males and females.

In Study II, 8 male and 8 female smokers received 0, 15, and 30 ug/kg nicotine @ 30 mins for 2.5 hrs, with each dose on a separate day. Between dosings, subjects were allowed to smoke their preferred brand of cigarette ad lib while reading, watching T.V., etc. Similar to Study I, replacement with 15 and 30 ug/kg nicotine significantly suppressed number of cigarettes smoked (by 18% and 32%, respectively), number of puffs (by 17% and 36%), and carbon monoxide boost (by 21% and 34%), and increased latency to smoking (by 40% and 55%), but there were few significant differences between the two nicotine doses. Magnitude of smoking suppression due to 15 ug/kg tended to be greater in males vs. females. However, plasma nicotine was significantly higher following 15 and 30 ug/kg vs. placebo, suggesting only partial compensation in smoking behavior with acute nasal nicotine pre-load.

These results indicate that self-reported desire to smoke (Study I) and smoking behavior (Study II) are significantly suppressed in male and female smokers following nicotine replacement via nasal spray. Nevertheless, the magnitude of the suppression, or compensation, in smoking behavior during Study II was less than would be expected in a strict "nicotine regulation" model of smoking behavior. Thus, these findings also support the notion that smoking behavior is partly influenced by factors other than nicotine regulation.

ACKNOWLEDGMENT: Supported by NIDA Grant DA-07865.

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REDUCING LONG-TERM NICOTINE GUM USE: THE ROLE OF NON-PHARMACOLOGICAL FACTORS

J. C. TATE, J. M. SCHMITZ AND R. SPIGA

A small subgroup of nicorette users demonstrate behavioral dependence on the gum, or persistent use despite a clear recommendation to stop. Recently, investigators have begun to look for the factors that might account for dependence on nicotine replacement therapies. We are conducting a prospective, placebo-controlled experimental study of nicotine withdrawal symptoms during gradual tapering of gum consumption among long-term nicorette users. Subjects are randomly assigned to either reduction only (daily 2 mg. nicotine gum is reduced by 1 piece per week), or reduction with placebo substitution (as daily 2 mg. nicotine gum is reduced by one piece per week, 0 mg. placebo is increased by one piece per week, so that total gum per day remains constant). Based on the hypothesis that behavioral dependence on nicotine gum is due, in part, to various non-pharmacological reinforcing effects of the gum, we predict that less nicotine withdrawal symptomatology will be reported during reduction without placebo substitution than reduction only. METHOD: Two ex-smokers with a mean rate of 18 pieces of Nicorette per day for an average of 3.3 years have participated to date. Throughout the study Ss recorded daily gum consumption and rated severity of nicotine withdrawal symptoms (NWF: Hughes & Hatsukami, 1984). Weekly measures included POMS, Nicorette Side Effects Scale, resting heart rate, BP, CO, weight and urine drug screen. RESULTS: Preliminary results indicate greater withdrawal symptomatology occurring in the nicotine reduction *without* substitution condition. Dramatic increases in symptomatology, mood, and weight were found during the final weeks of reduction, when total pieces of nicotine gum was less than 50% baseline rate. In contrast, as total daily nicotine dose was decreased *with* placebo substitution, only slight increases in nicotine withdrawal symptoms were reported, suggesting that the availability of the same total number of gums, albeit placebo, may have mitigated withdrawal symptoms. DISCUSSION: This present study is the first to examine the effects of a gradual reduction approach for cessation of nicotine gum on withdrawal symptomatology. The advantage of continuous monitoring and placebo replacement is that these procedures permit observation of the subtle effects of nicotine reduction as well as the effects of non-pharmacological factors (gum). Results of this ongoing study suggest that the availability of the same total number of gums, albeit placebo, may have mitigated withdrawal symptoms. Compared to nicotine gum, the newer replacement therapies, i.e., transdermal nicotine systems, should be less effected by non-pharmacological factors during cessation procedures.

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TOBACCO SMOKING AMONG METHADONE MAINTENANCE PATIENTS: PRELIMINARY INVESTIGATIONS

J. M. SCHMITZ, J. GRABOWSKI AND H. RHOADES

Cigarette smoking rates among clients in methadone maintenance treatment (MMT) are very high, ranging from 82-98%. This paper reports the results of three ongoing studies designed to examine: (1) the interaction of methadone administration and smoking; (2) the efficacy of contingent reinforcement procedures in promoting reduced tobacco use; (3) a behaviorally-based smoking cessation program for this population. In STUDY 1, four male methadone patients (M smoking rate = 34; M yrs smoked = 12.5) underwent successive methadone dose changes every two weeks during the eight week study period. Dose increases (50mg to 80mg) and dose decreases (80mg to 50mg) were delivered in a blind procedure. Dependent measures include daily self-report records of smoking, twice weekly CO measurement, and urine drug screen. Results to date show the predicted methadone dose-related changes in smoking for two of the four Ss. Average smoking rates for these Ss were 32.8, 28, 36.05, 24.95 when methadone doses were 80mg., 50mg., 80mg., 50., respectively. Mean CO levels have not reflected corresponding increases in smoking rate. These preliminary findings demonstrate that methadone can produce substantial increases in cigarette smoking. In STUDY 2, a within-subjects reversal design is being used to evaluate CO as the target for a contingent reinforcement intervention to promote reduced smoking. During 2-week contingency phases, a monetary payment of $7.00 is available for CO readings 50% or less of the average reading obtained during the previous noncontingency phase. Data from three completed Ss show that CO readings and smoking rate were generally reduced during the contingent reinforcement intervention compared to non-contingency phases. Two Ss reduced their CO readings below the CO criterion on at least four of the possible eight days that contingent reinforcement was available. The general return to original baseline levels when the contingency was withdrawn suggests that this behavioral intervention may have a short term effect on overall cigarette consumption and CO. STUDY 3 extends Study 2 by using a contingent reinforcement procedure in a smoking cessation treatment intervention. In this single-case study, a changing criterion design was used to reinforce stepwise reductions in smoking. During the 8-week treatment, weekly criterion rate of smoking was set at 80% of previous week with monetary consequences for goal achievement. Measures of smoking changed in an orderly manner during the study. The subject quit smoking at week 6 (CO<8ppm) and maintained abstinence for the remainder of the study. Suggestions for future smoking research with MMT clients can be derived from these preliminary studies.

ACKNOWLEDGEMENTS: Supported by NIDA Grant DA 06143.

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ACUTE AND RESIDUAL EFFECTS OF SMOKED MARIJUANA ON HUMAN PERFORMANCE

S. J. HEISHMAN; W. B. PICKWORTH; E. B. BUNKER AND J. E. HENNINGFIELD

Previous findings from our laboratory demonstrated that smoked marijuana can impair performance on certain cognitive tasks for up to 24 hours. This residual impairment was characterized by decreased accuracy and increased response time, was most evident in digit recall and serial addition/subtraction tasks, and was most clearly produced by conditions in which subjects smoked 3 or 4 active marijuana cigarettes (2.6% THC) over a 4-hour period.

The purpose of the present study was to determine if minimal exposure to marijuana would produce performance decrements the day after smoking. Thus, subjects were administered 8 puffs from cigarettes containing either 0, 1.8, or 3.6% THC, and the same battery of psychomotor and cognitive performance tasks as in the previous study was assessed periodically to 25 hours postdrug.

Nine healthy, males reporting a history of moderate marijuana use resided on a residential research unit. Subjects participated in three experimental sessions in which they smoked one NIDA marijuana cigarette containing either 0, 1.8, or 3.6% THC according to a paced smoking procedure (8 puffs per cigarette, 40 sec interpuff interval). The order of drug conditions was randomized, and marijuana was administered under double blind conditions. A battery of physiological, subjective, and performance measures was administered predrug and 0.25, 1, 1.75, 3.5, 5.5, 23, 24, and 25 hours postdrug. Psychomotor and cognitive performance measures included the following tasks: circular lights (eye-hand coordination), serial addition/subtraction, logical reasoning, digit recall, and manikin (spatial skills). Subjects practiced the tasks before the study began until stable performance was attained.

Data from each of the performance measures were analyzed by a 2-way ANOVA, with marijuana dose and time postdrug as factors. Results indicated that smoking one marijuana cigarette produced minimal acute performance impairment; response rate was decreased and response time was increased on several cognitive tasks. There was no evidence of impaired cognitive or psychomotor performance the day after smoking.

Specifically, marijuana had no effect on the circular lights and manikin tasks. On the serial addition/subtraction task, marijuana significantly decreased number of attempted trials and increased mean response time. There was a trend toward decreased response accuracy. On the logical reasoning task, marijuana decreased number of attempted responses, but had no effect on percent correct responses or mean response time. On the digit recall task, marijuana produced an increase in response time and a decreased trend in percent correct responses, but had no effect on number of attempted trials.

These results indicate that minimal exposure to marijuana (8 puffs) does not impair cognitive or psychomotor performance, as measured in this study, the day after smoking. These data are consistent with other recent studies in which comparable doses of marijuana were given.

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BEHAVIORAL EFFECTS OF SMOKED MARIJUANA IN HUMANS

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Acute effects of smoked marijuana on heart rate, drug ratings, and task performance, including DSST, repeated acquisition of response sequences, number recognition and repeated acquisition of task sequences were examined. Six subjects, reporting occasional marijuana use, participated in daily 3.5 hr sessions. Marijuana (0.0, 2.0 or 3.5% Δ9-THC) was administered at the start of each session, with monetary contingencies associated with minimum puff and breathhold durations. Heart rate was monitored immediately following drug administration; task performance was continuous over a 3-hr interval; and drug ratings were completed following sessions. Acquisition of task sequences was maintained by monetary contingencies; no contingencies were associated with performance of other tasks. Heart rate and ratings of dose "Potency" and "High" were increased, and several dimensions of task performance, including DSST rate and accuracy, sequence-acquisition efficiency, and number recognition accuracy and response time, were consistently disrupted by marijuana, often in a dose-related fashion. In contrast, task sequence acquisition was disrupted during initial sessions only, suggesting differential tolerance development. The relative sensitivity of these measures varied across subjects, and no single measure, such as heart rate or drug ratings, could be used to predict marijuana's behavioral effects. Marijuana puff durations were decreased at the highest dose, but dose-related changes in heart rate and task performance indicated that this change in smoking topography did not result in complete compensation for THC concentration in marijuana smoke.

ACKNOWLEDGEMENTS: This research was supported by Grant No. DA-03476 from the National Institute on Drug Abuse, and was approved by Johns Hopkins Medical School Joint Committee on Clinical Investigation.

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SUBJECTIVE RESPONSES TO DIAZEPAM IN HUMANS: EFFECTS OF RATE OF ONSET

H. DE WIT, J. AMBRE AND S. DUDISH

It is commonly assumed that drugs with rapid onset produce greater euphoria (and hence have higher potential for abuse) than drugs with slower onset of effects. This relationship has been noted in comparisons across different drugs within the same class, and in comparisons with the same drug across different routes of administration. However, few studies have examined this relationship within the same drug and via the same route of administration. The present study was designed to explore the relationship between onset rate and euphoria using orally-administered diazepam (DZ). Nine male social drinkers participated in three sessions (slow DZ, rapid DA and placebo), conducted double-blind and in counterbalanced order. DZ was administered orally in either a slow onset condition (six doses of 4 mg DZ every 30 min) or a rapid onset condition (a single dose of 20 mg DZ). The doses were selected to produce comparable peak blood levels in the two conditions. Subjective, behavioral and physiological effects, and plasma DZ levels were measured at regular intervals. The two dosing conditions produced similar peak plasma levels of DZ (548 ng/ml in the slow onset condition and 60 ng/ml in the rapid onset condition). However, the peak occurred after 201 min in the slow condition and 62 min in the rapid onset condition. The physiological, psychomotor and sedative effects of DZ were similar in the slow and rapid conditions. However, on a widely-used measure of drug-induced euphoria (the MBG scale of the ARCI) DZ increased scores significantly more in the rapid condition than in the slow condition. Further, subjects showed more signs of intoxication in the rapid, as compared to the slow onset condition. These results provide empirical support for the commonly-held belief that rate of onset influences drug-induced euphoria. They suggest, further, that the potential for abuse of new therapeutic agents could be minimized by developing drugs or drug formulations with slower onset of effects.

ACKNOWLEDGMENT: This research was supported by NIDA grant DA02812.

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EFFECTS OF REINFORCEMENT HISTORY ON BENZODIAZEPINE DISRUPTION OF MATCHING-TO-SAMPLE (MTS) PERFORMANCE

J. D. ROACHE; D. R. CHEREK; R. A. MEISCH AND R. SPIGA

Normal male subjects participated in studies of visual pattern MTS performance examined under three different levels of pattern discriminability and two different contingencies of monetary reinforcement. Under the ACCURACY contingency, money earnings depended only on accurate responding but under the TIME contingency, earnings depended on both speed and accuracy. Subjects were not instructed regarding the contingencies.

Performance was an orderly function of pattern discriminability. The least discriminable patterns exerted less stimulus control in that responding was slower and less accurate than observed with the most discriminable patterns. Behavioral studies in 4 subjects showed that two out of four were sensitive to contingency changes in an A-B-A-B double reversal design. Performance under the TIME contingency was faster and less accurate as compared with the ACCURACY contingency.

Ten subjects were randomly assigned to one of the two contingency conditions for triazolam dose-response determinations. Again schedule control was observed in that baseline accuracies were less with the TIME contingency subjects. Triazolam doses of 4.0 and 8.0 ug/kg produced dose-related decreases in performance accuracy indicating a disruption of stimulus control. Disruption was greatest for the least discriminable stimulus condition. Subjects under the ACCURACYcontingency showed significantly less disruption from triazolam than subjects under the TIME contingency. Four subjects in each of these groups were “crossed-over” to the opposite contingency and triazolam dose response was again determined. Most all subjects showed greater accuracy disruptions on this second triazolam determination. However, history effects also were apparent in that subjects with the TIME contingency history now showed greater accuracy disruptions than previously observed in those subjects who had first been tested under the ACCURACY contingency.

These data suggest that reinforcement only for accurate responding may attenuate drug-induced disruption of stimulus control. Also, histories of reinforcement involving speed for accuracy tradeoffs may enhance drug-induced performance impairment.

Supported by NIDA grant DA-05716

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ACUTE BEHAVIORAL EFFECTS OF CLINICALLY RECOMMENDED DOSES OF TRIAZOLAM AND TEMAZEPAM IN NORMAL SUBJECTS

C. R. RUSH; S. T. HIGGINS; J. R. HUGHES AND W. K. BICKEL

The adverse effects of triazolam purportedly occur more frequently and are more severe than those of other benzodiazepine hypnotics. The purpose of this experiment was to empirically assess the validly of such claims by comparing the behavioral effects of triazolam to those of a prototypical 1,4-benzodiazepine hypnotic, temazepam. Six healthy men participated in a double-blind, crossover trial in which they received acute doses of triazolam (0.25 and 0.5 mg/70kg), temazepam (15 and 30 mg/70kq), and placebo. Drug effects were assessed using a measure of learning, two recall measures, a psychomotor task, and self-reports assessing drug effects. Triazolam, but not temazepam, significantly impaired learning. Both drugs disrupted psychomotor performance and recall, but triazolam was more disruptive. Both drugs also increased subject ratings of sedation, but triazolam generally produced greater effects. The present experiment demonstrated that clinically recommended doses of triazolam produced greater behavioral impairment than temazepam. However, triazolam also produced significantly greater subject-ratings of sedation than temazepam suggesting that the doses tested probably were not clinically equivalent. Future research needs to establish equivalent doses of triazolam and temazepam on a clinical measure (e.g., hypnotic efficacy), or, at the very least, on a measure that likely covaries with hypnotic efficacy (e.g., self-reported sleepiness). Between-drug comparison studies could then compare several clinically equivalent doses to determine the relative liability associated with their use. Such research would determine which benzodiazepine hypnotics are associated with the least behavioral impairment, if indeed differences exist.

This research was supported in part by a US Public Health Predoctoral Fellowship Award (CRR) DA-05382, First Independent Research Support and Transition Award (STH) DA-04545, Research Grant (WKB) DA-06205, Research Grant (JRH) DA-04843, and Research Scientist Development Award (JRH) DA-00109 from the National Institute on Drug Abuse, and a General Clinical Research Center Award RR-109 from the National Institutes of Health. Rush, C.R., Higgins, S.T., Hughes, J.R., and Bickel, W.K. Departments of Psychiatry and Psychology, University of Vermont.

CONTEXTUAL CONTROL OF TRIAZOLAM REINFORCEMENT

K. SILVERMAN, G. K. MUMFORD AND R. R. GRFFITHS

This study assessed the influence of environmental context on triazolam reinforcement in 4 recreational sedative users. During the first phase, each subject was exposed to each of two color-coded compounds, placebo and triazolam (.25 mg or .5 mg), in each of three environmental contexts. The compounds were administered orally in capsules at 7:30 AM each day. Four consecutive 50-minute environmental context sessions were scheduled following drug administration at 60-minute intervals beginning at 6:30 AM. During part of each environmental context session, subjects were required to relax on a bed; during the remainder of each session, subjects performed a computer vigilance task. During the vigilance task, subjects sat at a computer terminal and were required to press a key immediately after a star appeared in the center of the screen. The star appeared briefly at unpredictable times. The three environmental contexts differed only in the proportion of the session occupied by the relaxation component in each 50-minute context session: Environmental context sessions either included 5 min, 25 min, or 45 min of the relaxation component. On any given day, the duration of the relaxation component was the same for all 4 context sessions. After being exposed to each compound in each of the three environmental contexts, subjects participated in a drug vs. money choice phase in which they chose between 20 different monetary values and each of their two color-coded compounds. Each day subjects were instructed to make those choices separately considering each of the three environmental contexts, 5 min, 25 min, and 45 min of relaxation. The choices were made using a novel multiple-choice procedure in which subjects made all 120 drug vs. money choices each day, but only one choice each day was reinforced. Subjects reliably chose all monetary values over placebo. Choice of triazolam over money was an increasing function of the length of the relaxation component within environmental context sessions. This experiment demonstrates that triazolam's reinforcing effects can be modulated by the environmental context in which self-administration occurs.

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REINFORCING AND SUBJECTIVE EFFECTS OF ETHANOL AND DIAZEPAM: EVALUATION IN THE SAME INDIVIDUALS

P. DOTY AND H. DE WIT

Non-drug-abusing volunteers vary widely in their subjective and behavioral responses to ethanol and diazepam. The present study was designed to examine whether responses to these two drugs were related in the same individuals. Nineteen normal healthy males and females participated in two double-blind, double-dummy studies, assessing preference for either ethanol (0.5 g/kg) vs. placebo or diazepam (20 mg) vs. placebo. Order of drug evaluation was counterbalanced across subjects. Each study consisted of seven sessions, four sampling sessions followed by three choice sessions. The number of occasions (out of three) on which subjects chose drug over placebo was the primary measure of preference. Subjective measures and psychomotor performance were evaluated at regular intervals throughout each session. Choice of ethanol was not related to choice of diazepam. Ratings of "liking" of the two drugs was moderately correlated (r=0.66). Subjective responses to the two drugs were generally not correlated within individuals. These results suggest that subjective and behavioral responses to ethanol and diazepam are not related in the same individuals.

AKNOWLEDGEMENTS: This research was supported by NIDA grant DA02812.

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EFFECTS OF RESPONSE COST AND UNIT DOSE ON THE SELF ADMINISTRATION OF ALCOHOL IN SOCIAL DRINKERS

M. L. VAN ETTEN; S. T. HIGGINS; W. K. BICKEL AND J. R. HUGHES

Prior laboratory studies in nonhumans and alcoholic humans have demonstrated that alcohol consumption varies as an orderly function of changes in response cost unit dose. For example, alcohol self-administration decreases as fixed-ratio requirement increases in both rats and rhesus monkeys, and increases in dose or concentration increase consumption up to a maximum after which further increases in dose suppress intake (Henningfield and Meisch, 1978, Meisch and Thompson, 1973 and Meisch and Thompson, 1974). Similarly in alcoholics, increasing the effort to obtain alcohol decreases alcohol self-administration, and increases in the dose of alcohol increases total consumption (Bigelow and Liebson, 1972 and Bigelow, Griffiths, and Liebson, 1977). To our knowledge, no research has focused on the effects of cost or dose on alcohol self-administration in social drinkers under controlled laboratory conditions. The present study is an ongoing investigation of this topic. Three male social drinkers (12-36 drinks/week), aged 21-22 years, have completed the study thus far. Subjects self-administered alcohol during 2 hr sessions twice weekly. Response requirement (FR 100-1600) and dose (2 and 4 oz of commercial beer) were varied separately across sessions. As FR increased, consumption generally decreased in a positively decelerating fashion. Maximum consumption was greater with the 4 oz than the 2 oz reinforcer. Overall rates of responding changed in an inverted-U-shaped manner as a function of increasing FR value. Higher rates of responding were maintained by the 2 oz reinforcer in 2 of 3 subjects, with the third subject showing no differences in rates across the two reinforcer magnitudes. The orderly relations between FR value and alcohol self-administration observed in this study extend prior findings in nonhumans and alcoholics to social drinkers. Consistencies were evident across measures of consumption and overall rates of responding. The positively decelerating functions relating consumption to increases in cost (i.e. FR value) observed in this study are consistent with prior findings involving several different species and drugs. The effects of varying unit dose of alcohol on these measures also were generally consistent with prior findings in nonhumans and alcoholics. Such consistencies in the functional relationships observed with nonhumans, alcoholics, and social drinkers support a position that a common set of variables control alcohol self-administration across these diverse subject populations.

*References may be obtained from the senior author.

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EFFECTS OF ETHANOL AND INSTRUCTIONS ON HUMAN FREE-OPERANT COOPERATIVE RESPONDING

D. ESHAGHPOUR AND R. SPIGA

Human free-operant cooperative responding, as affected by ethanol at doses of 0.5, 0.75 and 1.0 g/kg, was studied in twelve healthy male volunteers. Subjects participated, Monday through Friday, in five 30 minute sessions daily. Subjects were given either ethanol or placebo doses 30 minutes before the second session. Two schedule components alternated during each of the five sessions. The first schedule component maintained button pressing, "work alone" behavior, by presenting points exchangeable for money on a random (RI) 60 second schedule. Points were added to a counter marked "Your Earnings." Occasionally points were added to another counter marked "Other's Earnings" on a RT 60 second schedule. A concurrent RI 60 RI 60 second schedule, during the second schedule component, maintained button pressing in the experimental and control manipulations. Subjects were randomly assigned to either a social or non-social instructional condition. Subjects in the social condition were instructed that they could earn points by either working with or independently of another person. Points earned by cooperative behavior, in the social condition, were added to both the counter marked "Other's Earnings" and to the counter marked "Your Earnings." Subjects in the social condition had visual access to the fictious other's earnings. The non-social subjects did not have visual access to the fictious other person's earnings and were told that reaction time was measured. Otherwise, reinforcement contingencies remained identical for the social and non-social conditions. In the social condition, cooperative rate and time allocation decreased at the 0.5 and 0.75 g/kg ethanol doses and increased at the 1.00 g/kg ethanol dose. In the non-social condition the topographically identical but non-social alternative decreased at the 1.00 g/kg dose.

[1] Substance Abuse Research Center, University of Texas Health Science Center, Houston. Supported by NIDA Grant 6633.

STUDIES IN HUMAN DRUG SELF-ADMINISTRATION: METHADONE AND ETHANOL

R. SPIGA; J. GRABOWSKI; P. SILVERMAN; R. A. MEISCH AND G. LEMAIRE[1]

Human responding maintained by oral delivery of methadone or ethanol was examined as a function of work requirement and drug concentration. Completing a response requirement on one button dispensed 10 ml of drug solution. Completing the equivalent response requirement on a second, concurrently available, button dispensed 10 ml of vehicle into a cup. The appearance of the letters "A" and "B", indicating that the concurrent responses were available, appeared on the monitor screen. Instructions indicating that water or methadone solution was being dispensed into cups or was available also appeared on the monitor screen. The letters "A" and "B" reappeared on the monitor screen only if the full 10 ml of liquid had been consumed and the empty cup returned to the holder. Under work requirements of 32, 64 and 128 response/delivery (50 and 100 responses/delivery for the ethanol subject) drug concentration was systematically reduced. Sessions were terminated after 60 minutes or 50 deliveries at the highest concentration, 100 deliveries at the middle concentration and 200 at the lowest concentration. The frequency of deliveries were varied across concentrations to permit consumption of a standard amount of methadone or no more than 1 g/kg ethanol during a session. For the methadone study any remaining methadone was administered 30 minutes post-session. The frequency of deliveries and the amount of drug consumed was an orderly function of drug concentration and response requirement. These results, consistent with oral self-administration data obtained with non-humans, demonstrates the greater reinforcing efficacy of increased drug concentration in humans. The procedures generating these data contribute to our understanding of the behavioral mechanisms of methadone taking and ethanol drinking.

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DRUG DISCRIMINATION BY HUMANS: A COMPREHENSIVE COMPARISON WITH NONHUMANS

J. B. KAMIEN; W. K. BICKEL; J. R. HUGHES; S. T. HIGGINS AND B. SMITH

Drug discrimination (DD) procedures differentially reinforce behavior depending on the presence or absence of specific drug stimuli. The DD paradigm has been widely adopted by behavioral pharmacologists due to its specificity of stimulus control, concordance with drug action at cellular levels and its use as a preclinical model of subject-rated effects in humans. With the successful extension of DD to humans, a critical mass of human DD studies developed allowing generalities to be discerned and compared to representative nonhuman DD research. Twenty-eight studies of human DD are reviewed, including studies of amphetamine, opioid, benzodiazepine, caffeine, nicotine, marijuana and ethanol discriminative stimuli. Comparison of methodology and interpretation between human and nonhuman studies reveals a common heritage, except the use of instructions greatly facilitates DD acquisition in humans. Findings were qualitatively similar between humans and nonhumans. Potency relationships were quantitatively similar between humans and most, but not all, other species. Areas of human DD needing additional empirical evaluation include the influence of instructions, the effects of training dose and the effects of antagonists. Additionally, barbiturates, antihistamines, nicotine and marijuana are under-represented in human DD.

ACKNOWLEDGEMENTS: This research was supported by NIDA Grants DA-06205, DA-04545 and DA 00109.

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MULTIPLE CHOICE PROCEDURE (DRUG vs. MONEY): AN EFFICIENT APPROACH FOR ASSESSING THE REINFORCING EFFECTS OF DRUGS

J. R. TROISI, II, K. SILVERMAN AND R. R. GRIFFITHS

A novel choice procedure was designed to efficiently assess the reinforcing effects of drugs. Participants were six healthy male volunteers with histories sedative drug abuse. Initially, subjects participated in a forced-exposure phase. On each day of this phase subjects orally ingested color-coded capsules under double-blind conditions containing either placebo, 200, or 400mg/70kg sodium pentobarbital. Each of the three drug conditions was administered on three separate occasions in a block random sequence. Next, subjects participated in a five-day test phase in which they chose between different monetary values and each of their three color-coded capsules. On each day, subjects were given 132 choice-trials in which they chose between each of their three color-coded capsules and each of 44 different monetary values ranging from $0.50 to $30. Subjects were required to choose either the capsule color or the money on each trial. The choice-trials were numbered on a questionnaire for 1 to 132. After making all the choices, the subject randomly drew one chip from a container holding 132 chips numbered from 1 to 132. The number selected determined which of the 132 choices would be reinforced on that day. The subject then received the item chosen on that selected trial. If the monetary value had been chosen, the amount of money specified on that trial was added to the subject's earnings, but the subject did not receive any drug that day. If the color-coded capsule had been chosen, the subject received the capsule 15 minutes later, but no money was added to the subject's earnings. Choice of drug over money was an increasing function of dose. These data show that pentobarbital produced dose-related reinforcing effects under the circumstances studied. This result is consistent with previous demonstrations of pentobarbital reinforcement in sedative abusers, and therefore provides validation for this multiple-choice procedure. In summary, the multiple-choice procedure has two essential features: 1) each day each subject make multiple drug choice; and 2) only one of these randomly selected choices is reinforced. By providing only intermittent reinforcement of drug choices in this manner, this procedure may provide an efficient method for assessing the relative reinforcing effects of drugs. [NIDA Grant DA03889]

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RISK FACTOR FOR HIV-1 INFECTION AMONG STREET RECRUITED INTRAVENOUS DRUG USERS IN NEW YORK CITY

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The paper tries to identify risk HIV risk factors among a group of street recruited IV drug users in New York city.

METHODS:

Subjects were recruited by ex-addict outreach workers in areas of active drug use in the Bronx, Brooklyn and Queens in New York city during Jan. 1987-April 1988. Interviews were conducted with 325 subjects who had injected since 1977. Pre-test counselling and venipuncture were done on 278 subjects. Subjects were interviewed about their drug injection frequencies during two year periods starting in 1977 to last 30 days before interviews, specific injection practices during 1985 86, 1987 and the last 30 days, sexual behaviors and medical history.

FINDINGS:

52% of 278 subjects are seropositive. Serostatus was not significantly related to gender, race/ethnicity, level of education, age or drug treatment status. In bivariate analyses, seropositivity is significantly ($p < .05$) related to the following factors: residence in the Bronx as against in Brooklyn or Queens, injecting for more than seven years, total drug injection frequency during each time period from 1979 until the last 30 days before interviews, frequency of cocaine injections during each time period from 1983 to last 30 days, frequency of speedball injection during 1985-86 and 1987, injecting in shooting galleries and using previously used cookers during 1985-86. Any episode of sexually transmitted disease ever is weakly ($p < .06$) related to seropositivity although any episode of sexually transmitted disease occurring in or after 1975, is not related to seropositivity. Variables screened at $p < .10$ at the bivariate level were entered into a logistic regression model. In one final stepwise and backward regression analysis, frequency of total drug injection during 1985-86, injecting for more than seven years, residence in the Bronx and history of any sexually transmitted disease remain significant at $p < .05$ level. not being hispanic remain significant. In another, a dichotomous composite indicator of needle risks during 1985-86 replaces total drug injection frequency.

CONCLUSION:

The study confirms previous findings that frequency of intravenous injection and years of injection are risk factors for HIV. The finding that any episode of STD on or after 1975, approximately the time HIV was becoming a risk, is not related to serostatus may imply that for STDs are indicators of high risk life styles rather than direct factors in HIV transmission. Risky drug and needle use behavior taking place in 1985-86 is a strong predictor of seropositivity.

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AIDS Risk Among Female Sexual Partners of Injection Drug Users: Implications for Prevention

S. Tortu, M. Beardsley and S. Deren

Since 1983, women infected with HIV as a result of a sexual relationship with a seropositive drug user have been the most rapidly growing subgroup of adults with AIDS. The increase has been especially dramatic among African-Americans and Latina women. Because little information has been available about these women, their special needs for risk reduction have generally not been addressed by service providers and prevention specialists. This research reports on a sample of 222 female sexual partners, recruited as part of an inner-city AIDS risk reduction project. Information regarding demographic characteristics, AIDS knowledge, sexual risk factors, non-injected drug use, and health status was collected via self-report from 3 groups of women; those with single sex partners, those with multiple partners who exchange sex for drugs and/or money, and those with multiple partners who do not exchange sex.

Results indicated that a high level of AIDS knowledge existed among these primarily Black and Latina women (mean of 13 correct on 16-item test). Overall, the women reported high levels of unprotected sex, considerable use of crack, and a high prevalence of STDs. They also had few economic resources; many had not completed high school, and almost one in ten was homeless.

In comparing the three groups, it is clear that, in most instances, the women who exchange sex for drugs and/or money are at greatest risk for AIDS and also suffer the greatest economic and social hardships. For example, women who exchange sex reported a mean monthly frequency of 78 unprotected sex acts, while the other two groups both reported a mean of 42. Women who exchange reported crack use at a mean monthly frequency of 87 while means for the other groups were 38.7 (single partners) and 51.9 (multiple partners/no exchange). Women who exchange also had the highest prevalence of STDs, were most likely to receive income from illegal sources, and were most likely to have been in jail or prison.

Outreach and prevention efforts for women sex partners should be situated in locations where women sex partners are likely to be found: ob-gyn and family planning clinics, housing projects, prostitution strolls, STD clinics, etc. It must also be recognized that the severe economic and social hardships faced by these women may impede their efforts to practice risk reduction. Finally, given the high levels of risk in many inner-city neighborhoods, it is likely that the number of seropositive people in these communities will continue to increase dramatically. This trend will have a devastating effect on already distressed communities. Efforts to put into place coordinated, community-based medical and social assistance for families affected by the epidemic should begin immediately.

ACKNOWLEDGEMENTS. This research was funded by NIDA grant R18DA05746
AFFILIATION. National Development and Research Institutes, Inc.

COMBINING FIELD, LABORATORY, AND INTERVENTION STRATEGIES FOR HIV PREVENTION

C. B. MCCOY; N. WEATHERBY; P. SHAPSHAK; D. D. CHITWOOD; D. MASH; S. M. SHAH; J. C. ARGUELLO; J. E. RIVERS AND E. L. KHOURY

Needles and syringes shared by injecting drug users (IDUs) are primary vectors in the transmission of HIV, the AIDS virus. In studies to detect and halt the spread of HIV among IDUs, researchers at the University of Miami have combined epidemiologic, clinical, and laboratory strategies in related studies involving IDUs and their injection equipment and practices. In addition to recruiting and testing study participants for HIV serostatus, used needle/syringe units have been collected from Miami shooting galleries (locations where injecting drug users rent/share injection equipment) to test for the presence of antibodies to HIV. A 1988 study found that of those needles/syringes appearing to contain blood residue, a total of 20% were positive for antibodies to HIV. A 1991 study conducted by this research team used the same methodology to assess the effects of bleach cleansing on needles/syringes collected from shooting galleries. The focus on bleach (5.25%, volume/volume, sodium hypochlorite) as a cleansing agent is due to its low cost and ready availability. After randomizing visibly bloody needles into two groups, a laboratory staff member cleansed one group with bleach, simulating the technique taught to IDUs in the Miami Outreach Intervention. All needle/syringe units were rinsed with phosphate-buffered saline (PBS). Western Blot testing of the PBS rinses revealed that 60% of the uncleansed needles were positive for HIV antibodies, while none of the bleach cleansed needles were antibody positive. A related study was conducted to investigate the precise exposure time required to inactivate HIV. All experiments were performed in triplicate and exposure times of less than one minute were repeated in triplicate. Undiluted bleach inactivated HIV at exposures of 30 seconds or longer. These findings have implications for health care workers and for IDUs using bleach to cleanse their needles.

ACKNOWLEDGEMENTS

This work is supported by NIDA grants DA06910, DA04433, DA05349, DA04787.

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DEMAND FOR AIDS PREVENTION SUPPLIES AMONG INJECTION DRUG USERS IN METHADONE MAINTENANCE

J. LONDON; J. L. SORENSEN; K. DELUCCHI; R. WOLFE AND R. DUMONTET

Methadone maintenance treatment programs can be important sites for AIDS prevention efforts with injection drug users. This study was designed to determine whether methadone maintained clients would request AIDS prevention supply types such as condoms (including the new female condoms), bleach, dental dams, spermicidal gel, and needle and syringe sets. Thirty-six methadone maintained clients at San Francisco General Hospital were shown a series of six supply types. They were asked to specify how many they would take home with them if they were offered free at the methadone clinic. Subjects were also asked to report their first choice of supply type and their reason for that choice. Female injection drug users ranked the needle and syringe sets as their number one choice. Males, however, ranked needle and syringe sets as well as condoms (male version) as their number one choice. An average of 15 needle and syringe sets were requested by this sample of clients. Methadone maintained clients selected needle and syringe sets because they would be useful in the event that they relapsed while in treatment. Women selected twice as many total supplies, on average, than men (88 versus 48, $p < .05$). This study suggests that methadone maintained clients would avail themselves of a variety of HIV prevention supplies, including needle and syringe sets, if they were offered. The unexpectedly strong demand for needle and syringe sets among methadone maintained clients may have implications for the use of needle exchange schemes in outpatient drug abuse programs.

ACKNOWLEDGEMENTS
This study was supported by: NIMH/NIDA P50MH42459
NIDA R18DA06097

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CONDOM USE IN A METHADONE POPULATION

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As part of the research program of the NIDA-funded Comprehensive Vocational Enhancement Program (CVEP), data on use of condoms were collected from 208 clients who had sexual relations in the last 30 days. It was hypothesized that there would be a correlation between condom use and each of a number of other variables: employment in the year before entry, absence of incarceration history, absence or recent heavy alcohol use, and absence of recent heavy cocaine use. Each of these variables has previously been found to be associated with treatment success.

It was found that the demographic characteristics of these sexually active persons closely resembled the demographic characteristics of the larger sample of 390 clients. Almost three-fifths (58%) of these sexually active persons had not used condoms in the last 30 days. No correlation between condom use and any of the hypothetically related variables was found. It was found that persons who had more sex partners were significantly more likely to use condoms than others.

The data point to the need for educational efforts targeted toward sexually active methadone clients. Since variables associated with treatment success are not associated with condom use, it is concluded that sexual risk behaviors constitute a domain separate from high risk drug behaviors. Studies are needed to determine what factors are associated with high risk sexual behaviors.

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HIV Status and Risky Behavior: Do They Affect Motivation for Treatment?

J. McCusker; C. Bigelow; R. Frost; R. Hindin and M. Vickers-Lahti

The potential of drug abuse treatment in AIDS prevention depends in part upon the ability of treatment programs to attract and retain HIV-infected and high-risk clients. This study aimed to study associations of HIV status and HIV risky behavior with variables assessing readiness for treatment among clients admitted to two residential drug-free treatment programs (n=550).

Following consent to participate in Project IMPACT, site-specific randomized trials of programs of various duration, data were collected by interview within two weeks of admission. Independent variables included: self-reported HIV status and risky injection practices during the three months before admission. Dependent variables included: scores on scales measuring stages of behavior change (precontemplation and action); pros and cons of drug use; perceived importance of treatment for drug problems; and depression. Associations between HIV status, risky behavior, and the dependent variables were evaluated with univariable and multivariable statistical methods, the latter controlling for drug use history, demographic variables, and social desirability.

Seven percent (7%) of clients were HIV positive, 55% HIV negative, and 38% unaware of their status; 57% had not recently injected drugs, 20% were IVDUs who didn't borrow works or always cleaned with bleach, while 23% borrowed and sometimes or never bleached before reuse. HIV positive clients were more likely to be in the action stage of change and endorsed more cons of drug use. HIV negative clients were more likely to be in the precontemplation stage and perceived treatment as less important. Risky behavior was not associated with the dependent variables once social desirability and other variables were controlled.

These findings suggest that HIV status but not risky behavior is associated with motivation for treatment. It will be important to assess the effects of HIV status upon retention rates and outcomes.

ACKNOWLEDGEMENTS

This research was supported by NIDA grant no R18DA06151.

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ENHANCED INTERVENTION WITH SUBSTANCE ABUSERS AT HIGH RISK FOR HIV INJECTION: A CASE MANAGEMENT/-ADVOCACY APPROACH

A. JAFFE; J. POLING; R. SCHOTTENFELD; P. O'CONNOR AND B. ROUNSAVILLE

This study explored the effectiveness of intensive Case Management/Advocacy (CMA) in an outreach setting. Subjects (N = 38) were intravenous heroin users and cocaine abusers at high risk for HIV infection and transmission. The intervention was designed to overcome internal and external barriers to treatment-seeking, improve treatment compliance, and address patient's other related needs beyond substance use. This was compared to standard evaluation and referral with minimal advocacy. Subjects were randomly assigned to either intensive case management/advocacy (N = 19) or standard intervention (N = 19) for a three month period. The CMA condition resulted in significantly higher rates of treatment enrollment (22% vs. 3%). In addition the CMA group exhibited a greater decrease in drug use, state anxiety, and depression from time one (intake) to time two (six weeks later). Implications for substance abuse treatment and AIDS prevention are discussed.

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CRACK SMOKING AND DRUG INJECTION: COMPOUNDED RISKS FOR HIV

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Risk factors for HIV were assessed among 246 drug users from Miami, Denver and San Francisco. Respondents were classified according to three drug profiles: injectors only, crack smokers only, and injectors/crack smokers. Results showed an increased risk for infection through sexual transmission associated with the use of crack cocaine, particularly among those who also injected. Respondents reporting injecting and smoking were more likely to have had sex with another drug injector, exchanged sex, drugs and/or money, used drugs before or during sex, traded sex for crack, and not to have used protective barriers. They also injected more than injectors only, smoked crack as often as smokers only, and indicated higher frequencies, overall, of drug use in the 30 days and 48 hours prior to their interview. Higher rates of gonorrhea and syphilis reported by crack-only smokers, closely followed by smokers who also injected, are indicators of the threat this drug poses for heterosexual transmission of HIV.

Supported by the National Institute on Drug Abuse grants DA-06912, DA-06908 and DA-06910.

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DRUG USE BEHAVIORS AMONG ASIAN AMERICANS IN SAN FRANCISCO

T. NEMOTO; J. GUYDISH; M. YOUNG AND W. CLARK

This study investigated Asian American samples (N=1,578) representing 3.6% of all admissions to county-funded drug abuse treatment programs in San Francisco, excluding alcohol treatment programs, from January 1986 through December 1990 (N=43,811). Analyses included clients who were admitted to the programs repeatedly during the five year study period. Asian Americans were determined by self-reported responses to a question about ethnic background (Chinese, Japanese, Filipino, and other Asian American group) at admission. Associations between ethnicity and other variables were tested using Chi-square tests. A total 1578 Asian Americans consisted of 499 Chinese Americans (32%), 213 Japanese Americans (14%), 429 Filipino Americans (27%) and 437 other Asian Americans (28%). There was a significant association between ethnicity and primary substance abuse problems, $p<.001$. Compared to other groups, Chinese Americans used more sedatives (15%). About three fourths of other Asian Americans mentioned heroin as a primary drug. Route of administration was confounded by primary drug use. However, there was a significant association between ethnicity and route of administration, $p<.001$. Chinese Americans were less likely to take drugs by injection and more likely to take drugs orally, compared with other groups. Chinese Americans (36%) were less likely to be admitted to detoxification programs compared with Japanese (53%), Filipino (51%), and other Asian Americans (67%). Close to 50% of Chinese Americans were admitted to out-patient programs. Higher numbers of Chinese (10%) and Japanese Americans (8%) were admitted to residential programs compared with Filipino (4%) and other Asian Americans (4%). Demographic questions revealed that about one third of Japanese Americans were living alone compared with Chinese (19%), Filipino (17%), and other Asian Americans (19%). Japanese Americans (28%) were less likely to have either full-time or part-time jobs compared with Chinese (39%), Filipino (32%), and other Asian Americans (34%).

We found several significant associations between ethnicity and drug behaviors. Chinese Americans were more likely to take sedatives orally and to be admitted to out-patient drug treatment programs. Japanese Americans were more likely to take heroin by injection and to live alone, and less likely to have jobs. Filipino and other Asian Americans were less likely to be admitted to residential programs compared with Chinese and Japanese Americans. Filipino Americans were closer to averages for the full Asian American sample on the major study variables. Other Asian Americans were more likely to use heroin by injection and to be admitted to detoxification programs.

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DOMINICANS AND PUERTO RICANS: DIFFERENCES IN DRUG USE PATTERNS AND HIV RISK BEHAVIORS

S. DEREN; M. SHEDLIN; J. SANCHEZ; M. CLATTS; R. DAVIS AND K. MILLER

Higher AIDS infection rates have been reported for Blacks and Hispanics. Data regarding AIDS cases or AIDS-related risk behaviors among Hispanics generally do not distinguish among different Hispanic groups. Data from two studies was compared in order to examine risk behaviors among Latinos: (1) a NIDA-funded study conducted in Harlem NY which recruited Puerto Rican IDUs and sex partners and (2) a CDC funded study conducted in Washington Heights NY which recruited Dominican crack users, IDUs, sex workers and clients of sex workers Both studies used structured and ethnographic interviews.

The total samples consisted of 178 Dominicans and 499 Puerto Ricans. Groups selected for comparison were female sex workers (Dominicans: n=77; Puerto Ricans: n=48) and male crack users (Dominicans: n= 51; Puerto Ricans: n= 161).

Interview and ethnographic data indicated that Dominican sex workers who work in brothels(bayus) engaged in higher levels of condom use (61% report always using condoms) as compared with those working outside of bayus(32%) and Puerto Rican street prostitutes (10%; $p<.001$). Puerto Rican and Dominican non-bayu sex workers were more likely to report non-injected drug use than bayu sex workers (e.g., 92% and 96% as compared with 22%, respectively, reported ever used cocaine, $p<.001$). Injection drug use was less frequently found among Dominican drug users, and non-injected drug use was more frequently reported by Puerto Rican than Dominican male crack users. 98% vs 51% reported non-injected heroin use, $p<.001$). Ethnic and subcultural differences were found in needle use and its meaning, for example, there were strong norms against injection drug use in the Dominican sample.

Dominican and Puerto Rican risk groups were found to have significant differences in their risk behaviors. Furthermore, risk behaviors among Dominican prostitues varied depending on the **location** of their prostitution. Outreach and prevention efforts must address differences in risk behaviors among Latino groups and subgroups, as well as differences in cultural meanings.

ACKNOWLEDGEMENTS. This research was funded by NIDA grant R18DA05746 and CDC Cooperative Agreement U62/CCU204540.
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ADHERENCE TO ZIDOVUDINE (AZT) IN HIV-INFECTED INJECTION DRUG USERS

T. L. WALL; J. L. SORENSEN; J. LONDON; K. L. DELUCCHI; S. J. FERRANDO; C. ABBOTT; P. MORRIS AND S. L. BATKI

Zidovudine (AZT) has been shown to be an effective element of secondary prevention of HIV disease. Successful treatment, however, requires that patients adhere to prescribed therapeutic regimens. This study was undertaken to determine the degree to which HIV-infected injection drug users in methadone maintenance treatment adhered to their prescribed AZT regimens and to assess two different measures of AZT adherence: self report and mean cell volume (MCV) of erythrocytes. Elevation of MCV above the normal range (greater than 100 fL) has been shown to be an indirect side effect of AZT treatment. This study is the first phase of a larger intervention study designed to increase adherence to AZT in these patients.

A brief self-report questionnaire to assess adherence to AZT was developed. All of the 57 HIV-infected injection drug users in methadone maintenance treatment at San Francisco General Hospital, Substance Abuse Services were interviewed. Comparison data and most recent MCV values were also collected from patients medical charts.

On average, the study population was 42 years old and had 11 years of education. Ninety-three percent were unemployed, 56 percent were male, and 56 percent were minorities. Subjects were prescribed an average of three medications in addition to methadone. Thirty-three percent of subjects did not correctly identify their prescribed medications. Forty-nine percent reported that AZT was the medication they most often missed taking. From the questionnaire, a three-item AZT adherence subscale was found to have a high level of internal consistency (a=.82). Fifty-six percent of the subjects either reported poor adherence to AZT or did not show characteristic MCV elevations. There was not, however, a strong correlation between these two measures.

These results suggest a significant difficulty with AZT adherence in HIV-infected injection drug users. Special interventions may be required to bolster the likelihood of this population to adhere to therapeutic regimens. In addition, other measures may be. needed to accurately assess adherence to AZT

ACKNOWLEDGMENTS

Supported by grants from the American Foundation for AIDS Research and the National Institute on Drug Abuse (DA06097).

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DETECTION OF CYTOKINES AND HIV-1 IN THE BRAIN; EFFECTS OF COCAINE AND COCAETHYLENE (CE) ON HIV-1 REPLICATION IN NEURAL CELLS, IN VITRO

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The long-range goal of this laboratory is to determine the effects of illicit drugs on pathogenesis in the brain. We are investigating HIV-l and cytokines in the central nervous system (CNS) and the effects of cocaine and CE on HIV-1 replication. Cytokines (TNF-alpha, IL-1ß, and IL-6) are implicated in pathogenesis of encephalitis in post-mortem AIDS CNS tissue. Cytokines and HIV-l are detected using immunohistochemistry, *in situ* hybridization, and reverse transcription/PCR amplification. We hypothesize that cytokines arc produced in inflammatory foci in the CNS lesions and correlate with tissue damage. TNF-alpha was detected in brain **tissue** from four cases of AIDS, three cases of multiple sclerosis and two cases of subacute sclerosing panencephalitis (SSPE) and not in non-inflammatory controls including two cases of Alzheimer's disease and two non-neurological disease controls. Immunoreactive cells were localized in inflammatory lesions: areas containing mononuclear cell infiltrates, microglial nodules, and astrocytosis in all the AIDS cases. IL-1ß was localized in astrocytes and mononuclear cells in inflammatory lesions in cases of AIDS and SSPE. IL-6 was detected primarily in endothelial cells in the Golgi apparatus, confirming the in situ production of this cytokine. CE is produced after ingestion of both cocaine and alcohol and may have profound physiological effects. Cocaine users are possibly at risk for accelerated progression of AIDS disease. Treatment at physiological µM concentrations with cocaine and CE pre- and post-infection stimulated HIV-1 replication 1.2 to 2.1 fold in transformed lymphocytes and normal peripheral blood lymphocytes. HIV-1 replication was stimulated at 11 to 15 days post-treatment. CE stimulated HIV-1 production in chronically infected H-9 cells as well in neuroblastoma and astrocytoma cell lines. Ethanol resulted in smaller effects that may be due to non-specific membrane effects. Cocaine and CE effects may be due to cell surface receptor-mediated actions. Effects may also be at the molecular level of the control of transcription of HIV-I since effects are delayed up to two weeks after the initial single treatment. Possibly, cocaine and CE exacerbate pathogenic effects of HIV-l mediated by cytokines in the brain. We are commencing in vivo studies of a cohort of seropositive drug users to characterize the stimulatory effects of cocaine and CE on HIV-1 virus load and infectivity. This work is supported in part by NIDA grants DA04787, DA06227, and DA06910.

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INTERLEUKIN-1α ACTIVATES C-FOS PROTO-ONCOGENE IN THE RAT BRAIN[1]

S. L. CHANG[1], J. E. ZADINA[2] AND T. REN[1]

Interleukin (IL-1) is a primary inducer of several components of the systemic "acute phase" immune response. It is now known that IL-l is synthesized by cells of neuronal as well as hematological and dermasomal origin (Rothwell 1991). In the present study, we used FOS proto-oncogene protein activation by IL-I to identify the sites of action of IL-1 in rat brain.

Adult male rats (Harlan Sprague-Dawley, Indianapolis, IN) were randomly assigned to two groups, one to receive 200 ng of recombinant human interleukin-1α (rhIL-1α, Immunex, Seattle, WA) in 5 µl of 100 mM Tris/1% BSA or the control vehicle by direct intracerebraventricle (ICV) infusion under Nembutal (50 mg/Kg/ml) anesthesia. At 30 min after infusion, the c-fos mRNA levels isolated from hypothalamus were elevated about 100% ($p < 0.05$) relative to those of rats given rhIL-1α for 2 min. Values from the two min treatment group were not significantly different from those of control vehicle. There was no significant increase in c-fos mRNA in the striatum.

To determine whether the IL-1 activation of c-fos mRNA was associated with increases in FOS protein levels in the rat brain, we performed FOS immunocytochemistry. Two groups of four rats were randomly assigned to receive 200 ng of rhIL-1α in 5 µl of 100 mM Tris/1% BSA or 5 µl of 100 mM Tris/1% BSA alone, by cannulated ICV infusion in unanesthetized animals. Three hours after infusion, the rats were perfused, the brains were removed, and FOS immunocytochemistry was conducted by using the avidin-biotin-peroxidase method, following procedures previously described (Chang et al. 1988) with minor modifications. The anti-FOS antiserum was obtained from Oncogene Scientific Inc. IVC infusion of rhIL-1α induced FOS immunoreactivity in several nuclei. In this study, we focus on hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. FOS immunoreactivity in PVN and SON was markedly induced in the rats treated with rhIL-1α. Virtually no immunostained nuclei were detected in these two areas in the rats with control vehicle. Two other control groups, one given cannulation surgery, another untreated, also showed no immunostained nuclei. These data suggest 1) rhIL-1α activates c-fos mRNA rapidly and transiently in the hypothalamus; 20 PVN and SON are sites of action of IL-1α in spite of the relative absence of IL-1 binding sites in these nuclei (Farrar et al. 1987).

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This work is supported by NIDA grants, DA05969 and DA07058, SLC.

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INTERLEUKIN-2 MODULATES THE EXPRESSION OF NALOXONE-RESISTANT RECEPTORS FOR β-ENDORPHIN ON MURINE SPLENOCYTES IN RESPONSE TO CONCANAVALIN A

B. M. SHARP, K. M. LINNER AND N. A. SHAHABI

High affinity, naloxone-resistant receptors for β-endorphin are expressed by normal murine splenocytes after incubation in vitro. We have previously shown that concanavalin A (con A) enhanced the specific binding of β-endorphin to these mixed splenocyte cultures. Thus, we compared the effect of con A on mixed splcenocyte versus splenic T cell cultures and determined whether interleukin-2 (IL-2), a critical T cell growth factor, could modify this response. Incubating mixed splenocytes from CD1 female mice for 48th with con A (1-10 μg/ml) resulted in a significant dose-dependent increase in specific binding of β-endorphin that was approximately three and five fold above baseline with 7.5 and 10.0 μg/ml, respectively. Similarly, specific binding to splenic T cells, obtained by panning with anti-IgM/TgG, was enhanced by con A after 48 h (values are % of control for con A 1, 2.5, 5 and 10 μg/ml, mean ± sem, N=3): 78±13, 140±31, 199±13 and 277±14, respectively. In mixed splenocyte cultures, 0.5 and 5.0 ng/ml IL-2, alone, tended to reduce specific binding by 15-30% of baseline at 48 h. In addition, IL-2 significantly reversed the enhancement of β-endorphin binding by con A 5 μg/ml when mixed splenocytes were cultured in the presence of both agents for 48h. The values for specific binding of b-endorphin (cpm/5 x 10^6 cells; mean ± scm, N=4) were: 6319±366 for control; 14327±2841 for con A; 12668±1486 for con A + IL-2 0.5 ng/ml; 9460±2173 for con A + IL-2 2.5 ng/ml and 7439±846 for con A + lL-2 5.0 ng/ml. In summary, con A enhanced the expression of naloxone-resistant receptors for β-endorphin in mixed splenocyte as well as in splenic T cell cultures; this was reversed by IL-2.

ACKNOWLEDGEMENTS:

Supported by NIDA 04196.

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MORPHINE-INDUCED IMMUNE ALTERATIONS: EVIDENCE FOR β-ADRENERGIC RECEPTOR INVOLVEMENT

K. FECHO, D. T. LYSLE AND L. A. DYKSTRA

There is evidence suggesting that morphine-induced alterations of immune status are mediated through the central nervous system. For example, the systemic administration of morphine, but not of N-methylmorphine, has been found to produce a naltrexone-reversible suppression of spienic natural killer (NK) cell activity (Shavit et al. 1984; 1986). Furthermore, the central administration of morphine (either intracerebroventricularly or by microinjections directly into the periaqueductal gray region) has been shown to suppress splenic NK cell activity in a naltrexone-sensitive manner (Shavit et al. 1986; Weber & Pert 1989). However, little is known about how the activation of central opiate receptors by morphine translates into peripheral immune alterations. One possible mediator of morphine's effects on the immune system is the ß-adrenergic system. Lymphoid organs receive direct sympathetic nervous system innervation (Feiten et al. 1985) and ß-adrenergic receptors are present on lymphocyte membranes (e.g., Loveland et al. 1981). In addition, the central administration of morphine results in an increase in plasma catecholamine levels (Appel et al. 1986).

The purpose of the present experiments was to investigate the involvement of the ß-adrenergic system in morphine-induced immune alterations. Prior to a subcutaneous (s.c.) injection of 15 mg/kg morphine or saline, male Lewis rats (N=180) were administered either the nonselective ß-adrenergic receptor antagonist nadolol, the selective $ß_1$-adrenergic receptor antagonist atenolol or the selective $ß_2$-adrenergic receptor antagonist ICI-118,551 in doses of 0, 0.125, 0.5, 2.0 or 8.0 mg/kg, s.c. All three antagonists blocked the suppressive effects of morphine on the proliferative responses of splenic lymphocytes to the T-cell mitogens concanavalin-A (Con-A) and phytohemagglutinin (PHA), the B-cell mitogen lipopolysaccharide, and the T- and B-cell mitogenic combination of ionomycin and phorbol myristate acetate. In contrast, none of the antagonists exhibited any effect on the morphine-induced suppression of the proliferative responses of blood lymphocytes to Con-A or PHA; likewise, there was no antagonism of the morphine-induced suppression of splenic NK cell activity.

Although the immunosuppressive effects of morphine appear to involve multiple mechanisms, these data clearly implicate the involvement of both $ß_1$- and $ß_2$- adrenergic receptors. Moreover, since both nadoiol and atenolol are very hydrophilic compounds and are therefore unable to readily penetrate the blood-brain-barrier, the results suggest the involvement of peripheral $ß_1$- and $ß_2$- adrenergic receptors, specifically, as mediators of morphine's immunomodulatory effects.

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PAVLOVIAN CONDITIONING OF MORPHINE-INDUCED IMMUNE ALTERATIONS: EVIDENCE FOR OPIOID RECEPTOR INVOLVEMENT DURING TRAINING

M. E. COUSSONS, L. A. DYKSTRA AND D. T. LYSLE

Administration of morphine to animals has been shown to be associated with a decrease in a number of immune parameters (Bayer, et al., 1990; Bryant et al., 1988). Additionally, behavioral studies have shown that environmental stimuli paired with morphine administration can elicit morphine-like effects (Eikelboom and Stewart, 1979). Moreover, rats develop a strong place preference for environments in which morphine has been administered, suggesting that the appetitive properties of morphine can be conditioned to environmental stimuli (Carr et al., 1989). The present study provide the first demonstration that morphine-induced immune alterations can become conditioned to environmental stimuli, and that opioid receptors are involved in the conditioning process. The first experiment was designed to determine whether morphine-induced immune alterations could become conditioned to environmental stimuli, and to determine some of the parameters necessary for such conditioning. Lewis rats received either 0,2,4,8 or 16 days of conditioning sessions during each of which a subcutaneous injection of morphine (15 mg/kg) was immediately followed by a one-hour exposure to a distinctive environment, a standard rodent conditioning chamber. When rats were subsequently reexposed to the distinctive environment in the absence of morphine, immunological alterations similar to those produced by morphine occurred. Experiment 2 was performed to confirm that the immune alterations observed in the first experiment were indeed the result of a Pavlovian conditioning process. The experimental group received two conditioning sessions during each of which a subcutaneous injection of morphine sulfate was paired with exposure to a distinctive environment. Reexposure to the distinctive environment resulted in pronounced immune alterations including decreased mitogenic responsiveness of lymphocytes, decreased natural killer cell activity, and decreased interlcukin-2 production. Control procedures indicated that these alterations were the result of a Pavlovian conditioning process. Experiment 3 assessed whether the pharmacological effects of morphine were responsible for the conditioned immune alterations. Naltrexone administered during training was found to antagonize the conditioned immune alterations. Taken together, these studies indicate that morphine-induced immune alterations can become classically-conditioned to environmental stimuli paired with morphine administration, and that opioid receptors are involved in the establishment of these conditioned immune alterations.

REFERENCES: Available upon request from senior author.

ACKNOWLEDGEMENTS: PHS grant MH46284, DA02749 and DA07244

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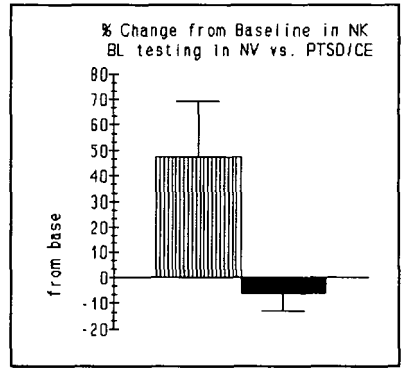
ABNORMAL NATURAL KILLER CELL (NK) ACTIVITY IN POST-TRAUMATIC STRESS DISORDER (PTSD) SUBJECTS

S. PINTO; R. YEHUDA; E. L. GILLER AND M. J. KREEK

We have previously shown [SP, MJK] a reduction in NK activity as well as atypical neuroendocrine (NE) responsiveness to stress in patients with addictive diseases. Other studies in our laboratory have shown a direct relationship between alteration in NK activity and abnormalities in the NE system. We initiated NE and NK studies on patients suffering from PTSD [RY, EG] because of the high prevalence of chemical dependency and the alteration in NE activity observed in this population. Eleven male volunteer subjects including 8 subjects, (41-47 yr), diagnosed with Vietnam PTSD, and 3 subjects (44-48 yr) who are Vietnam combat-exposed (CE) but who did not meet the criteria for PTSD were studied along with 8 normal volunteers (22-39 yr). Subjects were hospitalized the afternoon prior to the study and kept under controlled conditions. Basal (BL) testing on one day, was followed by a metyrapone (MT) provocative test performed on a second day in each subject. NK activity was determined from peripheral blood mononuclear cells (PBMC) by measurement of ^{51}Cr release from K562 target cells. All data from one of the PTSD patient was omitted due to NK assay problems.



In the BL study, reduction in NK activity between 9am and 1pm was observed in PTSD/CE subjects as contrasted with an increase in NK activity in the NV subjects. However, during the MT test, an increase in NK activity was observed in both PTSD/CE and NV subjects between 9am and 1pm. In the BL test, the percent change from baseline for the PTSD/CE groups differed significantly from the NV group ($p<0.05$) at all three target effector ratios (1:25,:50,:100). Changes in NK activity were not significantly different in the two study groups during MT testing. NK activity paralled changes in plasma cortisol levels on each study days.

ACKOWLEDGEMENT: Supported in part by NIDA-DA5130.

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THE CENTER FOR ADDICTION AND PREGNANCY: PRELIMINARY RESULTS OF AN INTENSIVE MULTIDISCIPLINARY PROGRAM FOR POLYSUBSTANCE ABUSING WOMEN

L. M. JANSSON; P. M. GAZAWAY; V. E. CULLINS; G. R. HUGGINS AND A. GOLDEN

The increased awareness and detection of illicit drug use by pregnant women revealed a paucity of resources to treat this unique population. The Center for Addiction and Pregnancy (CAP) incorporates the specialties of obstetrics, pediatrics, drug treatment/mental health and family planning (see Table 1) to address the multiple domains of the pregnant substance using woman's care.

In the first year of operation, 66 CAP women delivered 70 babies (4 sets of twins). The mean patient age was 27.7 years. Ethnically, 80.3% were African-American, 18.2% white and 1.5% other. They had an average 11.6 years of schooling. Seventy-eight percent had used cocaine for a mean of 2.2. years, 52% had used heroin for a mean of 2.4 years; 48% had been heavy drinkers for a mean of 3.3 years; and 14% had used sedatives for less than one year. The mean gestational age at delivery was 38.7 weeks (see Figure 1), with 86.4% of women delivering at or after 37 weeks gestation. The Cesarean birth rate was 12.9%. The mean birth weight and head circumference was 2804.3g (see Figure 2) and 32.7 cm, with 87.1% infants average, 8.6% small and 4.3% large for gestational age. Mean one and five minute Apgars were 7.6 and 8.7 respectively. Seven point one percent of infants were born to HIV positive mothers. 29.5% of patients had meconium stained amniotic fluid. Twenty-eight point six percent of infant urine drug screens were positive for cocaine and/or opiates at delivery. Nine infants (12.9%) required admission to the neonatal intensive care unit (NICU); mean length of NICU stay was 7.9 days (excluding one infant who is currently in NICU at the time of this writing). Recent drug use had no influence upon delivery EGA ($p=0.1$), mode of delivery ($p=0.7$) or birth weight ($p=0.5$). However, recent use was associated with the presence of meconium ($p<0.01$).

Finally, more than 80% of women elected and received long term contraception in the form of Norplant (54.5%) or tubal ligation (27.3%) in the immediate post partum period.

These preliminary results indicate that intensive multidisciplinary care can provide good perinatal outcomes in polysubstance abusing women.

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THE IMPACT OF INTENSIVE PRENATAL AND SUBSTANCE ABUSE CARE ON PREGNANCY OUTCOME

J. S. KNISELY; J. T. CHRISTMAS; M. DINSMOORE; E. SPEAR AND S. H SCHNOLL

Investigations of the effects of substance abuse during pregnancy have revealed high prevalence rates of obstetrical complications such as spontaneous abortion, intrauterine growth retardation, intrauterine fetal demise, congenital anomalies, preterm labor and preterm delivery. Also, cocaine exposure in utero has been associated with neonatal behavioral deficits and developmental delays. Recent evidence has suggested a relationship between cocaine exposure and fetal growth, however, dramatic affects have not been observed. The purpose of the present study is to evaluate the effects of substance abuse treatment and prenatal care on pregnancy outcome in substance-abusing pregnant women.

Substance users were recruited from the Center for Perinatal Addiction (CPA) and retrospectively divided into two groups: 1) women enrolled in treatment for less than 30 days at time of delivery (n=11) and 2) women enrolled in treatment for at least 30 days at time of delivery (n=33). Controls (n=160) were recruited from the obstetric clinic of a large metropolitan university and were screened for drug use via urine toxicology and a questionnaire. Measures collected included body weight, length, head circumference, gestational age, and APGAR scores at one and five minutes. This information was obtained from infant charts and/or birth certificates.

Ninety-three percent of cocaine abusers were polydrug users. More than half of the women used cannabis and/or alcohol in addition to cocaine. Analysis of variance demonstrated no difference in mean body weight ($p = .67$), gestational age ($p = .94$), or APGAR scores ($p = .54$) when comparing the three groups. Length of time from admission in the treatment program to delivery was positively correlated and length of drug exposure was negatively correlated with weight, length, head circumference, gestation age and APGAR scores. These preliminary results suggest that other factors in addition to cocaine exposure need to be considered when evaluating the pregnancy outcome of substance abusers. The lack of differences found between these groups may result from the impact of other variables such as socioeconomic status, amount of prenatal care, proper nutrition, etc. Also, it seems that intensive substance abuse treatment and prenatal care are associated with remarkably normal pregnancy outcome. (Supported by MDA Grant #DA06094).

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PRENATAL CARE DELIVERED IN A DRUG ABUSE SETTING: BIRTH OUTCOMES COMPARED TO ACOG STANDARDS

P. M. Gazaway, B. A. Shipley, R. K. Brooner and L. J. Felch

Drug and alcohol abuse during pregnancy are associated with poor obstetric performance and outcomes. However, integration of substance abuse treatment and prenatal care has been shown to improve compliance with obstetric care and enhance perinatal outcomes (e.g., Suffet 1984).

PURPOSE: The perinatal outcomes of opioid dependent, methadone maintained, pregnant women receiving integrated prenatal care and substance abuse treatment were compared to data from the general obstetric population. Secondly, the effect of a concurrent cocaine use disorder upon outcomes was examined.

METHODS: Opioid dependent pregnant patients (N=37) were admitted to integrated prenatal care and drug treatment that used methadone as one component of care. They had a mean age of 28 years, 11 years education, 43% were an ethnic minority, 85% were unemployed, and 6% were HIV seropositive. Their mean daily dose was 44 mg and 51% had a current cocaine use disorder. Obstetric visits were scheduled bimonthly until 32 weeks and weekly afterwards. Data were collected prospectively and compared to standards of the American College of Obstetricians and Gynecologists' and to obstetric outcomes of the general population.

RESULTS: Compared to the national average, methadone maintained pregnant women utilized prenatal care less and had poorer perinatal outcomes. Only 34% of the patients were registered in the first trimester vs a national average of 75%, they had a median of 9 visits vs 12, gained less weight (10 lbs vs 30 lbs for term births and 6 lbs vs 26 Ibs for preterm births), and had a lower median birthweight (2,695 gms vs 3,370 gms). Low birthweight occurred in 27% vs 7%. Only 14% had Caesarcan delivery vs the national average of 23% and none had low Apgars.

A current diagnosis of cocaine abuse or dependence also had a negative effect upon obstetric performance. Fewer of the cocaine abusing patients were seen in the first trimester compared to those without a cocaine diagnosis (13% vs 59%; p=0.006), they had a higher mean gestational age at registration (23 wks vs 17 wks; p=0.027) a lower number of prenatal visits (6 vs 9; p=0.031), and lower maternal weight gain (61 lbs vs 9 lbs; p=0.012). The cocaine abusing group also had a lower delivery age (37 vs 39 weeks; p=0.012) and a higher rate of preterm birth (63% vs 23%; p=0.024). Cocaine abuse had no significant effect upon the incidence of low birth weight, Apgar scores, or mean birth weight.

DISCUSSION: These data show a high rate of continued obstetric problems when outcomes are compared to the general population, particularly among those abusing cocaine. While integrating obstetric care with drug abuse treatment is beneficial, more effective interventions to reduce cocaine use and improve nutrition are also needed.

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COCAINE ABUSE DURING PREGNANCY

J. GROSSMAN; R. S. SCHOTTENFELD; R. VISCARELLO AND J. PAKES

PURPOSE

This study is part of an on-going project to conduct drug abuse screening in a prenatal clinic to determine the prevalence of cocaine/crack use in pregnant women, and to identify the characteristics and treatment needs of eligible subjects. The study includes a controlled clinical trial to compare the effectiveness of different treatment models.

METHOD

All women who register for prenatal care at Yale-New Haven Hospital are screened for cocaine use during pregnancy based on a substance abuse interview and urine testing. Exclusion criteria include current dependence on opiates or major psychiatric disorder. Enrolled subjects are randomized to a comprehensive day treatment program or weekly clinic based treatment. Data are collected at intake, delivery, 3 and 6 months postpartum.

RESULTS

The prevalence of self-reported cocaine use during pregnancy was 13% (N=778) of clinic registrants. Based on urine toxicologies, 9% were positive for cocaine metabolites; 29% of these women denied ever using cocaine, and 49% denied use during pregnancy. There were significant differences in substance use, demographic and personal characteristics between cocaine users and the clinic population. During year one, 120 women were enrolled as subjects.

CONCLUSION

Based on preliminary findings, eligibility must be determined by a combination of history-taking and urine toxicologies. Because eligible subjects have multiple medical, familial and environmental risk factors, programs must offer comprehensive, family-centered services.

ACKNOWLEDGEMENT

The research was supported by the NIDA Grant DA 06915

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RETENTION IN TREATMENT OF PERINATAL SUBSTANCE ABUSERS

D. L. HALLER; R. K. ELSWICK; K. S. DAWSON; J. S. KNISELY AND S. H. SCHNOLL

Problems have existed in recruiting and maintaining pregnant addicts in treatment. We were thus interested in identifying factors predictive of early dropout. Forty-nine patients at the Center for Perinatal Addiction participated in the study. We looked at residential status (program based vs. community based), pregnancy trimester, treatment resistance score (MMPI), and diagnosis of ASP as possible contributors to premature dropout. Survival analyses were conducted using the Cox proportional hazards model procedure. Results suggested that residence status in our transitional housing unit was highly related to retention in day treatment ($p < .002$). Patients not living in the THU were 3.3 times more likely to drop out. There was a trend for patients in their 1st trimester to be more likely to remain in treatment as compared to those in their 2nd trimester ($p < 0.028$) or those entering treatment post delivery ($P < 0.066$). Those in their 2nd trimester were 4.8 times (and post delivery were 3.4 times) more likely to dropout over those in their 1st trimester. Interestingly, neither treatment resistance scores nor diagnosis of ASP played a significant role. Thus, the environmental factors (as compared to the psychological factors) explored seem more critical to retention. This research was supported by NIDA Grant #DA06094.

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MICROTREMORS DURING A SUSTAINED MOTOR TASK FROM BOYS PREVIOUSLY EXPOSED TO OPIATES IN UTERO

J. SPENCER; X. Guo; P. SUESS; J. HICKEY AND R. HERNING

Motoric problems such as tremors or jerkiness can exist in infants exposed to illicit drugs such as cocaine or heroin in utero. To establish if these effects may continue into childhood, boys ages 8-11, exposed to opioids in utero, were evaluated for the presence of microtremors using power spectral analysis. This group (N=12) showed significant increases in integrated amplitude, across time, (peak frequency of 5.9 hz), for a simple postural extended microtremor or complex force-induced, intentional microtremor (peak frequency of 4.9 and 9.2 hz) recorded from the finger and involving the extensor digitorium muscle. Performance deficits, using a sustained concentration task, were simultaneously observed while recording the intentional microtremor. Children (N-12), not exposed to drugs in utero, but who grew up in environments in which drugs were used, or a second matched control group did not show differences in any tremor amplitude, and they did better on the performance task. Subtle, and possible long term physiological effects, related to in utero drug exposure, may be uncovered by measuring muscle tremors which are produced by increasing task demand and sustaining performance over time. In selective opioids exposed subjects, electroencephalographic (EEG) tracing from pre-rolandic areas indicated an increase in Beta 1 and Beta 2 integrated amplitudes which coincided with an increase in extended-postural microtremors. These differences were not noted in age-matched controls.

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PROVIDING MEDICAL CARE TO METHADONE CLINIC PATIENTS: A CONTROLLED STUDY OF REFERRAL VERSUS ON-SITE CARE

A. UMBRICHT-SCHNEITER; D. H. GINN; K. M. PABST AND G. E. BIGELOW

Intravenous drug abusers are at high risk for a variety of concurrent medical conditions, and many arc medically underserved. However as most drug abuse clinics have few resources, they refer patients elsewhere for medical cart. Our study was aimed at better understanding the medical needs of patients admitted to methadone treatment, comparing the efficacy of referral versus offering medical care at the methadone site, and assessing the characteristics of patients accepting HIV testing.

Patients were evaluated at admission to a methadone clinic for four target medical conditions: hypertension, PPD conversion, HIV infection, and treatable sexually transmitted discases. Patients were randomized into 2 groups: the On-Site group was offered medical care at the methadone site, the Referred group was offered medical care at a nearby clinic. Medical treatment was free of charge at both sites. Compliance was recorded by patient interview at 4 and 8 weeks, and by chart review.

Of 161 patients screened, 75 (47 %) had at least one of the target medical conditions. Fifty-one patients were randomized. Twenty-three patients (92%) in the On-site group (N=25) received further medical care, with a treatment rate per diagnosis of 88%, and an average of 3.1 ± 1.8 visits per patient. Only 9 (35%) patients in the Referral group (N=26) rcceived further medical care, for a treatment rate per diagnosis of 28%, and an average of 0.4 ± 0.6 visits per patient. These differences were significant with $p < .01$. Accceptance for HIV testing (82% overall) was greater in patients with young children ($p < .01$) or on public assistance ($p < .05$), and less in patients with private insurance ($p < .05$).

Conclusion: This study confirms the high prevalence of concurrent medical conditions among patients admitted to drug treatment clinics. The efficacy of providing medical care on the drug treatment site is much superior to that of the usual referral procedure. Even with optimal conditions, referral results in unacceptable loss of patients to medical care. Thus, primary care on the drug treatment site is an effective and valuable public health measure.

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IMIPRAMINE FOR DEPRESSED METHADONE PATIENTS

E. V. Nunes, F. M. Quitkin, R. Brady, S. Donovan, D. Deliyannides and T. Post-Keonig

Methadone maintenance is frequently complicated by continued drug abuse and associated HIV-high risk behaviors. Some of these patients may have affective disorder and use illicit drugs to "self-medicate". Available studies of tricyclic antidepressant treatment in depressed methadone patients have yielded equivocal results with some reporting improvement in depression but little evidence for reduced drug abuse. These studies relied on cross-sectional symptoms to diagnose depression, whereas longitudinal studies have suggested that most depression in opiate addicts is transient, perhaps representing organic mood syndromes or adjustment reactions to psychosocial stressors, rather than "true" affective disorder. Concordantly several of the previous trials had high placebo response rates.

We therefore used lifetime psychiatric history, elicited by experienced research psychiatrists, to select drug abusing methadone patients with DSM-III-R depressive disorders which are either primary (antedate substance abuse) or chronic (at least 3 months duration in the current episode, and persisting during at least one month of stable methadone treatment).

In a preliminary 12 week open label trial of imipramine 9/17 (53%) improved in both mood and drug abuse, achieving stretches of abstinence of at least 4 weeks. In an ongoing double blind trial 109 eligible patients were randomized and 69 have completed a minimum adequate trial of six weeks (37% dropout rate). The dropout rate is slightly higher on imipramine (41%) than placebo (31%). due to more side effect dropout on imipramine. Cocaine was the most common drug of abuse (56%) followed by heroin (41%). Among study completers 18/34 (53%) have achieved a favorable response on imipramine (much improved depression and at least a 75% reduction is self-report illicit drug use) compared to 2/35 (6%) on placebo. Among imipramine responders a little under half (8/18) are abstinent with clean urines at end study. The randomization was stratified by gender and by high versus low drug use at baseline. The results were consistent across strata.

This suggests a potential strategy for improving the treatment of illicit drug use in a small subgroup of methadone patients. We estimate that 10% to 15% of methadone patients meet our criteria for primary or chronic depression. The low placebo response rate suggests that our criteria have succeeded in avoiding the selection of transient mood syndromes. The fact that many imipramine responders continue to abuse drugs, albeit at reduced rates, suggests that a pure self-medication model does not.

AFFILIATION: New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons

FLUOXETINE TREATMENT OF DUALLY DIAGNOSED METHADONE MAINTAINED OPIOID ADDICTS

I. Petrakis; G. Cushing,; L. Gordon and B. Rounsaville

Methadone maintenance is an effective treatment for opioid addiction but additional treatments are needed for dually diagnosed opioid addicts. Depression is common among opioid addicts, and continued opioid, cocaine and sedative/hypnotic use undermines the effectiveness of methadone programs. Fluoxetine, a serotonin uptake inhibitor, is an antidepressant with a favorable side effect profile and may also be effective in reducing some compulsive/addictive behaviors in animals and humans. Twenty methadone maintained opioid addicts, who were referred for either depression or persistent substance abuse, had 20-60 mgs (depending on tolerance to side effects) of open-label fluoxetine added to their methadone for 12 weeks. Sixteen of the 20 patients completed the study. Fifteen patients met criteria for Major Depression or Dysthymia and had a Hamilton Depression Score (HDS) > 14 or a Beck Depression Inventory (BD1) > 12. The other 5 patients were included for persistent substance use as defined by 3 successive urine specimens positive for illicit substances. Eight of the patients in the depressed group also persistently used illicit substances. The HDS of the depressed patients decreased from a mean of 14.26 pretreatment to mean of 10.08 at endpoint (F=6.11, p=2 with no difference between substance users and those "depressed only"; the BD1 decreased from 15.93 pretreatment to 8.50 at endpoint (F=17.27, p = .001) with no difference between those abusing drugs and those "depressed only". The mean number of dirty urines for the dually diagnosed was 71%, compared to 100% in the "drug use only" group. These results suggest that fluoxetine had a modest antidepressant effect and little effect on illicit drug use in methadone maintained opioid addicts. A double blind placebo study is ongoing. This work is supported by NIDA grants 5-T32-DA07238-04, 5-R18-DA-6190-02, and 5-R18-DAO6963-02.

AFFILIATION: Yale University, New Haven, CT

ALTERNATIVES TO METHADONE MAINTENANCE: LAUDANUM, BUPRENORPHINE

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Methadone maintenance has been clearly shown to be helpful for treatment of opioid dependence. However, methadone is not always available. We report our experience with two alternatives to methadone maintenance pharmacotherapy in opiate addicts. The purpose of this study is to evaluate the impact of opiate maintenance pharrnacotherapy (OMP) on the biopsychosocial status of opiate addicts in a cultural environment (France) that is not favorable to OMP and where methadone is not available. Buprenorphine, which has been shown in some studies to be potentially as useful as methadone, and laudanum (opium tincture) which, to our knowledge, has not been reported previously in the scientific literature for OMP, are used in this study of a group of 18 DSM III-R opioid dependent subjects. At time of initiation of OMP mean age was 33 years, sex ratio male/female 14/4, average duration of drug use 11.2 years. Six patients received laudanum p.o., 15g daily; 12 patients received buprenorphine sublingual 2 to 4 mg daily. This group of patients was selected because of persistent relapse and impairment after an average of 5.7 drug-free oriented treatments. Initial evaluation and follow-up were made by way of a 150 minutes semi-structured interview using the Lifetime Retrospective Evaluation Score Table (Grabot et al.) and the Addiction Severity Index (McLellan et al. Both these instruments allow for a quantitative evaluation of addicted patients. Results show that body weight [Kg] and scores [scale 0 (extremely bad) to 6 (excellent)] for physical and psychological health, socio-profesional status and family relationships go respectively from 55;2.1;2,2.5;2.4 before OMP to 61;3.7;3.7;3.3;3.6 after 14 months of OMP. These increases in scores are statistically different (except socio-professional status) with both parametric (Student t test $p<0.01$) and non-parametric tests (Wilcoxon t test $p<0.01$). These results show that highly impaired opiate addicts doing poorly in drug-free treatment can respond to OMP even though methadone is not available and the idea of OMP is not favored.

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THREE METHODS OF AMBULATORY OPIATE DETOXIFICATION: PRELIMINARY RESULTS OF A RANDOMIZED CLINICAL TRIAL

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INTRODUCTION: Ambulatory opiate detoxification (AOD) serves as an important avenue for substance abusers to enter drug treatment and medical care. (O'Connor et al. 1992) has demonstrated that acute opiate detoxification can be effectively and safely carried out in a primary care setting using clonidine (C) and clonidine plus naltrexone (C/N) in open clinical trials of the two agents. Effectiveness of buprenorphine (B) as a transitional agent between the opioid-addicted state and the initiation of naltrexone therapy in AOD has also been shown in a randomized non-blinded comparative trial of C, C/N and B (Weiss, 1992).

PURPOSE: This is a randomized, double-blind prospective study to compare C, C/N, and B as methods of AOD, and preliminary results are reported.

RESULTS: Thirty-nine opiate addicted substance abusers were referred to our medical clinic for AOD. This group had a mean age of 31 years, 72% were male. 90% used cocaine, 49% were intravenous drug users, 62% were unemployed, 70% had no source of primary care, and 33% had never been in drug treatment. Overall, 85% of clients were successfully detoxified with the initiation of a blocking dose of naltrexone--by treatment groups, 77% (10.13) of C, 86% (12/14) of C/N, and 92% (11/12) of B.

CONCLUSION: Buprenorphine compares favorably with C and C/N as a method of AOD.

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ACKNOWLEDGEMENT: This is supported by NIDA Demonstration Grant R18 DA0693, (improving cocaine and opiate abuse treatment) and PHS Grant P32 DA07238.

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MARIJUANA USE IN A METHADONE-MAINTENANCE POPULATION

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Polysubstance abuse continues to be an impediment to rehabilitation efforts in the treatment of narcotic dependent persons. To assess the often-overlooked contribution of marijuana use to this phenomenon, urine toxicoloqy (radio-immuno assay) reports were reviewed for 568 persons enrolled in a methadone maintenance treatment program. Based upon clinical concensus that stabilization on methadone usually occurs within 90-days, only persons in treatment for more than that period were sampled. The population was defined as 70% male and 30% female; 65% Hispanic, 30% Black and 5% other. The mean age was 34 years. The coincident use of marijuana with opiates, cocaine or alcohol was reviewed, in addition to use defined by gender, weekly medication take home schedule and methadone dose.

Twenty-five percent (n=145) of the population had used marijuana at least once during the study period. Significant chi-squares emerged for the variable combinations of marijuana and alcohol (x^2=7.2, p<.01), and marijuana and gender (x^2=10.36, p<.001). The results indicate an inverse and independent relationship between marijuana and alcohol use, i.e., the vast majority (n=206, 94%) used marijuana (n=133, 61%) or alcohol alone (n=73, 33%); 12 (6%) used both. Marijuana use was also strongly associated with males (80%) compared to females (20%). These results concerning gender support findings in the drug abuse literature indicating a higher incidence of marijuana use among males. No significant differences in observed and expected frequencies emerged for the variable combinations of marijuana and cocaine, opiates, methadone dosage and weekly medication schedule, respectively.

While the incidence of marijuana use (25%) is significant in this methadone program, it does not indicate a clear threat to several gross indicators of progress in the treatment of opiate addiction. Future research should consider ethnicity as a variable and also address personality characteristics which differentiate males and females in their use of marijuana. Additionally, potential interactions among personality, physiological and mood altering characteristics in determining preference for marijuana and/or alcohol require further investigation.

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BUPRENORPHINE DOSE RANGING FOR COMBINED COCAINE AND OPIATE DEPENDENCE

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PURPOSE

To assess buprenorphine (BUP) dose effects on cocaine and opiate use in cocaine abusing opiate dependent subjects.

METHODS

15 subjects were maintained on BUP for 21 days at each dose in an ascending and tapering schedule of BUP 2 mg to 16 mg sl. Subjects were assessed using twice weekly urine toxicology and weekly self report ratings of cocaine and opiate use, opiate withdrawal symptomatology, cocaine craving and cocaine effects.

RESULTS

Higher BUP dose led to greater reduction in opiate use as measured by urine toxicology and self report. At 2, 4, 8 mg during ascending and tapering phases, 27 - 33% of subjects were entirely opiate free for 3 weeks, while 65% were opiate free at 16 mg and 75% at 12 mg during tapering ($F=2.13$, $df = 7,124$, $p < 0.05$). There were also significant BUP dose effects on cocaine urine toxicology and self report measures. The proportion of cocaine positive urines was lowest during tapering (51-53% compared to ascending phases 67-69% for BUP 4.8 and 12 mg). Self reported cocaine use and craving decreased during the ascending protocol and reached their lowest level during tapering. There were no BUP dose effects on the quality of cocaine high reported by subjects who continued cocaine use.

CONCLUSION

Results of the study indicate that BUP dose has a significant impact on opiate and cocaine use and that longer time on BUP may attenuate cocaine craving. Regardless of dose, however, buprenorphine alone is unlikely to lead to complete abstinence from cocaine, suggesting the need for pharmacologic or psychosocial adjuncts to augment BUP effects.

ACKNOWLEDGEMENT

Supported by NIDA Grants DA 5R18 DA06190 and DA06266

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EFFECTS OF BUPRENORPHINE ON NEEDLE SHARING, DRUG USE AND DRUG CRAVING IN MEN WITH COMBINED HEROIN & COCAINE DEPENDENCE

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Buprenorphine reduced heroin and cocaine use over a 12 week period in men with DSM-III-R dual dependence on cocaine and opiates (Gastfriend et al., 1992). This report examines buprenorphine's effects on needle sharing, drug use and craving, and the relationship between craving and drug use over 6 months of outpatient maintenance. After a 1 month inpatient induction, subjects received buprenorphine 4 or 8 mg SL qd under single blind conditions over 6 months. Subjects reported subjective outcomes using a daily diary form and supervised urines were collected twice weekly.

At baseline, almost all subjects reported having shared needles. Buprenorphine maintenance was associated with reductions in needle use (58%) and needle sharing (48%) and reductions in the number of days per week of heroin use (from 6.9 to 1.2) and cocaine use (from 4.9 to 0.9). Self-report outcomes correlated strongly with urine screens ($r=.723$, $p<.001$ for heroin and $r=.673$, $p=.001$ for cocaine), supporting the validity of the daily diary format. There was no loss of effect over 6 months on reduction of heroin dependence. There was a trend for a progressive decrease in cocaine use over time ($p=.058$).

Buprenorphine was also associated with a significant decrease in daily drug craving between week 1 and 6 month means in both dosage groups. In the 4 mg treatment group, craving for opiates decreased by 79% ($p<.001$) and craving for cocaine decreased 68% ($p=.029$). In the 8 mg group, craving for opiates decreased by 83% ($p=.001$) and craving for cocaine decreased 82% ($p=.003$). This decrease remained stable throughout the maintenance period. Finally, we explored the possibility that craving might predict outcome. Week 1 (drug free) cocaine craving was significantly correlated with 6 month cocaine use ($p=.020$) and cocaine+opiate use ($p=.029$). Subsequent cocaine craving was less consistently correlated with outcome. Craving for heroin or speedball did not correlate with outcome.

Results from this first study of men with DSM-IIIR combined heroin and cocaine dependence indicate that buprenorphine provides a lasting, beneficial effect for both heroin and cocaine dependence. Buprenorphine also shows promise for reducing needle sharing, a major risk factor for HIV transmission. These data demonstrate a significant anti-craving effect for buprenorphine. Differential dose effects between 4 and 8 mg did not emerge. Controlled, double-blind studies are underway to clarify the dose-response characteristics of buprenorphine's effects on combined heroin and cocaine dependence in humans.

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Supported by NIDA Grants DA 06116, DA 00064, DA 00101, and DA 05944

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EEG AND BEHAVIORAL EFFECTS OF I.V. COCAINE AND MORPHINE IN COCAINE- AND OPIATE DEPENDENT SUBJECTS DURING BUPRENORPHINE TREATMENT

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Chronic treatment with buprenorphine reduces opiate self-administration and recently has been shown to reduce cocaine self-administration as well. Treatment of dually-dependent polydrug abusers is a difficult task so the availability of a single drug that would treat both dependencies represents a major advance in drug abuse treatment strategies. While the mechanism of buprenorphine's effects on opiate abuse are known, its effects on cocaine abuse are not completely understood. Techniques to measure acute drug effects (and blockade of these effects) have typically used subjective questionnaires. Topographic brain mapping is a quantitative procedure for measuring the electrical activity of the brain during very specific periods in time. The present study was conducted to explore the utility of using EEG topographic brain mapping as an adjunct measure of drug-induced intoxication and to determine if buprenorphine alters the morphine and cocaine induced effects.

Six healthy adult male volunteers with a history of opiate and cocaine dependence (i.e., *speedballs)* provided informed consent for participation in this study. Drug-free subjects were admitted to the Treatment Research Unit on day 1 of a 30-day program. On day 10 subjects received a 1 mg dose of buprenorphinc (s. 1) which was increased on consecutive days to 2,4,6 and 8 mg until day 24. Three of the subjects remained at 4 mg. On days 7, 8 and 9 and again on days 21.22 and 23 the subjects were prepared with 19 scalp EEG electrodes and given i.v. challenges of either cocaine (30 mg), morphine (10 mg) or placebo (1 ml) in random order. EEG activity was measured during eyes closed before and during 3 periods after i.v. injection: 11-14, 22-25 and 47-50 min. Subjects reported changes in mood via rating scales. The latency to detection of cocaine and morphine effects was measured using a foot-pedal device.

Morphine produced increases in EEG alpha activity and subjective reports of euphoria. Both doses of buprenorphine attenuated the EEG and behavioral response to morphine. On the other hand, cocaine produced neither significant alpha increase nor euphoria in these post-dependent subjects. No significant effect of buprenorphine was seen although general alpha activity was reduced in two subjects.

Buprenorphine blocked the EEG and behavioral effects of morphine. It appears that the 30 mg cocaine dose was too low to produce significant EEG and behavioral changes in these dually-dependent subjects. Finally, these results suggest that EEG topographic mapping is an effective objective measure of drug-induced intoxication.

ACKNOWLEDGEMENTS: Supported in part by Grants DA00064, DA00101, DA00115, DA03994 and DA06116 from the National Institute on Drug Abuse.

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ACUPUNCTURE REDUCES COCAINE ABUSE IN METHADONE-MAINTAINED PATIENTS

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We conducted an eight-week pilot study of auricular acupuncture for the treatment of cocaine addiction in methadone-maintained patients. Thirty-two patients participated in this study (mean age± s.d., 34, 7.9 years; 14 males, 18 females; mean methadone dose± s.d., 65, 18 mg). All patients were chronic cocaine users who met DSM-III-R criteria for cocaine dependence (mean number of years abusing cocaine+ s.d., 13.4, 7.7; mean amount spent on cocaine in the week previous to entry into study± s.d., $347, 310). Pre- and post-treatment assessments included Beck Depression Inventory, Selves questionnaire, and cue-elicited cocaine craving and aversion ratings. Patients received six weeks of daily acupuncture treatments, followed by two weeks of treatments thrice weekly. Urine screens for benzoylecgonine were taken twice weekly. Treatments consisted of the insertion of five disposable acupuncture needles (.20 gauge) in each ear by a trained acupuncturist. The following points were used: stomach, lung, kidney, sympathetic, and "shen men." Needles remained in place for 50 minutes. Seventeen patients completed the study. Of these, 14 abstained from cocaine for at least the last two weeks of the study. In this group of abstainers depression decreased significantly ($p<.009$). Post-treatment cue-elicited craving for cocaine decreased significantly ($p<.05$); aversion to cocaine cues increased significantly ($p<.05$). These 14 patients also had a significantly greater identification with their non-addict, ideal sense of self, and a significantly lower identification with their addict sense of self compared to pre-treatment levels ($p<.01$). There were no reported side-effects or observed complications from the acupuncture treatments. At one month follow-up, 12 of these 14 patients continued abstinent as verified by urine screens. These results suggest that auriculor acupuncture may be a relatively low-cost, low-risk means of initiating abstinence from cocaine abuse. Controlled studies of acupuncture are needed in this population. The development of an appropriate control condition for acupuncture needle insertion will be a critical issue. Research supported by NIDA Grants #727E-41-47799 and #5R18-DA-06190. Acupuncture needles donated by Seirin Co., Ltd. (Japan).

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OPEN-LABEL CARBAMAZEPINE REDUCES COCAINE USE IN COCAINE-DEPENDENT PATIENTS WITH AND WITHOUT ABNORMAL EEG

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The anti-convulsant carbamazepine has attracted much attention as a possible treatment for cocaine dependence. The mechanism of action proposed for its efficacy is interruption of neuronal kindling. We report here the results of outpatient cocaine-dependents, treated with carbamazepine. Because some of these patients had abnormal EEG at treatment entry, comparisons of the treatment response to carbamazepine based on EEG status were made.

Study subjects were a convenience sample of 22 cocaine-dependent(DSM-III-R criteria). Men, mean age 27 years, mean cocaine use 7 years, mean number of days that they used cocaine
per month 11, and mean longest prior abstinence 2 weeks. Subjects received carbamazepine (started at 200 mg daily and increased 200 per week to 800 mg daily for one week, then dropped to 200 mg daily), plus counseling for 8 weeks. Mean reported last cocaine use before beginning treatment was 5 days. Fourteen patients smoked coca paste and 8 snorted cocaine intranasally. Ten patients had abnormal EEG.

The mean retention time in treatment was 7 weeks; 77% of patients completed the 8-week treatment. Eleven patients reported abstinence throughout treatment, and 19 patients (86%) achieved their longest abstinence during treatment. The mean reported longest abstinence increased significantly ($p<0.001$) from 11 days before treatment to 35 days during treatment.

No seizures occurred during the study. Patients with abnormal EEG had significantly longer ($p<0.001$) retention time in treatment (mean 7.8 weeks vs. 6.3 weeks). There were no significant differences between the two groups in length of longest abstinence or other clinical variables.

These results add to the evidence of the usefulness of carbamazepine plus counseling for treatment of cocaine dependence in cocaine dependent patients in Latin-America. However, the open-label design and absence of objective tests to confirm self-reported drug use and medication compliance mean these results must be considered tentative, and need to be confirmed by double-blind, controlled clinical trials. The significant difference in retention time in treatment between EEG normal and EEG-abnormal individuals suggests the need for further studies to determine the patterns of drug abuse, treatment response, and effectivenes of carbamazepine in cocaine abusers with EEG abnormalities.

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COCAINE-USING METHADONE PATIENTS SHOW DECLINES IN COCAINE USE AND DYSPHORIA DURING COGNITIVE-BEHAVIORAL TREATMENT

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Cocaine use is a serious problem in the methadone maintenance population. This study presents preliminary outcome data on methadone patients who received enhanced outpatient treatment adapted from Rawson's neurobehavioral model for stimulant abuse. The main features of the model are: 1. cognitive-behavioral therapy (cognitive restructuring and coping skills training); 2. relapse prevention techniques (identifying triggers, risk avoidance); and 3. therapeutic alliance. Patients are guided through sequential stages of recovery from cocaine abuse and are taught specific strategies such as thought-stopping, scheduling and alternative activities. Consistent positive reinforcement is used to engage and maintain patients in treatment. All subjects met DSM-III-R criteria for cocaine dependence (by the SCID) and attended at least two individual therapy sessions and two group sessions per week. Cocaine use, cocaine craving, cocaine use symptoms and mood were measured at study intake and weekly thereafter. Cocaine use was measured as the number of self-reported days in the past week that cocaine or crack were used. Cocaine craving measures were frequency of craving and frequency of acting on craving. Cocaine use symptoms were 20 common physical and psychological consequences of chronic or intense use. Mood was measured by the Profile of Mood States (POMS). Our current sample represents the first 30 patients who completed five weeks of treatment: men (50%), women (50%); Hispanic (63%), black (17%), white/other (20%); mean age = 37 years; unemployed (65%). At study intake 46% were sniffing cocaine, 50% were using crack, 46% were injecting cocaine, and 37% were using heroin (often as a heroin/cocaine "speedball"). Prominent additional current psychiatric diagnoses were: major depression (32%), anxiety disorders (32%), adult anti-social personality (45%). Paired comparisons between subjects' intake and week five data show reductions in number of days using cocaine in the past week, the frequency of cravings, frequency of acting on cravings when they occurred, and cocaine use symptoms (all $p < .05$, two-tailed paired t-test). There were declines on the POMS mood scales of Anxiety, Depression, Hostility and Confusion, as well as on Total Mood Disturbance Score (all $p<.05$), but not on Vigor and Fatigue. Abstinence from cocaine/crack was reported by 13 subjects (43%) at week five, which was confirmed by negative urinalysis during week five for nine of these subjects; four subjects may not have reported accurately. The results are preliminary, because they could represent a "honeymoon" period in treatment. A comprehensive evaluation that includes voluntary random assignment of subjects to neurobehavioral treatment and a low-intensity control group (once a week cocaine group) with six- and fifteen-month follow-ups is in progress.

ACKNOWLEDGMENTS: Supported by NIDA Grant No. R18DA06959.

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DESIPRAMINE IN THE TREATMENT OF "CRACK" COCAINE DEPENDENCE PRELIMINARY RESULTS

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We have conducted the preliminary analysis of one arm of a 2 x 2 randomized, double-blind placebo-controlled study of desipramine (DMI) treatment and enhanced psychotherapeutic continuity of care in "crack" cocaine dependence. Hypothesis included that DMI: decreases cocaine craving, increases abstinence rates; and enhances treatment retention.

Methods: The subjects were male veterans, of whom 85% were African-American, 76% were unemployed, and 32% were homeless. Abuse or dependence on other substances was not an exclusion criterion, as long as primary drug of choice was crack. Exclusion criteria included medical contraindications to DMI, biopolar disorder, and schizophrenia. Subjects were started on DMI or placebo on Day 5 of a 2-week inpatient stay on the SFVAMC Substance Abuse Unit at 50 mg qD, and advanced 50 mg qD to a total of 200 mg qD. DMI levels were obtained in hospital at Day 10. At the end of the two weeks, subjects were followed in the outpatient clinic. The medication phase of the study continued for a total of 8 weeks, with an overall study duration of 6 months.

Results: Data from the first 82 subjects were analyzed (DMI N = 41, Placebo N = 40). Mean DMI blood levels were 156 ± 162 ng/ml at Week 2. At Week 3, they were 129 ± 112ng/ml.

Sixty-seven percent of subjects entered outpatient treatment, regardless of medication group status. Of those subjects who entered the outpatient phase, there was strong positive correlation between Week 2 DMI levels and number of days in treatment (Pearson r = 0.50, p = .025), despite the absence of statistically significant differences in overall days in treatment (DMI: 101+ 14 days; Placebo: 89 + 12 days). There were no statistically significant differences in abstinence rates at Weeks 3 or 8; in measures of craving; POMS subscores; or in measures of subjective cocaine withdrawal symptoms. No statistical differences were found between or within subject treatment groups on the basis of depression and dysthymia, or PTSD. No differences were observed in subjects using only cocaine and no other illicit substances or alcohol.

Discussion: These preliminary analyses suggest that desipramine may have a quantitative dose-response relationship to factors which contribute to relatively lengthy treatment retention (up to the six months of the study). In this study, however, no one single factor for this DMI effect appears to be explanatory. Craving, point prevalence of abstinence and other measures showed no differences between treatment groups. Instead, it appears that a combination of effects are at work, including interactions between DMI and the relatively high intensity of psychotherapeutic intervention and enhanced continuity of care (see S.M. Hall et al., "Early Treatment of 'Crack' Cocaine Abuse," this volume). DMI does appear to abolish the direct effects of cocaine-related intrusive thinking (see Tunis et al., "Assessing Thoughts about Cocaine Abstinence," this volume).

ACKNOWLEDGEMENT: Dept. of Veterans Affairs Merit Review and NIDA grant 1R18 DA06097. **AFFILIATION:** San Francisco Department of Veterans Affairs Medical Center, University of California, San Francisco.

A DESIPRAMINE CEILING IN COCAINE ABUSERS

H. KHALSA; F. H. GAWIN; R. RAWSON; K. CARROL AND P. JATLOW

Desipramine plasma concentrations were assessed 24 hours and one week after initiating treatment in a sample of twenty-four cocaine abusers. The subjects had been randomly assigned to desipramine treatment as part of a previously reported six-week, double-blind, cocaine abuse treatment trial. Both the 24-hour and one-week concentrations were highly related to later treatment outcome. Paradoxically, individuals with lower early desipramine concentrations sustained abstinence, while those with high levels did not. No subject with a 24-hour desipramine concentration above 65 ng/ml or with a one-week concentration above 280 ng/ml achieved abstinence.

These findings suggest that early desipramine plasma assessments might be a simple, effective, rapid predictor of desipramine treatment outcome in cocaine abusers, and that uniform early assessment of desipramine levels with rapid desipramine adjustment should be used as a method to improve responses in desipramine-treated cocaine abusers.

To further assess these intriguing findings, two recent studies of double-blind desipramine treatment (n=48 and n=90) that had monitored plasma levels were retrospectively examined. These studies were consistent with the original observation of a "ceiling". A prospective fixed-dose study of desipramine is now underway.

If a ceiling for desipramine in cocaine abusers is confirmed, then important implications for clinical management exist. A desipramine ceiling also provides an explanation for mixed results with desipramine in two cocaine studies where desipramine effects on cocaine use in methadone-maintained subjects were not robust. Methadone substantially raises plasma desipramine levels, and a ceiling was not considered in these trials.

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FLUPENTHIXOL TREATMENT OF CRACK USERS: INITIAL DOUBLE-BLIND RESULTS

F. H. GAWIN; M. E. KHALSA; J. BROWN AND P. JATLOW

Clinical research has demonstrated that tricyrlic antidepressants facilitate abstinence in outpatient cocaine abuse if they arc given in correct time and dosage ranges. Prceclinical research demonstrates that decrements in reward responsivity follow chronic stimulant administration, and clinical observations show that anhedonic symptoms can perpetuate cocaine abuse even in the absence of other major depressive symptoms. Oral medications appear to be less effective for "crack" abuse because cocaine smokers present increased psychological devastation compared to earlier abusers of cocaine (mainly intranasal users) and thus have very poor compliance to oral medication regimens. A previous open study reported that flupenthlsol decanoate (10-20 mg/q/2 wks) facilitated abstinence in outpatient crack cocaine abusers who had not responded to multiple prior attempts of non-pharmocological treatment. Cocaine craving decreased within one week and abstinence was maintained during the study in nine of ten abusers given flupenthixol. We arc conducting the first double-blind study of flupenthisol in cocaine abuse treatment. The study is a double-blind comparison of placebo, desipramine, and flupenthisol in 90 crack cocaine abusers. Measures collected include background and demographics; history of cocaine; alcohol, tobacco and other drug use; medical, psychiatric, and drug treatments received; work and criminal history; weekly **assessments** of cocaine and other drug use; drug craving; indicts of depression, anxiety and stress; medication side effects; non-pharmacological treatment received; social support; and level of activity during the week. Assessments are now completed for almost half of the sample (n=42). Subjects met DSM-III-R criteria for cocaine dependence and received desipramine (n=14), flupenthixol (n=14): or placebo (n=14) for six weeks in a double blind design. Minimal psychotherapy was provided to better isolate pure neuropharmacological effects from psychosocial intervention and to better approximate the reatities of urban treatment.

Engagement in treatment for a second visit was 73% for those on flupenthixol, 50% for those on desipramine and 28% for those on placebo (p=.07). Retention of subjects who received adequate medication exposure for a third visit (> 14 days) was 45% for those on flupenthixol, 43% for those on desipramine, and 7% for those on placebo (p=0.06).

Our results thus far show that Flupenthixol and desipramine markedly facilitate engagement in treatment in the context of minimal psychotherapy. Flupenthixol decanoate is superior to desipramine, and both are far superior to placebo in maximizing initial engagement. Early data on facilitating abstinence initiation are less dramatic, but encouraging.

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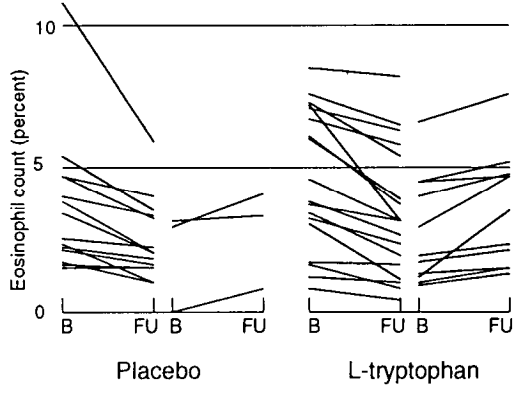
L-TRYPTOPHAN TREATMENT OF COCAINE DEPENDENCY AND THE EOSINOPHILIA MYALGIA SYNDROME

D. E. SMITH; D. R. WESSON; S. STEFFENS AND K. JUE

In November of 1989, the FDA suspended clinical trials involving L-tryptophan and banned L-tryptophan from sale in the U.S. because of the association of L-tryptophan with the Eosinophilia Myalgia Syndrome (EMS). Before that time, L-tryptophan was commonly used in drug treatment programs to treat cocaine withdrawal symptoms and cocaine craving. Clinicians and patients believed that L-tryptophan reduced symptoms of withdrawal and decreased cocaine cravings, although its pharmacological efficacy for treatment of cocaine withdrawal had not been established by controlled clinical trial. When EMS was first reported, we were midway through a placebo-controlled, randomized clinical trial of L-tryptophan with inpatients who were undergoing treatment for cocaine dependence. In our study, subjects were treated with 5 grams of L-tryptophan for up to 28 days. Both the L-tryptophan and the placebo used in this study were obtained from Arther, Inc. of Mountain Lakes, N. J.

Figure 1. Baseline and Follow-up Eosinophil Counts. For both groups, the right-hand column shows subjects whose eosinophils increased. The normal eosinophil count is 0-8 percent.



After the FDA report of EMS, we suspended our study. At that time, one-hundred and eighteen (118) subjects had been randomized to either placebo or L-tryptophan. We followed-up all subjects who could be contacted. We spoke with 75 subjects directly and, for 22 other subjects, we spoke with relatives who had information about the current health status of those subjects. One subject had committed suicide. We were unable to obtain information on 20 subjects. Forty-six subjects (17 placebo- and 29 L-tryptophan-treated subjects) agreed to follow-up laboratory evaluation. Subjects were paid $20 for the follow-up visit. The time between last treatment with L-tryptophan and the follow-up visit ranged from 3 to 30 months. No subjects reported taking L-tryptophan on their own following treatment, and no subjects reported symptoms suggestive of EMS.

Among our study subjects, we found no evidence that L-tryptophan treatment increased eosinophil count or produced EMS. AFFILIATION: Merritt Peralta Institute, Oakland, CA

FLUOXETINE AND COUNSELING FOR PCP ABUSE

L. COVI; J. M. HESS; N. A. KREITER AND J. H. JAFFE

While the first known US. PCP abuse epidemic occurred in 1967 but faded out, a somewhat lingering and rather regional endemic use has been noticed in Los Angeles, Washington/Baltimore and New York. Tennant et al. (1981), treated PCP abuser with desipramine but found no difference from placebo treatment. Fluoxetine has been recently reported to be more effective than placebo in PCP withdrawal (Loiselle and Giannini, 1988).

In this study forty-six outpatient PCP abusers who were not randomized placebo controlled fluoxetine study. Each of three weekly visits included urine testing, interviews on drug usage, monitoring of vital signs and side effects. Mood scales and craving scales were administered weekly. All participants received individual counseling for 50 minutes, twice a week by masters level counselors, who followed an outline describing a modified interpersonal counseling (Rounsaville 1985). Fluoxetine dosage began at 20 mg and, in a few cases, increased to either 40 Diphenhydramine 12.5 mg capsules were employed. Fluoxetine blood levels were obtained every other week.

Data for the 34 subjects, 18 on fluoxetine and 16 on placebo, who were fully compliant with protocol and in the case of the fluoxetinc subjects had fluoxetine/norfluoxetine blood levels above 100 ng/ml, were analyzed using an analysis of variance for repeated measures. Of 158 eligible callers 108 were given appointments and 60 attended the first evaluation visit. Forty-six completed evaluation and signed informed consent and 45 began treatment. Both fluoxetine and placebo treated groups showed significant improvement in drug use, urine positivity, mood depression, mood anxiety and craving measures over time but no differences were found between fluoxetine and placebo. The improvement over time is attributable to the effect of counseling.

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NICOTINE POLACRILEX AND POST-SMOKING CESSATION WEIGHT GAIN: DOSE AND GENDER EFFECTS

S. J. LEISCHOW; D. P. L. SACHS, A. G. BOSTROM AND M. D. HANSEN

Because of the equivocal relationship between nicotine replacement and post-cessation weight gain (Gross et al. 1989; Killen et al. 1990), the present study was designed to prospectively assess Nicotine dose effects on post-cessation diet, serum nicotine, and weight change. Eighty-nine Ss who enrolled in a 4 week smoking cessation trial were randomly assigned to use either 0.2, or 4 mg nicotine polacrilex in a fixed dose schedule (one piece/hour while awake). At each weekly visit, Ss (1) received behavioral strategies to remain abstinent, (2) received medication for the next week and returned all used and unused medication from the previous week, (3) had vital signs assessed, (4) provided a breath CO sample so that smoking status could be verified and a blood sample so that serum nicotine levels achieved by each dose could be evaluated. Seventy Ss also maintained 5 day food records one week pre-quit, one week post-quit, and 4 weeks post-quit.

Only the 35 Ss (16♀, 19 ♂)) who did not relapse at any point during the 4 weeks and who were completely abstinent during the last week of the study were included in the data analysis. There were no differences between the treatment groups or genders on baseline caloric intake or serum nicotine, but a gender difference was observed on baseline weight (males: 81.4 kg, females: 63.9 kg [$F = 22.9$, $p < 0.001$]).

At the end of the 4 week study, there were no gender or treatment group differences in energy intake (mean = 112 kcal increase across groups) or nicotine polacrilex use (mean = .9 pieces per hour). However. serum nicotine and body weight chances were found. Serum nicotine levels in males decreased -6.57 and -7.34 ng/ml in the 0 & 2 mg groups relative to baseline, respectively, and increased 7.72 ng/ml in the 4 mg group. In females, serum nicotine levels were -8.76, 11.27, & 7.64 ng/ml in the same groups, respectively. While gender differences were not significant, treatment group differences were significant ($F = 5.53$, $p = 0.009$), as was the group by gender interaction ($F = 4.22$, $p = 0.025$). The significant serum results appear due to the gender differences in 2 mg response: serum levels increased from baseline in women, but decreased in men.

Nicotine polacrilex doses were associated with gender differences in post-cessation weight gain. Males gained, on average, 1.60, 1 .45, and 1.18 kg in the 0,2, and 4 mg treatment groups, respectively (n.s.). However, weight change in females was 1.69, 0.33, and -0.26 kg in the 0, 2, and 4 mg treatment groups, respectively ($F = 4.39$, $p = 0.04$). The linear trend in female weight change by dose was also significant ($F = 8.11$. $p = 0.01$). When weight change was assessed as a function of change in actual serum nicotine levels (collapsing 'treatment groups), a significant correlation was found for females ($r = -0.52$, $p < 0.05$), but not males ($r = 0.13$, n.s.). Thus, as serum nicotine increased from baseline levels in females, post-cessation weight gain decreased.

The present prospective study found that the higher the dose of nicotine polacrilex used by females for 4 weeks after smoking cessation, the less weight they gained. Males gained weight regardless of nicotine polacrilex dose. The suppressed weight gain in females was associated with increased serum nicotine, while increased serum nicotine (even relative to baseline levels) was not related to weight suppression in males. While the present results are based upon a small sample and thus require replication, they are encouraging for those females who are concerned about weight gain after smoking cessation.

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NIDA/MDD's Preclinical Testing Programs for Development of Medications for Cocaine and Opiate Addiction

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COCAINE TREATMENT DISCOVERY PROGRAM (CTDP)

NIDA/MDD's mission is to develop medications for the treatment of drug addiction. MDD's primary goal is to identify potential treatments for the medical management of cocaine abuse. Preclinically, this is achieved by testing compounds with specific activities, acquired from academic researchers, commercial sources and pharmaceutical companies, through a decision-based screening program. This screening program consists of in vitro biochemical analyses such as dopamine transporter binding and uptake determinations and in vivo pharmacological evaluations such as mouse locomotor activity, rat drug discrimination and rat self-administration studies. A compound's advancement through the screening program is dependent on results at each stage of testing. "Promising" compounds may be further profiled for assessment of in vitro biogenic amine activities, potential for self-administration, and species generality in primates. These tests are performed through NIDA contracts or interagency agreements awarded to SRI International, the Medical College of Virginia, NIDA/Addiction Research Center, NIH/NIDDK and the Washington D.C. Veteran's Administration. Currently, compounds with potential activity at the dopamine transporter and selected CNS-active compounds are being screened for their potential utility as either substitution or blocker-type medications for the treatment of cocaine abuse.

OPIATE TREATMENT DISCOVERY PROGRAM (OTDP)

The MDD is also interested in identifying next generation opiate pharmacotherapies. For this program, opiates and opioid peptides are initially tested for in vitro opiate subtype activity through a NIDA contract at SRI International. Subsequent in vivo testing of "interesting" compounds is accomplished through the CPDD opiate testing program.

MDD DATABASE

Data obtained from a variety of sources including the opiate and cocaine treatment discovery programs, and the drug abuse literature, are being entered into a structure-activity database. This database, which is accessible to interested scientists on a dial-up basis, contains chemical information in a MACCS (Molecular Design Ltd) system and biological data in an Oracle system. The MACCS/Oracle system is installed on a dedicated Microvax 3300. A user friendly graphical interface which integrates the chemical and biological databases is provided to enhance structure-activity investigations. This database will serve as a tool to assist in the design of novel compounds for potential use as drug abuse treatment agents. Affiliation: Medications Dev. Div. (MDD), NIDA, Rockville, MD 20857

A PROBLEM-SOLVING SYSTEM OF INSTRUCTION (CINE') ON THE PHARMACOLOGY OF DRUG DEPENDENCE

D. HUTCHEON; S. GERTNER; D. M. HAVELIN AND E. FLYNN

Our objective is to show how advances in microcomputer technology including the use of interactive, multimedia products can be applied to promote understanding of basic concepts in the pharmacology of drug dependence. Programs include problem-solving instructional modules that are tutorial in nature and contain animated graphics and short video clips. Topics such as drug testing, laboratory analysis physiological effects of different drugs and treatment procedures can be presented in these computer modules for use by individuals or groups in a variety of educational settings.

Modules are prepared which use object-oriented programming and recently developed analog/digital systems to present laboratory exercises and case reports dealing with the actions and kinetics of the commonly abused drugs. Pre- and post-test questions linked with tutorial information and references cover concepts of physical dependence, tolerance, withdrawal and antagonism. As an example a program is presented illustrating how central and cardiovascular responses to cocaine provide data for analysis and relate to the potential roles of adrenergic, dopaminergic and 5-HT agonists and antagonists in treating cocaine toxicity and preventing relapse.

Advantages of the method of instruction on problems of drug dependence are that modules consisting of diskettes and a user's guide are easily distributable and can be used alone or as a supplement or complement to laboratory, lecture, and textbook learning. The modules are developed according to accepted psychological principles of learning. They provide for active involvement of the learner through assignments involving laboratory exercises and case studies requiring decision-making, calculations and interpretation of data.

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CYTOCHROME P450 CYP2D6 GENOTYPE IN HUMAN COCAINE ADDICTS

E. T. BUCHERT; R. L. WOOSLEY; L. WEINHOLD AND D.A. GORELICK

One pathway for cocaine metabolism in humans is oxidation by the Cytochrome P540 enzyme system, presumably the P4502D6 which binds cocaine in human liver (Tyndale et al. 1991). Genetic polymorphism in the CYP2D6 gene which codes for P4502D6 may explain interindividual variability in response to cocaine. In order to investigate this possibility, we are analyzing the CYP2D6 genotypes of cocaine addicts. Our preliminary study determined the frequency of the CYP2D6-B allele, the most common of the CYP2D6 mutations, in 14 black and 11 white cocaine-dependent research volunteers, as 0.107 and 0.136, respectively. This frequency is roughly consistent with findings in the general population (Broly et al. 1991 and Relling et al. 1991) and in our control groups. We found no homozygous CYP2D6-B individuals among our cocaine-dependent volunteers. Homozygotes (Wild Type/Wild Type) did not differ from heterozygotes (Wild Type/B) in age or self reported drug history. Preliminary review of data suggests that the two groups also did not differ in cardiovascular or subjective response to acute cocaine--25 mg i.v.

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A META-ANALYSIS OF MORPHINE EFFECTS IN NON-DEPENDENT HUMAN SUBJECTS

M. Farre, X. Lamas, V. Moreno* and J. Cami

The methods developed at the U.S. Public Health Service Addiction Research Center over the past 30 years have provided the basis for the evaluation of opioids for abuse liability in humans. Although these methods have remained relatively uniform, no efforts have been made to join the results from different studies. Meta-analysis technique allows to statistically combine the results of previous research. The present meta-analysis was designed to evaluate whether there was a dose-response relation between morphine doses and the magnitude of some variables commonly used in the assessment of the physiological, subjective and behavioral effects produced by the prototypic opioid agonist morphine.

METHODS: We carried out a comprehensive review of published studies that included the acute i.m. or s.c. administration of morphine to non-dependent male opioid abusers. Admission criteria for the studies to be selected were: double-blind, crossover, randomized and placebo-controlled. Scores from scales derived from the Single Dose Questionnaire (opioid classification, "liking" and adjective ratings), MBG scale of the ARCI and pupillary diameter measures acted as dependent variables. Log transformation of the morphine dose, stratifying by studies, was used as predictor variable. Logistic regression models were applied to study the dose-effect relation for categorical dependent variables, whereas multiple regression models were calculated for quantitative dependent variables. The number of subjects in each study was considered as a weighing factor. Homogeneity between studies was explored by residuals analysis. Random effects models were subsequently applied, but they did not substantially improve the fitting of data in the models. Finally, the models were used to calculate the doses of morphine needed to produce a given effect and their confidence intervals.

RESULTS: Thirty-one studies (total number of subjects = 307) were included in the analysis. Although some degree of heterogeneity was observed, a dose-response function could be demonstrated for the studied variables. Doses producing an average effect ranged from 7 mg (95% confidence interval: <1-206) (observer-reported "liking") to 12 mg (<1-612) (subject-reported "liking"). Dose producing an average effect in peak pupillary changes was 9 mg (1-78). The dose producing 50% of possible correct opioid classifications was 17 mg (11-25). MBG scale appeared to be a somewhat less sensitive index, with 25% of maximum scores produced by a 20 mg (7-64) dose.

CONCLUSIONS: The quantitative data derived from this work provide information about dose-effect morphine functions, and allow to calculate morphine doses capable to produce a given effect. The presence of some degree of heterogeneity between studies along with the broad confidence intervals observed could be due mainly to changes in the characteristics of subjects populations or experimental procedures over the period of time evaluated. Differences in sensitivity observed confirm that combination of several indexes is desirable when assessing morphine effects. Supported by a CTRAN grant.

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COMPARATIVE EFFECTS OF PENTAZOCINE, NALOXONE AND MORPHINE IN OPIOID-DEPENDENT HUMAN SUBJECTS

X. Lamas, M. Farre, T. Teran, B. Ugena and J. Cami

Previous research has demonstrated that mixed agonist-antagonist opioid drugs produce antagonist-like effects in opioid-dependent human subjects In morphine-dependent subjects the mixed agonist-antagonist opioid analgesic pentazocine precipitated a withdrawal syndrome resembling that produced by nalorphine, but no direct comparisons with the pure antagonist naloxone have been made. The purpose of the present study was to evaluate pentazocine's agonist and antagonist properties relative. to prototypic agonist (morphine) and antagonist (naloxone) opioid drugs and to characterize the withdrawal syndrome produced by the administration of pentazocine.

METHODS: Six male physically dependent opioid abusers maintained on methadone 30 mg daily PO participated as inpatient volunteers. Subjects ranged in age from 26 to 34 years and weighed between 55 and 76 Kg. Participants were individually tested in 9 sessions separated by at least 24 hr. A training session in which no drugs were given was followed by 8 experimental sessions, in which drugs were administered according to a doubleblind, randomized block order design, with the highest doses of the treatments included in the second block. Drug conditions tested were: Morphine (20,40 and 60 mg), naloxone (0.1 and 0.2 mg), pentazozine (45 and 60 mg) and saline, given intramuscularly. Physiological measures (blood pressure heart rate, respiratory rate temperature and pupil diameter) and subjective effects and observer rating forms were collected before drug administration and seven times postdrug administration (20,40,60,80,180 and 240 min postdrug). Subject - and observer-reported questionnaires included six visual analog scales a pharmocological class questionnaire, an adjective rating scale divided into three subscalcs (agonist scale, antagonist scale and mixed agonist-antagonisl scale), and a Spanish version of the 49 item short form of the ARCI.

RESULTS: Morphine produced typical mu-agonist effects, with significant increases in the subjects- and observer-reported "liking", MBG scale of the ARCI and in ratings on the agonist scale. Morphine 60 mg significantly decreased pupil diameter. Correct identifications of morphine increased as a function of the dose. Naloxone precipitatcd withdrawal symptoms that were measurable on a number of subjective and physiological measures. The 0.2 mg dose significantly increased scores on "any effect," "bad effects" antagonist scale, and LSD scale of the ARCI. A significant increasc in pupillary diameter was observed. Subjects consistantly identified naloxone as an antagonist. Pentazocine precipitated a withdrawal syndrome resembling that of naloxone, but the effects were not dose-related. Moreover, pentazocine increased scores on the mixed agonist-antagonist scale. "Confusion" and "lightheaded" scores were significantly higher on pentazocine than on naloxone. Pentazocine was indistinctly classified as an antagonist, alcohol or hallucinogen.

CONCLUSIONS: The results of the present study suggest that pentazocine precipitates an opioid abstinence syndrome in methadonedependent human subjects somewhat different to that produced by naloxone. This differences could be due to differences in receptor activities of pentazocine and naloxone, perhaps related to pentazocine's kappa agonist activity. These results indicate that the abuse liability of pentazocine in opioid-dependent subjects is probably low. This research was supported by a CITRAN grant and by Andomaco Laboratories.

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SUBJECTIVE, BEHAVIORAL AND PHYSIOLOGICAL RESPONSES TO INTRAVENOUS DEZOCINE IN HEALTHY VOLUNTEERS

J. P. ZACNY; J. L. LICHTOR; J. G. ZARAGOZA AND H. DE WIT

Dezocine is an agonist-antagonist opiate that acts at the mu receptor, and is used for management of pain in hospitals and surgicenters. Dezocine functions as a reinforcer in rhesus monkeys, and produces positive subjective effects similar to those of morphine in former opiate addicts. The subjective effects of dezocine have not been studied in healthy normals, so the abuse potential of this drug in the general population is not known. The purpose of our study, then, was to characterize the mood-altering and psychomotor effects of dezocine in healthy volunteers. A within-subjects, randomized design was used in which ten normal healthy volunteers (6 males, 4 females) were injected with 0, 2.5, 5.0 and 10 mg/70 kg of dezocine in a double-blind fashion. Subjects completed several subjective effects questionnaires (e.g., Addiction Research Center Inventory) before, and at periodic intervals for up to 5 h after drug injection. Psychomotor performance (e.g., eye-hand coordination) and several physiological measures (e.g., pupil size, respiration rate) were also assessed at these times. Dezocine produced increases in MBG ("Euphoria") scores of the ARCI, increases in ratings of drug liking, as well as other subjective effects that might be considered as pleasant ('good mood,' 'drunken,' 'coasting,' 'happy' ratings) (all $p<0.05$). At the same time, the drug had effects (increased dysphoria and sedation) that typically are not reported by addicts. Dezocine produced psychomotor impairment and miosis (constriction of the pupils) in a dose-dependent fashion. Some but not all of dezocine's effects were dose-related - in particular, those subjective effects which might be considered as pleasant (MBG scale of the ARCI) were not dose-related. The observation that dezocine produces euphoria and increased drug liking ratings in individuals without histories of drug abuse suggests that hospitals and surgicenters should have strict accountability procedures with this drug.

ACKNOWLEDGEMENTS

Supported by NIDA Grant DA02812, University of Chicago Anesthesia Research Fund, Chicago Anesthesia and Critical Care Research Foundation

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ANALGESIC EFFICACY OF CONTROLLED-RELEASE OXYCODONE vs. IMMEDIATE-RELEASE OXYCODONE ALONE AND IN COMBINATION WITH ACETAMINOPHEN IN POSTOPERATIVE PAIN: A PRELIMINARY STUDY

A. Sunshine, N. Olson; A. Colon; L. Gonzalez; R. Fitzmartin and J. Rivera

INTRODUCTION: Oxycodone is a synthetic opioid agonist which may be given orally. The purpose of this single dose, double-blind, randomized, parallel group study was to determine the relative analgesic efficacy of graded doses of controlled release oxycodone compared to immediate release oxycodone, immediate release oxycodone in combination with acetaminophen and placebo in patients with moderate or severe pain following abdominal or gynecological surgery.

METHODS: One hundred eighty-two hospitalized patients were randomly assigned to receive a single dose of one of the six study treatments: controlled release oxycodone 10 mg, 20 mg, or 30 mg (CR OXY), immediate release oxycodone 15mg (IR OXY), immediate release oxycodone 10mg in combination with acetaminophen 650mg (IR OXY/APAP) or placebo. Analgesia was assessed over 12 hours based on pain intensity and pain relief. Pain intensity was rated on a scale of 0 (none); 1 (slight); 2 (moderate) or 3 (severe). Pain relief was rated as 0 (none); 1 (a little); 2 (moderate); 3 (a lot); or 4 (complete). Subjective measures of onset and duration of "meaningful" pain relief were determined by the patient using a stopwatch. Survival analysis for onset and duration for those patients with onset was performed.

RESULTS: A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak PID, with CR OXY 20mg and 30mg being significantly better than the 10mg dose. All active treatments were significantly superior to placebo for SPID and TOTPAR. Peak PID and peak pain relief were observed approximately 2-4 hrs after dosing. CR OXY 10mg had significantly ($p<0.05$) better relief scores than placebo (hr 3-11). IR OXY (hr 10) and IR OXY/APAP (hr 10 and 11). CR OXY 20mg had significantly ($p<0.05$) better relief scores than placebo (hr 2-12). IR OXY (hr 10-12) and IR OXY/APAP (hrs 9-12). CR OXY 30mg had significantly ($p<0.05$) better relief scores compared to placebo (hr 2-12), IR OXY (hr 10), and IR OXY/APAP (hrs 9-12). PID scores showed that IR OXY was significantly superior to CR OXY 10mg (hrs 1 and 2). IR OXY/APAP was significantly superior to the doses of CR OXY at hr 1, and to CR OXY 10mg from hr 2 through 5.

Onset occurred in 93% of the patients who received CR OXY 20mg compared to 83% of the patients who received IR OXY. For those patients with onset, the median times to onset were 58 min for CR OXY 20mg and 41 min for IR OXY. CR OXY 10mg showed a median duration of relief greater than 720 min compared to 590 min for CR OXY 20mg, and 575 min for CR OXY 30mg. Onset time was significantly shorter for the IR OXY and the IR OXY/APAP treatment groups compared to the 3 CR OXY treatments. Duration of relief showed that CR OXY 10mg, 20mg and 30mg had significantly ($p<0.05$) longer duration of effect compared to IROXY and IR OXY/APAP. In addition, all three CR OXY preparations had significantly ($p<0.05$) longer times to remedication than IR OXY/APAP.

CONCLUSION: CR OXY is clearly an effective oral analgesic for the relief of moderate to severe postoperative pain. Median onset time for CR OXY was 20-30 minutes longer than IR OXY. CR OXY has a longer duration of effect compared to IR OXY or IR OXY/APAP. Onset of action occurred in 1 hr and duration of effect was from 10 to 12 hr. Both IR OXY and IR OXY/APAP had a duration of 6-8 hours.

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A Novel Approach to Assessing Pain Threshold in Human Subjects

J. H. Lee and M. Stitzer

Introduction: The purpose of this study was to test the reliability of an innovative radiant heat methodology for assessing analgesic response in human subjects that is based on the methods frequently used in animal analgesic research. New methodologies to assess analgesic response in humans are needed to better integrate pre-clinical and clinical data. The present study compared a radiant heat method to electrical stimulation.

Methods: For the radiant heat task a modified tail flick apparatus was used. The subject's finger is placed over a 3mm hole through which the light from a projection bulb (100 watt) radiates from below. Above the finger is **a** photocell, thus with the finger covering the light source, light is prevented from hitting the photocell. When the subject removes his/her finger the light hits the photocell, automatically stopping the timer and turning off the light. The latency (in seconds) for finger withdrawal was recorded. For the electrical stimulation tasks, subjects placed the middle and index finger of the dominant hand on top of two electrodes from which they received a brief series of increasingly intense electrical stimulations. Initial current applied **was** below sensation threshold (.35 mA, 0.6 second duration) the current was increased by 5 mA for each successive stimulus presentation, with pulses delivered once every 5 seconds until the subject terminated the test trial. Maximum stimulus intensity (mAmps) delivered was recorded. On each test day, subjects received 5 test trials with a 10 minute interval between trials. All 14 subjects were tested twice on both electrical stimulation and radiant heat in a counterbalanced design across 4 testing days.

Results: Finger withdrawal latencies for the radiant heat task did not differ significantly across test trials or test days ($\bar{x}$ = 7.66 sec., Day 1 and $\bar{x}$ = 7.62 sec., Day 2). Finger withdrawal scores for electrical stimulation increased significantly across both test trials and test days (mean ranged from 1.4 mA on trial 1, Day 1 to 2.2 mA on trial 5, Day 2).

Discussion: These data show that radiant heat method generates consistent latencies across trials and days, whereas shock trends over time. The radiant heat task appears promising as a sensitive and reliable test of drug induced analgesia.

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PHARMACOLOGIC EFFECTS OF INTRANASAL ("SNORTED") HEROIN

E. J. CONE AND B. HOLICKY

The intranasal route of administration is frequently used as an alternate method of heroin abuse by addicts. Although it has been known for many years that heroin was used in this manner, little information has been available on the efficacy of heroin administration by this route. We evaluated the pharmacologic effects of heroin by the intranasal and intramuscular routes. Six male subjects with recent histories of heroin abuse provided informed consent and resided on the research unit during the study. Subjects were administered an intramuscular injection (saline or 6 mg heroin hydrochloride) and inhaled 100 mg of a powder (lactose or lactose + 6 mg heroin hydrochloride or lactose + 12 mg heroin hydrochloride). Heroin doses were administered in random order under blind, double dummy conditions. Physiologic and behavioral measures were collected prior to and periodically after dosing. Effects from intranasally administered heroin were generally dose-related and similar in time course to intramuscular administered heroin. The magnitude of the effects from the higher intranasal dose were similar to or less than those observed for the intramuscular dose indicating an approximate relative potency of 50% for intranasal heroin.

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BUPRENORPHINE: DURATION OF BLOCKADE OF EFFECTS OF INTRA-MUSCULAR OPIOIDS

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Buprenorphine, a mixed opioid agonist/antagonist, has been shown to block the effects of exogenous opioids. This study examined the duration of blockade of intramuscular hydromorphone effects by several doses of buprenorphine.

Methods: Six opioid-dependent inpatients were maintained on daily sublingual doses of buprenorphine at 2,6, and 12 mg in a randomized, balanced sequence. Patients were maintained on each dose for at least five days, after which placebo buprenorphine was substituted in a single blind fashion for the next three days. Hydromorphone challenges were administered on each of the three placebo days. Challenges consisted of the sequential administration at 90 minute intervals of placebo, 6 mg, and 12 mg of intramuscular hydromorphone, followed by monitoring of physiological and subjective effects. Mean ratings after active hydromorphone administration were analyzed by two factor (buprenorphine dose, and duration off active buprenorphine) repeated measures ANOVA.

Results: There was a main effect of buprenorphine dose on subjective "high" ($F[2,10]=5.05$, $p=.03$) with 12 mg of buprenorphine providing greater blockade of "high" than 2 mg of buprenorphine ($F[1,5]=12.21$; $p=.02$). There was no significant main effect of duration off active buprenorphine on this measure ($F[2,10]=1.27$, NS) nor an interaction of buprenorphine dose with duration ($F[4,20]=1.03$, NS).

Conclusion: The current data suggest that buprenorphine's blockade of subjective opiate "high" persists for at least 72 hours after the last dose of buprenorphine.

This work was done at the Treatment Research Unit, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508

COMPARISON OF THE ACUTE EFFECTS OF BUPRENORPHINE AND METHADONE IN NON-DEPENDENT HUMANS

S. L. WALSH; K. L. PRESTON; M. L. STITZER; I. A. LIEBSON AND G. E. BIGELOW

INTRODUCTION: Buprenorphine, a mixed opioid agonist-antagonist, is currently being investigated as a new treatment for opioid addiction. The purpose of this study was to compare the acute subjective and physiological effects of buprenorphine to those of methadone over a wide range of doses, and to assess the ability of buprenorphine and methadone to alter the effects of a subsequently administered opioid agonist.

METHOD: Seven non-dependent male inpatient subjects with histories of opioid abuse were tested once weekly with methadone (0, 3.75, 15, and 60 mg, p.o.) and buprenorphine (0.5, 2, 8, 16 and 32 mg, s.1.) using a double-blind, double-dummy, Latin-square design. Twenty-four hours after dosing, subjects participated in a second experimental session in which they received cumulative doses of hydromorphone (0, 1 and 4 mg, i.m.). Subjects were monitored intensively on a number of physiological and subjective variables before and for 108 hours following the fist drug administration.

PRELIMINARY RESULTS: Both methadone and buprenorphine produced typical opioid agonist effects including pupillary constriction, respiratory depression and elevations on measures of positive drug effects. Methadone (60 mg) and buprenorphine (8-32 mg) produced comparable decreases in respiratory rate (~ 4 breaths/mm) and arterial oxygen saturation (-3%). On subjective report measures of "drug effect," "good effect," and "drug liking," score elevations after 0.5 mg buprenorphine were comparable in magnitude to those produced by 15 mg methadone, while 8 mg buprenorphine was comparable to 60 mg methadone. Subjective and physiological indices revealed that 16 and 32 mg buprenorphine produced effects equivalent to those of 8 mg buprenorphine, indicating a ceiling on these effects. In the opioid agonist challenge sessions, 15 mg methadone slightly enhanced, while 0.5 mg buprenorphine partially attenuated, the effects of hydromorphone. Higher doses, 60 mg methadone and 8-32 mg buprenorphine, attenuated the physiological and subjective effects of hydromorphone.

DISCUSSION: Buprenorphine and methadone have profiles that are typical of mu agonists; however, there is a ceiling on the effects of buprenorphine which is consistent with its classification as a partial agonist. Buprenorphine doses of 8, 16, and 32 mg s.1. were approximately equivalent to one another and to 60 mg methadone p.o. on both physiological and subjective measures. These long-acting opioids can attenuate the effects of an opioid challenge even following **acute** administration.

ACKNOWLEDGEMENTS
This work was supported by NIDA grants DA06120, DA07209 and DA00050.

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BUPRENORPHINE EFFECTS IN METHADONE-MAINTAINED SUBJECTS

H. L. JUNE; K. L. PRESTON; G. E. BIGELOW AND M. L. STITZER

Introduction. The interactions between methadone and buprenorphine are of both scientific and practical interest. In the event that buprenorphine becomes available as a new treatment for opiate abuse, an understanding of methadone-buprenorphine interactions will be relevant to the abuse liability of buprenorphine in methadone-maintained patients and also to the development of protocols for clinical transitions from methadone to buprenorphine treatment. The purpose of this study was to examine the effects of buprenorphine in methadone-maintained subjects to determine whether an agonist or antagonist effects profile would be observed.

Methods. Subjects were six opiate-dependent males maintained on methadone 60 mg/day for at least 2 weeks prior to the study. Subjects participated while residing on a residential research facility. During the study, seven test sessions were conducted at weekly intervals during which the following test drugs were examined: placebo, methadone 15, 30 and 60 mg p.o. and buprenorphine 2, 4 and 8 mg s.1. Test drugs were administered in random order under double blind conditions at 40.5 hours after the last methadone dose. Physiological, observer and subjective effects were measured for the next 6 hours.

Results. Methadone 60 mg produced opiate agonist effects including pupillary constriction and elevated "good drug effects" and "liking" scores. In contrast, buprenorphine precipitated signs and symptoms of opiate withdrawal including elevated scores on a withdrawal symptom checklist, elevated "bad drug effects" and "withdrawal sickness" scores and elevated scores on an observer rating of objective withdrawal signs. The intensity of withdrawal signs and symptoms was directly related to buprenorphine dose up to 8 mg s.1. Onset of precipitated effects was about one hour after test dose administration at 4 and 8 mg buprenorphine.

Implications. Buprenorphine acted as an antagonist, precipitating withdrawal, rather than an agonist in subjects maintained on 60 mg methadone/day even when test doses were given at 40.5 hours after the last methadone dose. This observation suggests that buprenorphine should have negligible abuse liability in patients already maintained on moderate to high doses of methadone. With regard to methadone-buprenorphine transitions, the data suggest that patients maintained on moderate methadone doses may not be able to switch directly to buprenorphine treatment at doses of 2 mg or higher. However, transitions that involve lower methadone and/or buprenorphine doses are not ruled out by these findings.

ACKNOWLEDGEMENT:
Research supported by USPHS grant R18 DA06120 from the National Institute on Drug Abuse

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DETECTABILITY OF BUPRENORPHINE DOSE ALTERATIONS IN OPIOID-DEPENDENT HUMANS

L. AMASS; W. K. BICKEL; S. T. HIGGINS; J. R. HUGHES AND T. PETERSON

Buprenorphine is a low efficacy μ-opioid agonist and a promising pharmacotherapy for narcotic dependence. The purpose of this study was to characterize the effects of double-blind, single-day buprenorphine dose alterations in opioid-dependent humans. Pour, outpatient opioid-dependent male subjects participated. Subjects' spent an average $349 per week **on** opioids during the month prior to the study and reported **an** average 11.4 years of regular opioid use. Subjects initially received sublingual buprenorphine in ascending daily doses of 2, 4 and 8 mg/70 kg over the first three study days and were maintained on 8 mg/70 kg daily (i.e., the stable dose). After at least 4 days of stable dosing, subjects participated in 16 test sessions where one of seven test doses was substituted for the stable dose. Participation in test sessions was contingent on the subject providing an opioid-negative urine sample, and each test session was separated by a minimum of two days of stable dosing. Test doses, masked for taste, were 0, 2, 4, 8, 12, 14, and 16 mg/70 kg of buprenorphine. Subjects received each of the test doses twice in a randomized block fashion, except for the 8 mg/70 kg test dose, which was administered four times. Self-reports, observer-ratings, and physiological measures of opioid effects were assessed before and at 30, 60 90, 120 min and 24 hours following drug administration. Subjects' estimations of both magnitude and direction of dose alterations were sensitive to dose decreases but not to dose increases. Visual analog scale ratings of "drug effect" and "high" were sensitive only to dose increases. Self-reported withdrawal ratings increased following only the 0 mg/70 kg and 2 mg/70 kg test doses, and remained elevated above pre-drug levels at 24 hours. All active buprenorphine doses produced miosis, but pupil diameter returned to pre-drug levels within 24 hours. Other physiological measures were not sensitive to dose alterations, suggesting that doubling the buprenorphine dose was tolerated well. This profile of behavioral and physiological effects is consistent with buprenorphine's actions as low efficacy μ-agonist, findings reported previously with methadone, and the effects of acute buprenorphine in non-dependent opioid users. Moreover, 75% reduction of buprenorphine dose produces persistent elevations in self-reported withdrawal. Thus, abrupt or accelerated buprenorphine detoxification may induce an abstinence syndrome that in turn may precipitate relapse. These data also confirm unpublished results from a controlled, outpatient clinical trial in this laboratory demonstrating poor treatment outcomes following rapid buprenorphine detoxifications.

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COCAINE PRECIPITATION OF PATIENT-INDUCED OPIATE WITHDRAWAL IN OPIATE-DEPENDENT INDIVIDUALS

S. STINE AND S. SATEL

In our clinical programs we observed that many opiate addicts reported typical opiate abstinence symptoms after using cocaine. The interaction of cocaine and opiates is highly significant for clinical effects have been reported including decreased withdrawal after naloxone in patients who have a cocaine use history and increased cocaine use in methadone programs. In order to study patient-identified opiate withdrawal after cocaine use, we constructed a 16 item clinician-administered questionnaire. The 35 subjects were 94% male, 43% black, and had an average age of 37. Most subjects had experienced opiate withdrawal after cocaine use (77%). although they were not in opiate withdrawal at the time they initiated the cocaine. Among the subjects reporting opiate-like withdrawal symptoms after cocaine use (the 77% above), the most frequent interval endorsed since last heroin use as "1-6 hours" (66.7%) (see figure 1). Frequency and severity of specific symptoms is also reported (see figure 2). A minority of subjects questioned (37%) stated that cocaine "relieved opiate withdrawal" if they used cocaine after opiate withdrawal symptoms had begun, and that relief occurred only while they were high from the cocaine administration and lasted 1/2 to 1 hour. After this period opiate withdrawal symptoms were even more severe than those usually experienced. These observations suggest that a large proportion of opiate addicts experienced symptoms they identify as opiate withdrawal after cocaine use. A smaller proportion can also experience relief of these symptoms after cocaine use. The short duration of this latter effect, only experienced during euphoria, suggests that the cocaine high masked rather than attenuated opiate withdrawal symptoms. We propose a noradrenergic mechanism for this effect: acute cocaine may exacerbate the noradrenergic hyperactivity associated with opiate abstinence. This hypothesis should be tested experimentally, using appropriate adrenergic ligands such as yohimbine.

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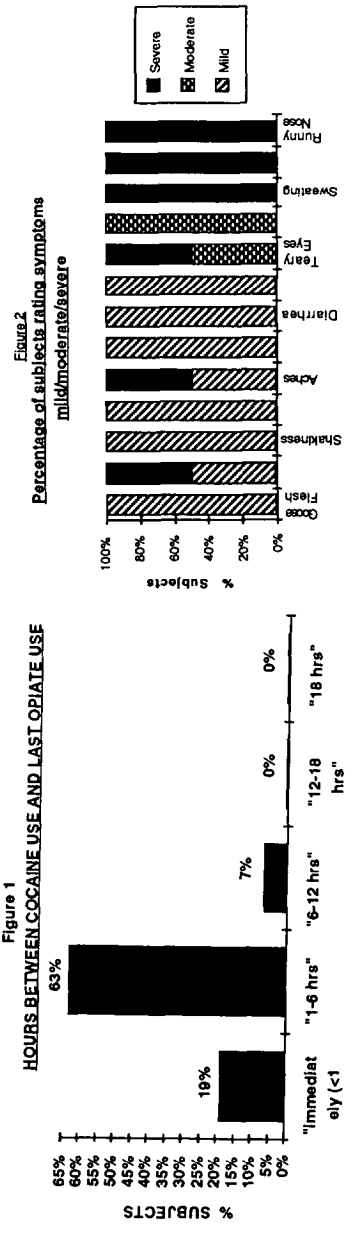

ENHANCED COCAINE EFFECTS DURING METHADONE MAINTENANCE

K. L. PRESTON; J. T. SULLIVAN; E. C. STRAW AND G. E. BIGELOW

Cocaine abuse has become a serious problem among methadone maintenance patients. The present study was conducted to determine whether methadone maintenance alters the pharmacological effects of cocaine. Twenty current users of IV cocaine who were not seeking treatment for their cocaine abuse participated while living on a research unit. Ten were receiving methadone 50 mg p.o. daily as treatment for their opioid abuse; ten were opioid abusers who were not physically dependent on opioids and who provided opioid-free urines throughout the study. There were no differences between the two groups on race, weight, years of cocaine or opioid use, or current frequency of illicit cocaine or opioid use. Acute IV cocaine challenge doses of 0, 12.5, 25, and 50 mg were given in randomized order under double-blind conditions. Physiologic and subject-rated responses were measured pre-injection and for 2 hr after the injection. In the maintenance group, cocaine challenge sessions occurred 15.5 hr after the daily methadone dose. Cocaine significantly increased heart rate and blood pressure and ratings of Drug Effect, Rush, Good Effects, Liking and Desire for Cocaine. There were significant differences between the methadone-dependent and nondependent groups that could be categorized into two types: 1) Differences related to chronic methadone administration and not associated with changes in response to cocaine (respiration, skin temperature and pupil diameter) and 2) Differences due to modulation of the response to cocaine (Drug Effect, Rush, Good Effects, Liking, Desire for Cocaine and heart rate). Cocaine-induced increases in Drug Effect, Rush, Good Effects, Liking, Desire for Cocaine and heart rate were greater in the methadone maintenance patients compared to the nondependent group. These results indicate that the effects of cocaine may be enhanced in methadone maintained individuals, suggesting a pharmacological basis for the high rates of cocaine abuse among methadone maintenance patients. Supported by USPHS grants DA-05196 and DA-00050.

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INTRAVENOUS COCAINE CHALLENGES DURING NALTREXONE MAINTENANCE

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An earlier human study had suggested that naloxone augmented the acute reinforcing effects of cocaine (Byck et al., 1982), but more recent primate work has found an attenuation of cocaine self administration with naltrexone and buprenorphine, a partial opioid agonist (Mello et al., 1991). To examine this issue intravenous challenges with placebo and three cocaine dosages ranging from 0.125 to 0.5 mg/kg were administered to five subjects using a "within subjects" design during placebo and active naltrexone (NTX) maintenance at a fixed dose of 50 mg daily for at least ten days. The dollar "value of drug given" reported after cocaine was decreased under the NTX condition. Physiologically, peak heart rate after cocaine was higher on NTX than on placebo, but there were no significant differences in blood pressure between the NTX and placebo conditions. Thus, as demonstrated in recent primate studies, chronic naltrexone appears to attenuate acute cocaine reinforcement.

Supported by NIDA DA04060, DA001112 (TRK).

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BUPRENORPHINE ATTENUATES DRUG CRAVING IN MEN WITH CONCURRENT HEROIN AND COCAINE DEPENDENCE

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Persistent craving for heroin, cocaine, and concurrently both drugs "speedball" is often associated with high probability of relapse to drug self-administration in dually-dependent heroin and cocaine abusers. We have evaluated the effectiveness of buprenorphine in reducing drug craving in a controlled, inpatient treatment research unit. Twenty men (mean age =33) were admitted to the clinical research ward for methadone detoxification and remained on the unit for 30 days. The first 9 days were drug-free followed by administration of ascending doses of sublingual buprenorphinc (for a total dose of 4 or 8 mg per day) during 5 consecutive days. Subjects were then maintained on buprenorphine for 15 consecutive days prior to discharge to an outpatient buprenorphine treatment program. During the 30 day inpatient period, subjects were requested to provide reports of their craving for cocaine, heroin and speedball every thirty minutes between 8 a.m. and 11:30 p.m. A total of 17,649 half-hourly reports were submitted representing a 95% completion rate for the 20 men. Subjects were also asked to complete and submit a craving intensity scale ("not at all" to "overwhelming"), a craving scale relating to high-risk situations and a craving scale relating to drug cues. Significant (p=0.0001) decrements in heroin craving were observed over the course of the study on all 4 self-reports. There was a significant (p=0.0001) increment in craving for no drug. There were significant decrements in craving for cocaine (p=0.0001) and speedball (p=0.0001) on the 3/4 craving scales. Baseline heroin craving scores were usually the highest and decreased the most over the course of buprenorphine treatment. Baseline cocaine craving tended to be lower than heroin and "speedball" craving scores and the decrements in craving were the smallest. Decreases in craving for heroin tended to occur earlier than decreases in cocaine and speedball craving scores. Decreases in craving for either heroin, cocaine or "speedball" also tended to occur earlier in subjects on 4 mg than those on 8 mg of buprenorphine. However, this difference between 4 mg and 8 mg of buprenorphine did not reach significance. The magnitude of decrease in craving on the 30 minute assessments, the Daily Diary, the High-Risk Environment Scale and the Conditioned Cues Scale were 58%. 55%, 56% and 61% respectively for heroin, 0%, 19%, 47% and 20% respectively for cocaine and 1%, 32%, 53% and 36% respectively for speedball.

ACKNOWLEDGMENT:

This research was supported by NIDA grant DA06116.

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EFFECTS OF ACUTE BUPRENORPHINE ON RESPONSES TO INTRANASAL COCAINE

M. I. ROSEN; H. R. PEARSALL; C. J. MCDOUGLE; L. H. PRICE; S. W. WOODS AND T. R. KOSTEN

Five patients addicted to both intravenous cocaine and heroin were admitted to the hospital and detoxified from opiates. Patients intranasally self-administered among of cocaine before being randomized to start 5 days of double dummy treatment with active buprenorphine 2mg/d sublingually and placebo benzotropine, or the converse, with cocaine challenges on days 3 and 5. Patients were crossed over to the opposite condition with cocaine challenges again repeated on day 3 and 5.

Results: Several trends which did not reach statistical significance were noted Buprenorphine appeared to enhance patients' ratings of cocaine-induced pleasurable effects and to reduce dysphoric effects. Cocaine-induced pulse, SBP, and DBP were numerically greater on buprenorphine. Buprenorphine's enhancement of cocaine effects appeared to be more prominent on day 3 than on day 5, suggesting that cocaine may interact differently with acutely vs. chronically administered buprenorphine.

This work was done at the Treatment Research Unit, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508

ACUTE INTERACTIONS OF BUPRENORPHINE WITH INTRAVENOUS COCAINE AND MORPHINE

S. K. TEOH; J. H. MENDELSON; N. K. MELLO; J. KUEHNLE; P. SINTAVANARONG AND E. RHOADES

Recent preclinical and clinical studies suggest that buprenorphine, an opioid mixed agonist-antagonist, may be useful for the treatment of dual dependence on cocaine and opiates. This report describes an inpatient clinical evaluation of the safety of buprenorphine alone and in combination with single doses of cocaine and morphine. Twenty subjects with a DSM-III-R diagnosis of concurrent cocaine and opioid dependence were randomly assigned to maintenance treatment with 4 or 8 mg of sublingual buprenorphine for 21 days. The physiological effects of a single-blind challenge dose of cocaine (30 mg/i.v.), morphine (10 mg/i.v.) and i.v. saline placebo were measured before and during buprenorphine maintenance. Cardiovascular responses to cocaine and to morphine were equivalent under drug-free and buprenorphine maintenance conditions. Respiration and temperature changes in response to cocaine were also equivalent before and during buprenorphine maintenance. Respiratory rates were slightly lower following morphine administration during maintenance on 8 mg buprenorphine, but this was not statistically significant. EKG and blood chemistry measures were normal before and during buprenorphine maintenance. These data suggest that daily maintenance on buprenorphine is not associated with adverse side effects or toxic interactions with an acute dose of intravenous cocaine or morphine.

ACKNOWLEDEGEMENTS

This research was supported in part by Grants DA 00101, DA 00064 and DA06116 from the National Institute on Drug Abuse. We are grateful to the staff on the NIDA Treatment Research Unit at the Alcohol and Drug Abuse Research Center, McLean Hospital for their many contributions to these studies.

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EVOKED POTENTIAL EXCITABILITY CYCLES DURING EARLY COCAINE ABSTINENCE

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Somatosensory evoked potential (SEP) excitability cycles, using right median nerve stimulation, were recorded in a sample of 22 early abstinent chronic cocaine abusers. These male subjects could be classified into three groups based on their respective duration of abstinence at the time of the first SEP recording session (DDF): 1) less than 8 days abstinent (N=10); 2) 10 to 21 days abstinent (N=6); 3) greater than 25 days abstinent (N=6). They were compared to 8 age-matched male controls using SEP amplitude ratios for ISIs 5, 10, 15, 20, 35, 55, and 90 msec. Repeated measures analysis of variance for each ISI used recording site (20 leads) as repeated measures and the four groups as the between groups measure. Data for the analyses were the ratios of R2 to R1 SEP amplitudes from each scalp lead at 14, 19, 23, 27, 31, and 45 msec post-stimulus for a given ISI. Recording site (20 leads of 10/20 system) were repeated measures and the four groups the between groups measure. Significant main effects for groups or significant lead by group interactions were found for P14, P23, P27, and N30. The majority of these effects involved ISIs between 5 and 20 msec and the 55 msec ISI. During both 23 msec and 27 msec activity and at all six ISIs, all DDF groups had greater than normal recovery activity contralaterally, and less than normal recovery ipsilaterally. This was particularly so for both the less than 8 DDF and the 10 to 21 DDF groups. At 55 msec ISI, marked facilitation was seen.

These preliminary data on cocaine abstinent abusers, suggests differences in SEP recovery between contralateral and ipsilateral scalp regions in relation to the duration of of abstinence; particularly in those abstinent between 10 and 21 days. The data support the viability of SEP recovery cycle studies in demonstrating CNS alterations subsequent to chronic cocaine use. The conceptual framework for SEPs and recovery cycle profiles assumes addictive neurophysiological interactions between synaptic potentials of neurons and their influences. Excitatory synaptic activities at basal dendrites of deep cortical pyramidal cells are suggested to be responsible for negative components of the evoked potential. Positive components appear to be related to activation of apical dendrites on superficial pyramids. If this is the case, then the marked contralateral facilitation of 23 and 27 msec activity implicates projections into layers I and II. These are also where major extrathalamic subcortical projections ramify. These extrathalamic subcortical nuclei contain cells of origin of the major catecholamine systems of the central nervous system. Chronic use of cocaine is thought to down regulate the catecholamine systems. The extent to which 23 and 27 msec facilitation in early abstinent subjects is directly related to such down regulation awaits further study.

Supported, in part, by DA06728 from NIDA and MH12507 from NIMH.

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A COMPARISON OF THE ARTERIAL KINETICS OF SMOKED AND INTRAVENOUS COCAINE

S. M. EVANS; E. J. CONE; A. P. MARCO AND J. E. HENNINGFIELD

Smoked cocaine ("crack") is widely thought to have greater addictive effects than other routes of cocaine administration, including intravenous administration. This could be due to 1) the possibility that smoked cocaine is delivered more rapidly and efficiently to the brain than intravenous cocaine and/or 2) nonpharmacological aspects of stimuli associated with smoking. The purpose of the present study was to directly compare the kinetics of intravenous and smoked cocaine in both arterial and venous blood, while measuring standard subjective and physiological effects. Male subjects, with recent histories of both intravenous and smoked cocaine, participated. One session day consisted of 4 smoked cocaine sessions spaced 90 minutes apart in ascending order (sham, 12.5, 25, 50, mg "crack"). The other session day consisted of 4 intravenous cocaine sessions spaced 90 minutes apart in ascending order (0,8,16,32 mg). For the two highest doses of each route of administration measures were taken at the following times: predrug, 5 sec into drug administration, at the completion of drug administration (Time 0) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 15, 20, 30, 45, 60, 75 and 90 min after the completion of drug administration. At each of these times the following measures were taken simultaneously: arterial blood samples, venous blood sample, heart rate, blood pressure, and visual analog ratings of subjective effects. Preliminary results from 2 subjects indicate the arterial cocaine concentrations can be substantially increased relative to venous cocaine concentrations, for both routes of administration. These high arterial concentrations may contribute to the cardiotoxicity and high addictiveness of cocaine.

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COMPARISON OF INTRAVENOUS COCAINE ON BLOOD FLOW IN THE PERIPHERAL AND PULMONARY CIRCULATIONS

J. T. SULLIVAN; K. L. PRESTON; P. M. BECKER; R. A. WISE; F. WIGLEY AND D. R. JASINSKI

Diffusing capacity for carbon monoxide (Dco) is low in cocaine users but normalizes with abstinence. Since cocaine has vasoconstrictive properties in the peripheral circulation (as demonstrated by fall in skin temperature), we hypothesized that cocaine might also cause pulmonary vasoconstriction leading to a reduction in DCO. Twelve adult males with histories of drug abuse received 0, 25 or 50mg of iv cocaine, on 3 consecutive test days. Doses were administered double blind, according to four 3 x 3 latin squares. Single breath Dco was measured in duplicate 10 and 20 min before, and 5 and 10 min after infusion. Indices of peripheral circulation were determined by continuous measurement of digital cutaneous blood flow (as measured by laser doppler flowmetry) and skin temperature. Subjective, behavioral and cardiovascular responses (RR and BP) were also determined. Results showed that cocaine prevented the fall in Dco seen after placebo ($p<.05$). This was related to increased CO back pressure due to repeated measurements. Accordingly the results suggest that iv cocaine increases pulmonary capillary blood volume at the time of maximum central and peripheral effects. Cocaine significantly decreased skin blood flow and temperature in a dose related manner, with a significant lag in temperature changes as compared to blood flow changes. The plot of change in blood flow vs change in temperature shows a clockwise hysteresis curve. Cocaine also showed typical subjective, behavioral, chronotropic and pressor responses. The results suggest that; the peripheral circulation is more sensitive to cocaine than the pulmonary circulation; that redistribution of blood, from the peripheral to the central circulation (due to vasoconstriction) may attenuate the effects of cocaine on the pulmonary circulation. Other potential explanations for the increase in Dco include an increase in cardiac output or a differential vasoconstrictor response on pulmonary veins leading to an increase in capillary blood volume.

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Concurrent Cocaine-Ethanol INGESTION IN HUMANS: PHARMACOLOGY, PHYSIOLOGY, BEHAVIOR, AND THE ROLE OF COCAETHYLENE

E. F. McCance-Katz; L. H. Price; C. J. McDougle; T. R. Kosten and P. I. Jatlow

Simultaneous abuse of cocaine and ethanol is a common occurrence. Cocaethylene (EC), the ethyl ester of benzoylecgonine, has been detected in the urine of patients reporting concurrent use of cocaine and ethanol, and high levels have been found in the blood of victims of fatal drug overdose. Like cocaine, EC binds to the dopamine transporter, blocks dopamine uptake, and causes increased extracellular concentrations of dopamine in the nucleus accumbens following systemic administration.

A pilot study was undertaken to evaluate the interaction of cocaine and ethanol in humans and lo prospectively document the formation of EC. Four cocaine/ethanol challenges were administered in a randomized, double-blind sequence to each subject (n=6) over an 8-day period. The four test days included the following drug administration schedule: cocaine (2mg/kg) ethanol (1g/kg); cocaine (2mg/kg)/ethanol placebo; cocaine placebo/ethanol (1g/kg); cocaine placebo/ethanol placebo. Cocaine administration was intranasal followed by oral ethanol administration. Physiological and subjective (visual analog scales, "High" scale) measures, plasma cocaine, EC, and ethanol levels were assessed.

EC was found in the plasma only following administration of both cocaine and ethanol. EC was initially detected in the 30 min sample at a plasma concentration of 10 ± 4 ng/ml (mean ± SEM), with peak plasma concentrations of 62 ± 7 ng/ml occurring at 115 ± 9 min. Peak EC concentrations were found to be approximately 115 those of cocaine. The apparent elimination half-life of EC was 148 ± 15 minutes, about twice that observed for cocaine Cocaine levels following cocaine/ethanol administration were significantly higher than during cocaine alone ($p<0.001$), but elimination constants for cocaine under the two conditions were approximately equal. Heart rate was significantly increased following cocaine/ethanol administration as compared to that of cocaine alone ($p<0.002$) or ethanol alone ($p<0.001$). Euphorogenic effects (cocaine "high" and overall "high") were both enhanced and prolonged following active cocaine/ethanol administration. Cocaine/ethanol produced a greater overall "high", which was sustained for the entire 360-minute test session and was significantly greater than the overall "high" state reported for the other test conditions (cocaine/ethanol vs. cocaine/placebo ethanol $p<0.014$, cocaine/ethanol vs. placebo cocaine/ethanol $p<0.025$).

This study prospectively contirms that cocaethylene is formed in humans engaging in concurrent use of cocaine and ethanol. Plasma cocaine concentrations were greater following cocaine/ethanol administration. Euphorogenic effects were both enhanced and prolonged, and heart rate was significantly increased following cocaine/ethanol administration as compared to administration of cocaine or ethanol alone. Our data suggest that cocaethylene may accumulate relative to cocaine during binge use.

ACKNOWLEDGEMENTS

Supported in part by grants DA-04060, DA-00112, MH-25642, MH-30929 from the U.S. Public Health Service and by the Department of Mental Health, State of Connecticut.

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EFFECTS OF THE INTERACTION BETWEEN ETHANOL, AND PSYCHOSTIMULANT DRUGS ON HUMAN PSYCHOMOTOR PERFORMANCE

M. PEREZ-REYES

Consumption of ethanol produces consistent decrements in psychomotor performance. Frequently, however, ethanol is consumed in combination with CNS stimulant drugs which theoretically should antagonize its decremental psychomotor effects. We have investigated the effects of the interaction between a fixed oral dose of ethanol (0.85 g/kg) and either two dose levels of oral dextroamphetamine (0.09 and 0.18 mg/kg) or snorted cocaine (1.25 and 1.9 mg/kg). Male, paid volunteers, familiar with the effects of the study drugs, were tested in a placebo-controlled, single-blind, randomly-assigned, latin-square, cross-over design. The following variables were measured: subjective ratings of ethanol, dextroamphetamine, and cocaine intoxication; cardiovascular parameters; accuracy and latency of response in the Simulator Evaluation of Drug Impairment (SEDI task): blood ethanol levels by breath analyzer; and plasma concentrations of dextroamphetamine, cocaine, and cocaethylene by gas chromatography. Results indicate that ethanol significantly increased the ratings of dextroamphetamine and cocaine "high" as well as the heart rate accelerating effects of both drugs. Neither dextroamphetamine nor cocaine decreased the subjective ratings of ethanol intoxication. Dextroamphetamine, in a dose-response fashion, significantly decreased the ethanol-induced decrements in performance. Surprisingly, neither dose of cocaine was able to antagonize this decremental effect of ethanol.

Supported by Grant DA04484, National Institute on Drug Abuse.

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ETHANOL, PENTOBARBITAL AND INDOMETHACIN INTERACTIONS IN HUMAN VOLUNTEERS

W. B. Pickworth, E. B. Bunker, N. Snidow, J. Nichels and J. E. Henningfield

Results from animal studies suggest that prostaglandin synthesis inhibitors (PGSIs) such as indomethacin diminish some of the behavioral and physiologic effects of ethanol. The purpose of this study was to determine if pretreatment with indomethacin altered ethanol- or pentobarbital-induced changes in, subjective, physiologic or performance effects in humans. Six volunteers were pretreated with placebo or indomethacin (0.166, 0.347. 0.66 and 1.33 mg/kg) 1 hr before ethanol (1 Gm/kg consumed over 15 min). In the same subjects, indomethacin (0.66 mg/kg) or placebo was given 1 hr before pentobarbital (1.33 and 4.0 mg/kg, orally). Physiologic, subjective and performance measures were collected before any drug, the pretreatment and up to 4 hrs after ethanol or pentobarbital.

Indomethacin alone had no significant effects on any of these measures. Blood alcohol levels peaked at 120 mg %, a level that caused significant performance decrements and subjective effects. Indomethacin did not change the peak level of blood alcohol. The lower doses of indomethacin diminished ethanol-induced increases in PCAG scores, drug liking, bad effects and tired scales. Decreases in DSST accuracy and speed after ethanol were prevented by lower doses of indomethacin and the pretreatment improved hand steadiness and card sorting. The performance impairment caused by ethanol on the letter search and rapid arithmetic tasks was not prevented. Indomethacin did not prevent the increases in PCAG and drug liking scores after the high pentobarbital dose. Indomethacin exaggerated the subjective effects and performance impairment induced by the lower dose of pentobarbital. Taken together, indomethacin antagonism was small, irregular, and not dose related. While the results support a palliative role of PGSIs on ethanol-induced performance and subjective effects, their magnitude does not appear to be of clinical significance. Furthermore, it appears that many performance and subjective effects of pentobarbital and ethanol are not mediated through prostaglandin-dependent processes.

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SUBJECTIVE AND PSYCHOMOTOR EFFECTS OF FLUNITRAZEPAM IN HEALTHY VOLUNTEERS

M. T. Teran, M. Farre, X. Lamas, B. Ugena and J. Cami

Flunitrazepam is a benzodiazepine derivative used as hypnotic drug that is marketed in several European countries. Epidemiological surveys in Spain and Malaysia indicate that flunitrazepam is misused by opioid dependent subjects in order to relieve abstinence symptoms and to obtain "high". The present study was designed to characterize the subjective and psychomotor effects of flunitrazepam and to provide information about the doses useful in future studies on drug abuse liability.

METHODS: Ten healthy male volunteers without history of drug abuse or dependence participated in the study. They received in an outpatient setting single doses of flunitrazepam (1,2 mg), diazepam (5 mg), d-l-amphetamine (10 mg), and placebo. The study design was randomized, double-blind, and cross-over. Drug effects were evaluated using performance objective tasks (DSST, balance, Maddox-Wing), subjective effects questionnaires (49-item ARCI, 72-item POMS, visual analog scales, drug identification), and physiological measures (blood pressure, heart and respiratory rate).

RESULTS: Flunitrazepam produced dose-related effects on subjective and behavioral measures. Both doses impaired the performance on DSST and balance with increases in the PCAG scale. The 2 mg dose produced increases in ratings of "bad effects" and "drunkenness". No differences were found between placebo, diazepam, and amphetamine except for scores of the BG scale (increased by amphetamine). Subjects identified both doses of flunitrazepam as a sedative (90% and 100% for 1 and 2 mg), the dose of 5 mg of diazepam as placebo (60%) or sedative-stimulant (20%-20%), and the dose of 10 mg of d-l-amphetamine as placebo (50%) or stimulant (50%). Placebo was correctly identified in 70% of cases.

CONCLUSIONS: Flunitrazepam 1 mg and 2 mg produced sedative dose-related effects, with an impairment of the psychomotor performance. These effects seems to be aversive in healthy volunteers.

*This study was supported by grants FIS 91/0686 and CITRAN.

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SENSITIVITY TO NICOTINE IN SMOKERS AND NEVER-SMOKERS

O. F. POMERLEAU; C. S. POMERLEAU; O. G. CAMERON AND M. HARIHARAN.

Using an intranasal aerosol method to administer controlled doses of nicotine, we compared sensitivity to nicotine in never-smokers with sensitivity in a) minimally-deprived smokers and b) overnight-deprived smokers, using change in heart rate as an index. **Never-smokers vs. minimally-deprived smokers.** Subjects were 10 never-smokers and 10 dependent smokers; there were no significant differences in age or Body Mass Index (BMI=Kg/m^2) between the 2 groups, and both sexes were equally represented. A 50 µl spray (7 psi for < 1 sec) of a sterile aqueous solution of nicotine bitartrate was administered intranasally (one spray per nostril) in less than 5 sec. Intranasal administration of nicotine produced an immediate sharp rise in plasma nicotine followed by decay, resembling the pattern associated with cigarette smoking. A dose of 1.50 mg nicotine produced a peak plasma nicotine increment of 11.5 ± 2.3 ng/ml (mean ±s.e.m.) in the smokers. The first 3 never-smokers received 0.50 mg nicotine, which produced a peak plasma nicotine increment of 12.0 ±5.8 ng/ml; the remaining 7 received 0.25 mg nicotine, which resulted in a peak plasma nicotine increment of 7.5 ± 1.2 ng/ml. The ratio of peak plasma nicotine increment per unit dose of nicotine was 28.1 ±3.9 ng/ml/mg in the never-smokers and 7.7 ± 1.5 ng/ml/mg in the smokers ($t = 4.90$; $p = .000$). This finding suggests that the smokers were more pharmacokinetically tolerant to nicotine than never-smokers. In order to correct for the difference in plasma nicotine accumulation in comparisons of pharmacodynamic (functional) sensitivity between smokers and never-smokers, we divided physiological reactivity (peak change in heart rate) by peak change in plasma nicotine for each subject. In the smokers, sensitivity to nicotine was inversely related to cotinine level ($r = -.69$, $p = .028$), indicating that heavy smokers were less sensitive to nicotine than light smokers, as predicted. Surprisingly, however, the average sensitivity to nicotine for never-smokers was *similar* to that of the smokers; we had expected that both light and heavy smokers, having had years of exposure to nicotine, would show considerably less sensitivity to nicotine than never-smokers--i.e., they would exhibit extensive functional tolerance. **Never-smokers vs. overnight-deprived smokers.** Smokers in the above comparison were tested in the context of *ad libitum* smoking. To minimize the possible effects of acute tolerance, we compared the 5 male never-smokers with 12 male smokers--6 light smokers (cotinine < 100 ng/ml) and 6 heavy smokers (cotinine > 100 ng/ml)--who had abstained from smoking overnight. The three resulting groups *were* similar with respect to age and BMI. The smokers received 1.00 mg nicotine; although all the never-smokers had received 0.25 mg nicotine, plasma nicotine boost was very similar across groups (8.9±2.6, 6.9 ±1.3, and 7.5 ±1.7 ng/ml in heavy smokers, light smokers, and never-smokers respectively)--replicating our observation of greater pharmacokinetic tolerance in smokers. We found that the heavy smokers were actually *more* reactive to nicotine than either light smokers or never-smokers (heart rate boost was 22.7 ±4.3, 18.7 ±3.8, and 14.2 ±3.9 bpm, respectively). **Conclusion.** Overall, these findings suggest that persons who become smokers may actually be constitutionally more sensitive to nicotine than people who do not take up the habit. Thus, individual differences in sensitivity *prior* to exposure to nicotine may play a greater role in determining subsequent smoking status and nicotine dependence than has been previously recognized.

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OCULAR MEASURES AND MARIJUANA DETECTION IN HUMANS

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Changes in static and dynamic pupillary measures (diameter before and after a light flash, amplitude of constriction, and constriction velocity) are not strongly correlated with drug-induced changes in cognitive and motor performance or subjective effects (Pickworth et al, CPDD 1991). In the present study, two recently developed instruments were evaluated for their ability to detect marijuana-induced changes: the PPA (Pulse Medical Instruments) measured Maxwellian Stimulation pupillary response and anisocoria; and the EM/2 (Drug Detection Systems) measured horizontal and vertical nystagmus, bilateral monocular smooth pursuit tracking and pupillary escape. These ocular and pupillary measures were collected before and up to 24 hr after subjects smoked a marijuana cigarette containing 0, 1.8 or 3.6% THC. Dose conditions were quasi-randomly presented to ten adult male residential volunteers in a double blind fashion. Treatments were separated by at least 48 hours.

Response to a series of alternating (generic swing) Maxwellian (open-loop, fovial targeted) light flashes was significantly changed by the high dose of THC: amplitude of constriction, time to 50% recovery, and constriction and dilation velocities decreased; whereas initial diameter and constriction latency increased.

The high dose of THC significantly diminished responses to prolonged (5 and 8 sec) light stimuli, causing a 16% increase in minimum and final diameter, and mean diameter during pupillary escape. Prestimulus diameter, hippus and slope of recovery (escape) were, however, not significantly altered. Averaged angular velocity during horizontal monocular smooth pursuit tracking decreased after THC administration and persisted for up to 4 hours post-drug.

These results extend previous findings that marijuana causes ocular changes in humans. However, ocular measures are not well correlated with performance measures in individual subjects -- suggesting a limited utility for their use in impairment screening.

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CEREBRAL EVOKED POTENTIALS IN CHRONIC MARIJUANA USERS

J. STRAUMANIS, F. STRUVE AND G. PATRICK

Cognitive (P300), auditory (AEP), right and left somatosensory (RSEP, LSEP), and visual (VEP) evoked potentials were evaluated in two groups of chronic marijuana users and a psychiatrically screened control group. One group (long term) had smoked marijuana for over 15 years, the other (moderate) for 3-6 years. Subjects were matched for age and sex for two comparisons; one comparisons; one comparing 13 long term users with 13 moderate users and 13 controls, the other comparing 18 moderate users with 18 controls. The auditory and visual P300 was elicited with a "oddball" paradigm where the target stimulus occurred 15% of the time. AEP was elicited with 80 db binaural clicks, SEP with 0.1 MSEC 10 MA above threshold shocks over R and L median nerve, VEP with checkerboard reversal. Latency and amplitude of selected EP peaks was measured: (1) P300-NI, P2, N2, P3 (2) AEP-P30, N1, P2, N2, (3) SEP-N18, P40, N60, P90, N140, P180, (4) VEP-P100.

Controls vs. Moderate Users: (1) AEP-no significant amplitude, latency differences. (2) VEP-no significant latency or amplitude differences. (3) RSEP and LSEP-no significant amplitude differences. Prolonged RSEP N140 and P180 latencies THC group (13 1 vs. 146 MSEC; 175 vs. 2 16 MSEC). Prolonged LSEP P180 latency, trend for N140 in THC group (174 vs. 211 MSEC; 134 vs. 141 MSEC). (4) P300-no latency differences, smaller P30 amplitude in THC group. Aud P300 (11.3uv vs. 7.6uv). Vis P300 (8.3uv vs. 6.2uv).

Controls vs. Moderate Users vs. Long Term Users: (1) AEP-no significant amplitude or latency differences cxcept for larger P1 in long term users (2) VEP-no significant amplitude or latency differences (3) RSEP and LSEP-no significant latency differences except for longer P180 in moderate and long term users. No significant amplitude differences except for larger RSEP P180 amplitude in long term users (4) P300-no latency differences and only a trend for P300 amplitude reduction with THC. We did not replicate the previously noted P300 latency increase with THC. We did replicate the reduced P300 amplitude seen previously with patient THC users. There were no obvious P300 topographic differences between the groups. SEP P90, N140, P180 and AEP N1 and P2 amplitudes are reduced in schizophrenia (cognitive disorder), and P300 latency is prolonged in schizophrenia and dementia. We expected, but did not find, similar changes with chronic THC use.

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GENETIC DIFFERENCES IN THE DEVELOPMENT AND PERSISTENCE OF THE ANTICONVULSANT EFFECTS OF CARBAMAZEPINE AGAINST COCAINE SEIZURES

K. SHIMOSATO, S. R. GOLDBERG AND R. J. MARLEY.

Cocaine is capable of inducing convulsions in animals and humans. Furthermore, there are genetic differences in susceptibility to cocaine-induced seizures. Carbamazepine (CBZ) is widely used for treatment of various forms of convulsive disorders and it has been suggested that CBZ may be useful for the treatment of some of cocaine's toxic side effects. Recent studies in our laboratory have shown that CBZ acts to inhibit cocaine-induced seizures in a genotype-specific manner. In these studies, however, the duration of CBZ treatment appeared to be an important determinant of its efficacy for inhibiting cocaine-induced seizures. The present studies were initiated to investigate the time course for the development and persistence of the anticonvulsant effects of CBZ against seizures induced by the acute administration of cocaine. We have employed a pharmacogenetic approach using the same animal models (BALB/cByJ, C57BL/6J, and SJL/J) that we had previously characterized for differences in response to cocaine and CBZ. The levels of CBZ and its active metabolite, CBZ-10, 11-epoxide, in plasma and brain tissue at various time points during and after chronic CBZ administration were also determined. There were genetic differences associated with the anticonvulsant effects of CBZ against cocaine-induced seizure. The most notable difference between the genotypes was the observation that the mechanisms underlying CBZ's anticonvulsant effects were much less labile in BALB mice, than in the C57 or SJL mice.

The development and persistence of the anticonvulsant effects of CBZ against cocaine seizures were indeed dependent on the duration of CBZ administration. From two to seven days of chronic CBZ treatment were required to achieve maximal anticonvulsant efficacy. However, once the anticonvulsant effects of CBZ were manifest, these effects persisted for up to 5 days after stopping CBZ treatment. Furthermore, there was a negative relationship between seizure susceptibility and the levels of CBZ and CBZ-10, 11-epoxide in plasma and brain, such that lower levels of CBZ and CBZ-10, 11-epoxide were associated with an increased resistance to cocaine seizures. The levels of CBZ and CBZ-10, 11-epoxide decreased to undetectable levels over the duration of the treatment period, presumably due to the auto induction of the enzymes responsible for the metabolism of CBZ and CBZ-10, 11-epoxide following chronic CBZ administration. These studies suggest that the increased resistance to cocaine seizures observed following chronic CBZ administration could result from changes in the pharmacokinetic mechanisms responsible for the metabolism and/or distribution of cocaine. We have speculated that CBZ auto-induction of the P-450 isozyme, responsible for cocaine oxidative metabolism, may be responsible for the decreases in cocaine seizure susceptibility following chronic CBZ.

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1-PHENYLCYCLOALKANECARBOXYLIC ACID DERIVATIVES AS POTENTIAL ANTICONVULSANT AGENTS

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Carbetapentane (CBP, 2-[2-(diethylamino)ethoxy]-ethyl-1-phenyl-1-cyclopentyl carboxylate) is an antitussive drug that demonstrates anticonvulsant activity in the rat maximal electroshock (MES) test and potentiates the anticonvulsant action of the prototypic antiepileptic drug diphenylhydantoin. The mechanism of its pharmacologic actions are unknown. Carbetapentane binds to high and low affinity binding sites labeled with [^{3}H]Dextromethorphan and it has been speculated that the anticonvulsant activity of this drug may be mediated through one or both of these sites.

A series of analogs based on CBP was prepared as potential novel anticonvulsant drugs and as pharmacological tools to study the as yet undefined relationship between dextromethorphan, phencyclidine (PCP) and sigma binding sites. Analogs were prepared in which the ester function was replaced with a methylene ether, an amide, or either a secondary or tertiary methylene amine. The cycloalkyl ring was increased in size to a cyclohexyl ring, decreased to a cyclopropyl ring or eliminated. Mono-substituted phenyl ring analogs were also prepared. These compounds were first evaluated for their ability to protect against seizures in the rat MES test.

In this series of compounds three of the analogs were effective anticonvulsants, with the ether derivative being more potent than the parent compound. Optimum structural features for anticonvulsant activity are a cylopentyl ring, an unsubstituted phenyl ring and either an ester or ether linkage. All other modifications explored resulted in inactive compounds. The most potent anticonvulsant agent (ether analog) in this test was further evaluated in other models of convulsive action including the flurothyl seizure threshold and NMDA-induced seizure models, in rats. In the flurothyl model, CBP is proconvulsant at 4-times it's MES ED_{50} dose and the ether analog has no effect at doses up to 7-times it's MES ED_{50}. Results of preliminary experiments indicate that centrally administered CBP and the ether analog fail to prevent NMDA convulsions but effect a small delay to their onset. The binding profile of these analogs at dextromethorphan, sigma and PCP sites is currently being investigated to determine whether a functional correlate exists between anticonvulsant activity and receptor binding affinity.

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COMPARISON OF EEG CHANGES WITH RECURRENT EXPOSURE TO MORPHINE AND COCAINE

K. GRASING AND Q. T. LIN

Exposure to either cocaine or opioids can produce an alert EEG with active behavior. The effect of opioids on arousal is biphasic: a desynchronized EEG and increased motor activity occurs after treatment with low doses, while EEG amplitude is increased with stuporous behavior following relatively high doses. With repeated doses, opioid excitatory effects become more pronounced. Also, reductions in EEG power occur to a greater extent in animals that contingently self-administer morphine than in yoked-control subjects that passively receive an identical pattern of drug infusions.

Adult male Sprague-Dawley rats with chronically implanted cortical EEG electrodes received increasing daily doses of cocaine or morphine, administered as an intravenous infusion over six hours. The EEG was continuously digitized at 256 Hz for four second epochs with Fast Fourier Transformations performed on-line. Epochs with excessive spectral amplitude across 0.0 to 1.0 Hz were rejected as artifact. EEG power and power spectra were normalized by obtaining the percent change during drug treatments relative to predrug periods. Ultradian variability was obtained through the standard deviation of total power during drug infusions. Independent one-way ANOVA's were performed across EEG measures for effects of dose on EEG power and variability.

Both morphine and cocaine markedly reduced ultradian variation in the EEG, with morphine being slightly more potent for this effect.

EEG power was reduced by intermediate doses of either morphine or cocaine. However, treatment with cocaine resulted in greater reductions in EEG power. Power spectra at these doses were similar for both agents, and resembled spectra from alert control periods. The highest dose of morphine administered (10 mg/kg-hr) caused large increases in EEG power that were not observed after high doses of cocaine.

In conclusion, similarities exist between the excitatory EEG effects of intermediate doses of morphine and cocaine. However, cocaine reduces EEG power to a greater extent than cocaine, while morphine is slightly more potent in reducing ultradian variability in EEG power. Affiliation: Depts of Med. & Clin. Pharmaco., R. W. Johnson Sch. of Med., New Brunswick, NJ

EFFECTS OF CHRONIC MORPHINE ADMINISTRATION AND NALOXONE ON EEG, EEG POWER SPECTRA AND BEHAVIOR IN TWO INBRED RAT STRAINS

L. MAYO-MICHELSON AND G. A. YOUNG

Utilizing behavioral and electroencephalographic (EEG) assessments, two inbred rat strains, Lewis (LEW) and Fischer 344 (F344). were exposed to morphine (iv) over a period of seven days in order to discern differences in tolerance development. Following morphine injection, the LEW group demonstrated a greater mean total amount, as well as a greater rate of reduction, of stuporous behavior across the seven days tested. The LEW rats exhibited a positive linear profile of opiate-induced hyperexcitability, while a quadratic profile emerged for the F344 group. Differences in patterns of latency to onset of slow-wave sleep between the two strains were also exposed; the F344 rats exhibited a greater change (as reduction of suppression) across the seven days tested. EEG analysis of spectral parameters utilizing an ANOVA with repeated measures revealed that peak frequency, mean frequency, and edge frequency differed as a function of inbred rat strain. All spectra parameters differed as a function of duration of morphine injection; linear trends were indicated for both strains. Naloxone was administered (iv) following the seven days of morphine in order to delineate dependence differences. The LEW animals reflected a greater amount of behavioral responses, e.g., wet dog shakes, diarrhea, body stretch, sluggish behavior. However, the F344 rats demonstrated a greater alteration in two spectral parameters assessed, peak frequency and total power. Genetic variability appears to play a major role in both morphine tolerance and dependence as indicated by differences in EEG and behavioral responses. (Supported by grant DA01050).

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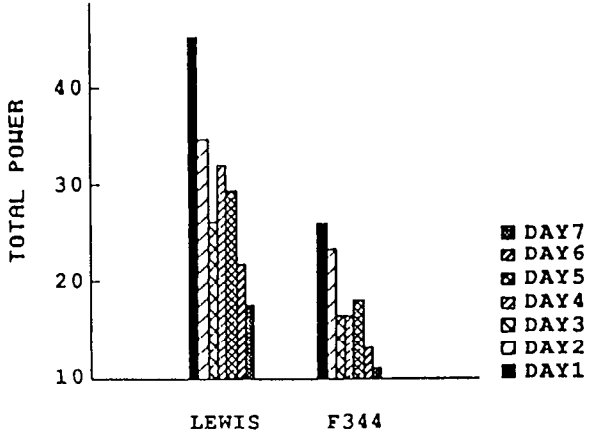

COMPARATIVE EFFECTS OF THE KAPPA OPIOID AGONISTS U=50,488H, SPIRADOLINE AND DuP 747 ON EEG, EEG POWER SPECTRA AND BEHAVIOR

G. A. YOUNG; G. M. HUDSON; H. STAMIDIS AND G. F. STEINFELS

The present data indicate that the κ opioid agonists U50,488H, spiradoline and DuP 747 produced qualitatively similar effects on EEG, EEG power spectra and behavior. However, the quantitative effects of spiradoline on these parameters were greater than those for U50,488H and DuP 747. Female Sprague-Dawley rats were implanted with cortical EEG electrodes and i.v. cannulae. I.v. administration of U50,488H and DuP 747 produced occasional high-voltage EEG slow-wave bursts. Spiradoline produced more numerous and more pronounced high-voltage EEG slow-wave bursts than either U-50,488H or DuP 747. U-50,488H, spiradoline and DuP 747 produced increases in EEG spectral power in the 2.5-7.5 Hz band as a predominant spectral peak. Spiradoline-induced increases in 2.5-7.5 Hz spectral power were significantly greater than those produced by either U-50,488H or DuP 747, and spiradoline-induced spectral power increased linearly as a function of spiradoline dose. Moreover, spiradoline produced EEG and EEG power spectral effects that were quantitatively and qualitatively similar to those produced by several benzomorphans. Behaviorally, U-50,488H, spiradoline and DuP 747 produced incidents of sedation, ataxia, ptosis, straub tail, hunching of the back, and backing-up. (Supported in part by NIDA Grant DA-01050 and a DuPont Merck Research Grant.)

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β-FNA INHIBITS DPDPE-INDUCED INCREASES IN MORPHINE EEG AND EEG POWER SPECTRA

H. STAMIDIS AND G. A. YOUNG

In the present study, the effects of β-FNA on DPDPE-induced increases in morphine EEG and EEG power spectra were assessed. Adult female Sprague Dawley rats were implanted with cortical EEG electrodes and permanent indwelling i.c.v. and i.v. cannulae. Rats were administered i.c.v. β-FNA at 20 nmoles or i.c.v. sterile water. 18-24 hrs later, rats were administered i.c.v. DPDPE at 2.5 nmoles or i.c.v. sterile water followed, 10 min later, by i.v. morphine at 3 mg/kg. Morphine-induced changes in EEG global (1-50 Hz) spectral parameters, the duration of morphine-induced high voltage EEG bursts, the period of EEG and behavioral excitation, and the latency to onset of slow-wave sleep were statistically analyzed using a one-way analysis of variance. β-FNA pretreatment significantly decreased morphine-induced total spectral power seen in the DPDPE + morphine group. β-FNA pretreatment also significantly decreased the duration of morphine-induced EEG bursts, the period of EEG and behavioral excitation, and the latency to onset of slow-wave sleep in the DPDPE + morphine group. These data, therefore, suggest that DPDPE may be increasing the effects of morphine on EEG through *delta* opioid receptors associated within the *mu-delta* opioid receptor complex. (Supported by Grant DA-01050.)

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REGULATORY EFFECTS OF SIGMA LIGANDS ON U-50,488H-INDUCED EEG POWER SPECTRA CHANGES

G. M. HUDSON; H. STAMIDIS; G. A. YOUNG AND G. F. STEINFELS

The present data indicate that the σ antagonists rimcazole and DuPont Merck S-7389-4 apparently "released" or "unmasked" κ opioid effects of U-50,488H on EEG, EEG power spectra and behavior. I.v. administration of U-50,488H after i.v. saline pretreatment produced occasional high-voltage EEG slow-wave bursts that were associated with relatively small increases in spectral power in the 2.5-7.5 Hz band as a spectral peak and with behavioral incidents of sedation, ataxia, ptosis, straub tail, hunching of the back, and backing-up. After pretreatment with the σ antagonists rimcazole and DuPont Merck S-7389-4, U-50,488H administration produced significantly larger increases in absolute EEG spectral power, both over the 1-50 Hz range and in the 2.5 to 5.0 and 5.0 to 7.5 Hz bands, than after saline pretreatment; rimcazole pretreatment eliminated U-50,488H-induced incidents of ataxia, ptosis, hunching of the back and backing-up. The U-50,488H-induced effects on EEG spectral power after rimcazole and DuPont Merck S-7389-4 pretreatment in the present study were analogous to those previously shown for (±)- and (-)-ketocyclazocine. In summary, effects of U-50,488H on EEG, EEG power spectra and behavior may reflect interactions between κ opioid and σ (non-opioid) receptor-effector systems. (Supported in part by a DuPont Merck Research Grant and NIDA Grant DA-01050.)

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LONG-TERM POTENTIATION AT THE HIPPOCAMPAL MOSSY FIBER-CA3 SYNAPSE: A MODEL OF SYNAPTIC PLASTICITY IN A REWARD PATHWAY

B. E. DERRICK, S. B. RODRIGUEZ AND J. L. MARTINEZ, JR.

Synaptic plasticity within neural reward pathways is suggested to underlie the persistent neural modifications associated with drug dependence. Long-term potentiation (LTP) has been studied extensively as a potential mechanism of synaptic modifications subserving memory storage in the brain. The hippocampal mossy fiber-CA3 synapse displays LTP, but unlike many synapses in the hippocampus, LTP at the mossy fiber synapse is not blocked by antagonists of the N-methyl D-aspartate (NMDA) glutamate receptor. The mossy fibers contain and release opioid peptides, and they display a form of LTP that is blocked by opioid receptor antagonists. The mossy fibers support naloxone-sensitive intracranial self-stimulation, and animals will self-administer mu opioid receptor agonists into the CA3 region. Thus LTP at the mossy fiber synapse is an example of plasticity occurring in a neural reward pathway.

Our studies focus on the mechanisms of mossy fiber LTP induction in the adult rat in vivo. Mossy fiber LTP is blocked by the mu opioid receptor selective antagonist CTOP in a dose-dependent manner. By contrast, CTOP does not affect mossy fiber responses evoked at low frequencies, nor does it affect mossy fiber LTP once it is established. CTOP also attenuates both the magnitude and the time constant of decay of mossy fiber posttetanic potentiation, which suggests that mu opioid receptors may contribute to mossy fiber LTP via presynaptic actions at mossy fiber terminals. In addition, mossy fiber LTP, in contrast to NMDA receptor-dependent LTP, shows little decay in vivo and may therefore represent a long-lasting form of synaptic plasticity.

These data suggest that mu opioid receptors may mediate both rewarding and plastic processes at the mossy fiber synapse. We suggest that LTP at the mossy fiber synapse may be one mechanism underlying persistent synaptic changes associated with opioid dependence, and that the mossy fiber synapse may be an important site for both the rewarding and the associative mechanisms of opiate dependence.

ACKNOWLEDGEMENTS

Supported by DA05374 to B.E.D. and DA04195 to J.L.M., Jr.

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SINGLE DOSE SUPPRESSION OF MORPHINE WITHDRAWAL SIGNS BY BUPRENORPHINE, MORPHINE, AND BUTORPHANOL IN MALE CYNOMOLGUS MONKEYS

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Buprenorphine is an opioid analgesic currently under evaluation as a treatment for opioid dependence. This experiment was conducted to characterize buprenorphine's agonist/antagonist profile using morphine-dependent Cynomolgus monkey (*Macaca fascicularis*). Twelve male cynomolgus monkeys were maintained on morphine (3.0 mg/kg, q.i.d.) for 6 months. On evaluation days monkeys were scored for opiate withdrawal signs 18 hours after the last dose of morphine. Subcutaneous injections of either buprenorphine (1, 3, 10, 30, or 100 µg/kg), morphine 3, 6 or 12 mg/kg), butorphanol (.01, .1, 1.0 or 3.2 mg/kg), naloxone (.01, .05 or .1 mg/kg) or saline were given and observations continued for an additional 2 hours. Observers were blind to the experimental treatments. As reported by Yanagita et al. (1981) using rhesus monkeys, all doses of buprenorphine increased withdrawal signs such as backward gait, rearing, chafing face, chain biting, vomiting, masturbation, and vocalization after intimidation; increased tremor, defecation, and urination occurred after the high doses. Fighting after intimidation and yawns were suppressed by buprenorphine. Morphine completely suppressed all signs of withdrawal within 30 minutes of injection. Low doses of butorphanol suppressed some signs while the highest dose almost completely eliminated all withdrawal signs.

1. Morphine-dependent cynomologus monkeys are a good model for testing drugs for opiate-like activity.

2. Over the dose range studied, buprenorphine exerted only µ antagonist-like effects with respect to morphine withdrawal signs.

3. In contrast to buprenorphine, butorphanol produced µ agonist-like effects on morphine withdrawal signs.

4. Some signs such as depressed posture, drowsiness, yawn and fighting after intimidation negatively correlated with the severity of morphine withdrawal.

ACKNOWLEDGMENTS:

This research was supported, in part by, NIDA Grant DA-00115.

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EFFECTS OF NALTRIBEN (NTB) ON THE DEVELOPMENT AND EXPRESSION OF CHRONIC DEPENDENCE ON MORPHINE

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Recently, the involvement of delta opioid receptors in the development of morphine-dependence has been reported (Abdelhamid et al., 1991). Naltriben (NTB), an equilibrium delta;! receptor antagonist, is a benzofuran analog of NTI and is much more potent in antagonizing DSLET-induced antinociception than NTI when administered systemically (Sofuoglu et al., 1991). In the present study, the effects of NTB on the development and the expression of chronic dependence on morphine were studied in male Swiss-Webster mice. The degree of chronic dependence was estimated by the ED_{50} values of naloxone (s.c.) required to precipitate withdrawal jumping and diarrhea 72 hr after morphine-pellet (75 mg base) implantation. NTB administered s.c. itself precipitated withdrawal jumping and diarrhea in morphine-dependent mice (72 hr after morphine-pellet implantation), suggesting that $delta_2$ receptors are involved in morphine-dependence, and the ED_{50} values of NTB were 6.3 μmol/kg for jumping and 5.8 μmol/kg for diarrhea. The highest dose of NTB which did not precipitate jumping or diarrhea was 2 μmol/kg. NTB 2 and 10 μmol/kg, s.c. increased the ED_{50} value of DSLET (i.t.) for antinociception by 3.8- and 15.5-fold respectively without affecting the ED_{50} value of morphine (s.c.) for antinociception. The peak time of NTB action was 30 min and the delta-inhibition lasted for at least 4 hr and dissipitated in 8 hr after s.c. administration. NTB (0.1 - 2 μmol/kg) administered 30 min before naloxone-challenge did not affect the ED_{50} values of naloxone for both withdrawal signs. Chronic treatment with NTB (2 and 10 μmol/kg, s.c. administrations at 30 min before, 24 hr and 48 hr after morphine-pellet implantation) did not affect the ED_{50} values of naloxone for both withdrawal signs. However, continuous blockade of $delta_2$ receptors with 5'-NTII (a nonequilibrium $delta_2$ receptor antagonist, 1 - 10 nmol, i.c.v. injections at 24 hr before, just before, 24 and 48 hr after morphine-pellet implantation) significantly inhibited both withdrawal signs. These data suggest that $delta_2$ opioid receptors are involved in morphine-dependence and that continuous blockade rather than intermittent blockade of $delta_2$ receptors is neccessary to inhibit the development of morphine-dependence.

Supported by USPHS grants from NIDA.

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HIBERNATION-INDUCED REDUCTION OF MORPHINE PHYSICAL DEPENDENCE IN GROUND SQUIRRELS: PRELIMINARY DOSE-RESPONSE STUDIES

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Earlier work suggested that adaptive mechanisms of the hibernating brain, not attributable to central nervous system (CNS) depression alone (The Pharmacologist 33:192, 1991), may also reduce the development of morphine physical dependence. We have shown (FASEB J. 6:A985, 1992) that the strength of dependence produced in the nonhibernating state of Citellus lateralis increased as a function of dose and duration of morphine administration. In the present study, we compared the strength of dependence produced during hibernation to our earlier data obtained during the nonhibernating state.

C. lateralis were implanted with a chronic cannula guide directed to the right lateral ventricle. Following recovery from surgery and resumption of hibernation bouts of sufficient length, morphine (3.44, 6.88 or 13.75 µg/µl in sterile 0.9% NaCl) or sterile 0.9% NaCl was infused at 1 µl/hr using an osmotic minipump. At the end of the prescribed period of infusion (1, 3, or 6 days), the animals were given sufficient time to return to the nonhibernating state (a process requiring about two hrs). Dependence was then measured using the naloxone (1 mg/kg, s.c.) evoked abstinence syndrome.

The results showed that the strength of dependence developed during hibernation was markedly reduced (up to 79%) compared to that developed during the nonhibernating state (t-test, $p<0.05$). Whereas significant dose- and duration-response trends (least-squares linear regression, $p<0.02$) were found for dependence produced during the nonhibernating state, none were observed for dependence produced in the hibernating state. However, a significant dose-response relationship was observed for morphine action on the CNS control of hibernation: morphine reduced hibernation bout duration up to 90%.

These results demonstrate that the strength of morphine dependence produced during the state of hibernation is significantly less than that produced during the nonhibernating state. Whereas no dose-response or duration-response dependence relationships were apparent for hibernation, the dose-dependent reduction of hibernation bout duration demonstrates that morphine is capable of generating dose-dependent neuronal actions in the hibernating brain. Continuing work will investigate the mechanisms responsible for the diminished capacity of the hibernating CNS to develop morphine dependence.

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TOLERANCE TO MORPHINE ANALGESIA: PRELIMINARY STUDIES USING THE SKIN-TWITCH ASSAY IN THE GROUND SQUIRREL HIBERNATOR MODEL, CITELLUS LATERALLIS

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Previous studies of morphine action in our laboratory have suggested that Citellus lateralis is a model in which the normally high liability of the central nervous system (CNS) for the development of morphine dependence becomes suppressed by the adaptive mechanisms associated with hibernation. We have shown that morphine physical dependence develops in a typical fashion during the nonhibernating state, but is significantly reduced during hibernation. The present study was designed to determine if tolerance to morphine analgesia occurs in the nonhibernating state of C. lateralis and to establish the baseline conditions for determining if tolerance to morphine analgesia is reduced during hibernation.

Morphine (1.7 µg/µl) or 0.9% NaCl [vehicle) was infused (osmotic minipump; 1 µl/hr) for six days in nonhibernating animals via a cannula inserted into a chronic guide directed to the right lateral ventricle. Analgesia was assessed at 24-hr intervals by measuring the latency of the skin-twitch response (STR) to a radiant heat stimulus delivered to unrestrained animals. At the end of the infusion period, morphine dependence was measured using the naloxone (1 mg/kg, s.c.) evoked abstinence syndrome. Baseline STR latency measures during hibernation were obtained under optimum conditions for hibernation [ambient temperature [T_a], 5°C) using the same method of analgesia assessment as for nonhibernating animals.

The results showed that the morphine-infused nonhibernating animals demonstrated increasing analgesia which peaked on day 2, followed by the development of tolerance which was completed by day 3. The development of tolerance was confirmed by trend analysis in which the data were smoothed and subjected to regression analysis (cubic trend significant, $p<0.01$). The morphine-infused animals also demonstrated dependence. Hibernating animals displayed baseline STR latencies that were comparable to, but elevated above! those measured in nonhibernating animals. Additional experiments on nonhibernating animals showed that baseline latency values increased as a function of season and of the reduced T_a associated with hibernation tests.

These data demonstrate that tolerance to morphine analgesia occurs in the nonhibernating state of C. lateralis. Continuing work will determine if tolerance to morphine analgesia is reduced during the hibernating state.

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ARE THE HYPOTHERMIC EFFECTS OF CAFFEINE MODULATED BY OPIATE RECEPTORS?

M. J. DURCAN AND P. F. MORGAN

Caffeine, and other methylxanthines, induces a dose dependent reduction in core body temperature in mice. The mechanism of this methylxanthine-induced hypothermia is at present unclear, however, the efficacy of compounds to induce a 2°C drop in core body temperature correlates highly with their calcium independent phosphodiesterase inhibiting effects (Durcan and Morgan, 1991). In these experiments, the effects of pretreatment with the opiate antagonists naloxone and naltrexone on caffeine-induced hypothermia were investigated.

Naive male NIH Swiss mice weighing between 21 and 25 g were used. Core body temperature was measured using a rectal probe and digital thermometer immediately prior to treatment with 3 mg/kg naloxone (i.p.) or distilled water vehicle. After 20 min, core body temperature was again measured immediately prior to administration of caffeine (30-140 mg/kg, i.p.) or distilled water vehicle and further remeasured 20 min later. Naloxone had no significant intrinsic effect on core body temperature whereas caffeine administration dose dependently reduced it; however, the caffeine-induced reduction in core body temperature was significantly attenuated in mice pretreated with naloxone. In a second experiment mice were treated in an identical fashion except that varying doses of naloxone (0.3-30 mg/kg) were administered to animals subsequently treated with caffeine (100 mg/kg) or vehicle. In this experiment only the highest dose of naloxone (30 mg/kg) had any intrinsic effects on core body temperature (a reduction seen 20 minutes after administration) and the caffeine treatment reduced body temperature. Pretreatment with all doses of naloxone except the lowest dose used (0.3 mg/kg) significantly attenuated the hypothermic effect of caffeine. Subsequent experiments have revealed very similar results following pretreatment with another opiate receptor antagonist, naltrexone.

These results suggest that opiate receptors, but not adrenergic, serotoninergic, dopaminergic or benzodiazepine receptors (antagonists of which were also investigated), play a role in attenuating the hypothermic action of caffeine and possibly other methylxanthines. The mechanism of this hypothermic effect remains to be fully elucidated but it may involve the release of endogenous opioids.

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EFFECTS OF SELECTIVE OPIOID AGONISTS AND AMBIENT TEMPERATURE ON THERMOREGULATION IN THE RAT?

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PL-017 (1.86 nmol), dynorphin A1-17 (4.65 nmol), or DPDPE (4.64 nmol), selective for μ, κ, and δ receptors, respectively, was injected into the right lateral ventricle of unrestrained, male, S-D rats. At ambient temperatures of 5° and 30°C, brain surface temperature (Tb), oxygen consumption (V_{O2}) and heat exchange (Q) were measured over a 3-hr post-injection period in a gradient-layer calorimeter. PL-017, at 30°C, caused a significant increase in Tb (1.23° ± 0.22°C). Increased Tb supported by a significant decrease in Q (-1.23 ± 0.36 cal/g/hr), and a 60-70% increase in V_{O2}, both occurring 15 min post-injection. At 5°, PL-017 decreased V_{O2} and Q significantly, resulting in hypothermia (-1.75° ± 0.08°C). Thirty-min pre-treatment with CTAP (0.75 nmol), a μ-selective antagonist, blocked these effects. At 30°C ambient, dynorphin A1-17 induced decreases in Q, which differed significantly from saline controls. The reduction in Q and a small increase in V_{O2} resulted in an increase in Tb when compared to saline controls. Dynorphin-induced changes at 30°C were blocked by the r-selective antagonist, nor-BNI (25 nmol; 15 min pre-treatment). Post-injection thermoregulatory responses to dynoprhin at 5°C varied widely from animal to animal, with lethality (32%, within 60 min post-injection) becoming a significant factor. Thirty-five percent of the animals tested at 50 showed no reaction to icv dynorhin. The remainder of the animals demonstrated varying increased Tb, primarily due to a decrease in Q throughout the post-injection period. These changes were blocked by the d-selective antagonist, naltrindole (1 nmol; 15-min pre-treatment). At 5°C, DPDPE reduced Q significantly, maintaining Tb, at pre-injection control levels. We have demonstrated that a change in ambient temperature from 20°C modifies the thermoregulatory effect when selective opioid agonists interact with their receptors.

ACKNOWLEDGMENT

This research was supported in part by NIDA grants DA T32DA07237 and DA 00376.

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RESPIRATORY EFFECTS OF Mu AND MIXED-ACTION OPIOID AGONISTS

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Previous studies have shown that μ-selective, but not κ-selective, opioid agonists have marked respiratory-depressant effects. The present studies were conducted to evaluate the respiratory effects of mixed-action opioids by comparing the effects of the μ-selective opioids levorphanol (0.1-3.0 mg/kg), methadone (0.03-3.0 mg/kg), and codeine (0.3-30.0 mg/kg) with those of mixed-action opioids buprenorphine (0.0003-3.0 mg/kg), butorphanol (0.003-0.3 mg/kg), and nalbuphine (0.03-3.0 mg/kg). Experiments were conducted in awake, seated rhesus monkeys breathing air or CO, (3, 4, and 5%) mixed in air. Results indicated that respiration was stimulated by CO_2 in a concentration-dependent manner. Levorphanol and methadone depressed respiration in a dose-related manner and, at the highest doses, also suppressed the respiratory-stimulant effects of CO_2. Codeine also depressed respiration, but at doses less than 30 mg/kg did not greatly alter the respiratory-stimulant effects of CO_2. Butorphanol had effects comparable to those of levorphanol and methadone: respiration was depressed in a dose-related manner and the respiratory-stimulant effects of CO, were nearly abolished by the highest dose. Buprenorphine depressed respiration to a lesser extent than butorphanol or μ-selective opioids and, at the highest doses, decreased the respiratory-stimulant effects of CO, to no less than 50% of control. Nalbuphine, like levorphanol and methadone, depressed respiration in a dose-related manner, and, like buprenorphine, reduced the respiratory-stimulant effects of CO, to approximately 50% of control. These results suggest that the respiratory effects of buprenorphine and nalbuphine are not likely to restrict their therapeutic utility whereas the respiratory-depressant effects of butorphanol should be considered in its clinical applications.

Supported by USPHS grants .MH07658, MH14275, RR00168, and DA03774.

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COMPARISON OF THE EFFECTS OF COCAINE AND COAETHYLENE ON CARDIOVASCULAR FUNCTION IN SQUIRREL MONKEYS

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Cocaethylene is an active metabolite of cocaine formed when cocaine is used in the presence of ethanol. Significant levels of cocaethylene have been detected in human postmortem blood and brain (Hearn et al., J. Neurochem. 56:698, 1991) and it has been reported to be more potent than cocaine in mediating lethality in mice (Hearn et al., Pharmacol. Biochem. Behav. 39:531, 1991). However, cocaethylene is less potent than cocaine in producing psychomotor stimulant effects in rats and mice (Jatlow et al., Life Sci. 48: 1787-1794, 1991; Katz et al., Life Sci. 50: 1351-1361, 1992). Further, cocaethylene has been reported to be less, or equipotent to cocaine in producing cocaine-like discriminative stimulus effects in rats and squirrel monkeys (Katz et al., Life Sci. 50: 1351-1361, 1992; Woodward et al., J. Pharmacol. 197: 235-236, 1991). To delineate the potential cardio-toxicity of cocaethylene, we compared the effects of cocaine and cocaethylene on cardiovascular function in squirrel monkeys. In addition, the reinforcing effects of these two compounds were also studied in squirrel monkeys to determine whether they function similarly behaviorally. For the cardiovascular studies, cocaine was studied in 3 subjects and cocaethylene in 5 subjects. Both cocaine and cocaethylene (0.1-3.0 mg/kg) produced clear increases in blood pressure (BP) and heart rate (HR). However, for both the peak effects and duration of action, cocaethylene was not more potent than cocaine. While these data are preliminary, they indicate that cocaethylene does not produce any greater increases in BP and HR than cocaine itself. For the self-administration studies, 2 monkeys were trained to respond on a FI 3-min schedule for 56 µg/kg cocaine. Various doses of cocaine and cocaethylene were then substituted during single sessions. An inverted U-shaped function was observed for both cocaine and cocaethylene and, as with the cardiovascular effects, both compounds produced equivalent maximal effects and appeared equipotent. Therefore, cocaine and cocaethylene appear equipotent for both cardiovascular and reinforcing effects in squirrel monkeys.

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COCAINE EXPOSURE MODIFIES THE NEUROENDOCRINE RESPONSES TO THE 5-HT_{1C}/5-HT_2 AGONIST DOI

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Cocaine interferes with serotonergic neurotransmission by inhibiting serotonin (5-HT) reuptake (Eur. J. Pharmacol, 7:270, 1969). The influence of chronic cocaine on serotonergic function is only beginning to be assessed. Reports of chronic cocaine's effects on 5-HT content have been inconsistent. (J. Neurosci. Res. 3:95, 1977; Neuropharmacol. 17:559, 1978; Brain Res. Bull, 21:233, 1988; Drug Alcohol Depend. 27:51, 1991). Also, chronic cocaine does not alter the density of 5-HT receptors (Brain Res. 552:27, 1991), while behavioral responses to the 5-$HT_{1c/2}$ agonist DOI are enhanced by chronic cocaine (Pharmacol, Biochem, Behav. 41:519, 1992).

Serotonergic neurons stimulate the secretion of several hormones including ACTH, corticosterone, prolactin, oxytocin and renin (Annu. Rev. Pharmacol, Toxicol. 31:289, 1991). Thus, hormonal responses to 5-HT agonists and releasers can evaluate 5-HT function. We have previously determined that chronic cocaine produces deficits in 5-HT neuronal function. The ability of the 5-HT releaser p-chloroamphetamine to stimulate ACTH, corticosterone, prolactin and renin secretion is reduced by 7 or 30 days of cocaine exposure (Neurooharmacol. 31:169, 1992; Brain Res. 580:6, 1992). The present study examined whether the cocaine-induced deficits in presynaptic 5-HT function lead to modifications in the sensitivity of postsynaptic receptors.

Adult, male Sprague-Dawley rats (N=8/group) received cocaine HCl (donated by NIDA) in doses of 0, 5, or 15 mg.kg, i.p. twice daily for 7 days. Rats were then administered the 5-$HT_{1c/2}$ agonist DOI (0. 0.5, 2 or 10 mg/kg i.p.) 42 hours after the final cocaine injection. Rats were sacrificed 30 minutes after DOI injections and blood samples were collected for subsequent radioimmunoassays of plasma ACTH, corticosterone, prolactin, oxytocin and renin concentrations.

The 5-$HT_{1c/2}$ agonist, DOI, dose-dependently increased ACTH, corticosterone, prolactin, oxytocin and renin secretions. Cocaine exposure for 7 days potentiated the DOI-induced stimulation of plasma ACTH ($F_{(6.78)} = 2.71$, $p<.05$), corticosterone ($F_{(2,83)} = 5.52$, $p<.01$). and prolactin ($F_{(6,80)} = 2.33$, $p<.05$) concentrations. In contrast, the DOI-induced elevation of oxytocin secretion was inhibited by cocaine exposure ($p <.05$, Newman-Keuls'), and DOI-s enhancement of plasma renin concentration was unaltered by cocaine injections. The data suggest that repeated cocaine exposure produces supersensitivity of the 5-HT_{1C} or 5-HT_2 receptors that mediate ACTH, corticosterone and prolactin secretion. The 5-HT_{1c2} receptors that mediate oxytocin secretion become subsensitive, while the 5-HT receptors mediating renin secretion appear to be unaltered by cocaineexposure. (Supported by DA04865). AFFILIATION: Dept. of Pharmacology, Loyola University Chicago, 2160 S. First Ave., Maywood, IL 60153

STIMULATION OF HYPOTHALAMIC OXYTOCIN mRNA IN CULTURED NEURONS

L. J. SIMS; M. F. CALLAHAN; G. TSAI AND M. MORRIS

A hypothalamic tissue culture system has been developed using isolated cells of the paravenbicu1ar nuclear region (PVN). The objective is to obtain an enriched population of oxytocin (OT) neurons for the study of drug/endocrine interactions. Oxytocin, a peptide hormone known for its reproductive effects, is also involved in autonomic function and may influence tolerance and dependence. We are interested in evaluating the effects of drugs that affect dopaminergic neurotransmission on PVN OT neurons. The present studies were performed to assess the effects of KCl, a depolarizing agent, on OT immunoreactive (OT-ir) neurons in PVN cultures. Activation of OT-ir cells was identified with cfos immunocytochemistry and OT mRNA levels were determined using *in situ* hybridization.

Brains were removed from 1-2 day rat neonates and the PVN was microdissected for use in primary culture. The tissue was treated with dispase and triturated and cells were plated onto chamber slides. On day 5, cultures were treated for 1 hour with 40 or 50 mM KC1 and fixed at appropriate time points after treatment. Cultures to be used for *in situ* were processed for OT immunocytochemistry and hybridized with an ^{35}S labeled 30mer OT probe ($3\text{-}4x10^5$ cpm/100µl). Slides were washed with a final stringency of 0.5XSSC at 55° C. Slides were coated with emulsion, developed for autoradiographic analysis and analyzed using a computer image analysis system. To identify activated neurons, fixed cultures were processed immunocytochemically with cfos antibody using the Vector Elite avidin-biotin system. cFos immunoreactivity was visualized with nickel enhanced 3,3'diaminobenzidine tetrahydrochloride (DAB) to produce a purple reaction product. Cultures were processed immunocytochemically for oxytocin neurophysin using the avidin-biotin system. In this case, OT was visualized with DAB to produce a brown reaction product. OT-ir and OT/cfos-ir cells were counted to determine the percentage of cells activated by KC1 treatment.

An increase in OT mRNA was identified after a 1 hour treatment with 40 mM KCl. The levels of mRNA were determined based upon grain intensity over individual cells and are expressed as intensity units (IU). OT mRNA was increased at 1 hour post-treatment ($170.1\pm7.4x10^3$ IU/cell) and remained elevated through 24 hours ($175.5\pm7.5x10^3$ IU/cell), compared to controls ($121.7\pm4.3x10^3$ IU/cell). The greatest increase in OT mRNA was detected at 4 hours post-treatment, in which cells contained $258.2\pm9.9x10^3$ IU/cell. Dual immunocytochemistry for cfos and OT showed that the percentage of double labeled OT/cfos-ir neurons increased after a 1 hour treatment with 50 mM KCl. A significant increase in OT/cfos-ir neurons was found at 1 hour post-treatment, where 74.8±3% of OT neurons were activated, compared to 24.7±5% at time 0. No significant increases were detected at 30 minutes (30.8±9%) or 4 hours (29.2±7%) post-treatment. These studies demonstrate that this PVN tissue culture system is suitable to evaluate the effects of drug induced changes in an identified population of neurosecretory cells. Acute activation can be identified with cfos immunocytochemistry and longer term changes in mRNA identified with *in situ* hybridization. (Supported by PMA & N.C. Biotechnology Center)

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NECESSITY OF 5-HT IN OPIATE-INDUCED PROLACTIN SECRETION

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Mu opiates and 5HT serve as modulators of prolactin secretion during stress and suckling. The mechanisms by which mu opiates and 5-HT control prolactin release are unclear. Both mu opiates and 5-HT may stimulate prolactin release by decreasing the tonic inhibitory influence of dopamine and/or by stimulating a hypothalamic prolactin releasing factor. Furthermore, it has been hypothesized that mu opiate stimulation of prolactin release is a 5-HT-dependent event.

To further characterize the interaction between mu opiate and 5-HT modulation of prolactin release, the ability of specific opiate and 5-HT antagonists to block agonist-induced prolactin release was tested. 30 day old male Sprague-Dawley rats were injected sc with either naloxone (2 mg/kg) or ketanserin (5 mg/kg) 30 min prior to injection with morphine or a number of 5-HT agonists. Rats were killed 20 min after agonist treatment and blood collected for serum, prolactin levels were then determined by RIA. Naloxone pretreatment blocked the elevation of prolactin levels produced by morphine and the 5-HT agonists DOI, quipazine and parachloroamphetamine (PCA), but not m-CPP. In contrast, ketanserin failed to block the stimulatory effects of morphine, DOI, quipazine, m-CPP and PCA. Although ketanserin (a $5\text{-HT}_{2/1c}$ receptor antagonist) failed to block morphine-induced prolactin secretion, p-CPA (a 5-HT synthesis inhibitor) attenuated the elevation of prolactin by morphine.

In conclusion, there appears to be a reciprocal modulation rather than a 5-HT dependency between mu opiate and 5-HT neurons which mediate prolactin release.

ACKNOWLEDGEMENTS

This work was supported by NIDA research grant DA 02739.

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CELLS OF A SPECIFIC GLIAL FATE MEDIATE OPIATE-DEPENDENT GROWTH: ROLE OF TYPE 1 ASTROCYTES

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Opioids affect glial growth in the developing brain, Not only are glia targets of opioid action, but some developing glia express the proenkephalin gene. The growth of type 1 astrocytes can be altered by opiates, whereas the growth of type 2 astrocytes is unaffected. Moreover, type 1 astrocytes express the proenkephalin gene suggesting that opioids may regulate their growth by autocrine and/or paracrine mechanisms, To determine whether opioids affect the growth of, or are expressed by, other types of developing glia: (i) opiate-dependent growth was assessed in cultures enriched in astrocytes, astrocytes and preoligodendroglia, or preoligodendroglia alone; and (ii) proenkephalin mRNA expression was assessed in mixed-glial cultures using *in situ* hybridization. Cultures from newborn ICR mouse cerebra were exposed to 10 nM, 1 or 100 μM morphine or [Met^5]-enkephalin for 48-72 h prior to [^{3}H]-thymidine incorporation (0.2 μCi/ml/16 h). [^{3}H]-Thymidine autoradiography was combined with immunocytochemical markers for astrocytes (glial fibrillary acidic protein; GFAP) and preoligodendroglia (04 courtesy Dr. M. Schachner) in double- and triple-labeling paradigms. [^{3}H]Thymidine labeling index and cell numbers/μm^2 were assessed in type 1 astrocytes and preoligodendroglia. Proenkephalin mRNA expression was assessed using specific [^{35}S]-labeled cRNA probes and combined with GFAP immunocytochemistry. [Met^5]-enkephalin or morphine at all concentrations significantly inhibited the growth of type 1 astrocytes in a naloxone-reversible manner. In preoligodendroglial-enriched cultures, however, opioids did not affect preoligodendroglial numbers or labeling index. Yet, in mixed-glial cultures, 1 μM concentrations of [Met^5]-enkephalin, but not morphine, increased the preoligodendroglial labeling index compared to cultures treated with naloxone alone (Newman-Keuls; $P<0.05$). This unexpected effect may result from [Met^5]-enkephalin acting on type 1 astrocytes, e.g., decreasing the number of type 1 astrocytes may indirectly promote preoligodendroglial replication. Why naloxone alone has an effect might be explained by the findings of others that type 1 astrocyte cultures release opioids *in vitro*. This was presently confirmed, in part, because the proenkephalin gene was expressed by type 1 astrocytes. In summary, developing type 1 astrocytes express the proenkephalin gene and are developmentally responsive to opioids. Alternatively, type 2 astrocytes and preoligodendroglia (O-2A lineage) do not express the proenkephalin gene and lack opioid responsiveness. Type 1 astrocytes may mediate the effects of opioids on other cell types and appear to be critical intermediaries in opiate-dependent neural growth.

Supported by NIDA grant DA 06204

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AGE-RELATED CHANGES IN KAPPA OPIOD RECEPTORS IN THE GUINEA PIG BRAIN: A QUANTITATIVE AUTORADIOGRAPHIC STUDY

J. M. HILLER, L.-Q. FAN AND E. J. SIMON

Investigation into the effect of aging on κ opioid receptors in the brains of guinea pigs was carried out in animals aged one, six, 24 and 36 months. Quantitative autoradiography was employed to monitor the concentration of receptors in various anatomical regions at five rostro-caudal regions in each age group. Areas of high levels of κ1 binding were found in laminae V,VI of the neocortex and in the internal band of the periallocortical, dorsal agranular insular cortex. Among the non-cortical areas examined, the nucleus accumbens and the substantia nigra exhibited κ binding levels equal to those observed in the deep neocortical areas. In all cases, where an age related change in the level of κ receptors was detected, the direction of the change was that of decreased binding with advancing age. Statistical analysis of the data revealed that the one month old animal possessed the highest level of κ binding among all age groups examined. While the vast majority of age-related decreases in κ1 binding levels occurred in laminae V,VI of the neocortical regions, levels of κ binding in the striatum and the substantia nigra were found to be similarly depressed. The percent decreases in binding varied from 20 to 42% in different anatomical areas. The age of onset of the observed changes is of interest. Thus, the number of cortical areas showing statistically significant changes were; five at six months, 12 at 24 months and 14 at 36 months. These, progressive, anatomically selective, reductions in κ opioid binding occurred mainly in regions of the neocortex which are characterized by their motor, sensory and associative functions. It is within these three areas of function that diminutions in performance are most apparent in senescence.

ACKNOWLEDGEMENTS

This work was supported by Grant DA 08945 from NIA to JMH and Grant DA 00017 from NIDA to EJS.

AFFILIATION

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LESIONING OF THE NUCLEUS BASALIS OF MEYNERT HAS DIFFERENTIAL EFFECTS OF Mu, DELTA AND KAPPA QPIOID RECEPTOR BINDING IN RAT BRAIN: A QUANTITATIVE AUTORADIOGRAPHPIC STUDY

D. Ofri; L-Q. Fan; E. J. Simon and J. M. Hiller

Impairment of the cortical cholinergic system in laboratory animals has been a central feature in recent attempts to construct an animal model for Alzheimer's Disease (AD). It has been demonstrated that cholinergic fibers originating in the nucleus basalis of Meynert (nbM) project widely to cerebral cortices. Following unilateral ibotenic acid lesioning of the nbM in rat brain, the specific laminar and regional distribution of μ, α and kappa opioid receptor binding was assessed in lesioned and control hemispheres, using quantitative autoradiography. A significant decrease (50% or greater) in choline acetyltransferase activity in the ipsilateral prefrontal cortex confirmed the efficacy of the lesioning. It was notable that the direction of the statistically significant changes in binding was dependent upon the type of opioid receptor being assessed, i.e., both κ and δ binding was increased and μ binding was decreased in the lesioned hemisphere. In almost every cortical region where a divergence from control binding was observed, the change was located in the most lateral aspects of that anatomical structure. Of the 91 regions measured, δ binding was increased by 15%-24% in the following regions: laminae V,VI of the frontal cortex (FC), laminae III,IV and V,VI of the occipital cortex (OC). outer layers of the perirhinal cortex and the retrosplenial granular cortex. In the lesioned hemisphere κ binding in laminae I.II and V,VI of the OC increased by 72% and 20%. respectively, and in area CA3 of the hippocampus by 49%. In contrast, μ opioid binding exhibited decreases in laminae III,IV of the FC (15%) and in the entorhinal cortex (16%) while laminae I,II of the forelimb cortex exhibited the largest decease (27%). In the current study we found that this lesion is associated with changes in opioid binding that are similar to some of the changes we have previously observed in homogenates of post-mortem brain from AD patients[1], i.e., the large increase in κ binding and the decrease in μ binding. Therefore, despite the limited nature of this animal model, the similarities found with respect to opioid receptor changes in nbM lesioned rats and AD brains suggest some relevance of the model to this disease.

1. Hiller, J. M., Itzhak, Y. and Simon, E. J. Brain Res, 406:17-23. 1987.

This work supported by Grant AG 08945 from NIA to JMH and Grant DA 00017 from NIDA to EJS.

AFFILIATION: Depts. of Psychiatry and Pharmacology, N.Y.U. Med. Ctr., N.Y.

IN VITRO EFFECTS OF THE CANNABINOID, CP 55,940, AND OF ITS (+)-ENANTIOMER, CP56,667

R. G. PERTWEE; L. A. STEVENSON; S. R. FERNANDO AND A. D. CORBETT

This investigation was directed at extending our search for smooth muscle preparations in which cannabinoids produce stereoselective inhibition of electrically-evoked twitches (Pertwee et al. 1992), since a comparison of the relative potencies of cannabinoids in different tissues could well resolve the question of whether there is more than one type of cannabinoid receptor.

Myenteric plexus-longitudinal muscle strips were dissected from the small intestines of male Dunkin-Hartley guinea-pigs or MF1 mice and vasa deferentia from Dunkin-Hartley guinea-pigs, Sprague-Dawley rats or MF1 or TO mice. Tissues were mounted in 4 ml baths containing Krebs solution kept at 37°C and bubbled with 95% O_2 and 5% CO_2. Mouse vasa deferentia were set up in Mg++-free solutions. Tissues were stimulated supramaximally with single pulses (guinea-pig intestinal tissue; 0.1 Hz) or with trains of pulses, 30 pulses for 3 s (guinea-pig vas deferens), 11 for 0.5 s (mouse intestinal tissue) or 3 for 0.5 s. Train frequencies were 0.033 Hz (guinea-pig vas deferens), 0.1 Hz (rat and mouse vas deferens) or 0.2 Hz (mouse intestinal tissue). Pulse duration was 1.0 ms (guinea-pig vas deferens) or 0.5 ms. Isometric contractions were recorded. Cannabinoids were dispersed in Tween/saline (Pertwee et al. 1992).

Concentrations of CP 55,940 that decreased twitch heights by 50% (IC_{50}) were 0.18, 0.21, 55 and 86 nM respectively in the vasa deferentia of MF1 mice, TO mice, rats and guinea-pigs and 0.77 nM in the guinea-pig myenteric plexus preparation. The corresponding IC_{50} values of CP 56,667, the psychotropically less active (+)-enantiomer of CP 55,940, were much greater (13.2, 12.5, >1000, >1000 and 100 nM respectively). In the mouse myenteric plexus preparation, CP 55,940 produced a maximum inhibition of the twitch response of only 47% (at a concentration of 100 nM). CP 56,667 was 27 times less potent. The drug vehicle, Tween 80, and the non-psychotropic cannabinoid, cannabidiol (100 nM), were inactive. We conclude that all the preparations that we investigated could be of use in the search for multiple cannabinoid receptors.

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ACKNOWLEDGEMENTS

We thank Pfizer for CP 55,940 and CP 56,667 and the Nuffield Foundation for financial support. AFFILIATION: Dept. Biomed. Sci, Marischal Col., Univ of Aberdeen, Aberdeen AB9 1AS Scotland

FURTHER CHARACTERIZATION OF THE CANNABINOID RECEPTOR WITH ^{3}H- 11-OH-Δ^9-THC-DMH BINDING IN RAT BRAIN SLICES: AUTORADIOGRAPHY, DISPLACEMENT STUDIES AND CORRELATION TO IN VIVO PHARMACOLOGICAL POTENCIES

B. F. Thomas and B. R. Martin

Although the existence of a specific receptor in the central nervous system responsible for the effects produced by marijuana has recently gained experimental support (Howlett et al., 1986; Devane et al., 1988; Herkenham et al., 1990; Matsuda et al., 1990. Haycock et al., 1990), a number of criteria for a receptor-mediated mechanism of action have not been met, such as the existence of a specific cannabinoid receptor antagonist. Furthermore, the structures of the radiolabeled analogs which have been used to study this receptor site (^{3}H-CP-55,940 and ^{3}H-WIN-55212-2) differ markedly from the naturally occurring cannabinoid, Δ^9-THC, which raises the question as to whether the binding site for these two compounds is in fact responsible for the pharmacological effects produced by marijuana. The objective of this study was to compare the binding of a "classical" cannabinoid analog, ^{3}H-11-OH-Δ^9-THC-DMH, to that of the non-classical bicyclic analog ^{3}H-CP-55,940. The binding characteristics of ^{3}H-11-OH-Δ^9-THC-DMH and 3H-CP-55.940 were compared in a rat brain-section assay developed by Herkenham et al (1990). 3H-11-OH-Δ^9-THC-DMH and 3H-CP-55,940 possessed similar affinities (K_D's of 29 ± 9 and 19 ± 3, respectively), binding site densities (B_{max} of 3.2 ± 0.4 and 4.3 ± 0.6 pmol/mg protein, respectively) and binding site localization. In order to characterize the pharmacological significance of 3H-11-OH-Δ^9-THC-DMH binding, competition studies were performed to determine K_I values of selected cannabinoid analogs. All of the cannabinoids tested displaced the binding of 3H-11-OH-Δ^9-THC-DMH with the exception of (+)-11-OH-Δ^8-THC-DMH, an inactive cannabinoid. The K_I values (nM ± SEM, n = 3) were: Δ^9-THC, 2200 ± 100; CP-55,940, 52 ± 5; (-)-Δ^8-THC-DMH, 18 ± 9; (-)-11-OH-Δ^8-THC-DMH, 6 ± 1; (+)-11-OH-Δ^8-THC-DMH, >1000; and WIN-55212-2, 322 ± 108. Linear regression analysis between the log of each cannabinoid K_I value and *in vivo* potency in mice (log ED_{50} value, moles/kg) yielded correlation coefficients of 0.98,0.99, 0.86 and 0.96 for decreasing spontaneous activity, increasing tail-flick latency, decreasing rectal temperature, and producing catalepsy, respectively. Therefore, these studies support the hypothesis that the site labeled with 3H-11-OH-Δ^9-THC-DMH, as well as ^{3}H-CP-55,940., is responsible for some of the behavioral effects seen upon cannabinoid administration.

ACKNOWLEDGMENTS: This work was supported by NIDA research grant DA-03672 and training grant DA-07027.

AFFILIATIONS: Research Triangle Institute, Research Triangle Park, NC and Medical College of Virginia/Virginia Commonwealth University, Richmond, VA

THE ANTINOCICEPTIVE ACTION OF CP-55,940 MICROINJECTED INTO THE PERIAQUEDUCTAL GRAY (PAG) SHOWS REGIONAL SPECIFICITY

A. H. Lichtman & B. R. Martin.

The cannabinoids have long been shown to produce both antinociception and catalepsy in laboratory rodents. The PAG plays an important role in the activation of descending antinociceptive systems and contains a higher concentration of cannabinoid binding sites than other brain stem structures. Therefore, the primary goal of this study was to determine whether intracerebral administration of CP-55,940, a potent bicyclic cannabinoid, to several sites in the PAG would produce any behavioral effects in rats. In order to ascertain whether the effects were stereoselective CP-56,667, the inactive stereoisomer of CP-55,940, was also assessed.

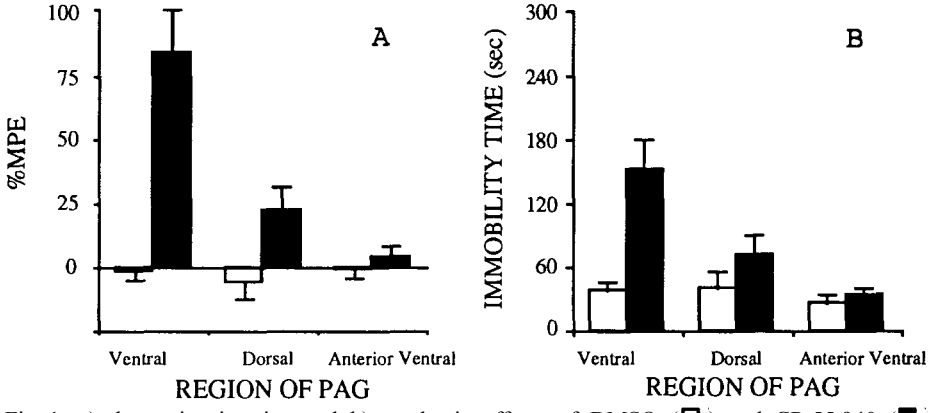

Fig 1. a) the antinociceptive and b) cataleptic effects of DMSO (□) and CP-55,940 (■) when administered into three separate regions of the PAG. Subjects were assessed in the tail-flick test and in the ring immobility test at 20 min and 40 min, respectively.

Intracerebral injections of the bicyclic cannabinoid, CP-55,940 (15 μg), into the posterior ventrolateral PAG of rats produced both antinociception (Fig 1a) and catalepsy (Fig lb). Administration of CP-56,667 to this region failed to have any effects (data not shown). Finally, administration of CP-55,940 to either the posterior dorsolateral PAG or the anterior ventrolateral PAG failed to have any significant effects in either the tail-flick test or the ring immobility test. These results indicate that the antinociceptive and cataleptic effects of cannabinoids microinjected into the PAG exhibit both stereoselectivity and regional specificity.

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CALCIUM CHANNEL ACTIVATORS AND BLOCKERS: EFFECT ON NICOTINE-INDUCED ANTINOCICEPTION

M. I. DAMAJ AND B. R. MARTIN

There is good evidence that nicotinic receptor activation results in an increase in intrasynaptosomal and intracellular calcium concentration. The purpose of the present study was to investigate the influence of the voltage-dependent calcium channel (L-type channel) on the central nicotine receptor using in vivo techniques. For this study we have chosen to measure nicotine-induced antinociception in mice by modulating nicotine's agonistic effect by dihydropyridine receptor agonist and antagonists.

Male ICR mice received in the first part of the experiment 0.75 mg/kg of (±) BAY K 8644 10 min before treatment with nicotine (0.01, 0.02, 0.05, 0.3 and 1 mg/kg). In the second part mice received nifedipine, nimodipine and verapamil at different doses (2. 5 and 15 mg/kg, i.p.) 20 min before treatment with nicotine (1.5 mg/kg, s.c.). There were 12 animals in each group. The antinociceptive effect was measured by the tail-flick method. BAY K 8644 and the calcium antagonists alone had no effect on the tail flick test. On the other hand, BAY K 8644 enhanced the antinociceptive effect in mice by 5- to 20-fold. For example, nicotine (0.05 mg/kg) alone produced no significant effect (%MPE = 5%), whereas BAYK 8644 pretreatment increased this MPE to 74%. At higher doses of nicotine (0.25, 0.5 and 1.5 mg/kg), the enhancement by BAYK8644 was only slight and %MPE reached after these doses were 76%, 81% and 100%, respectively. The calcium antagonists reduced the analgesic effect of nicotine in a dose-related manner especially for nifedipine and nimodipinc. Verapamil at the doses of 5 and 15 mg/kg reduced the response of nicotine (1.5 mg/kg) from 72% to 43%. Nifedipine and nimodipinc at the dose of 15 mg/kg reduced the activity to 10.6% and 22.1% respectively. These findings are consistent with the biochemical observations that calcium plays a role in the pharmacological actions of nicotine. (Supported by PHS grant #DA-05274.)

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ANABOLIC STEROIDS: EVIDENCE IN MICE FOR THE PRODUCTION OF INDIRECTLY-MEDIATED BEHAVIORAL EFFECTS AT DOSES RELEVANT TO HUMAN ABUSE PATTERNS

D.R. COMPTON

Passage of the Anabolic Steroids Control Act of 1990 was primarily precipitated by growing fears over the wide spread prevalence of this abuse problem (Buckley et al., 1988; Hough 1990; Johnson et al 1989; Terney and McLain 1990; Yesalis et al., 1989). Yet, little is known about the pharmacological effects of this class of drugs other than their anabolic-androgenic properties. If the potential detrimental effects are to be elucidated, it is important that pharmacological models mimic the human abuse pattern. Testosterone and the synthetic analog nandrolone are typical examples of drugs which are abused at doses varying from 10 to 100 times that required to treat medical conditions (Anonymous 1990; Kisling et al. 1989; Strauss et al. 1985). Besides the potential hazards of anabolic steroid abuse, polydrug abuse is also a problem (Dezelsky et al. 1985; McKillop 1987; Kleiner et al. 1990). Abuse of non-steroid drugs (e.g. cocaine and marijuana) by anabolic steroid abusing individuals was found to be similar to that of the general population, so it is possible that symptoms believed to be related to steroid abuse may be due to the co-abused drugs (Anonymous 1991; Pope and Katz 1988; Pope and Katz 1990). Thus, it is reasonable to investigate the modification of behaviors induced by other drugs of abuse.

METHODS & RESULTS-- In order to determine the acute behavioral effects of anabolic steroids, testosterone propionate (TES) or nandrolone decanoate (NAN) were administered i.p. to male ICR mice in the dose range of 50 to 500 mg/kg, and effects measured between 5 min and 3 hr. These formulations possess half-lives in the mouse of 3-5 days, so the bioavailable dose was actually smaller. Neither steroid altered spontaneous locomotor or forced (rotarod) activity. Although TES decreased body temperature (2-3 hr post-injection), the difference from control was too small (<2 °C) to be considered pharmacologically relevant. However, in terms of indirect effects, a 10 min NAN pretreatment reduced (by 30%) the dose of s.c. pentobarbital necessary to induce loss of righting-reflex, without altering the duration of the loss. Additionally, a 1 hr TES pretreatment increased the cataleptic effect of i.v. Δ^9-THC from 27% to 44% at 90 min. TES pretreatment also increased the cataleptic from 15% (near control) to 38% at 3 hr.

CONCLUSIONS-- Anabolic steroids appear to increase the duration action of cannabinoids. without altering the magnitude of the cannabinoid-mediated response. Alternatively, anabolic steroids increase the magnitude of the barbiturate-mediated response, without altering the duration of action. Thus, it appears that the relatively non-toxic anabolic steroid class of drugs may augment the behavioral toxicity produced by other classes of drugs. **REFERENCES--**Available upon request.

ACKNOWLEDGMENTS-- Supported by the Commonwealth of Virginia Center on Drug Abuse and NIDA grant DA-00490.

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6-MONOACETYLMORPHINE (6MAM) ACTS ON SUPRASPINAL AND SPINAL DELTA RECEPTORS TO PRODUCE ANALGESIA IN SWISS WEBSTER MICE

J. M. FUHMOTO AND J. J. RADY

Heroin is metabolized to 6MAM and morphine and the latter accounts for the major actions of heroin. Previously, we reported that heroin given intracerebroventricularly (i.c.v.) to Swiss Webster (SW) mice acted on δ receptors in the brain. Morphine given i.c.v. acted on μ receptors in the brain. In ICR mice, heroin actived μ receptors as did morphine. The present purpose was to extend the comparison between SW and ICR mice to GMAM.

In the brain of SW mice. 6MAM activated δ receptors: 6MAM, 8 μg i.c.v. 10 min (given before the tail flick test), produced 96.8% MPE. Naltrindole, i.c.v. 10 μg, 10 min, reduced MPE to 55%. This dose of naltrindole blocked DPDPE (delta agonist) action in both SW and ICR mice. In ICR mice, i.c.v. 6MAM action was not affected by i.c.v. naltrindole. Activation of δ receptors in the brain of SW mice was supported also by lack of both i.t. yohimbine and methysergide (which block descending aminergic pathways) to affect i.c.v. 6MAM analgesia. In the brain of ICR mice, 6MAM activated μ receptors: The response to i.c.v. 6MAM (94.9%) was inhibited by i.c.v. naloxone, 0.1 μg (52.9%). Naloxone inhibited i.c.v. DAMGO, 15 min, a μ agonist, in both ICR and SW mice. In the spinal cord of SW mice, 6MAM activated δ receptors: 6MAM, 2.5 μg i.t., 5 min, produced 90.4% MPE which was reduced to 42% with naltrindole, 10 μg i.t. Natrindole did not affect 6MAM analgesia in ICR mice. Natrindole blocked the action of i.t. DPDPE in both ICR and SW mice. In the spinal cord of ICR mice. 6MAM activated μ receptors: 6MAM, i.t. (88.4%) action was inhibited by i.t. naloxone 0.1 pg, 5 min (40.2%). Naloxone i.t. blocked the action of i.t. DAMGO in both ICR and SW mice but did not affect 6MAM action in SW mice.

In SW mice, 6MAM activated δ receptors in the brain and spinal cord: Heroin activates δ receptors in the brain but μ receptors in the spinal cord while morphine activates μ receptors at both sites. In SW mice, heroin does not act through formation of morphine.

Acknowledgement: Supported by DA00451.

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STUDY OF OPIOID PEPTIDES BY LASER DESORPTION MASS SPECTROMETRY

J. Z. CHOU; S. PINTO; M. J. KREEK AND B.T. CHAIT

Studies in our laboratory and elsewhere are now focusing on the role of endogenous opioid peptides in the biological basis of addictive diseases. Using matrix-assisted laser desorption mass spectrometry (LDMS) we are developing methods for determining the presence of these opioid peptides and their processed active peptides in human and animal body fluids and tissues. We report here preliminary findings using LDMS to study the processing of dynorphin A (Dyn A) and its family of peptides in human plasma.

Dynorphin standards used in this study included Dyn A (1-6), (1-7), (1-8), (1-9). (1-10), (1-13), (2-17) and Dyn A (1-17). Typically, a sample was applied to a probe tip in a solution containing 5 g/*l* α-cyano-4-hydrosycinnamic acid in 30% acetonitrile, 70% 0.1% trifluroacetic acid (TFA). LDMS appeared to tolerate well the large excess (5 orders of magnitude) of involatile inorganic buffer contamination over peptides. Dilution studies demonstrated that LDMS is a very sensitive method (fmole level). The results from the standards encouraged us to study the LDMS response to the neuropeptides spiked in plasma, which more closely resembles a biological system. The separation methods that we esploited include C_{18} Sep Pak columns, regenerated cellulose membrane filters, and a micro-bore HPLC system with C2/C18 reverse phase column. Spiked plasma samples were diluted with 5-10 times (v/v) of acidic aqueous solution. Filtration using membrane filters was found to be the most successful first step for removing plasma proteins. At the present time, the spiked dynorphin standards can still be clearly identified by LDMS even at an initial concentration of 10^{-7}M.

The study of *in vitro* dynorphin A (1-13) breakdown in human blood was carried out to establish the validity of sample handling procedures and to demonstrate the feasibility of the method. Dyn A (1-13) was injected into fresh blood taken from normal volunteer subjects. The major degradation products of that peptide are identified by LDMS as Dyn A (1-6), (1-8). (1-8) [or (4-12)], (3-12), (2-12) and Dyn A (1-12). The precursor (Dyn A(1-13)) concentration was about 10^{-5} M. The same breakdown products were identified when Dyn (1-13) was spiked into fresh human serum and plasma, indicating that the dynorphin-peptidase that broke down Dyn A (1-13) remained in fresh serum/plasma. The relative binding probability of dynorphm between plasma and red blood cells (RBC's) in blood was determined using ^{3}H-Dyn A (1-13) and (1-9), each of which is purified extensively by HPLC. The percentage of dynorphin found in plasma was 51 ± 6%, suggesting an equal partition between the plasma and RBC's. In summary, while considerable work is needed to bring the detection level of the peptides down to the level of endogenous dynorphin contained in human plasma, the mass spectra obtained from the spiked plasma and dynorphin break down study illustrate that the method has potential for the specific characterization of neuropeptides and the sensitive detection of the processing of these peptides in biological systems.

Acknowledgment: Supported in part by NIDA I-P50-DA05130, Aaron Diamond Foundation (MJK, SP and JZC); Aaron Diamond Postdoctoral Fellowship (JZC); NIDA-KOSDA00049 (MJK) and NIH RR00862 (BTC).

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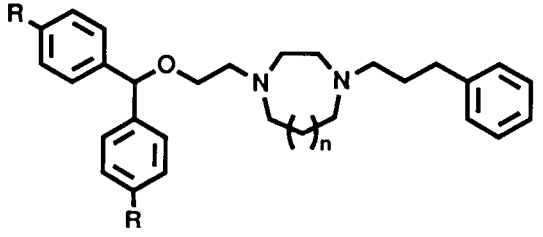
SYNTHESIS, RECEPTOR BINDING AND BEHAVIORAL STUDIES OF N-(2-DIPHENYL-METHOXYETHYL)-N'-(3PHENYL PROPYL) HOMOPIPERAZINE, (A NOVEL GBR 12935 ANALOG)

D. MATECKA[1]; L. RADESCA[1]; B. DE COSTA[1]; R. B. ROTHMAN[2]; C. DERSCH[2]; H. AKUNNE[2]; B. LEWIS[2]; J. PARTELLA[2]; H. XU[2]; A. PERT[3] AND K. C. RICE[1]

As part of our studies to gain further insight into the structure and function of the dopamine (DA) transport complex, and to establish structure activity relations in compounds structurally related to GBR12909 and GBR12935, we synthesized the title compound 1, in which the piperazine ring of the GBR series had been replaced by a homopiperazine function. In vitro studies with **1** showed results similar to those with GBR12935 and revealed the expected high affinity for the [^{3}H]GBR12935 binding site (IC_{50} = 6.7 nM). Unlike GBR12935, **1** displayed high selectivity for inhibition of [^{3}H]DA reuptake compared with [^{3}H]5HT reuptake showing IC_{50} values of 7.2 and 34000 nM, respectively.



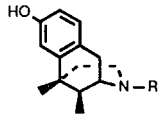
1: R = H, n = 1; GBR12909: R = F, n = 1; GBR12935: R = H, n = 0

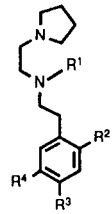
Quite surprisingly, however, **1** failed to act as a locomotor stimulant like GBR12935 and also was inactive in blocking cocaine induced locomotor stimulation. In order to understand these phenomena, we arc currently examining the hypothesis that **1** failed to enter the CNS by synthesizing and studying of [^{3}H]**1.** Plausible mechanisms for lack of penetration into the brain include: metabolic oxidation of the homopiperazine moiety and (or) inability to permeate blood brain barrier due to high lipophilicity resulting from high binding to blood proteins. Phenolic derivatives of GBR12935 and **1** were synthesized to test the lipophilicity hypothesis. They showed high affinity for [^{3}H]GBR12935 binding site (IC_{50} = 9.1 and 17.2 nM respectively), although the phenolic analog of **1 was** also inactive as a locomotor stimulant. These results suggest that these compounds might be undergoing extensive hepatic metabolism reducing the amount of parent drug available for entry into the brain. The synthesis of novel GBR analogs with structures that are less amenable to metabolic oxidation is in progress. **AFFILIATION:** [1]LMC, NIDDK, NIH, Bethesda, MD 20892; [2]LCP, NIDA, Baltimore, MD 21224,[3]BPB, NIMH, Bethesda, MD 20892

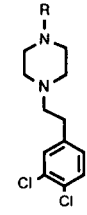
DESIGN, SYNTHESIS AND RECEPTOR BINDING PROPERTIES OF FLUORO AND IODO SUBSTITUTED SIGMA RECEPTOR LIGANDS AS POTENTIAL PET AND SPECT IMAGING AGENTS

X.-S. HE; L. RADESCA; C. DOMINGUEZ; L. DI PAOLO; W. D. BOWEN; W. WILLIAMS AND B. DE COSTA

Sigma receptors are non-opioid CNS binding sites that have been the focus of intense study because of their potential to offer new insights into the mechanisms of certain movement disorders, psychoses and neurodegeneration. The presence of sigma receptors in both the CNS and certain peripheral tissues offers a novel use of sigma ligands in both the imaging of peripheral structures such as liver as well as comparison of CNS sigma receptor distribution and density in normal and diseased states. We therefore synthesized fluoro- and iodo-substituted derivatives of three classes ((+)-benzomorphan **1.** ethylene diamine **2** and piperazine **3)** of highly potent and selective sigma receptor ligands in order to evaluate their potential as PET and SPECT imaging agents.







1. R = $CH_2CH{=}C(CH_3)_2$, (+)-Pentazocine;
(+)-**4**. R = $(CH_2)_4CH_2F$;
(-)-**4**. R = $(CH_2)_4CH_2F$.

2. $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = Cl$;
5. $R_1 = (CH_2)_4CH_2F$, $R_2 = H$, $R_3 = R_4 = Cl$;
6. $R_1 = CH_3$, $R_2 = I$, $R_3 = R_4 = Cl$;
7. $R_1 = CH_3$, $R_3 = I$, $R_2 = R_4 = H$;
8. $R_1 = CH_3$, $R_4 = I$, $R_2 = R_3 = H$.

3. R = $(CH_2)_2CH_3$;
9. R = $(CH_2)_2CH_2F$;
10. R = $(CH_2)_2CH_2I$;
11. R = $(CH_2)_4CH_2F$.

All of the F/I derivatives exhibited very high affinity and selectivity for sigma receptors labelled by [^{3}H]-(+)-3-PPP, [^{3}H]-(+)-pentazocine and [^{3}H]-DTG (Table). These ligands failed to bind significantly with either κ ([^{3}H]-Brem), PCP ([^{3}H]-TCP), D_2-dopamine ([^{3}H]-Sulp) or muscarinic cholinergic ([^{3}H]-QNB) receptors (not shown). These sites commonly cross-react with sigma receptor ligands and thus limit their utility. Within this series, compounds **6-9** proved to be amenable to labelling to high specific activity with ^{123}I for SPECT and ^{18}F for PET. The highest radiochemical yields (>93%) were obtained for the SPECT ligands 7 and 8 utilizing Sn/I exchange methodology. A 50% yield of [^{18}F]-**9** was accomplished by nucleophilic displacement of -O-SO_2CH_3 with $^{18}F^-$ from the corresponding methanesulfonate ester precursor.

Compd.	K_i (nM + SEM)		
	σ_1		σ_2
	[^{3}H](+)-3-PPP	[^{3}H](+)-Pent	[^{3}H]DTG
(+)-4	0.29±0.10	10.5±0.57	ND
(-)-4	73.6±7.1	38.9±29.4	ND
	4.22±0.84	5.07±0.84	ND
6	0.54±0.03	1.23±0.02	8.13±0.91
7	ND	2.90±0.12	38.1±5.7
8	ND	2.50±0.88	9.14±3.56
9	4.24±0.26	0.39±0.002	ND
10	1.32±0.42	1.19±0.06	ND
11	0.86±0.18	0.52±0.02	ND

Preliminary binding data with [^{123}I]-**7** revealed up to 97% specific binding in guinea pig brain thus indicating that this and related compounds may be suitable for the visualization and quantitation of sigma receptors in vivo.

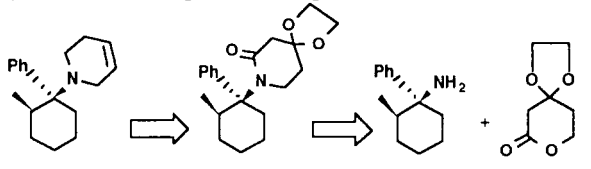
PROGRESS IN THE SYNTHESIS OF ENANTIOMERICALLY PURE PCP DERIVATIVES: 1-(1-PHENYL-2-METHYLCYCLOHEXYL)-1,2,3,6-TETRAHYDROPYRIDINES

N. A. GRAYSON, J. T. M. LINDERS AND K. C. RICE

Phencyclidine (1-(1-phenylcyclohexyl)piperidinc, PCP) is a drug of abuse which affects several different neurotransmitter systems, including the dopaminergic, cholinergic, and excitatory amino acid receptor systems. Some compounds with high affinity for the PCP binding site, such as PCP and MK-801, exhibit neuroprotective and anticonvulsant properties. The structure-activity relationships of various substituted 1-(1-phenylcyclohexyl)piperidines have therefore been the subject of our ongoing investigations into delineation and characterization of the PCP binding site. Previous studies have shown that unsaturation in the 3,4position of the piperidinc ring substantially enhances the binding affinity and may increase the neuroprotectivc effects of thesc compounds. The *trans*- 2-PCP, where the methyl substituent and the phenyl ring occupy different faces of the cyclohexyl ring, exhibits higher affinity than the corresponding *cis* -isomer. [1] We desired to synthesize PCP derivatives with optimal affinity for the PCP/NMDA receptor complex which could be used as tools for positron emission tomography (PET) studies in the mammalian brain. This could best be accomplished by combining the most attractive trails for high affinity in a compound such as 1 which can be labelled with ^{18}F.

Compound **1** could not be accessed via the Bruylants reaction, the classical approach to PCP dcrivatives[1], as previous investigations have indicated that the *trans*-isomer is not produced. In addition, experimental evidence shows that unlike the example of thienyl derivatives, a protective ketal functionality cannot be cleaved in the piperidine ring of a PCP derivative. The key intermediate in our proposed synthesis was therefore a ring-closed piperidinone compound such as 2, where the basic nature of the nitrogen is masked.

The synthesis of target compound 1 did not follow the original proposal due to the inaccessibilty of lactone **4.** Instead, the anhydride precursor of 4 was reacted directly with **3** to give a ring-opened amide derivative of **2.** The carbosylic acid functionality of this intermediate was easily reduced with lithium aluminum hydride or alane to produce the alcohol, but the amide functionality remained untouched. Various attempts to cyclize the ring-opened intermediate failed due to facile elimination of the alcohol or loss of the side-chain. Future synthetic efforts must therefore be concentrated on alternate methods of ring closure followed by elimination to produce compound **1.**



1 **2** **3** **4**

[1]Iorio, M. A.; Tomassini L. T.; Mattson M. V.; George C.; Jacobson, A. E., J Med Chem, 34 (8): 2615-2623, 1991; and references therein.

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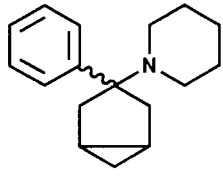
SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW CONFORMATIONALLY RESTRICTED PCP ANALOGS

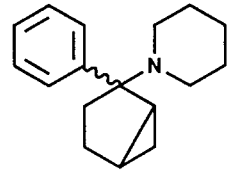
M. V. MATTSON; B. R. DECOSTA; J. T. M. LINDERS AND A. E. JACOBSON

PCP (1-(1-phenylcyclohexyl)piperidine) has been found to act as a noncompetitive antagonist for the NMDA-receptor ionophore complex. This receptor is involved in normal neuronal functions, as well as in excitotoxity and neurodegenerative diseases. In our program for the delineation of the structure and function of the PCP binding site associated with the NMDA receptor, we have recently concentrated on the synthesis and biological evaluation of isomeric methyl substituted PCP derivatives. Based on the conformations and binding affinities of these compounds, we have constructed a model of the PCP binding site. (J.T.M. Linders et al., 1992)

More information about the structural requirements of the binding site can be obtained from conformationally restricted analogs of PCP. For example, methano- and ethano-bridged analogs of PCP (C.F. Bigge et al., 1992) show higher affinity for the PCP binding site than PCP, while the adamantyl derivative (H. Weinstein et al., 1983), which combines both the Phax and Pheq conformations of the phenylcyclohexyl moiety, was found to be devoid of affinity. In contrast, replacing the cyclohexane ring with a bicyclo[3.1.0]hexane moiety restricts the conformational freedom without introducing additional steric bulk.



cis/trans I



cis/trans II

The affinity of these compounds for the PCP binding site (vs [^{3}H]TCP) ranges between 0.6 and 29 μM (PCP 0.065 μM). The low affinity can be explained by the preference for the Pheq conformation (**cis II**) and steric interaction of the cyclopropane ring with the binding site (**trans I** and **trans II**). **Trans-I** has been shown to exist in a pseudo-boat conformation (X-ray, courtesy of C. George, NRL, Washington, D.C.), which may not be recognized by the PCP binding site. Furthermore, **I** and **II** can be considered as substituted analogs of 1-(1-phenylcyclopentyl)piperidine, which is known to have significantly lower affinity than PCP for the PCP binding site.

REFERENCES: Available upon request.

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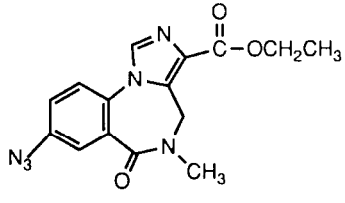
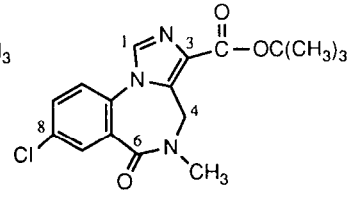
SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL $GABA_A$/BENZODIAZEPINE RECEPTOR LIGANDS SELECTIVE FOR THE DIAZEPAM INSENSITIVE (DI) SUBTYPE

Z.-Q. GU; G. WONG; P. SKOLNICK AND K. C. RICE

The diazepam insensitive subtype of benzodiazepine receptor (DI) represents a novel GABAA receptor isoform. The DI exhibits a ligand specificity distinguished from other diazepam sensitive (DS) sites by low affinities (>1 μm) for benzodiazepines (e.g. diazepam, flunitrazepam), triazolobenzodiazepines (e.g. triazolam) and triazolopyridazines (e.g. CL 218,872), but high affinities for imidazobenzodiazepinones, such as Ro 15-4513 (K_i = 3.1 nM, ethyl 5-methyl-8-azido-6-oxo-4H-imidazo[l,5-a][1,4]benzodiazepine 3-carboxylate, **I**). Recent studies have implicated the DI in the antagonism of some of the pharmacological effects of ethanol. These include: 1) the ability of Ro 15-4513, Ro 15-3505 and Ro 19-4603 to antagonize some of the biochemical and behavioral effects of ethanol, 2) the high affinity of these compounds for DI, 3) the lack of measurable DI in alcohol non-tolerant rats, 4) the predominant cerebellar localization of DI in humans, rodents, birds and fishes. Nonetheless, the involvement of DI in alcohol antagonism remains highly controversial due to the lack of benzodiazepine receptor selectivity of high affinity DI ligands. In order to define the structural requirements of high affinity to DI and to develop DI selective ligands, a novel series of 5,6-dihydro-5-methyl-8-chloro-6-oxo-4H-imidazo[l1,5-a][1,4]benzodiazepine 3-carboxylate compounds were designed and synthesized based upon previous structure-affinity relationship studies. These compounds exhibit a broad range of affinities at DI dependent upon the 3-position ester moiety. Differences in the steric tolerance at this ester moiety between DS and DI were observed and led to the development of a series of DI selective ligands. Among compounds evaluated, the tert-butyl analog (tert-butyl 5-methyl-8-chloro-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, **II**), possessed the highest affinity K_i = 1.7 nM versus 3.1 nM for Ro 15-4513) and selectivity for DI described to date. Such a compound should prove useful in elucidating the physiological and pharmacological role of this unique GABAA receptor subtype.



I



II

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PRESENCE OF METHADONE BINDING SITES ON HUMAN LUNG CANCER CELLS DISTINCT FROM THOSE FOUND IN RAT BRAIN

R. Maneckjee and J. D. Minna

Human lung cancer cells of various histologic types were found to express specific, saturable and high affinity (10^{-9} M) binding sites for methadone. These sites were found to be biologically active as methadone binding was accompanied by decreases in intracellular cAMP levels. However, these receptors do not appear to be coupled to a pertussis toxin-sensitive guanine, nucleotide-binding protein. Methadone significantly inhibited the in vitro growth of human lung cancer at nM concentrations. Growth inhibition was irreversible after a 24 hour exposure to the drug. Methadone also inhibited the in vivo growth of these cells in nude mice xenografts. The binding and growth inhibitory actions of methadone could be reversed by the opioid antagonist naloxone. suggesting involvement of opioid binding sites. Effects of methadone in these cells could be reversed by actinomycin-D and cycloheximide, suggesting requirement for new mRNA and protein synthesis. Biochemical and pharmacological characterization of these binding sites on lung cancer cells showed them to be distinct from those present in rat brain. Methadone has generally been considered to behave as a μ agonist. However, [^{3}H]-methadone binding to lung cancer cell membranes, in contrast to rat brain membranes, could be effectively displaced with ligands specific for the k, σ and PCP receptors, but not with μ and δ–specific ligands and appears to be relatively insensitive to protein modifying agents and GTP. The presence of methadone binding sites in human lung cancer cells different from those in brain and the significant growth inhibitory effect of methadone in these cells may be of clinical importance. This data suggests that methadone could be potentially useful in the treatment of human lung cancer.

References: Maneckjee, R. and Minna, J. D. Nonconventional opioid binding sites mediate growth inhibitory effects of methadone on human lung cancer cells. Proc. Natl. Sci. (USA) 89:1169-1173, 1992.

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ACTIVATING PROTEIN KINASE C RAPIDLY DOWNREGULATES NALOXONE-RESISTANT RECEPTORS FOR β-ENDORPHIN ON U937 CELLS

N. A . SHAHABI AND B. M. SHARP

Activation of protein kinase-C (PKC) has been reported to modify a variety of receptor-ligand interactions, including that of tumor necrosis factor-a with immune cells. Thus, we studied the effect of phorbol esters on the binding of β-endorphin to naloxone-resistant receptors on the promonocyte-like U937 cell line. After incubating intact U937 cells with phorbol 12-myristate, 13-acetate (PMA, 100 nM) at 22°C for 30 min, the specific binding of ^{125}I-β-endorphin was maximally reduced by approximately 40%. Only PMA (10-150 nM), and not the biologically inactive phorbol, 4α-phorbol 12,13-didecanoate (4α-PDD), caused this rapid, dose-dependent down-regulation. PMA did not interfere with the radioreceptor assay nor did it induce down-regulation when incubated with cell membrane. Scatchard analysis revealed that PMA significantly reduced both the number of receptors and Kd (10,640 receptors/cell and Kd=2.9±0.1 nM for control vs. 4,868 receptors/cell and Kd=1.5±0.7 nM for 150 nM PMA). The effect of PMA was abolished by preincubating cells with the inhibitors of PKC, N-(2-aminoethyl)-isoquinolinesulfonamide (H-9) or 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7). Down-regulation was reversible; removing 100 nM PMA from the media partially restored binding by 3h and completely by 24h. At 22°C internalization of ^{125}I-β-endorphin was not observed, and this was not altered by PMA. These results show that activation of PKC rapidly down-regulated the naloxone-resistant receptor for β-endorphin on intact U937 cells; the number of receptors available for interaction with the ligand was reduced by a mechanism independent of internalization.

ACKNOWLEDGEMENTS: Supported by NIDA 04196.

AFFILIATIONS: Minneapolis Medical Research Foundation and the Departments of Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis, MN.

MECHANISMS OF MODIFIED OPIOID RECEPTOR-G-PROTEIN FUNCTION IN NG108-15 CELLS

D. E. SELLEY AND S. R. CHILDERS

Opioid receptors are negatively coupled to adenylyl cyclase through a G-protein mechanism. Treatment of rat brain membranes at pH 4.5 prior to assay at pH 7.4 has been shown to: 1) increase the inhibition of adenylyl cyclase activity by opioid agonists, 2) decrease stimulation of adenylyl cyclase activity by receptor-mediated or direct (fluoride) activation of G_s, and 3) increase the inhibition of opioid agonist binding by sodium and guanine nucleoudes. The NG108-15 cell line, which contains only **δ** opioid receptors, has been chosen as a model system to investigate the mechanism of action of low pH pretreatment in altering opioid receptor-G-protein function. Data show that low pH pre-treatment of NG108-15 membranes increased the maximal inhibition of adenylyl cyclase by the opioid agonist DSLET, without changing the IC_{50} value or the basal enzyme activity. This increased inhibition was accompanied by decreased G_s-mediated stimulation of adenylyl cyclase activity, and increased inhibition of [^{3}H]DPDPE binding by sodium, but not by guanine nucleotides. Scatchard plots revealed no significant change in the K_D or B_{max} values of opioid agonist binding to NG108-15 membranes, indicating that the number of G-protein-coupled opioid receptors was unchanged. These results are similar to those previously obtained in rat brain membranes. In addition, the maximal inhibition of NG108-15 adenylyl cyclase by muscarinic and cannabinoid agonists was also increased by low pH pretreatment. Studies of the effect of sodium concentration on adenylyl cyclase activity in NG108-15 membranes revealed that low pH pretreatment: 1) decreased basal adenylyl cyclase activity in a manner that was inversely related to the sodium concentration and 2) increased opioid inhibition of adenylyl cyclase at sodium concentrations below that required to support opioid inhibition of the enzyme in control membranes. Studies of the effect of low pH pretreatment of NG108-15 membranes on DSLET-stimulated low K_m GTPase activity revealed that neither the maximal stimulation nor the ED_{50} value of the agonist was altered by the treatment, though there was a slight, but nonsignificant, decrease in basal low K_m GTPase activity. Similar sodium requirements for DLSET-stimulation of low K_m GTPase were observed between control and low pH-pretreated membranes. However, removal of sodium from the pretreatment buffers (replacement of sodium with ammonium salts) resulted in an increase in the maximal stimulation of low K_m GTPase by DSLET in pH 4.5-pretreated membranes. These results indicate that the mechanism of action by which low pH pretreatment modifies G-protein-mediated signal transduction in NG108-15 cell membranes may be related to the ability of the pretreatment to mimic or enhance the effects of sodium. Thus, acidification of membranes prior to assay is not only a convenient method for enhancing receptor-mediated inhibition of adenylyl cyclase, but may also provide insight into the complex regulatory function of sodium in this biochemical signalling pathway.

Supported by PHS grants DA-02904 and DA-07246 from NIDA.

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DOSE-DEPENDENT DOWNREGULATION OF OPIOID RECEPTORS IN MICE

B. C. YOBURN, A. DUTTAROY AND B. BILLINGS

The contribution of changes in opioid receptor density to opioid agonist potency has been well-documented. For example,. increases in receptor density following chronic opioid antagonist treatment are associated with supersensitivity to opioid agonist effects. However, the role that receptor downregulation plays in tolerance following chronic agonist treatment is not yet clear. Some studies have reported tolerance in the absence of receptor changes, while others report that downregulation as well as upregulation can accompany tolerance. In the present study, mice were infused (ALZET® Minipump) with etorphine (50-1000µg/kg/day) or fentanyl (0.03-5.0mg/kg/day) or implanted with a placebo pellet. On the 8th day of infusion mice were either sacrificed and saturation opioid binding studies ([^{3}HIDAMGO) conducted in brain, or mice were examined for analgesia (tailflick) in dose-response studies. Etorphine produced dose-dependent downregulation of binding site density (10-45%) with minimal effects on affinity. Dose-dependent tolerance (2-4-fold potency decrease) was observed following etorphine infusions. Fentanyl infusions upregulated (≈ +20%) receptor density at low doses (0.03-1 .0mg/kg/day) and downregulated (≈-25%) receptors at the highest dose (5,0mg/kg/day). The lowest dose produced a 2-fold reduction in fentanyl's analgesic potency. In a second experiment, mice were injected daily for 7 days with fentanyl (0.3mg/kg, s.c.). This dosing protocol produced upregulation (+25%) and tolerance (≈2-fold). In a final experiment, mice were injected acutely with etorphine (21 µg/kg, s.c.) and binding studies conducted periodically (15min-20hr). Acute etorphine reduced receptor density by 65% 15min following administration and this downregulation was completely gone by 16hr. These results suggested that etorphine-induced downregulation immediately following infusions may be due to interference with binding. Therefore, mice were infused with etorphine (50-500µg/kg/day) for 200hr, the pumps removed, and binding and analgesia studies conducted 16hr later. Under these conditions, dose-dependent downregulation was still observed, However, the lowest dose (50µg/kg/day) produced tolerance but not downregulation. Both downregulation and tolerance were observed with the highest dose (50µg/kg/day).

This study demonstrates that tolerance and opioid receptor downregulation are related to etorphine dose. Conversely, fentanyl infusions upregulated receptors and produced tolerance at low doses and downregulated receptors at higher doses. Similarly, daily s.c. fentanyl upregulated receptors and generated tolerance. Thus, while tolerance and downregulation can occur simultaneously, our data indicate that downregulation is not necessary for the development of tolerance. Furthermore, chronic opioid agonist treatment can produce concurrent upregulation and tolerance. The functional significance of opioid agonist-induced receptor regulation remains to be determined.
(Supported by NIDA; DA 04185)

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MORPHINE-3-GLUCURONIDE, SILENT REGULATOR OF MORPHINE ACTIONS

A. W. LIPKOWSRI*+; A. LANGLADE*#; P. F. OSGOOD*;
S. K. SZYFELBEIN* AND D. B. CARR*

The morphine remains the drug of choice for patients with severe pain. Glucuronidation of morphine is a major route for biotransformation in humans and other mammals. Recently attention has focused on the importance of morphine metabolites as effecters of opioid actions during chronic therapy. Morphine-3-glucuronide (M3G), a metabolite that lacks opioid receptor affinity or analgesic activity, is a major product of glucuronidation, rapidly generated after acute doses of morphine. During chronic morphine treatment the relative plasma concentrations of morphine, M3G and M6G are constant and independent of morphine dose. Such a stable ratio suggests the presence of an equilibrium between metabolic substrate and products, resulting from either deactivation of UDP-glucuronosyltransferase by end-products or by induction of reversed enzyme activity. Thus one might predict that co-administration of the opioid inactive metabolite M3G at the time of morphine administration might acutely shift the equilibrium between parent and daughter compounds, thereby raising the plasma concentration of morphine and increasing and/or prolonging its analgesic effect. Further, if chronic morphine (i.e., substrate) administration does induce metabolic processes that increase metabolite formation, such activation of clearance may contribute to morphine tolerance in vivo as manifest by an increasing dosage requirement to maintain a therapeutic effect during repetitive dosing. In this case, co-administration of M3G may prevent an increase in dosage requirement that arises through this mechanism.

To examine our prediction we conducted two experiments. In our first experiment we have tested whether co-injection of M3G modifies the acute analgesic activity of morphine. We found that M3G significantly increased the antinociceptive activity of morphine, and also increased the integrated antinociceptive response. The second experiment showed that M3G may prevent of the development tolerance to morphine. In rats, s.c. co-injection of M3G with morphine developing of tolerance to morphine was significantly lower compared to rats treated with morphine alone.

The obtained data shows that morphine-3-glucuronide which itself does not express any nociceptive activity has strong positive effect on morphine action when injected systematically.

On the base of our experiment, we see potential clinical use of M3G as a co-injected agent for systematically injected morphine, or other benzomorphan related opioid drugs. The additive of M3G to morphine may delay developing tolerance in long term morphine anesthesia.

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THE EFFECTS OF A 3-METHYL GROUP ON THE OPIOID RECEPTOR SELECTIVITY OF 4-PHENYLPIPERIDINES

M. FROMOWITZ; A. D. KHANOLKAR; G. W. PASTERNAK; V. CODY AND A. MAKRIYANNIS

Based on conformational energy calculations, it has been suggested that symmetrically substituted 4-phenylpiperidines such as meperidine, ketobemidone, and 3-demethylprodine will contain a pair of mirror image conformers (Froimowitz 1982). Ketobemidone HCl was studied by x-ray crystallography and found to contain both mirror images. This raises the question as to which conformer is responsible for opioid activity. To answer this, phenyl meta-hydroxylated and nonhydroxylated 3-methyl analogs of the compounds are being synthesized and resolved to provide compounds that are conformationally homogeneous.

Opioid receptor affinities (nM) for the nonhydroxylated 3-methyl compounds are shown below. Also included are the results for meperidine and ketobemidone. The affinities of all of the compounds is highest for u-receptors with little affinity for δ- and κ-receptors. In all three series, the β-3-methyl compound has higher affinity than the α-3-methyl compound. The compound with the highest affinity is β-prodine which is consistent with its high *in vivo* potency. The β-3-methyl group causes a ten-fold increase in affinity for n-receptors in the meperidine analog compared with the parent compound. Ketobemidone, which contains a phenyl meta-hydroxyl group, has extremely high affinity for u-receptors for which it has moderate selectivity.

name	4-group	3-CH_3	μ_1	μ_2	δ	κ_1	κ_3
meperidine	COOEt	none	320	>1000	>1000	>1000	>1000
ketobemidone	COEt	none	0.67	8.09	188	1910	107
	COOEt	α	430	>1000	>1000	>1000	>1000
	COOEt	β	33	211	>1000	>1000	818
	COEt	α	971	>1000	>1000	>1000	>1000
	COEt	β	202	>1000	>1000	>1000	>1000
α-prodine	OCOEt	α	76	501	>1000	>1000	>1000
β-prodine	OCOEt	β	19	100	>1000	>1000	485

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ACKNOWLEDGEMENTS: This work was supported by NIDA grant 04762 (to MF)

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REPEATED, DAILY COCAINE ADMINISTRATION PRODUCES CHANGES IN BASAL AND OPIOID-REGULATED ADENYLYL CYCLASE ACTIVITY IN RAT CAUDATE-PUTAMEN AND NUCLEUS ACCUBENS

S. IZENWASSER; E. M. UNTERWALD*; T. E. COTE; B. M. COX AND M. J. KREEK*

Cocaine is a psychomotor stimulant that inhibits the reuptake of dopamine into presynaptic dopaminergic terminals. Repeated exposure to cocaine has been shown to alter opioid receptor densities in rat brain. To investigate the functional consequences of cocaine-induced opioid receptor changes, adenyl cyclase activity was measured in rat caudate-putamen and nucleus accumbens following repeated cocaine administration. Activation of opioid receptors leads to inhibition of adenylyl cyclase activity. Male Fischer (CDF) rats were treated daily for 14 days with injections of saline or cocaine HCl (30 mg/kg/day i.p.) in three equal doses over a two hour period. On day 14,30 min after the last injection, animals were sacrificed, the brains were rapidly removed and the rostra1 portion of the caudate-putamen and/or nucleus accumbens were separately dissected on ice. The effects of DAMGO (a selective μ-opioid receptor agonist) and DPDPE (a selective δ-opioid receptor agonist) were examined on adenylyl cyclase activity in crude membrane preparations using a cAMP radioligand binding assay. There was a 50% decrease in basal adenylyl cyclase activity in caudate-putamen of cocaine-injected animals as compared with saline controls. Cocaine injections had no effect on basal adenylyl cyclase activity in nucleus accumbens. DAMGO and DPDPE maximally inhibited approximately 25% and 30%, respectively, of basal adenylyl cyclase in saline-treated animals. Cocaine administration greatly reduced the inhibition of adenylyl cyclase by DPDPE in both caudate-putamen and nucleus accumbens. There was, however, no change in the inhibition of adenylyl cyclase by DAMGO in either brain region following cocaine treatment. These results suggest that repeated cocaine administration results in a selective impairment of δ-opioid receptor mediated effector function in caudate-putamen and nucleus accumbens.

Supported by grants from NIDA (BMC, MJK) and Aaron Diamond Foundation (MJK).

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CHANGES IN STRIATAL DOPAMINE METABOLISM DURING THE DEVELOPMENT OF MORPHINE DEPENDENCE: PRELIMINARY OBSERVATIONS USING IN VIVO MICRODIALYSIS IN RATS

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Numerous studies over the past several years have examined the effects of morphine on the release and metabolism of dopamine (DA) in the brain. Utilizing in vitro brain homogenate methods, these studies indicated that acute morphine administration increased DA metabolism in the striatum and other areas, thereby suggesting that morphine-induced changes in DA neuronal function may be an important element in the development of physical dependence. In the present study, we tested this notion more directly, using in vivo microdialysis (MD) to obtain successive measures of DA and its metabolites during the early phase of the development of morphine dependence.

Sprague-Dawley rats were implanted with chronic guides for MD of the striatum. Morphine (two 75-mg pellets; s.c. implant) or placebo (two pellets) was given (12 hr) to pentobarbital anesthetized animals. MD samples were collected every 20 min for 2-hr baseline and hourly for 12-hr pellet exposure. Following recovery from anesthesia, dependence was measured by the naloxone-evoked abstinence syndrome. MD samples were analyzed for DA and its metabolites (DOPAC; HVA) using high performance liquid chromatography with electrochemical detection.

The results showed that morphine significantly increased the striatal efflux of DOPAC and HVA; DA was measured only sporadically, at low levels. HVA levels began to increase immediately following morphine administration, whereas DOPAC levels began to increase after a latency of 3 hr. Morphine effects on striatal DA metabolism were also evident in the metabolic disposition of DA. Increases in HVA concentration accompanied increases in DOPAC concentration up to DOPAC efflux values of about 40 fmol/min; thereafter, however, increases in DOPAC concentration were associated with decreases in HVA concentration. The morphine-treatcd animals demonstrated significant dependence after the MD sampling period.

These in vivo data lend further support to the hypothesis that morphine-induced changes in the regulation of dopaminergic function may be an important contributor to the development of physical dependence. These changes in the rat striatum include increases in the extracellular levels of DA metabolites and, above a threshold level of DOPAC efflux, a shift in the metabolic disposition of DA toward reduced levels of HVA.

ACKNOWLEDGMENT: Supported by NIDA Grant DA02254.
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ACUTE AND CHRONIC BUPRENORPHINE TREATMENT: DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS OF CONSCIOUS RAT

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Buprenorphine (BUP) is a synthetic opioid with mixed mu partial agonist and kappa antagonist activity which has been reported to be successful in the treatment of opioid addiction (Jasinski et al 1978) and possibly cocaine abuse (Mello et al 1989). In behavioral studies acute BUP appears to potentiate cocaine's ability to condition a place preference in rats (Brown et al 1991) whereas chronic BUP pretreatment attenuates this effect of cocaine (Kosten et al 1991). In this microdialysis study we have investigated the effects of both acute and chronic buprenorphine on dopamine release in the nucleus accumbens of conscious, freely moving rats.

Concentric dialysis probes were stereotaxically implanted into the nucleus accumbens of male Wistar rats (270-300g). 48 hours later the probe was perfused at 2 µl/minute with a physiological medium. Samples were collected every 20 minutes and the dopmaine content measured by HPLC-ECD. When release of dopamine into three consecutive samples was stable, drugs or saline were administered and sampling continued for the next 3 hours.

Acute BUP (0.01, 0.05, 0.1, 0.5, 1 and 5 mg/kg i.p.) increased basal dopamine release for at least 3 hours. The mean total percent increases over 3 hours were 496, 600, 1231, 1443, 606 and 874% respectively. No increases in release were seen in vehicle controls. Co-administration of the mu antagonist naltrexone (1.0 mg/kg i.p.) greatly inhibited the dopmainergic response to BUP (0.1 mg/kg i.p.). The mean total percent increase in dopamine release over 3 hours was 1328% in the SAL/BUP treated rats as compared with 313% in the NALT/BUP group. The response to a BUP (0.1 mg/kg i.p.) challenge 24 hours after chronic BUP pretreatment (0.5 mg/kg s.c., twice a day, 4 days) was also investigated. The mean total percent increase in dopamine release over 3 hours was attenuated by chronic BUP pretreatment (161%) as compared with chronic SAL pretreatment (821%).

Acute BUP (0.01 - 0.5 mg/kg) significantly increased dopamine release in rat nucleus accumbens. Whilst the higher doses (1 & 5 mg/kg) also caused significant increases compared with controls, these increases were less than those at the lower doses, suggesting a bell-shaped dose response curve. Inhibition of BUP-induced dopamine release by naltrexone indicates the involvement of the mu agonist activity of BUP. The decreased response to a BUP challenge after chronic treatment suggests development of tolerance to the dopamine-releasing effects of DA. In light of these findings we will now also examine the effects of chronic BUP pretreatment on cocaine-induced dopamine release.

REFERENCES -- available upon request from senior author.

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CATECHOLAMINE ANALYSIS BY HPLC AT FEMTOMOLE LEVEL

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In performing microdialysis analysis of catecholamines low pmol sensitivity is essential. A wide variety of catecholamine HPLC methods are available. Based on the experience we have gained from working with catecholamines on HPLC, we present here a method based on theory which was hoped to provide higher sensitivity in catecholamine analysis. HPLC analysis of basic amines like catecholamines has traditionally been particularly problematic. It appears that high hydrophobicity and extensive end-capping of columns with a mobile phase containing special solvent modifiers for amines is the optimal condition for catecholamine separation. The present method was developed by refinement of a previous method based on the above principles using radial compression column technology. By optimizing the chromatographic conditions a signal-noise level equivalent to 45 fmol dopamine was obtained. Concerns that the low buffer strength (~ 2.5 mM phosphate) employed would lead to an erratic retention was disproved, since a retention C.V. of 2.2% was found (N=10) for dopamine over a period of three days. The procedure allowed separation of norepinephrine, dopamine, DOPAC, 5-HT, 5-HIAA and HVA with a total run time of 25 min. The minimum value measurement of dopamine by this method was around 135 fmol per sample. With new custom designed small diameter columns, this method might be able to provide an additional improvement in sensitivity of catecholamine measurement.

However, this method proved not to be anymore sensitive or specific than more commonly used methods, including the method now in use in our laboratory (Maisonneuve et al., 1992).

ACKNOWLEDGEMENTS

Funded in part by NIDA Research Center DA05130;
Assistance of Ms. Jennifer Home-King is acknowledge.

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EFFECTS OF A SERIES OF ACUTE COCAINE INJECTIONS ON THE DOPAMINERGIC SYSTEMS IN RATS: AN IN VIVO MICRODIALYSIS STUDY

I. M. MAISNNEUVE, H. ALBECK AND M. J. KREEK

Although numerous studies have investigated the effects of cocaine on the dopaminergic systems, none of them have mimicked the human pattern of cocaine administration. Cocaine users self-administer cocaine frequently (q 10-30 min) over a period of several hours (2-24 hrs) and many users remain abstinent for several days. The aim of the present study was to determine how a rapid succession of cocaine injections alter dopamine (DA) levels.

In a rat model, using in vivo microdialysis, we studied in the nucleus accumbens and striatum the time course of extracellular DA levels induced by acute triple injections of cocaine (3x10 mg/kg, i.p.) administered over a period of 2 hrs. In both regions cocaine increased extracellular DA levels immediately after the first injection. The two last cocaine injections produced greater DA increases that did not differ from each other. DA metabolites levels were decreased by the administration of cocaine, except striatal HVA levels that were not altered. Cocaine's effects on DA levels were similar in the two regions, but the effects on DA metabolites were greater in the nucleus accumbens.

These results suggest that repeated injections of cocaine might maintain increased, but stable DA levels. By self-administering cocaine frequently over a few hours addicts may succeed in sustaining, but not increasing the drug-rewarding effect. Further studies are warranted to explore the chronic effects of this novel administration paradigm.

ACKNOWLEDGEMENTS: Supported by the Aaron Diamond Foundation

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INDUCTION OF THE PIROTO-ONCOGENE *C-FOS* FOLLOWING ACUTE AND CHRONIC COCAINE ADMINISTRATION IN RATS

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The proto-oncogene *c-fos* and its protein product (Fos) can be transiently induced in a regionally selective manner by numerous central nervous system manipulations including seizures, stress, and drug administration. Repeated, intermittent administration of cocaine results in the development of behavioral sensitization (at low doses) or kindling (at higher doses). The present study was designed to examine the effects on c-fos of acute and repeated cocaine administration in rats, in conjunction with observational measures of stereotypy and seizure occurrence.

Rats *were* injected with cocaine (40 mg/kg) or saline for 5 days, or saline for 4 days and cocaine on the last day (acute control). Rats were sacrificed either one-half hour (for mRNA) or two hours (for protein and immunohistochemistry) after the last injection. Total mRNA from the striatum and hippocampus was isolated and separated by gel electrophoresis. The gels were then transferred to nitrocellulose and probed for c-fos mRNA. Nuclear protein was isolated, separated by SDS-PAGE, transferred to nitrocellulose labelled for Fos and Fos-related antigens with a polyclonal antibody that recognizes the Fos m-peptide. For immunohistochemistry, rats were perfused with saline followed by 4% paraformaldehyde. The brains were sliced and processed for Fos-like immunoreactivity.

Rats with a single injection of cocaine showed a two to four-fold increase in c-fos mRNA and Fos protein in the striatum compared to the saline-injected controls. Rats with repeated injections displayed greater behavioral stereotypies, yet showed significantly attenuated increases in c-fos mRNA and protein in the striatum compared to a single injection. A Fos-related antigen (Fra) was also increased with cocaine administration, but this induction did not decrease with repeated administration. *In situ* immunohistochemistry showed that it was both the number of cells and the amount of Fos-like immunoreactivity that were increased after a single injection and diminished after five injections. No increases were found in the hippocampus, except in animals experiencing cocaine-induced seizures.

Repeated administration of cocaine changes the relative expression of Fos and Fras as behavioral sensitization develops. It is suggested that cocaine administration induces a sequence of events that leads to transient increases in gene transcription and translation of Fos in the striatum, which, in turn, may affect the transcription of genes for peptides (e.g., dynorphin and somatostatin) and receptors (e.g., p-receptors) that are altered by chronic cocaine. These effects of cocaine mediated at the level of gene expression may underlit the long-lasting behavioral and psychological consequences of cocaine use.

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DOPAMINE AND SEROTONIN BIOSYNTHESIS IN RAT BRAIN AFTER CHRONIC COCAINE

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It is well established that acute cocaine treatment increases extraneuronal DA ***in vivo*** via inhibition of the DA reuptake mechanism[1]. Interestingly, cocaine also decreases DA biosynthesis in a variety of projection areas[2], and this inhibitory action is presumably a feedback response mediated by elevated synaptic transmitter. Thus, cocaine's effects on DA neurotransmission are biphasic in nature characterized by an initial increase in extraneuronal DA that leads to a compensatory decrease in transmitter synthesis. It is noteworthy that cocaine also suppresses 5-HT biosynthesis' suggesting that 5-HT neurons and DA neurons are influenced by the drug in a similar manner. The purpose of the present study was to examine the effects of acute and chronic cocaine on DA and 5-HT synthesis in various brain regions implicated in drug reinforcement. Male rats were treated twice daily with cocaine (15 mg/kg, ip) or saline for one week. After 42 hr of abstinence, rats were challenged with either cocaine (15 mg/kg, ip) or saline (1 ml/kg, ip), followed by the aromatic L-amino acid decarboxylase inhibitor NSD-1015 (100 mg/kg, ip). Thirty minutes after NSD-1015 rats were decapitated, and discrete brain regions were microdissected from 300 pm frozen sections. Post-mortem tissue levels of DOPA and 5-HTP were quantified by HPLC-EC and used to estimate biosynthesis of DA and 5-HT, respectively. In chronic saline-treated rats, cocaine dramatically suppressed DA and 5-HT synthesis in all forebrain regions examined, including: medial prefrontal cortex, nucleus accumbens, caudate nucleus, olfactory tubercle and basolateral amygdala. The degree of inhibition ranged from 30%-65% and was more pronounced in 5-HT neurons compared to DA neurons in the same tissue sample. In general, chronic cocaine did not alter basal levels of DOPA or 5-HTP; a notable exception was lateral hypothalamus, where chronic cocaine significantly reduced basal DA synthesis to 75% of control. After repeated cocaine injections, the synthesis-inhibiting effect of cocaine was attenuated in many brain areas. These data suggest that, while acute cocaine decreases DA and 5-HT synthesis in forebrain, chronic cocaine is not neurotoxic to DA and 5-HT neurons. Furthermore, the mechanism(s) mediating cocaine-induced suppression of monoamine synthesis may become desensitized by chronic drug exposure.

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A STUDY ON THE MECHANISM BY WHICH DOPAMINE REUPTAKE BLOCKERS INHIBIT [^{3}H]MAZINDOL BINDING TO THE DOPAMINE TRANSPORTER

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The present study addressed the hypothesis that there exist multiple sites/states associated with the dopamine (DA) transporter in striatal membranes. Incubations with [^{3}H]mazindol proceeded for 18-24 hr at 4°C in 55.2 mM sodium phosphate buffer, pH 7.4, with a protease inhibitor cocktail. In order to obtain data suitable for quantitative curve fitting, it was necessary periodically to repurify the [^{3}H]mazindol by HPLC. Under these conditions, we observed greater than 80% specific binding. The method of binding surface analysis was used to characterize the interaction of GBR12935, BTCP, mazindol, and CFT with binding site/sites labeled by [^{3}H]-mazindol. Unlike results obtained with [^{3}H]GBR12935 and [^{3}H]BTCP (see Akunne et al, this volume), fitting the data to one and two site binding models (using MLAB-PC) demonstrated that the one site model fit the data as well as the two site model:

Parameter	Value ± SD
Bmax (fmol/mg)	16911 ± 1554
Mazindol (Kd, nM)	74.6 ± 7.1
GBR12935 (Kd. nM)	8.10 ± 0.47
CFT (Kd, nM)	49.7 ± 3.0
BTCP (Kd, nM)	44.0 ± 3.8

The data of two binding surfaces (520 data points) were fit to the one site and two site binding models. The SS for both models were 6306.

All agents tested (GBR12935, CFT, BTCP, cocaine, cis-flupenthixol, nomifensine, WIN35.065-2, bupropion, PCP and benzotropine) were competitive inhibitors.

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STRUCTURE-ACTIVITY-RELATIONSHIP OF N-SUBSTITUTED-N-NORMETAZOCINE (NSNM) ANALOGS FOR BINDING TO PCP AND μ OPIOID RECEPTORS

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Early studies of the benzomorphan group utilizing the N-allyl-analog of normetazocine (NANM, SKF 10,047) have shown that the (+)-isomers of NANM and related benzomorphans are relatively specific PCP-like drugs, whereas the (-)-isomers have typical mu and/or kappa opioid actions. Variation of substituents on the benzomorphan nucleus, particularly on the nitrogen, results in significant changes in biological responses. The present study showed that the binding potency and selectivity of N-substituted-normetazocine (NSNM) analogs to the PCP and mu opioid receptor sites are sensitive to changes in the N-substituent and to the stereochemistry of the benzomorphan. Optical antipodes of NSNM analogs were synthesized and evaluated for their ability to compete for 3H-TCP (KD = 7.7 nM) and ^{3}H-DAMGO (KD = 1.9 nM) binding to rat brain membranes as well as for their behavioral properties. The analogs demonstrated only modest stereoselectivity for the ^{3}H-TCP site with the greatest affinity residing in either the (-)- or (+)-isomer. (+)-N-Normetazocine (KI = 30 nM) displayed the highest affinity for the PCP receptor followed by (+)-metazocine (KI = 41 nM) and (-)-cyclazocine (KI = 48 nM), which are only slightly less potent. None of the other analogs, all of which possess larger N-substituents, showed appreciable affinity for the PCP site. As shown in other current studies (Balster personal communication) most compounds show a poor correlation between PCP-like behavioral effects and affinity for the PCP receptor. All of the analogs exhibited a large degree of stereoselectivity for the ^{3}H-DAMGO site with the greatest aftinity residing in the (-)-isomers. (-)-Cyclazocine (KI = 0.18 nM) and (-)-phenazocine (KI = 0.2 nM) are the most potent compounds for the mu opioid receptor. Additionally a good correlation exists between in vitro affinity for the opioid receptor and in vivo activity in antinociceptive assays. (Supported by NIDA grants DA-05721, DA-02396 and DA-00490)

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DISPOSITION OF ANTI-PCP FAB FRAGMENTS IN RATS

S. M. OWENS; M. B. MCCLURKAN; T. M. BADGER; D. J. IRBY AND J. L. VALENTINE

Treatment of drug toxicity is problematic for compounds like phencyclidine (PCP) which have no known antagonists. With the advent of technology for production of large amounts of monoclonal antibodies (MAb), it is now possible to use these antibodies as *in vivo* antagonists for treatment of PCP overdose. In the current study, the pharmacokinetics of an anti-PCP MAb Fab fragments (K_d=1.8 nM) were determined in rats (n=5). Sprague-Dawley rats were cannulated and dosed with 40 mg of unlabeled Fab with a tracer dose of anti-PCP [^{3}H]Fab. Blood was drawn at predetermined intervals and serum was analyzed for total radioactivity by liquid scintillation spectrometry. Serum and urine were analyzed for intact anti-PCP [^{3}H]Fab after fractionation on a HPLC molecular weight sizing column followed by quantitation by liquid scintillation spectrometry. The pharmacokinetic parameters for the Fab in rat serum were an apparent volume of distribution of 1.6±0.36 L/kg, terminal elimination $t_{1/2}$ of 6.9±1.2 hrs, and systemic and renal clearance of 2.8±0.9 and 0.64 ml/min/kg, respectively. Urinary excretion of intact Fab accounted for 23.2± 18.4% of the total dose. This study is an important first step toward deciding a rational use of anti-PCP MAb Fab fragments in the treatment of PCP overdose.

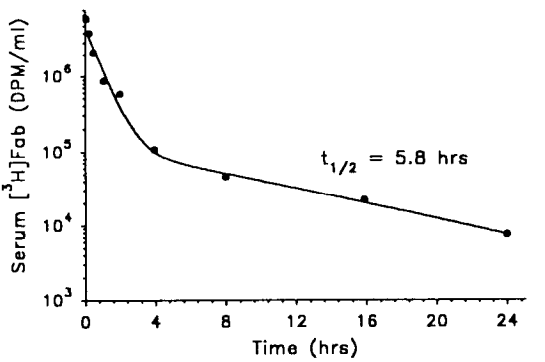

Figure 1. Representative plot of intact anti-PCP [^{3}H]Fab concentrations vs. time after an iv bolus dose of anti-PCP [^{3}H]Fab and 40 mg/kg unlabeled Fab in a rat.

ACKNOWLEDGEMENTS: This work was supported by NIDA grants DA07610 & DA041 36 and Research Scientist Development Award (SMO) K02 DA00110).

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DIFFERENTIAL REGULATION OF THE DEVELOPING NMDA RECEPTOR-CHANNEL COMPLEX BY PHENCYCLIDINE

R. SIRCAR

Phencyclindine (PCP) exhibits unique psychotomimetic, anticonvulsant and neuroprotective properties and reproduces the neuropsychological deficits of schizophrenia. PCP and PCP-like drugs selectively inhibit N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in a noncompetitive manner. PCP is known to cross both placental and blood-brain barrier with relative ease. During development, the NMDA receptor-channel complex has been shown to be involved in activity-dependent synaptic plasticity. To determine whether exposure to PCP during development modulates the NMDA receptor complex, [^{3}H]MK-801 binding was measured in postnatal rats treated chronically with PCP; [^{3}H]MK-801 binding was used as a marker for NMDA channel activity. Rat pups were injected (i.p.) daily with PCP (5 mg/kg) or saline beginning on postnatal day 5 till day 15. Animals were sacrificed on postnatal day 21 and crude synaptosomal membranes (csm) were prepared from their pooled frontal corticles and hippocampi (forebrain). Well-washed, frozen-thawed forebrain csm from experimental and control rat pups were incubated with graded concentrations of [^{3}H]MK-801 (0.1-300 nM), in the virtual absence of any excitatory amino acids (basal condtion) and also under various degrees of channel activation i.e. in the presence of L-glutamate and/or glucine. Under basal conditions, data from saturation studies indicate that PCP treatment produced a decrease in the density of high-affinity [^{3}H]MK-801 binding sites and an increase in the density of low-affinity sites compared to controls. When binding was carried out in the presence of 10 μM L-glutamate either alone or in the added presence of glycine there was no apparent difference in binding between the PCP- and saline-treated brains. But when [^{3}H]MK-801 binding was measured in the presence of glycine (10 μM) alone, the density of high-affinity binding in the PCP-treated rats was significantly lower than saline-treated animals. The affinities of [^{3}H]MK-801 binding did not apparently differ under any condition. Together, these data suggest that chronic exposure to PCP during postnatal period differentially regulates the NMDA receptor-channel complex.

ACKNOWLEDGEMENTS

This study was supported by the National Institute on Drug Abuse, (PHS Grant #7188), the National Alliance for Research on Schizophrenia and Depression, the National Alliance for Mentally Ill, and by the Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY.

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SIGMA LIGANDS HAVE REDUCED ABILITY TO INHIBIT THE MUSCARINIC PHOSPHOINOSITIDE RESPONSE IN CELLS DEFICIENT IN SIGMA-1 RECEPTORS

J. M. CUTE, B. R. DE COSTA AND W. D. BOWEN

We have previously presented evidence that sigma-1 receptors mediate the ability of sigma ligands to attenuate the stimulation of phosphoinositide (PPI) turnover by muscarinic agonists in rat brain synaptoneurosomes (Bowen et al. 1992). However, the finding that sigma ligands bind to muscarinic receptors with micromolar affinity has clouded the issue of sigma-1 receptor involvement in this effect. To test the requirement for sigma-l receptors we have further examined the effect of sigma ligands in cells which possess a muscarinic PPI response, but which do not possess a high density of sigma-l receptors. The potency of these ligands (3, 10, and 30 uM, unless mentioned otherwise) was then compared to that in rat brain synaptoneurosomes. PC12 pheochromocytoma cells and N1E-115 and SK-N-SH neuroblastomas contain a high density of sigma-2 sites (as well as a novel binding site for (+)-pentazocine; Vilner et al. this volume), but a low to negligible density of sigma-l sites (Vilner and Bowen 1992). In PC12 and N1E-115 cells, DTG and (+)-pentazocine inhibited 10 uM oxotremorine-M (oxo-M) stimulated PPI turnover with similar potency as in rat brain synaptoneurosomes. However, BD737 and BD1008 had considerably reduced potency in cell lines. Dextrallorphan (100 uM) and reduced haloperidol were essentially inactive in PC12 cells. In SK-N-SH cells, all of the above-mentioned sigma ligands were either inactive or showed markedly reduced potency compared to synaptoneurosmes. oxo-M dose curves (1 - 1000 uM) were performed in the absence and presence of (+)-pentazocine. We had previously shown in rat brain synaptoneurosomes that 10 uM (+)-pentazocine was a non-competitive inhibitor, markedly reducing the maximal stimulation with only a small effect on the EC_{50} (Bowen et al. 1992). In contrast, (+)-pentazocine (10 and 30 uM, respectively) was purely a competitive inhibitor in NIE-115 and SK-N-SH cells, having no effect on the maximal stimulation but causing a pronounced increase in the oxo-M EC_{50}. Similar results were obtained with DTG. These data suggest that co-localization of sigma-1 sites and muscarinic receptors in the same cell is required to produce the relatively potent, non-competitive inhibition of the PPI response. This is strong evidence that activation of sigma-l receptors attenuates signalling via muscarinic receptors. Weak, competitive inhibition may be the result of direct interaction of sigma ligands with muscarinic receptors.

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PRELIMINARY EVIDENCE FOR MULTIPLE α1 BINDING SITES/STATED LABELLED BY [^{3}H](+)-PENTAZOCINE IN GUINEA PIG BRAIN

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We have evaluated the interaction of analogs of GBR12909 (13) and dextromethorphan (33) with al binding sites labelled with [^{3}H](+)-pentazocine ([^{3}H]P). Incubations proceeded for 4-6 hr at 25° C in 5 mM TRIS-HCl, pH 8.2, along with a protease inhibitor cocktail. Structure-activity studies demonstrated a bimodal distribution of slope factors, with most compounds having slope factors of 1, or greater than 1. Only two compounds had consistently low slope factors: the apparent IC50 (nM ± SD) values and slope factor (N) of LR1109 and LR1127 were 50 ± 15.9 (N=0.46 ± 0.06) and 47.7 ± 11 (N = 0.58 ± 0.07). Slope factor less than 1 are consistent with a hypothesis of two binding sites. We therefore used binding surface analysis to resolve multiple binding sites. Two concentrations of [^{3}H]P (0.5 and 2.5 nM) were each displaced by 9 concentrations of 1) (+)-pentazocine, 2) LR1109 and 3) LR1127 in absence and presence of blockers (50 nM LR1109,200 nM LR1127, or 2 nM (+)-pentazocine). A two site binding model fit the data (214 data points) considerably better than a one site binding model:

Best-Fit Parameter Estimates of the Two site Model

Parameter	Site 1 (±SEM)	Site 2 (±SEM)
Bmax (fmol/mg protein	2400 ± 10	480±6
(+)-Pentazocine (Kd, nM)	4.9±0.1	0.075 ± 0.004
LR1109 (Ki, nM)	215±3	8.0 ± 0.4
LR1127 (Ki, nM)	250±4	7.1 ± 0.4

The data shown in Figure 3 were tit to the two site model, using MLAB-PC. The best-tit parameter estimates (±SEM) are reported above.

These data provide preliminary evidence for the extistence of multiple ϭ]l binding sites or states in guinea pig brain.

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PRELIMINARY EVIDENCE FOR A CONTAMINANT IN HEPPSO BUFFER WITH HIGH AFFINITY FOR σ1 BINDING SITES

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Previous studies using [^{3}H](+)-pentazocine ([3H]P) to label σ_1 receptors in guinea pig brain homogenates demonstrated discrepant results between batches of HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxy-propanesulfonic acid] buffer purchased two years apart: there appeared to be a competitive inhibitor present in the more recent batch of HEPPSO that was not present in either the earlier batch of HEPPSO or in TRIS-HCI buffer (Rothman - unpublished data). To characterize this factor, 100 ml of 0.2 M HEPPSO was acidified and extracted with 3 x 100 ml anhydrous ethyl ether or chloroform. The aqueous phase was made basic and extracted with 3 x 100 ml ether or chloroform. Under these conditions HEPPSO was retained totally in the aqueous phase. The organic phase was washed with 2 x 100 ml water and evaporated. The residue was resuspended in ethanol which was made 50% with water to a total volume of 1 ml and tested in the [^{3}H]P binding assay. As a control, HEPES was extracted in ether as described and also tested in the [^{3}H]P binding assay. An ether blank did not inhibit [^{3}H]P binding. As summarized below, HEPPSO and HEPES buffer inhibited [^{3}H]P binding to guinea pig brain membranes. The HEPPSO organic extract potently inhibited [^{3}H]P binding. The organic extract from HEPES was inhibitory only at very high doses. While extracted HEPPSO became less potent after ether extraction, extracted HEPES became more potent. The explanation for the latter observation requires further investigation.

	IC50(±SEM)	
	HEPPSO	HEPES
Buffer (mM)	3.12±0.50 (N=5)	77.2±34.5 (N=5)
Organic Extract (µl)	0.151±0.04 (N=9)	5.15±0.45 (N=2)
Extracted Buffer (mM)	12.7±0.99 (N=6)	18.0±3.6 (N=4)

In summary, HEPPSO preparations contain an inhibitor of [3H]P binding which is extractable into chloroform or ether and which can be recovered in ethanol. We hope to purify this factor by HPLC for subsequent structural identification by mass spectroscopy.

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SIGMA-1 AND SIGMA-2 BINDING SITES OF RAT KIDNEY

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There is now evidence from several laboratories for the existence of two subtypes of sigma sites, termed sigma-l and sigma-2 (Quirion et al. 1992). While (-)-benzomorphans do not distinguish the sites, sigma-2 sites have markedly reduced affinity for (+)-benzomorphans, resulting in (-)-isomers having higher affinity than (+)-isomers (Hellewell and Bowen 1990). We have previously shown using photoaffinity labeling and ligand binding that rat liver contains both of these sites (Bruce et al. 1990). Here, we characterize sigma binding sites in rat kidney. [^{3}H]DTG (which labels sigma-1 and sigma-2 sites) labeled sites with Kd = 45.8 nM and Bmax = 1,190 fmol/mg protein. [^{3}H](+)-Pentazocine (selective for sigma-1) labeled sites with Kd = 23.3 nM and Bmax = 229 fmol/mg protein. Both ligands gave linear Scatchard plots. Competition studies revealed that sites labeled by [^{3}H]DTG (3 nM) and [^{3}H](+)-pentazocine (3 nM) had profiles which differed mainly in affinity for (+)-benzomorphans. For [3H](+)-pentazocine-labeled sites: haloperidol > (+)-pentazocine > (-)-pentazocine > (+)-3-PPP > (+)-SKF 10,047 > (-)-SKF 10,047. When [^{3}H]DTG binding was carried out in the presence of 1 uM dextrallorphan (a condition which masks labeling of sigma-l receptors; Bruce et al. 1990): haloperidol = (-)-pentazocine > (+)-3-PPP > (+)-pentazocine = (-)-SKF 10,047 >> (+)-SKF 10,047. All curves were monophasic. Thus, [^{3}H](+)-pentazocine gave the typical sigma-1 profile, while [^{3}H]DTG gave the sigma-2 profile. The ratio of Bmax values for [^{3}H](+)-pentazocine and [^{3}H]DTG would suggest that rat kidney contains only 20% sigma-1 sites and 80% sigma-2 sites. Consistent with this notion, in the absence of the masking concentration of dextrallorphan, [^{3}H]DTG gave an overall sigma-2 profile and (+)-benzomorphans exhibited biphasic curves. The ratio of sigma-1 to sigma-2 in rat kidney is similar to the ratio in rat liver, which is 25% sigma-1 and 75% sigma-2 (Bruce et al. 1990). However, the density of each site in kidney is 10-fold lower compared to liver, and is more comparable to the densities found in rat brain. The presence of sigma sites in brain, liver, and kidney suggests important cellular functions for these sites.

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CHARACTERIZATION OF A NON-SIGMA-1, NON-SIGMA-2 BINDING SITE FOR [^{3}H](+)-PENTAZOCINE

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We have previously reported that several clonal cell lines including NB41A3 neuroblastoma, C6 glioma, and NG108-15 hybrid cells contain sigma-2 sites as determined by binding of [^{3}H]DTG (Vilner and Bowen 1992). However, the presence of sigma-1 sites was difficult to detect, as binding of the highly sigma-1 selective ligand, [^{3}H](+)-pentazocine was anomalous. Here we further characterize sites labeled by this radioligand and show that [^{3}H](+)-pentazocine labels a novel site in these cells. Binding was carried out on membranes prepared from these cells in 50 mM Tris-HCl, pH 8.0 at 25°C for 120 min. Non-specific binding was determined in the presence of 10 uM (+)-pentazocine. Saturation analysis revealed the presence of two sites (range of values in the three cell types): Kd1 = 3.0 - 7.0 nM, Bmax1 = 31.4 - 76.5 fmol/mg protein; Kd2 = 247 - 360 nM, Bmax2 = 946 - 5,431 fmol/mg protein. The Kd of the high affinity site is consistent with that of sigma-l, while the low affinity, high capacity site represents a novel binding site. Competition of 10 nM [^{3}H](+)-pentazocine with various sigma ligands revealed the following rank order of potency: haloperidol > (+)-pentazocine = dextrallorphan > (+)-3-PPP > DTG > (-)-pentazocine > fluphenazine = (+)-SKF 10,047 > (-)-SKF 10,047. MK-801, naloxone, and naltrexone were inactive. The data shows that this site has some of the characteristics of sigma-1 sites, such as enantioselectivity for (+)-benzomorphans over the (-)-isomer. This site also has some of the characteristics of sigma-2 sites, such as a Ki for haloperidol = 29 - 65 nM and only moderate affinity for (+)-3-PPP (Ki = 132 - 436 nM). However, certain characteristics clearly distinguish this site from either sigma-1 or sigma-2 sites. For example in NB41A3 cells, Ki's for (+)-pentazocine (98 nM), dextrallorphan (207 nM), and (+)-SKF 10,047 (418 nM) are intermediate between their sigma-1 and sigma-2 values, and DTG has an affinity (Ki = 1,028 nM) which is about 30 times lower than affinity at sigma-1 and sigma-2 sites (Hellewell and Bowen 1990; Vilner and Bowen 1992). This site was also found in high density in N1E-115 and SK-N-SH neuroblastomas. This site may represent a novel subtype of sigma binding site. Further work is needed to verify this.

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SENSITIZATION TO 5-HT_{1C} RECEPTOR AGONISTS IN ETHANOL (ETOH) WITHDRAWN RATS

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Recent evidence suggest that alteration in 5-hydroxytryptamine (5-HT) system in the brain may be associated with ETOH drinking and ETOH withdrawal (EW) related-anxiety. Drugs which reduce 5-HT neurotransmission in the brain reverse anxiety-like behaviors in a variety of animal models (Chopin and Briley, 1987). We have previously reported that buspirone (Lal et al., 1991), a 5-HT_{1A} agonist and mianserin (Prather et al, 1991). a 5-$HT_{2/1C}$ antagonist blocked anxiogenic behaviors observed during EW in rats. In these studies, a reduction in the open-arm activity in the elevated plus-maze (EPM) reflected an anxiogenic behavior caused by cessation of chronic ethanol. Using the same paradigm, we tested the hypothesis that 5-HT_{1C} receptors are up-regulated by chronic ETOH and after withdrawal this change is manifested as a sensitization to 5-HT_{1C} agonist drugs.

Long-Evans hooded rats were fed a liquid diet containing 4.5% ETOH for 5 d (Lal et al,. 1988) followed by a final dose of 3g/kg ETOH by gavage. Control animals received a liquid diet with dextrin isocalorically substituted for ETOH. Twelve hours after the last ETOH dose, rats were tested in EPM and the percent open arm entries (%OAE) and percent time spent (%OAT) in the open arms were measured. In rats fed the ETOH diet, the %OAE and %OAT were reduced during ETOH withdrawal. Pre-treatment with m-chlorophenyl-piperazine (mCPP), a 5-HT_{1C} agonist, further reduced the %OAE and %OAT, with a dose of 0.32 mg/kg producing a maximum reduction. A much higher dose (eight-fold) was required to produce the same effect in naive rats. Similarly, action of another $5HT_{1C}$ agonist, 1-NP (1-naphthylpiperazine), was enhanced. In contrast, DO1 (2,5-dimethoxy-4-ido-phenyl-2-aminopropane), a 5-HT_2 agonist, was equipotent in both naive and ETOH withdrawn rats. Further, Clozapine, a 5-HT_{1C} receptor antagonist, but not altanserine, a 5-HT_2 antagonist, reversed the EW-induced reduction in the %OAE. These data support the hypothesis that the 5-HT_{1C} receptors are sensitized during EW, and that antagonists with selective affinity for 5-HT_{1C} receptors may be beneficial in the treatment of anxiety precipitated by withdrawal from chronic ETOH (Supported by NIAAA grant No. AA06890).

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF A RIGID ANALOG OF NICOTINE

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In the search for potent centrally active nicotinic agents, an important question has been what the internal dimensions of the active site are. One approach to this question is to determine the active conformation by synthesizing analogs in which the nicotine structure is held in a particular conformation by 'bridging' units. If active, it is reasonable to suppose that the particular conformation represented by the rigid analog is the active conformation. Previous studies in this area (Kachur et al. 1986, Kanne and Abood 1988) have not been successful. We now report the preliminary results of a new rigid analog of nicotine, **1,** and its nor derivative, **2.**

1 R = -CH_3
2 R = -H

In the mouse tail-flick assay the ED_{50}'s (μM/kg) for **1** and **2** are 6.7 and 49.4 (nicotine ED_{50}=6.5, nornicotine=inactive).In disruption of spontaneous activity in the mouse, the ED_{50}'s (μM/kg) for **1** and **2** are 10.2 and 24.7 (nicotine ED_{50}=11.1, nomicotine=29,7).In displacing [^{3}H]-(+)-nicotine from rat brain homogenate, the K_i (nM) for **1** is 0.79-3.55 (nicotine K_i=0.7-2.4). In contrast, compound **1** failed to produce generalization in rats trained to discriminate nicotine from saline, though it augments the action of nicotine. The drug discrimination data suggests that **1** acts at an allosteric site, while the other *in vivo* and *in vitro* data support a more direct, agonistic mode of action for **1.** These results are still preliminary, and further work is needed before any firm conclusions can be drawn.

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ACKNOWLEDGEMENTS

This work was supported by National Institute on Drug Abuse grants DA05274-04, DA07027, DA00490-16 and by the German Research Council on Smoking and Health, Bonn, Germany.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON MORPHINE ANALGESIA

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Pharmacogenetic techniques allow for the examination of both genetic and environmental factors underlying phenotypes associated with drug response. Initial studies on inbred strains of mice obtained from Jackson Laboratories (JAX) indicated that the C57BL/6J strain was more sensitive to morphine analgesia as determined by the hot plate test than the SJL/J strain of mice. A Mendelian-cross breeding program was initiated to examine the genetic factors which may contribute to morphine-induced analgesia. C57BL and SJL mice obtained from JAX were crossed to produce F1, F2, backcross and additional parental generations. The initial genetic analysis of the Mendelian cross generations indicated that there is a significant genetic influence on sensitivity to morphine-induced analgesia characterized by significant heterosis or dominance towards reduced sensitivity with the F1 generation being significantly less sensitive to morphine-induced analgesia than either parental strain. Mathematical analysis of the generation means revealed that a simple additive-dominance model with no epistatic interactions between genes at different loci best described the data. A model with no genetic parameters did not fit the data. Environmental factors also appeared to affect sensitivity to morphine analgesia. C57BL and SJL mice raised in our facility did not differ in their analgesic response to morphine. Comparison of the ED56 values derived from the dose effect curves for SJL mice obtained directly from JAX with those reared in our facilities revealed that animals raised in our facility were more sensitive to morphine's analgesic effect. This finding suggested that environmental factors were also having a significant impact on the expression of genetic differences related to morphine's analgesic effect.

While the exact nature of these environmental factors remains to be determined, one variable that may possibly affect morphine-induced analgesia is intrastrain aggression. SJL mice from JAX are known to exhibit a high degree of intrastrain aggression, while SJL mice raised in our facilities showed little or no aggression. The level of aggression to which SJL mice had been exposed was assessed by evaluating the physical evidence of fighting i.e. the number of bite marks and scabs on each individual animal prior to analgesia testing. It was observed that exposure to aggression correlated significantly with sensitivity to morphine analgesia, such that those mice exposed to increasingly greater levels of aggression were the least sensitive to morphine. Thus, the changes observed in sensitivity to morphine-induced analgesia appear to be related to the degree of aggression to which these mice are exposed. This change could possibly result from the stress and/or prolonged exposure to painful stimuli associated with aggressive encounters.

LONG-LASTING MU AND KAPPA OPIOID ANTAGONISTIC AND SHORT-TERM KAPPA AGONISTIC EFFECTS OF 14β-(THIOGLYCOLAMIDO)-7,8-DIHYDRO-N(CYCLOPROPYLMETHYL)-NOR-MORPHINONE IN THE MOUSE

Q. JIANG; A. SEYED-MOZAFFARI; S. ARCHER AND J. M. BIDLACK

Opioid agonistic and antagonistic properties of 14β-(thioglycolamido)-7,8-dihydro-N(cyclopropylmethyl)-normorphinone (N-CPM-TAMO) were characterized in the 55 °C warm-water mouse tail-flick and acetic acid-induced writhing assays. All opioids were given by intracerebroventricular (*i.c.v.*) administrations and antinociceptions were tested at 10 min after *i.c.v.* injection in both assays. N-CPM-TAMO had no antinociceptive effect up to a dose of 300 nmol in the mouse tail-flick assay. However, pretreatment of mice with N-CPM-TAMO produced a time- and dose-dependent antagonism of morphine-induced antinociception, but not that of the δ agonist, [D-Pen^2,D-Pen^5]enkephalin (DPDPE). The antagonistic effect of N-CPM-TAMO (1 nmol) appeared at 8 hr after *i.c.v.* administration and lasted up to 72 hr, with a maximum at 16-24 hr. The antagonistic dose range for *i.c.v.* N-CPM-TAMO at -24 hr was from 0.03 to 1 nmol against 3 nmol morphine, which produced about 70% antinociception by itself. Similarly, pretreatment of mice with N-CPM-TAMO from 10 to 100 nmol at -24 hr also produced a dose-dependent antagonism of the κ-selective agonist, U50,488-induced antinociception. In the mouse writhing assay, N-CPM-TAMO produced a time- and dose-dependent antinociception after *i.c.v.* administration. The agonistic effect lasted less than 4 hr. The antinociceptive D_{50} value (and 95 % C.L.) for *i.c.v.* N-CPM-TAMO was 18.4 (10.6 - 31.9) nmol. This antinociceptive effect of N-CPM-TAMO was blocked by co-administration of the κ-selective antagonist, nor-binaltorphimine (nor-BNI), in a dose-dependent manner. Pretreatment with N-CPM-TAMO also produced a time- and dose-dependent antagonism of U50,488-induced antinociception. This antagonistic effect of N-CPM-TAMO was seen at 16 hr after administration and lasted up to 72 hr, with a maximum at 24 hr. The antagonistic dose range for *i.c.v.* N-CPM-TAMO at -24 hr was from 10 to 300 nmol against 10 nmol U50,488 which produced approximately 60% antinociception. Therefore, these data suggest that N-CPM-TAMO selectively acts as a long-term μ antagonist. In addition, higher doses of N-CPM-TAMO also produced short-term antinociception and long-lasting antagonism at κ opioid receptors.

Acknowledgement: This work was supported by NIDA grants DA03742 and DA01674.

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EVIDENCE THAT INTRACEREBROVENTRICULAR (I.C.V.) CALCIUM STIMULATES SPINAL DYNORPHIN RELEASE TO INHIBIT MORPHINE ANALGESIA IN MICE

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Abundant evidence indicates that a close relationship exists between opiate analgesia and calcium fluxes across neuronal membranes. Hano et al., (1964) demonstrated that i.c. injection of Ca++ antagonizes morphine analgesia, and conversely, the Ca++ chelator EGTA potentiates morphine analgesia. In addition, ionophores (X-537A or A23187) enhance the antagonistic effect of Ca++ on morphine analgesia (Harris et al., 1975; Vocci et al., 1980). Since the activity of ionophores is largely that of increasing intracellular Ca++ (Pressman 1976). it was postulated that Ca++ alters intracellular events to antagonize morphine analgesia (for review see Chapman and Way 1980).

It has been reported that raising the concentration of extracellular Ca++ stimulates an increase in cytosolic Ca++ in numerous systems (for two reviews see Borle 1981; Rasmussen and Barrett 1984). We have demonstrated that raising extracellular Ca++ stimulates an increase in free intracellular Ca++ in several neuronal preparations. In cultured PC-12 cells, raising extracellular Ca++ from 0.1 to 3 mM produced a 21 to 86% increase in free intracellular Ca++. In cultured dorsal root ganglia, raising extracellular Ca++ from 2 to 8 mM increased the levels of free intracellular Ca++ by 140% in the soma, 30% in neutric processes and 209% in neuritic varicosities. Verapamil (10 μM) attenuated 8 mM Ca++-stimulated increases by 30% in the soma, 49% in neuritic processes and 42% in neuritic varicosities. In mouse brain synaptosomes, raising extracellular Ca++ from 0.1 mM to 3.0 mM produced an 89% increase in free intracellular Ca++. The effects of opiates on Ca++ content in brain regions and synaptosomes supports the view that opioid exposure leads to reductions in levels of intracellular Ca++ (Cardenas and Ross 1976; Harris et al., 1976; Ross et al. 1974; Ross et al.. 1976). μ-Opioids have been shown to hyperpolarize neurons by opening membrane K+ channels (North and Williams 1985), and this may explain the ability of morphine to attenuate KCl-stimulated increases in free intracellular Ca++ (Welch et al. 1991). In synaptosomes we confirmed that morphine (1 μM) attenuates KCl-stimulated rises in free intracellular Ca++. However, raising extracellular Ca++ to 3 mM blocked the effect of morphine to attenuate KCl-stimulated levels in free intracellular Ca++. This indicates that morphine-induced analgesia may be blocked, in part, by the ability of Ca++ injected i.c.v. to increase free intracellular Ca++ levels, thereby obviating the inhibitory effects of morphine on Ca++ levels.

Other investigators have discovered that dynoprhin A inhibits the analgesic effects of opioids (Fujimoto and Arts 1990; Fujimoto and Holmes 1990; Song and Takemori 1991). Experiments were conducted to determine if Ca++ injected i.c.v. also stimulated dynorphin release in the spinal cord to inhibit opiate-induced analgesia in the tail-flick test. Morphine (1.5 mg/kg, s.c.) alone produced an 82±12%MPE. Morphine-induced analgesia was blocked when Ca++ (550 nmol) was injected i.c.v. (6±3 % MPE). Naloxone (2.8 fmoles) and nor-BNI (13.6 pmol) injected i.t. blocked the inhibition of morphine analgesia by Ca++. In addition, the antiserum to dynorphin (1-13) (100μg) injected i.t. blocked the inhibition of morphine analgesia Ca++. These data indicate that Ca++ may also block morphine analgesia, in part, by stimulating the release of dynorphin in the spinal cord.

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INTERACTION 0F INTRATHECALLY ADMINISTERED (I.T.) POTASSIUM CHANNEL OPENERS AND BLOCKERS WITH OPIATE SYSTEMS

S. P. WELCH AND D. L. DUNLOW

The type of the potassium channel upon which morphine acts has not been determined, although evidence suggests that the channel may be an ATP-gated potassium channel (Ocana et al., 1990; Vergoni et al., 1992). Morphine has been shown to hyperpolarize neurons by enhancement of the outflow of potassium (Chavkin, 1988). High doses of glucose to mice produces hyperglycemia and decreases the potency of morphine in vivo and in vitro (Simon and Dewey, 1981) possibly by the increased formation of intracellular ATP which blocks the ATP-gated potassium channels. The blockade of these channels would increase calcium entry, and counter the hyperpolarization induced by morphine. The potassium channel openers such as diazoxide, minoxidil, and lemakalim (BRL 38227) share with morphine the ability to open potassium channels. The potassium channel openers may represent a novel class of drugs for the management of pain. Thus, comparison of the profile of such drugs to morphine would be important in order to determine the opiate interactions of the drugs which could lead to possible side effects such as tolerance and dependence. We chose to evaluate the effects of the potassium channel ligands following administration to the spinal segmental area (i.t.) in combination with either peripherally (s.c.) or centrally (i.t.) administered morphine. We investigated the calcium-gate potassium channels blocked by apamin or charybdotoxin, as well as the ATP-gated potassium channel blocked by glyburide. In addition, we evaluated the effects of the potassium channel blockers, TEA and 4-AP in combination with morphine and the potassium channel openers. In studying the interaction of the potassium channel openers with opiate systems we attempted to block the antinociceptive effects of the potassium channel openers with the mu antagonist, naloxone, the kappa antagonist, norbinaltorphimine (nor-BNI), and the delta antagonist, ICI 174864 (ICI). We examined the cross-tolerance of the potassium channel openers with morphine in morphine-tolerant mice. We also compared the ability of apamin and glyburide to precipitate withdrawal in morphine dependent mice to that of naloxone.

Diazoxide (i.t.) produced antinociception (ED50 = 90 μg/mouse) which was blocked totally by the i.t. administration of nor-BNI (2 μg/mouse), ICI (0.5 μg/mouse), naloxone (1 μg/mouse), apamin (50 μg/moose)) and charybdotoxin (2.50 μg/mouse) and partially blocked by glyburide (300 μg/mouse). Minoxidil (i.t.) produced antinociception (ED_{50} = 200 μg/mouse) which was blocked totally by naloxone (AD_{50} = 0.03 mg/kg, s.c.) and naloxone (1 μg/mouse, i.t.), ICI (0.1 μg/mouse), and glyburide (100 μg/mouse), but not by nor-BNI, apamin, or charybdotoxin. Lemakalim (BRL 38227) produced antinociception (ED50 = 40 μg/mouse, i.t.) which was blocked totally by ICI (2 μg/mouse), glyburide, and partially by naloxone (1 μg/mouse, i.t.), but not blocked by apamin, charybdotoxin, or nor-BNI. Morphine (2 μg/mouse, i.t.) was blocked partially by glyburide (150 μg/mouse) and apamin, but not charybdotoxin, or galanin. These data indicate that opening of diverse K^+ channels in the spinal cord results in opiate-sensitive antinociception and conversely, that morphine produces antinociception by interaction with calcium and ATP-gated K^+ channels. Through these studies we observed opiate/potassium channel interactions which may provide a lead as to the mechanism of action of morphine, as well as the potassium channel openers, in the production of antinociception. This work was supported by DA06031, DA05274, DA01647. (References available from primary author). Affliliation: Dept. of PMC/TOX, MCV/VCU, Richmond, VA 23298

RECEPTOR SELECTIVITY OF THE ANALGESIC EFFECTS OF ICV MORPHINE IN THE COLD WATER TAIL-FLICK TEST IN RATS

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In analgesic assays, morphine usually acts as a relatively pure m agonist; however, this may have little to do with the selectivity of morphine for the μ-opioid receptor, but may be primarily due to the fact that δ and κ agonists are not efficacious in many analgesic assays. The cold water tail-flick test in the rat is somewhat unique in its sensitivity to the analgesic effects of both δ- and κ-opioid agonists (Adams et al., 1992; Tiseo et al., 1988); thus, a component of morphine-induced analgesia in this test might be mediated by δ- or κ-opioid receptors. To test this hypothesis, morphine was administered icv in combination with the nonselective opioid antagonist naloxone (NLX), as well as μ-, δ- and κ-selective antagonists. D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr (CTAP), naltrindole (NTI) and norbinaltorphimine (norBNI), respectively. Male rats, implanted with icv cannulae, were tested for latency to withdraw their tails from an ethylene glyco/water bath maintained at -3°C (average baseline latency=6.0 sec [range 2.0-17.6 sec, N=199]; cutoff time=60 sec). Naloxone (10μg) or NT1 (1.0μg) was co-administered icv with morphine. With CTAP (1.0 μg) and norBN1 (0.1-20μg), antagonist injection preceded agonist injection by 15 and 30 min, respectively. Tail-flick latency was tested at, 30.45 and 60 min after agonist injection. Morphine induced analgesia in a dose-related manner; administration of NLX or CTAP antagonized morphine in a competitive fashion. Administration of NTI had no effect at all on the morphine dose-effect curve. The K-selective dose of 0.1 μg norBNI did not affect the analgesia induced by morphine; higher doses (10-20 μg) of norBN1 did antagonize morphine, but were found to be nonselective. Thus, there does not appear to be a δ- or κ-opioid component to analgesia induced by morphine in the cold water tail-flick test, at least by the icv route.

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ACKNOWLEDGEMENT

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OPIOID RECEPTOR SELECTIVITY OF INTRATHECALLY ADMINISTERED NALTRINDOLE AND NALTRINDOLE BENZOFURAN IN THE RAT: STUDIES WITH THE CARRAGEENAN-INFLAMED PAW FLICK TEST

P. E. STEWART AND D. L. HAMMOND

Recent studies with the δ-selective opioid antagonist naltrindole (NTI) support the presence of δ-mediated antinociception in the spinal cord of the rat (Drower et al., 1991). Naltrindole benzofuran (NTB) is also reported to be a selective antagonist for the δ opioid receptor in the mouse (Sofuoglu et al., 1991). This study examined the selectivity and potency of NTI and NTB as opioid receptor antagonists using a rat model of hyperalgesia, the carrageenan-inflamed paw flick test (Hargreaves et al. 1988). Male Sprague-Dawley rats were injected s.c. with 2 mg carrageenan in one hindpaw. Three hr later, paw-flick latency was reduced to 2.5 sec from a baseline of 7 sec. Rats were then intrathecally injected with the δ-selective agonist cyclic[D-Pen^2, D-Pen^5]enkephalin (DPDPE) or the p-selective agonist [D-Ala^2, MePhe^4, Gly-ol^5] enkephalin (DAMGO) in the presence or absence of either intrathecal NTI or NTB. DPDPE and DAMGO each produced a dose-dependent increase in paw-flick latency with maximal response at 10 min post-injection and respective ED_{50}s of 30 µg and 0.04 µg. The antinociceptive action of DPDPE was antagonized by 30 µg NTI (2.5-fold rightward shift) and by 10 µg NTB (2.7-fold rightward shift). Thus, as predicted, NTB and NTI were antagonists at the δ opioid receptor with NTB being 3 times more potent than NTI. Surprisingly, the antinociceptive action of DAMGO was also antagonized by 30 µg NTI (6-fold rightward shift) and by 10 µg NTB (9.4-fold rightward shift). These data support the characterization of NTI and NTB as antagonists of the δ opioid receptor. However, in the carrageenan-inflamed paw flick test, NTI and NTB also antagonized the µ opioid agonist, DAMGO. These results suggest that NTI and NTB do not function as selective antagonists of the δ receptor in the spinal cord of the rat in the carrageenan-induced model of hyperalgesia.

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ACKNOWLEDGEMENTS

Paw flick tests were performed with the assistance of Kimberly Benson. Jonathan Washington performed the intrathecal implantations. Supported by PHS grant DA 07004 from the National Institute on Drug Abuse to D.L.H.

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BEHAVIORAL EVIDENCE FROM THE RAT HIND PAW FORMALIN TEST SUGGESTS THAT LOCAL ANESTHETICS MAY BE SUPERIOR TO OPIOIDS FOR PRE-EMPTIVE ANALGESIA

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Repeated stimulation of primary afferent fibers sensitizes both peripheral and spinal neurons in pain pathways. Pre-emptive analgesia may therefore improve post-operative pain management. Injection of formalin causes localized pain and inflammation. In the rat, it elicits a distinct biphasic excitatory response in spinal dorsal horn neurons (DHN) and a temporally similar behavioral response. Dickenson and Sullivan (1987) have shown that an i.th. mu opioid given prior to formalin inhibits both peaks of DHN excitation. When, however, opioid administration was delayed until after the acute formalin response, the inhibitory effect on the second (tonic) peak was less, arguably supporting the use of opioids for pre-emptive analgesia. We now compare the antinociceptive profile of s.c. and i.th. morphine with that of lidocaine (200µ1, 1%; injection through the popliteal fossa into the area of the sciatic nerve) against tonic phase formalin-induced flinching behavior (Wheeler-Aceto and Cowan 1991) following pre- or post-formalin administration. Unlike the differential response observed with DHN tiring, the antinociceptive A50 of morphine was not markedly changed by post-formalin dosing.

		Morphine	
		Pre-formalin A50	**Post-formalin A50**
s.c.	**(mg/kg)**	**0.35 (0.21-0.43)**	**0.13 (0.05-0.25)**
i.th.	**(mg)**	**0.15 (0.06-0.26)**	**0.17 (0.07-0.30)**

Morphine also dose-related antiedema activity but only when given before formalin, a finding more closely related to electrophysiological rather than behavioral data. Like morphine, pretreatment with lidocaine significantly decreases formalin-induced flinching (32±5) compared to control (103±14, $p<0.001$); when dosed post-formalin, however, even though the foot is insensitive to a thermal stimulus (50°C hot-water foot-flick), lidocaine (73±13; control = 80±6) no longer attenuates tonic flinching. Overall, these data support the notion that the tonic phase is dependent on activity in the acute phase and may be an example of adaptive change to tissue injury. The behavioral results suggest that local anesthetics may be superior to opioids for pre-emptive analgesia.

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ACKNOWLEDGEMENT: NIDA Training Grant T32 DA07237 and NIDA Research Grant DA03945

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35-HT_3 RECEPTOR ANTAGONIST BLOCK COCAINE-INDUCED LOCOMOTION VIA A *P*-CPA SENSITIVE MECHANISM

A. L. Svingos and R. J. Hitzemann

In mice the $5HT_3$ receptor antagonists zacopride and ICS 205-930, block the hyperactivity induced by an acute cocaine injection (Reith, 1990). We now report similar results in rats pretreated with (±) zacopridc (0.03 mg/kg, i.p.). ICS 205-930 (0.1 mg/kg, i.p.) or MDL 72222 (1.0 mg/kg, i.p.) fifteen minutes before the challenge with (-)cocaine (10.0 mg/kg, i.p.). (+)Zacopride significantly inhibited (approximately 50%) the effects of cocaine at a dose of 10 μg/kg. 5-HT_3 antagonists may attenuate cocaine-induced behaviors through effects on dopamine (DA) transport or release (Carboni et al., 1989, Madras et al., 1989). We investigated whether or not 5-HT_3 antagonists blocks the cocaine binding site on the DA transporter and/or effect the ability of DA to regulate this binding site. In well washed striatal membranes, neither zacopridc nor ICS 205-930 (10^{-9} to 10^{-5} M) inhibited [3H]2β-carbomethoxy-3β-(4-fluorophenyl) tropane (^{3}H]WIN 35,428) (0.3 nM) binding. Furthermore, neither of these compounds affected the ability of DA to block WIN 35,428 binding. To determine if 5-HT is required for the 5-HT_3 antagonist effect, we examined the interaction between cocaine and zacopride in rats pretreated with *p*-chlorophenylalanine (*p* -CPA) (3 days x 100 mg/kg/day). Following *p* -CPA pretreatment, zacopride was ineffective in blocking the locomotion induced by 10.0 and 3.0 mg/kg cocaine.

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RECEPTOR AND TRANSPORTER MOLECULES IN DRUG ADDICTION

[1]L. MATSUDA; [2]B. HOFFMAN; [3]O. CIVELLI AND [4]E. NOBLE

Lisa Matsuda reviewed the structure of cannabinoid receptor and functional expression of the cloned cDNA. Although there are a lot of well documented effects of cannabinoids (analgesia, anti-emesis, sedation, reduction of intraocular blood pressure, bronchodilation, anticonvulsant activity, anti-inflammatory effects), the mechanisms responsible for these are not yet known. The hydrophobicity of cannabanoids suggested that nonspecific mechanisms could contribute to their overall effects. However, recent evidence supported a mechanism involving a G protein-coupled receptor which inhibits adenylyl cyclase activity in a dose-dependent, reversible, steroeselective and pertussis toxin-sensitive manner. The development of potent cannabinoid analogs such as CP55940 has allowed the mapping of cannabinoid receptors in the brain. The cannabinoid receptor was cloned by isolating a cDNA clone (SKR6) from a rat cortex cDNA library, using a oligonucleotide probe derived from the sequence of bovine substance K receptor. The receptor sequence (473 amino acids) has seven hydrophobic domains, numerous residues that are highly conserved among G protein-coupled receptors, and several potential glycosylation sites. *In situ* hybridization revealed that SKR6 mRNA was abundant in brain. The highest expression was found in superficial and deep layers of cerebral cortex, the hippocampus and dentate gyrus, amygdala and hypothalamus. The comparison between [^{3}H]CP55940 and [^{35}S]SKR6 *in situ* hybridization showed that the receptors and mRNA were very high in the cortex and the hippocampus; however, in the substantia nigra and the globus pallidus where the receptor density was high although the signal for mRNA was low. A striking feature of SKR6 mRNA is its presence in the dentate gyrus, hippocampal formation and cerebral cortex; here, individual neurons express very high levels of message, while its level is moderate in the surrounding cells.

Expression of a G protein-coupled receptor responding to cannabinoids was obtained by transfecting Chinese hamster ovary cells with SKR6. In these cells, CP55940 and Δ^{9}-tetrahydrocannabinol (the major psychoactive constituent found in marijuana) inhibit the forskolin-stimulated accumulation of cyclic adenosine 5'-monophosphate (cyclic AMP). This effect was prevented by pertussis toxin treatment.

Beth Hoffman reviewed the molecular biology of the 5-hydroxytryptamine (5HT) transporter. 5-HT transporters are a site of action for some antidepressants and drugs of abuse, including amphetamine derivatives and cocaine. Antidepressants that block 5-HT uptake are used to treat depression, panic disorders, obsessive compulsive disorders, obesity and alcoholism. The 5-HT transporter allows platelets and most cells (which do not synthesize 5-HT) to concentrate 5-HT and thus store large amounts of the amine. This property was used to clone the transporter by using a rat basophilic leukemia cell line, the RBL2H3 cells. A cDNA library was constructed from mRNA extracted from RBL2H3 cells. Plasmids were used to transfect COS cells and a 5-HT uptake assay of the cDNA clones was performed. A single positive pool was identified and further subdivided. 5-HT uptake in transfected cells was potently inhibited by fluoxetine, paroxetine, cipalopram and clomipramine, which are selective for the 5-HT transporter. Dopamine and reserpine, an inhibitor of vesicular uptake, were not effective to block 5-HT uptake. Northern blot analysis allowed the demonstration of high levels of the mRNA in the lung, the gut and the brainstem. The spleen, stomach and uterus displayed low levels. *In situ* hybridization with

a 5-HT transporter specific oligonucleotide revealed the presence of mRNA for the transporter in specific arcas of the brain such as raphe nuclei.

Hydropathy analysis indicated 12 or 13 potential transmembrane domains. Comparison of the 5-HT transporter to other proteins indicates a high degree of conservation between the 5HT, noradrenalinc, dopamine and GABA transporters (respectively 91%, 90% and 66%). Two potential protein kinase C phosphorylation sites are found on the 5-HT transporter. Future goals are to investigate the regulation of the transporter by second messengers as well as its interactions with the presynaptic 5-HT receptors. It will be of interest to determine how drugs of abuse affect the transporter function.

Olivier Civelli reviewed the diversity of dopamine receptors. There are three principal DA pathways: (1) the nigrostriatal pathway; (2) the mesocorticolimbic pathway and (3) the tuberoinfundibular pathway. In the 1980's, dopamine was thought to exert its effects by binding to two G protein-coupled receptors, D1 and D2. SCH23390 was a specific antagonist acting at D_1 receptors, while D_2 receptors recognized with high affinity spiperone and haloperidol. The D_1 receptor is coupled to G_s and stimulates adenylyl cyclase. The D_2 receptor is coupled to G_i; activation leads to potassium channel opening, calcium current inhibition and inhibition of adcnylyl cyclase. Postsynaptic D_1 receptors are prototypically localized in the parathyroid gland whereas presynaptic and postsynaptic D_2 receptors are located in the pituitary gland.

The strategy used to clone the D_2 DA receptor was based on the sequence homology expected to exist among G protein-coupled receptors. A rat genomic library was screened with the ß-adrenoceptor coding sequence as a hybridization probe. This allowed the isolation of the clones encoding the ß1 adrenoceptor, 5-HT_{1A} receptors, the muscarinic m4 receptor and another clone, RGB2, that was later shown to encode the D_2 receptor. The RGB2 clone encodes a 415 amino acid protein with seven hydrophobic domains, and has significant sequence similarity with the other receptors in this gene family. Northern blot analysis showed that RGB2 mRNA sequences arc expressed throughout the rat brain, with high levels in the striatum and the pituitary gland. Dopamine inhibits adenylyl cyclase in cells transfected with the RGB2 cDNA.

Synthetic oligonucleotides corresponding to two highly conserved regions among all the G protein-coupled receptors were used as primers in the polymerase chain reaction. A full-length clone was isolated that was demonstrated to encode the D_1 receptor by showing that dopamine stimulated adenylyl cyclase in cells transfected with the clone. Several amino acid residues might play a role in ligand binding. Civelli presented the current view of the way in which these receptors bind dopamine; an aspartate residue in transmembrane domain III and two serine residues in transmembrane domain V could interact with the amino and hydroxyl groups of dopamine. The carboxyterminus contains a conserved Cys which might be palmitoylated and serve to anchor the receptor to the membrane.

Subsequently, two forms of human D_2 receptors were reported in human, rat and bovine. The two forms differ by alternative splicing, which either leaves ($D_{2,1ong}$) or removes ($D_{2,short}$) a 29 amino acid sequence in the putative third cytoplasmic loop of the receptor. The ratio of the two forms is tissue specific, but they do not differ in their pharmacological or biological activity.

A cDNA was next isolated which encoded a novel receptor related to the D_2 receptor, namely the D_3 receptor. The D_3 receptor structure is very similar to that of the D_2 receptor and, when expressed in eukaryotic cells, the D_3 receptor has a pharmacological profile similar to that of the D_2 receptor. However, its affinity for most neuroleptics was 10 to

100 times less than that of the D_3 receptor. The tissue distribution of the D_3 receptor overlaps with that of the D_2 receptor, with the exception of the islands of Calleja and the nucleus accumbens, where D_3 receptor levels much exceed those of D_2 receptors.

Analysis of the mRNA of the SK-N-MC cell line with doparnine receptor cDNA probes under conditions of low stringency revealed the existence of a D_2-related mRNA. After sequencing, the corresponding cDNA was found to encode a novel receptor (D_4). Most of the agonists and antagonists tested displayed similar affinities for D_4 and D_2 receptors. However, the D_4 receptor binds clozapine with an affinity 10 fold higher than the D_2 or D_3 receptor. This property is of interest since clozapine is a particular antipsychotic agent whose action is not associated with motor control side effects peculiar to other neuroleptics. These observations suggest that the D_4 receptor may be the primary target mediating the antipsychotic action of clozapine. D_4 receptors have been shown to be associated with the mesocorticolimbic system.

Finally, during a structural analysis of the human D_1 receptor gene, Civelli's group found that the human genome contains a sequence that is similar but not identical to the D_1 gene. These D_5 receptors have a pharmacological profile closely similar to D_1 receptors, but they have a ten-fold higher affinity for dopamine. Intracellular cAMP accumulation is stimulated by dopamine in cells transfected with the D_5 DNA. D_5 receptors are located mainly in the hippocampus, hypothalamus, parafascicular nuclei. Receptor genes for D_2, D_3 and D_4 possess introns, whereas the genes for D_1 and D_5 do not

Ernst Noble reviewed data concerning the association of the D_2 receptor gene with alcoholism and drug dependence, addressing the question "Is there a molecular basis for alcoholism and drug dependence?" Subjects were divided into groups of non-alcoholics and alcoholics. Analysis of the human genome showed that on chromosome II, there is locus Al allele of the D_2 receptor gene. The alcoholic group, when compared to the non-alcoholic group, showed a significantly greater association with the A1 allele of the D_2 receptor gene; 69% of severe alcoholics possess A_2 allele against 20% of the control subjects. A stronger association was found when severe alcoholics, rather than all alcoholics, were compared to non-alcoholics. Young children of alcoholics also had a significantly greater association with the Al allele that non-alcoholics, but not when compared to alcoholics.

Analysis of risk of alcoholism severity suggest that it is comprised of two independent components: family history and the presence of the Al allele. The Al allele may play an important role in reinforcement behavior itself and not only alcoholism. In order to test this, cocaine abusers and control subjects were tested; 51% of cocaine-dependent subjects display the A1 allele against 18% of the non-cocaine users. There was no difference between alcoholics or non-alcoholic cocaine-dependent users. This property suggests that it is drug dependence itself that correlates with the presence of the Al allele. In conclusion, A1 allele is not only associated with alcoholism but also plays an important role in different reward behaviors.

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OPIOID RECEPTOR SUBTYPES IN BRAIN-STIMULATION REWARD

C. KORNETSKY

Conan Kornetsky described how, in 1954, Olds and Milner showed that animals implanted with electrodes in certain brain areas will respond to receive brief bursts of electrical stimulation (also referred to as intracranial self-stimulation or ICSS). These investigators showed that certain parts of the brain produce acquisition and extinction curves that compare favorably with other types of reward. One of these brain areas, the medial forebrain bundle (MFB) in the lateral hypothalamus, has been described as a "reward center" since animals respond to receive electrical stimulation in this area. In contrast, animals work to turn off electrical stimulation in the mesencephalic reticular formation which indicated that electrical stimulation in this area was aversive rather than reinforcing. Other investigators subsequently showed that various drugs, such as morphine, chlorpromazine, and pentobarbital, lowered the rate of responding for ICSS when the electrode was implanted into the MFB. In addition to morphine, other μ opioid agonists such as heroin and sufentanil also lowered the threshold for ICSS into the MFB. The κ agonists U50488 and ethylketazocine (EKC) either had no effect on the threshold for ICSS or produced effects opposite to those of morphine-like drugs. The δ agonist DPDPE produced effects similar to morphine. The opioid antagonist naloxone and nalmifene had no effect on ICSS.

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PARTICIPATION OF μ, δ AND κ RECEPTOR IN THE EXPRESSION OF PHYSICAL OPIOID DEPENDENCE IN RATS

R. MALDONADO

R. Malaldonado has studied the effects of μ, δ and κ receptors in the expression of physical dependence in rats, by assessing withdrawal signs produced after chronic administration of various selective opioid agonists. After chronic intracerebroventricular (i.c.v.) treatment with the μ agonist DAMGO, the δ agonist DPDPE or the κ agonist U50488, Cowan and colleagues found that the severity of withdrawal symptoms precipitated by naloxone varied considerably. Withdrawal symptoms were most severe with chronic DAMGO treatment, less so with DPDPE and least severe with U50488. To further evaluate the extent to which opioid receptor subtypes are involved in the expression of physical dependence, rats were implanted with two 75 mg morphine pellets subcutaneously and selective antagonists were administered i.c.v. to precipitate withdrawal effects. Three days after implantation of the morphine pellet, the selective δ antagonist naltrindole (NTI; 62, 125, 250, 500, 1000 and 2000 ng) and the selective κ antagonist norbinaltorphimine (nor-BNI; 0.6, 1.2, 2.5, 5, 10, and 20 ng) were administered every 12 h. The selective μ antagonist CTAP (5, 50, 500 and 5000 ng) was administered every 24 h due to its long duration of action. Animals were observed for opiate withdrawal effects 10 min after antagonist administration. Teeth chattering, mastication and eye twitch were significantly increased after administration of CTAP. Mastication was the only withdrawal sign that was significantly increased after administration of NTI. Mastication, and to a lesser extent teeth chattering, were significantly increased after administration of nor-BNI. Overall (global) withdrawal scores showed that the most robust withdrawal signs occurred after administration of CTAP. Global withdrawal scores were significantly increased only after administration of the largest doses of NTI, which may have been due to blockade of μ rather than δ receptors. Global withdrawal scores also were significantly increased by nor-BNI. These data, and the fact that naloxone, which is a less selective μ antagonist than CTAP, produced a more severe withdrawal syndrome than CTAP, indicated that although μ receptors are primarily involved in dependence on and withdrawal from morphine, δ or κ receptors may modulate dependence and withdrawal from morphine. Thus, combinations of CTAP and NTI, as well as CTAP and nor-BNI, were administered to morphine-dependent, rats. Neither nor-BNI nor NTI co-administration affected the global withdrawal scores produced by CTAP. The conclusions made from these experiments were that (1) μ receptors play a critical role in the expression of physical dependence with morphine (2) κ and particularly δ receptors play a relatively minor role and (3) physical abstinence induced by μ antagonists are not modulated by δ or κ receptors.

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RECEPTOR-SELECTIVE BI-DIRECTIONAL MODULATION OF REWARD MECHANISMS BY OPIOIDS

A. HERZ

The conditioned place preference paradigm was used to study the modulation of reward mechanisms produced by opioids (*A. Herz* and colleagues). In a typical conditioned place preference paradigm, a box is used that consists of at least two distinct sides separated by a wall or door. For example, one side may be white with a smooth floor while the other side may be black with a grid floor. On one day, a drug is administered and the animal is placed in one side of the box; on another day, an inert vehicle used to dissolve the drug is administered and the animal is placed in the other side of the box. After several pairings, animals are given access to both sides and the time spent in each side of the box is measured. Results from several experiments using the conditioned place preference paradigm have shown that animals prefer the side paired with appetitive substances and avoid the side paired with aversive substances.

The effects of a number of selective opioid agonists and antagonists were evaluated in the conditioned place preference paradigm. Preference for the drug-paired side occurred with the μ agonists sufentanil, fentanyl and morphine while aversion for the drug-paired side occurred with the κ agonists U69593 and U50488. The μ receptor-selective peptide DAMGO also produced a place preference that was antagonized by the μ receptor-selective antagonist CTOP but not the δ receptor-selective antagonist ICI174864. The δ receptor-selective peptide DPDPE produced a place preference that was antagonized by ICI174864 but not CTOP. Naloxone and CTOP alone produced place aversions, ICI174864 had no effect and nor-BNI produced a slight place preference. ß-Endorphin produced a place preference that was antagonized by both ICI174864 and CTOP, which might indicated that an interaction occurred between μ and δ receptor-mediated effects after administration of ß-endorphin. In an attempt to localize the sites through which the rewarding effects of these various opioids are mediated, an experiment was performed in which medio-basal arcuate lesions were made and naloxone, morphine and U50488 were tested. While the effects of morphine and U50488 were not different in lesioned and sham lesioned animals, the place aversion produced by naloxone was abolished in lesioned rats. The conclusions from this series of experiments were that (1) μ and δ opioid agonists are reinforcing, (2) κ opioid agonists are aversive, and (3) continuous rewarding tone is mediated by ß-endorphin pathways.

Given the fact that several investigators have shown an interaction between opioid and dopamine systems, the effects of various opioids were tested in brain areas involved in dopamine activity. DAMGO produced a place preference after administration into the ventral tegmental area (VTA) and was not effective after administration into the nucleus accumbens (NAC), substantia nigra (SN), mediofrontal cortex (MFC), caudate putamen (CP) or lateral hypothalamus (LH). U50488 produced a place aversion after administration into the VTA, MFC, NAC and LH; U50488 was not effective in SN or CP. When the NAC was lesioned with 6-hydroxydopamine, morphine and U69593 lost their rewarding and aversive effects, respectively. In non-lesioned animals, the dopamine D_1 antagonist SCH 23390 antagonized the effects of both morphine and U69593. SCH 23390 produced a place aversion after systemic or NAC administration but not after administration into the VTA, CP or MFC. The dopamine D_2 antagonist sulpiride had no

effect. In the VTA, the μ agonist DAMGO increased and the μ antagonist CTOP decreased the release of dopamine. Neither DAMGO nor CTOP had an effect in the NAC. Conversely, the κ agonist U69593 decreased and the κ antagonist nor-BNI increased dopamine release in the NAC. Neither nor-BNI nor U69593 had an effect in the VTA.

A model was described involving dopamine neurons originating in the VTA which project to the NAC. GABA neurons, which are in turn affected by ß-endorphin, interact with dopamine neurons in the VTA. The interaction between ß-endorphin. GABA and the dopamine neurons results in an excitatory μ-mediated tonus. In the NAC, an inhibitory κ-mediated tonus exists. The interaction between opioid, GABA and dopamine neurons in these brain areas may be a useful model for understanding dependence and withdrawal produced by opioids.

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ROLE OF OPIOID RECEPTOR TYPES AND SUBTYPES IN OPIOID SELF-ADMINISTRATION

S. NEGUS

S. Negus described how, in traditional self-administration paradigms, pagonists are readily self-administered, κ agonists are typically not self-administered and it is not clear whether ∂ agonists are self-administered. The purpose of the study was to examine the role of μ,∂ andκτ receptors in the reinforcing effects of heroin (60 mg/kg/injection) in rats responding under a fixed ratio schedule (20 s time-out, daily 3 h sessions). When the unit doses of heroin were changed, the rate of responding for heroin changed and the pattern of responding changed from an even distribution to an extinction pattern. Several different opioid selective antagonists were used including the irreversible, μ receptor-selective antagonist ß-funaltrexamine (ß-FNA), the μ_1 receptor-selective antagonist naloxonazine, the ∂ receptor-selective antagonist NTI and the κ receptor-selective antagonist nor-BNI. ß-FNA, naloxonazine and NTI antagonized heroin-reinforced responding. However, only very large doses of NTI affected heroin self-administration which indicated that NTI antagonism of heroin was not due to blockade of ∂ı receptors, but instead was most likely due to blockade of μ receptors. Of animals tested with ß-FNA, some rats showed an extinction pattern of responding while other rats did not. Rats tested with naloxonazine did not show an extinction pattern of responding. Nor-BNI had no effect on heroin-reinforced responding. Thus, it appeared that neither ∂ nor κ receptors mediated the reinforcing effects of heroin. However, in order to assess whether ∂ or κ ıreceptor agonists modulate the reinforcing effects of heroin, the ∂ agonist DPDPE (i.c.v.) and κ agonist U50488 (s.c.), as well as the μ agonists heroin (s.c.) and DAMGO (i.c.v.), were administered during the heroin self-administration session. Both heroin and DAMGO decreased heroin-maintained responding. However, behaviorally-active doses of DPDPE and of U50488 did not alter rates of responding for heroin. Thus, the conclusions from these experiments were that (1) μ receptors, in particular μ receptors, mediate the reinforcing effects of heroin and (2) neither ∂ nor κ receptors arc involved in heroin self-administration as evidenced by the fact that neither DPDPE nor US0488 affect heroin self-administration.

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SIGNAL TRANSDUCTION MECHANISMS ASSOCIATED WITH OPIOID ACTION

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Opioid receptors are coupled to effecters via G proteins. Agonists at G protein-coupled receptors generally activate G proteins, and the properties of the particular G protein activated determine whether the effector (an enzyme or ion channel) is stimulated or inhibited. *Hiroshi Ueda* discussed an unusual finding: U50488, an agonist at the κ-opioid receptor, inhibits rather than activates G proteins.

In the inactive state, G proteins bind guanosine 5'-diphosphate (GDP). Activation of a G protein requires the exchange of GDP for guanosine 5'-triphosphate (GTP), and inactivation involves hydrolysis of the GTP to GDP. Addition of radiolabeled GTP to guinea pig cerebellar membranes eventually leads to formation of labeled GDP as labeled GTP is hydrolyzed. The labeled GDP is then released in exchange for GTP as another cycle begins. Activity of G proteins can therefore be assessed by measuring the release of radiolabeled GDP following the addition of labeled GTP. U50488 decreases the release of labeled GDP, indicating a decrease in G protein activity. Addition of the unlabeled, non-hydrolyzable, GTP analog ß,γ-iimidoguanosine 5'-triphosphate (GPPNHP) or unlabeled GDP increases the release of labeled GDP dose-dependently. U50488 shifts to the right the dose-response for GPPNHP, but not GDP, meaning that a higher concentration is required to produce a given effect. This result suggests that the decrease in G protein activity is due to a decrease in affinity for GTP rather than an increase in affinity for GDP.

A possible effector system regulated by this inhibition of G protein activity is phospholipase C (PLC). In the membrane preparations in which it inhibits G proteins, U50488 also inhibits GTP-stimulated PLC activity. Both effects are abolished by pertussis toxin. Experiments in which endogenous G proteins are inactivated and various G proteins are introduced in an attempt to reconstitute responses demonstrate that both effects are mediated by the G protein subtype.

Jurgen Hescheler focused on the specificity of the interaction between the signal-transducing heterotrimeric G proteins and the receptors which activate them. He began by pointing out that in addition to almost 100 G protein-coupled receptors, 16-20 G protein a subunits, four G protein B subunits and four G protein γ ; subunits have been cloned. Given the potential high degree of specificity offered by this multiplicity, do different receptors which couple to the same effector use different G protein subtypes?

Activation of both muscarinic and somatostatin receptors inhibits L-type calcium current in the pituitary GH3 cell line. Initial experiments examined the specificity of coupling of G protein a subunits. Oligonucleotides complementary to sequences of G protein α subunit mRNA (antisense oligonucleotides) were injected into the nuclei of GH3 cells. Antisense oligonucleotides complementary to a sequence common to all G protein a subunits abolished the inhibition of calcium current by both somatostatin and the muscarinic agonist carbachol, as measured using whole-cell voltage-clamp. Oligonucleotides complementary to a sequence found only in α_{o} subunits blocked the inhibition of the calcium current by both agonists, while oligonucleotides complementary to a sequence found only in α_{i} subunits had no effect. Determining further the specificity of interaction, knocking out the α_{o1} subunit blocked the inhibition of the calcium current by carbachol but not by somatostatin and eliminating the $\alpha_{o\ 2}$

subunit prevented inhibition of the calcium current by somatostatin but not by carbachol.

Having established that specificity exists for the a subunit, Hescheler went on to describe work examining the coupling specificity of the G protein B and γ subunits. Using the antisense oligonucleotide technique described above, it was shown that of the four known G protein ß subunits, only $ß_1$ is involved in coupling the somatostatin receptor to inhibition of L-type calcium current in GH3 cells, while only $ß_3$ is involved in coupling the muscarinic receptor to inhibition of the calcium current. It was similarly demonstrated that γ_3 is involved in the somatostatin and γ_4 in the muscarinic inhibition of the calcium current Thus specificity exists with each G protein subunit.

The identity of the G protein a subunits coupling μ and δ opioid receptors to inhibition of calcium current was determined using the human cell line SH-SY5Y. Since the G protein a subunits have been cloned from rat, it was not possible to use the antisense oligonucleotide approach described above due to a lack of homology. Instead, pertussis toxin was used to inactivate endogenous G protein a subunits coupling opioid, muscarinic and somatostatin receptors to inhibition of N-type calcium current. Purified G protein asubunits were then added to the cell by including them in the whole-cell electrode. A mixture of α_{o1} and α_{o2}, but not α_{o1} alone, reconstituted the inhibition of calcium current by the μ opioid receptor agonist DAMGO and the ∂-opioid receptor agonist DPDPE. These results imply that α_{o2} is the G protein a subunit which couples the μ and ∂ opioid receptors to inhibition of calcium current in SH-SY5Y cells.

Charles Chavkin discussed actions of opioids in the hippocampus at two levels: effects on ion currents in individual neurons and the roles of endogenous opioids in hippocampal circuitry. Exogenously applied μ opioid receptor agonists act on interneurons in the hippocampus. For the experiments investigating effects on ionic conductances, the CA1 and subiculum areas of the hippocampus were dissociated and interneurons were identified based on morphology and electrophysiological responses to opioids. Two populations of opioid-responding neurons are identifiable based on whole-cell voltage clamp responses to the μ opioid agonists PLO17 and DAMGO. In 30% of opioid-responding neurons, μ agonists activate a potassium current that exhibits inward rectification. The current is activated at rest and thus opioids hyperpolarize this type of neuron.

In the other 70% of opioid-responding cells, μ agonists potentiate a different potassium current, one which is activated with depolarizing steps to potentials positive to the resting potential. Since this current is not active at rest, PLO17 has no effect on testing membrane potential, but enhancement of this current may speed action potential repolarization. Experiments with the non-hydrolyzable GTP analog guanosine 5'-O-(3-thiotriphosphate)(GTPγS) indicate that the effect is mediated by a G protein. The cyclic adensine 5'-monophosphate AMP (cyclic AMP) analog 8-bromo-CAMP blocks the effect of opioids on the current; this suggests an action on through cyclic AMP second messenger system.

Little is known about the role of endogenous opioids found in the hippocampus. Chavkin described experiments whose objective was to understand the role of endogenous μ and κ selective opioids in the hippocampus. Using a slice preparation, electrical stimulation of the afferent perforant path reduces the binding of radiolabeled μ opioid receptor agonists in the hippocampus, indicating that such stimulation releases endogenous μ opioid receptor agonists. Exogenously applied μ agonists reduce the GABA synaptic potentials recorded in pyramidal cells by inhibiting GABA-containing intemeurons, but endogenous μ agonists released by stimulation apparently do not. Even so, when the opioid antagonist naloxone **was** applied the GABA response became larger. This effect was blocked by the ß-adrenergic antagonist propranolol. It is proposed that perforant path stimulation causes the release of opioids which have an inhibitory effect on adrenergic terminals. The latter would normally

release transmitter onto GABA interneurons, activating excitatory ß-adrenergic receptors. Consistent with this hypothesis, perforant path stimulation increases the displacement of radiolabeled propranolol, and this increase is potentiated by naloxone.

κOpioid receptors and the κ opioid receptor agonist dynorphin are found in the dentate gyrus. Stimulating the perforant path, which synapses in the dentate gyrus, or the mossy fibers, which project from the dentate gyrus to the CA3 hippocampal pyramidal cell layer, decreases the binding of radiolabeled κ agonist U69593. The decrease in binding resulting from perforant path, but not mossy fiber, stimulation was blocked by CNQX, indicating that the former effect was indirect and that displacement likely occurred as a result of release of endogenous κ ligands from mossy fibers. Antibodies to dynorphin A or dynorphin B, but not enkephalin, reduced the displacement of U69593, suggesting that both dynorphin A and dynorphin B are released upon stimulation.

These endogenous κ opioid receptor agonists appear to inhibit synaptic transmission between the perforant path afferents and granule cells of the dentate gyrus. Perforant path stimulation, in the presence of the $GABA_A$ antagonist bicuculline, evokes a glutamate EPSP in dentate gyrus granule cells. Exogenously applied U69593 decreases the size of the glutamate EPSP. High frequency perforant path stimulation also leads to a depression of the glutamate synaptic potential that is blocked by naloxone or the selective κ opioid receptor antagonist norbinaltorphimine. The depression lasts 5-10 min, suggesting the released κ agonists are active for extended periods. Given the location of the κ opioid receptors and the dynorphins, a model was proposed in which dentate gyrus granule cells have collaterals that feed back on the perforant path afferents to inhibit release of transmitter by releasing dynorphins which act at presynaptic κ opioid receptors.

As indicated above, opioids open potassium channels, close calcium channels and decrease transmitter release. *Annmarie Surprenant* posed the question: can either of the first two actions of opioids account for the third? After reviewing examples of each of the actions of opioids in widespread areas of the peripheral and central nervous systems and in cell lines, the effects on potassium channels and calcium channels were described in detail using as a model the submucous plexus preparation. In the submucous plexus, agonists acting at δ opioid, α_2 adrenergic and somatostatin receptors all increase an outward current that reverses at the potassium equilibrium potential. Recording from outside-out patches reveals that activation of these receptors increases the open probability for three sizes of potassium channels already active in the patch. Agonists at δ opioid, α_2 adrenergic and somatostatin receptors also decrease an N-type calcium current in submucous plexus neurons.

Having established that the actions of α_2 adrenergic receptor agonists on potassium and calcium currents are identical to those of δ opioid receptor agonists in this preparation, correlations between effects on ion channels and inhibition of transmitter release were made. The α_2-adrenergic inhibition of the nicotinic excitatory postsynaptic potential was used as a measure of presynaptic inhibition. A decrease in calcium current probably does not mediate the decrease in transmitter release because the concentration of agonist required to decrease calcium current is 5-10 times higher than that which decreases transmitter release; however, identical concentrations of calcium channel blockers such as cadmium, nickel or ω-conotoxin equally inhibit calcium currents transmitter release. There is also a difference in the time course of agonist effects on the calcium current and transmitter release. Calcium current reduction takes twice as long to begin after agonist is applied as does the decrease in transmitter release. On the other hand, dose-response relations for agonist-induced potassium current and transmitter release inhibition are identical, as are latencies to onset of these responses. A final argument against either a decrease in calcium current or an increase in potassium current mediating the inhibition of transmitter release is pertussis toxin sensitivity. Pertussis toxin blocks the effects of agonists on calcium and potassium currents, indicating a pertussis toxin-sensitive G protein is involved in these actions. Inhibition of

transmitter release is, however, insensitive to pertussis toxin. This implies that reduction of transmitter release involves a different, as yet unelucidated, signal transduction system than those mediating effects on the ion currents. It was hypothesized that agonist binding to the receptor leads to activation of a pertussis toxin-insensitive G protein which acts at a site on or close to the synaptic vesicle containing transmitter to decrease transmitter release.

In summary, although we know much about the signal transduction mechanisms associated with opioid action, it is clear that there are aspects that have yet to be elucidated. In the context of the presentations in this symposium, these include the mechanism of the _ opioid inhibition of G protein activity, the specificity of G protein coupling between a single receptor and multiple effecters, the signal transduction components involved in opioid activation of the voltage-dependent potassium channel in hippocampus and the mechanism of the inhibition of transmitter release by opioids.

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PHARMACOLOGY OF MULTIPLE OPIOID DELTA RECEPTORS

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The current state of the field was reviewed by *Frank Porreca* who gave an overview which summarized research on subtypes of opioid δ receptors. Evidence for differences in opioid δ receptors was presented in 1990 by Vaughn and colleagues (Eur. J. Pharmacol. 177: 99, 1990), who suggested that δ receptors in the brain and mouse isolated vas deferens (MVD) were different. This suggestion was based on the observation that [D-Ala^2,(2R,3S)deltaE,Phe^4,Leu^5]enkephalin methyl ester (CP-OMe), an enkephalin analog, competed for the binding of [^{3}H][D-Pen^2, p-Cl-Phe^4, D-Pen^5]enkephalin ([^{3}H]p-Cl-DPDPE) with different affinities in the brain and the MVD, whereas p-Cl-DPDPE itself competed with equal affinity in both preparations. Evidence for subtypes of opioid δ receptors within the brain came from work *in vivo* using two novel irreversible antagonists. [D-Ala^2, Leu^5, Cys^6]enkephalin (DALCE) was developed by Wayne Bowen and 5'-naltrindole isothiocyanate (5'-NTII) was developed in the laboratory of Phil Portoghese; both of these compounds have been shown to be non-competitive antagonists at δ receptors, though with differential selectivity against highly selective opioid δ agonists. These two compounds were used to demonstrate a two-way differential antagonism of the antinociceptive effects of [D-Pen^2, D-Pen^5]enkephalin (DPDPE, developed by Hank Mosberg) and [D-Ala^2, Glu^4]deltorphin (discovered in the Kriel/Erspamer laboratory), two selective opioid δ agonists. DALCE was found to block the antinociceptive actions of DPDPE but not [D-Ala^2, Glu^4]deltorphin while 5'-NTII blocked the antinociceptive effects of [D-Ala^2, Glu^4]deltorphin but not DPDPE. The demonstration of two-way differential antagonism was important in that it eliminated concerns regarding relative efficacy of the agonists. Similar results were obtained in the laboratory of Aki Takemori using competitive δ selective antagonists including naltrindole and naltriben and the δ selective agonists DPDPE and [D-Ser^2, Leu^5, Thr^6]enkephalin (DSLET). Subsequent work later demonstrated a two-way lack of cross-tolerance between the antinociceptive effects of the δ selective agonists DPDPE and [D-Ala^2, Glu^4]deltorphin, as well as the μ selective agonist [D-Ala^2, NMPhe^4, Gly-ol]enkephalin (DAMGO). Mice made tolerant to the effects of any one of these agonists were found not to be cross-tolerant to either of the other agonists. At this time, δ receptor subtypes were classified as δ_1 and δ_2; thus, δ receptors selectively antagonized by DALCE and activated by DPDPE are δ_1 receptors, whereas δ receptors selectively antagonized by 5'-NTII or naltriben and activated by [D-Ala^2, Glu^4]deltorphin or DSLET are δ_2 receptors. Based on studies of antagonism of opioid δ receptor modulation of opioid μ receptor antinociception, this classification is believed to correlate to the classification proposed by Richard Rothman and colleagues in the following manner: opioid δ_1 is similar to opioid $\delta_{1_{non\text{-}complexed}}$ opioid δ_2 is equivalent to opioid $\delta_{complexed}$. While [D-Ala^2, Glu^4]deltorphin is highly selective for the δ_2 ($\delta_{complexed}$), DPDPE acts predominately (but not exclusively) at the opioid δ_1 (i.e., $\delta_{1_{non\text{-}complexed}}$) receptor. DPDPE is able to produce its antinociceptive actions directly through the δ receptor and, additionally, modulate μ agonist antinociceptive potency via the δ_2 receptor.

Studies on endogenous activation of opioid receptors by physiological stimuli show that antinociception occuring in response to cold-water swim-stress (CWSS) in the mouse

appears to be due to endogenous activation of opioid δ_2 receptors. CWSS antinociception was antagonized by naloxone, ICI 174,864 (δ-antagonist) and 5'-NTII (δ_2 antagonist) but not by ß-FNA (μ antagonist), nor-BNI (κ antagonist) or DALCE (δ_1 antagonist). Also, antinociceptive cross-tolerance developed between CWSS antinociception and [D-Ala^2, Glu^4]deltorphin (δ_2 agonist) antinociception but not between CWSS antinociccption and DPDPE (δ_1 agonist) or DAMGO (μ agonist) antinociccption.

Recent work, in collaboration with Bob Raffa, shows possible species differences in δ receptor subtypes. CXBK mice, known to be deficient in supraspinal (but not spinal) μ receptors and to have a surplus of supraspinal δ receptors, were shown to be insensitive to the antinociceptive effects of supraspinally administered [D-Ala^2, Glu^4]deltorphin. whereas this route of administration produces antinociception in the progenitor CD-1 strain of mouse. However, [D-Ala^2, Glu^4]deltorphin was active in CXBK mice (as well as CD-1 mice) when given spinally. This suggests that CXBK mice may be deficient in supreaspinal opioid δ_2 receptors as well as opioid preceptors. Naloxonazine was unable to antagonize the actions of ∂_1 agonists in the CXBK mouse.

Strong support for these subtypes in brain has not yet been obtained by radioligand binding. Recent studies were described in which the affinities of opioid δ_1 and δ_2 ligands were shown to be differentially reduced by guanine nucleotides. DPDPE and [D-Ala^2, D-Leu^5]enkephalin (DADLE)(δ_1 agonists *in vivo)* were observed to decrease their affinity in the presence of sodium or ß,γ-imidoguanosine 5'-triphosphate (GPP(NH)P; by about 4-fold) and decrease even further in the presence of both (about 40 to 70-fold). In contrast [D-Ala^2, Asp^4]deltorphin and [D-Ala^2, Glu^4]deltorphin (δ_2 ligands *in vivo)* show no shift in affinity in the presence of sodium or Gpp(NH)p and a small shift in the presence of both (about 10 to 15-fold). These data were hypothesized to suggest that binding in membranes from mouse whole brain may represent binding only to opioid δ_1 receptors and that opioid δ_2 ligands may compete at this receptor as partial agonists or antagonists as indicated by their reduced regulation by guanine nucleotidcs.

The existence of subtypes has been sought in the MVD. DALCE was shown to product no antagonism of the opioid δ agonists DPDPE and [D-Ala^2, Glu^4]deltorphin under a variety of experimental conditions whereas incubation with 5'-NTII and a more recently characterized δ_2 antagonist, [D-Ala^2, Cys^4]deltorphin, produced antagonism of both DPDPE and [D-Ala^2, Glu^4]deltorphin. Furthermore, cross tolerance was demonstrated in this preparation between DPDPE and [D-Ala^2, Glu^4]deltorphin. Together, these data suggest that there is only one opioid δ receptor subtype in the MVD and that this subtype appears to be similar to the opioid δ_2 receptor - further data will be needed before this possibility can be established.

Returning to *in vivo* studies, the spinal cord was found to be similar to the MVD. That is, the antinociceptive actions of both DPDPE and [D-Ala^2, Glu^4]deltorphin were found to be antagonized by 5'-NTII but not by DALCE. Thus, it would appear that there is only one functional subtype of opioid ∂ receptor in the spinal cord and that this subtype is likely to be the opioid δ_2 receptor, similar to the subtype identified in the MVD.

In terms of identifying subtypes of opioid ∂ receptors *in vitro* then, one compound has been identified that may be useful. This compound, Tyr-L-Tic-Phe-Phe-OH (TIPP from Peter Schiller), is δ selective in radioligand binding, possessing greater than 25,000-fold selectivity for δ over either μ or κ receptors. In the MVD bioassay, it selectively antagonizes opioid δ agonists with greater than 10,000-fold potency over opioid μ agonists. This compound also shows a total lack of regulation by sodium and GPP(NH)P

in the mouse brain, again suggesting that this compound is an antagonist. Interestingly, using radioligand binding data from Robert Horvath and Henry Yamamura showed that TIPP has lower affinity for sites in the MVD than in the brain and also has lower affinity for sites in the spinal cord compared to sites in brain. These data *in vitro* support the notion that δ receptors in the MVD and spinal cord may be of a different subtype from those identified in brain using radioligand binding techniques as δ_1 receptors.

Lastly, the novel, non-peptide opioid δ compound BWB 373U86 (BW373) was shown to be a potent δ agonist in the MVD bioassay as well as a potent inhibitor of adenylyl cyclase activity in rat brain homogenate (data from Steve Childers). However, this compound was found to be insensitive to regulation by sodium and GPP(NH)P in mouse brain and in MVD binding assays, a rather odd finding in light of its agonist activity. BW373 was discussed subsequently by other speakers.

The selectivity of opioid peptides for the subtypes of opioid δ receptors was addressed by *Hank Mosberg* in a presentation entitled "Peptide ligands with δ receptor subtype selectivity". Dr. Mosberg pointed out some interesting structural differences between DPDPE (cyclic Tyr-D-Pen-Gly-Phe-D-Pen) and [Glu^4]deltorphin (Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH,) that may relate to δ/μ selectivity as well as δ subtype selectivity. First, these two compounds have different C-terminal extensions and, second, there is different placement of the Phe residue in DPDPE (4 position) compared to [D-Ala^2, Glu^4]deltorphin] (3 position). Strictly among analogs of deltorphin, there is a decreasing μ/δ selectivity ratio in affinity along the series [Glu^4], [Asp4], [Asn^4] and [Gly^4]deltorphin due to increased μ affinity in conjunction with no alteration of δ affinity. Also, in [Asp^4]deltorphin, there is a progressive loss of δ selectivity as one removes C-terminal residues one by one, due to rejection of the δ receptor but not of the μ receptor. Thus, the C-terminal end seems to be required for δ affinity (and thus selectivity) whereas the negative charge and bulk in position 4 seems to reduce μ affinity.

Reviewing the history of DPDPE we see that it was synthesized as a rigid molecule to perform conformational analysis of opioid δ receptor-ligand interactions. Unfortunately, it seems that DPDPE may have more flexibility than desired (or expected) because of the glycine residue in its backbone providing flexibility. There were two approaches that could be taken to stabilize DPDPE. One would be to alter the glycine residue through substitution and the other would be to remove the glycine altogether, resulting in a [des-Gly^3]DPDPE. This approach is logical because dermorphins were already known to lack the Gly^3 residue and yet retain opioid activity, although the cyclic dermorphins have μ selectivity. Cyclic [des-Gly^3]DPDPE types of molecules were thus synthesized. One compound, JOM-13, a cyclic Tyr-D-Cys-Phe-D-Pen, was found to have good ∂ affinity and fairly good selectivity for δ receptors.

In vivo studies with JOM-13 revealed antinociceptive action when given intracerebroventricularly (A_{50} of 0.96 nmoles). This antinociceptive effect was blocked by ICI 174,864 (∂ antagonist) and 5'-NTII (δ_2 antagonist), but not ß-FNA (μ antagonist) or DALCE (δ_1 antagonist). Therefore, JOM-13 appears to be a δ_2 ligand, similar to the deltorphins. It now seems likely that the C-terminal end of the deltorphins, required for δ affinity, may be required because of a conformational effect on the N-terminal part of the molecule via some as yet ill-defined turn structure. Evidence for this suggestion in [Asp^4]deltorphin stems from its similarity to the rigid structure of the restrained, cyclic JOM-13 as well as from NMR studies by Balboni et al. (Biophys. Biochem, res. Commun. **169,** 617, 1990). JOM-13 may cause the same type of conformation in the N-terminus due to the cyclization of the molecule via its disulfide bridge as seen in [Asp^4]deltorphin. As further evidence, JOM-13-NH_2 had slightly reduced δ affinity but

increased μ affinity compared to JOM-13-OH, similar to a comparison of [Asn^4]deltorphin and [Asp^4]deltorphin.

The potential advantages of truncated δ_2 ligand such as JOM-13 are multiple. Such a compound might have increased metabolic stability (although it appears that [Glu^4]deltorphin itself is stable) and its smaller size may lead to better bioavailability. Further, its conformational restriction may make it a better probe for conformational analysis of opioid δ receptor-ligand interactions. While JOM-13 is not as δ/μ selective as [Asp^4]deItorphin or [Glu^4]deltorphin, some analogs, such as [2-Na1^3] (2-napthylalanine) and [p-Cl-Phe^3], produce better δ selectivity, comparable to [Asp^{4}1 or [Glu^4]deltorphin. In conclusion, we now have better ligands for use in conformational analysis of opioid ∂ subtype receptor-ligand interactions.

The third speaker was *Kwen-Jen* Chang, discussing the "Identification of a novel, potent and selective non-peptide delta-selective agonist, BW373U86". The rationale for the δ ligand program at Burroughs Wellcome was to produce good analgesics that, because of their δ selectivity, would possess reduced side-effects. BW373 was shown to be more selective for δ versus μ, κ or E(in that order); the respective K_i values in radioligand binding were 1.8, 15, 34 and 85 nM. In the MVD preparation, BW373 was active with an IC_{50} value of 0.2 nM and was blocked by naltrindole in a concentration-dependent manner (1, 2 and 5 nM). A Schild plot for naltrindole versus BW373 in the MVD revealed a slope of 1.03 and a pA_2 of 9.43, consistent with the naltrindole pA_2 at opioid δ receptors. The inhibitory action of BW373 in MVD was not blocked by CTOP (μ antagonist). The GPI/MVD ratio for BW373 is 700, a value better than that for DADLE although not better than that for DPDPE (> 1,000) or [D-Ala^2, Asp^4]deltorphin (>15,000). Its potency in MVD is comparable to [D-Ala^2, Asp^4]deltorphin (0.1 nM) and DPDPE (3.6 nM). In radioligand binding experiments using [^{3}H]diprenorphine in N4TGI neuroblastoma cells, BW373 had no shift in affinity in the presence of GPP(NH)P (G-shift). In contrast, DPDPE and [D-Ala^2, Asp^4]deltorphin both had G-shifts in this cell line.

BW373 was first tested for antinociceptive activity by subcutaneous administration to rats. No antinociception was observed but the rats did show a naloxone-sensitive increase in locomotor activity. BW373 was also found to inhibit the acoustic startle reflex in a dose-dependent, naloxone-sensitive manner. Because it had an effect in rats, but no antinociceptive activity, it was next tested in the mouse warm-water tail-flick test. It was found to produce antinociception in the mouse when given intraperitoneally and intrathecally. However, in this test, BW373 (intraperitoneal) was blocked by naloxone but not by δ antagonists such as naltrindole, suggesting non-δ activity. In the acetic acid writhing test, BW373 was active when administered by the intracerebroventricular, intrathecal, intraperitoneal routes but not by the oral route. Here, BW373 antinociception was blocked by δ antagonists as well as by naloxone, suggesting action at opioid δ receptors.

In morphine-dependent animals, BW373 does not substitute for morphine, does not precipitate withdrawal from morphine and does not block naloxone precipitated withdrawal. When BW373 is given to mice by continuous osmotic minipump infusion for six days, no withdrawal is precipitated by either naltrindole or naloxone. When BW373 was co-infused by minipump with morphine, it did suppress naloxone precipitated abstinence syndrome in these mice, an effect which could be blocked by naltrindole. This suggests that BW373 could have some usefulness in preventing withdrawal.

In conclusion, this compound seems to modulate the effects of μ opioids in dependence studies and does produce some antinociceptive effects at opioid δ1 receptors. Burroughs Wellcome hopes in the future to achieve the overall goal of their δ program to develop a good δ--selective analgesic with reduced side-effects.

Aki Takemori spoke next on "Selective agonists and antagonists for delta opioid receptors" developed in conjunction with Phil Portoghese. There are several important compounds that have been used in δ pharmacology, such as naltrindole, as well as newer useful compounds such as naltriben (NTB), the benzyl derivative of naltrindole. When administered subcutaneously or into the cerebral ventricles, naltriben selectively blocks the antinociceptive effects of DSLET but not of DPDPE, DAMGO or DADLE, suggesting the existence of subtypes of opioid δ receptors. Also in support of subtypes of opioid δ receptors, a lack of cross tolerance was demonstrated between the antinociceptive effects of DSLET and DPDPE.

Interestingly, [^{3}H]DSLET has been shown to bind to a larger number of sites in spinal cord than either DPDPE or DADLE. Further, DPDPE and DADLE compete better against [^{3}H]DPDPE and [^{3}H]DADLE than they do against [^{3}H]DSLET, whereas DSLET competes better against [^{3}H]DSLET than against either [^{3}H]DPDPE or [^{3}H]DADLE. When naltriben is used as a competing ligand against [^{3}H]DSLET or [^{3}H]DADLE, it has the same affinity against both ligands in brain homogenate but better affinity against [^{3}H]DSLET in spinal cord homogenate. These results suggest the possibility of selective δ_1 and δ_2 binding assays.

Turning to the naltrindole isothiocyanates (NTII), there are four derivatives with the isothiocyanate group at either the 4', 5', 6', or 7' positions. All four of these derivatives are irreversible ligands with the 7' as the most potent but least selective for δ receptors. However, 5'-NTII is the only derivative that is selective for subtypes of opioid δ receptors.

Several new compounds are the subject of recent study. They are BHM (hydromorphone derivative), BNTX (naltrexone derivative), SIOM (oxymorphindole derivative) and SINTX (naltrexone derivative). In the GPI and MVD preparations, BHM and SIOM have slight agonist activity. As antagonists, all four compounds have dissociation equilibrium constants (K_e) that are consistent with δ selectivity (but no δ subtype selectivity). In radioligand binding, all four compounds are selective for δ compared to μ and κ. Interestingly, BNTX also shows 108-fold higher affinity against [^{3}H]DADLE (δ_1 ligand) than [^{3}H]DSLET (δ_2 ligand), suggesting selectivity for the ∂_1 receptor.

In vivo, BNTX, subcutaneous or intracerebroventricular, blocks antinociception induced by DPDPE (intracerebroventricular) but not that caused by DSLET (intracetebroventricular), morphine (subcutaneous) or U50488 (subcutaneous), indicating that BNTX is a selective δ_1 antagonist. BHM appears to be a selective δ_1 agonist, producing antinociception that is blocked by BNTX (δ_1 antagonist) but not by naltriben , δ_2 antagonist), nor-BNI (δ_1 antagonist) or ß-FNA (μ antagonist). SINTX (intracerebroventricular) was able to block the antinociceptive effects of morphine, DPDPE and DSLET but not U50488. SIOM was an agonist which was blocked by BNTX more than by naltriben and not blocked by nor-BNI or ß-FNA. Thus, of these four compounds, BHM and BNTX appear to be very useful selective opioid δ_1 ligands as an agonist and antagonist, respectively. Further, these compounds seem to be the first good non-peptide δ ligands to be successfully developed.

Sandra Comer spoke on the "Delta-receptor-mediation of convulsions and refractoriness" produced in mice by BW373. In earlier drug discrimination studies with pigeons, it was found that μ and κ receptor agonists do not substitute for BW373. The δ agonists DSLET and DPDPE also do not substitute for BW373. In addition, BW373 does not substitute for morphine or bremazocine in this paradigm. Lastly, naltrindole blocks the discrimination of BW373 but not of morphine or bremazocine. In mouse antinociceptive assays, naltrindole was capable of antagonizing the effects of BW373 with greater potency than against morphine and with much greater potency than against bremazocine (i.e., no block). In comparison with other δ agonists, naltrindole antagonizes the effects of [D-Ala^2, Glu^4]deltorphin > BW373 > DPDPE. Thus, it appears that the discriminative and analgesic effects of BW373 are mediated through opioid δ receptors but not necessarily the same receptors that are activated by DPDPE and [D-Ala^2, Glu^4]deltorphin.

In mice, BW373 was observed to cause non-lethal, partly clonic, convulsions with Straub-tail and catalepsy. Experiments were conducted to answer the following four questions: a) are BW373 induced convulsions mediated via opioid receptors, b) are other opioids capable of inducing convulsions, c) what will happen to BW373 induced convulsions upon chronic administration of BW373, and d) will selective antagonists block the induction of convulsions by BW373? Results indicate that increasing the dose of BW373 shortens the latency to convulsion and increases the percentage of mice having a convulsion. The convulsion dose-effect curve was shifted to the right by naltrexone and naltrindole although naltrindole was 10 times more potent than naltrexone. No other opioids tested were observed to produce convulsions. Pentylcnetetrazol (PTZ), another convulsion inducing agent, produced convulsions similar to those produced by BW373, but the convulsions were multiple and near-lethal. MDZ (PTZ antagonist) blocks convulsions induced by PTZ but not by BW373, whereas naltrindole blocked BW373-induced convulsions but not PTZ-induced convulsions. Previous exposure to BW373 (24 hr prior) produced a rightward and downward shift in subsequently constructed BW373 dose-effect curve. Also, 2-week administration of a sub-effective (no convulsions) dose of BW373 could produce a downward shift in the subsequent dose-effect curve of BW373-induced convulsions, i.e., a small tolerance could be produced with sub-effective doses. To determine how long this refractoriness to subsequent convulsions lasts, the time course of refractoriness was determined for administration of 3.2, 10, and 32 mg/kg of BW373. Mice in these three groups showed refractoriness to subsequent convulsions for one, four, and 16 days, respectively. So, one convulsion can protect against subsequent convulsions for quite a long time. When naltrindole was administered up to one hour following the first convulsion, refractoriness could be prevented. However, if naltrindole was given 2 or more hours after the first convulsion, refractoriness was still observed. The naltrindole block of refractoriness induction was dose-related when naltrindole was given immediately after the first convulsion. The highest dose of naltrexone tested could also block the induction of refractoriness by the first BW373-induced convulsion.

In summary, BW373 induces convulsions that are sensitive to naltrindole and naltrexone. The magnitude and degree of refractoriness to subsequent convulsions following the first convulsion is dose-related and naltrindole-sensitive and naltrindole must be given within one hour of the first convulsion to block the refractoriness. The conclusion, then, is that BW373 acts at opioid δ receptors to produce convulsions and that this receptor appears to be the same receptor at which BW373 produces antinociception.

Linda Dykstra continued the discussion of BW373U86 in her presentation "Behavioral effects of a novel and selective opioid delta agonist in the monkey". The studies she described had the purpose of investigating BW373 in Rhesus and squirrel monkeys, and represented the first evaluation of a peripherally given δ agonist in the primate. The first question was, does BW373 produce antinociception in monkeys using the shock titration procedure? Using L-methadone in this paradigm, a 100% effect is achieved. BW373

seemed to produce some antinociception, but later it was determined that the subjects were experiencing convulsions of 5 - 10 min duration during testing, thus producing erroneous results. Even so, naltrindole could block the apparent antinociceptive effects of BW373 but not those of L-methadone. In a separate study, lower doses of BW373 which produced no convulsions could potentiate the antinociceptive response to L-methadone, i.e., the L-methadone dose-response curve was shifted to the left. This potentiation effect of BW373 is blocked dose-relatedly by naltrindole. BW373 could also shift the morphine dose-response curve to the left in morphine tolerant monkeys.

The next series of studies were conducted to determine if BW373 was u-like in its actions. In schedule-controlled behavior, monkeys were responding for food and this responding was decreased by BW373 in an naltrindole-sensitive manner. *In vivo* pA_2 analysis in this paradigm revealed the following:

Antagonist	pA_2 vs. Levorphanol	pA_2 vs. BW373
Naltrexone	7.66	5.99
Naltrindole	5.49	7.43

The naltrexone pA_2 versus BW373 was non-μ-like (compared to pA_2 versus levorphanol) while the naltrindole pA_2 versus BW373 was δ-like. In respiration studies, BW373 produced no decrease in respiration using either air or 5% CO_2, whereas L-methadone did decrease respiration. Also, a study of self-administration was conducted to determine μ-like abuse liability. Animals trained to self-administer either alfentanil or cocaine would not self-administer BW373. In monkeys trained to discriminate withdrawal, BW373 administration did not prevent subjects from responding for withdrawal after removal of chronic alfentanil, i.e., BW373 did not substitute for alfentanil. Further, BW373 does not produce responding in animals trained to discriminate either codeine, fentanyl, or U50,488. Lastly, BW373 was examined in a repeated acquisition model of learning. BW373 was found to decrease responding and increase the percentage of errors in this model; that is, BW373 interfered with learning. This effect of BW373 was sensitive to naltrindole and even naltrexone in higher doses. In this model, μ and κ agonists do not produce these effects.

The conclusion of these studies, then, is that BW373 potentiates μ agonists in a δ antagonist-sensitive manner, possesses minimal respiration effects, and does not appear to have any μ-like abuse liability.

In summary, the symposium established a classification of δ receptor subtypes and compounds selective for these subtypes. It is anticipated that future progress may yield molecules which will be therapeutically useful in the treatment of pain either as direct ∂ selective analgesics or as potentiators of μ selective analgesics. The possibility of success is increased by the knowledge of δ receptor subtypes, for which there is now ample evidence as well as the discovery of a relatively selective non-peptide δ receptor agonist. The discovery of non-peptide δ selective compounds in the laboratories of Ken Chang, Aki Takemori and Phil Portoghese continues to generate excitement.

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BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XVI. DRUG EVALUATION COMMITTEE OF THE COLLEGE OF PROBLEMS OF DRUG DEPENDENCE, INC. (1992).

A. E. JACOBSON

The CPDD has been involved with research on drugs of abuse for more than 50 years. The Drug Evaluation Committee (DEC) has been assigned by the CPDD to oversee various aspects of this effort. The DEC is devoted to research on drugs of abuse and the determination of the physical dependence potential and abuse liability of specific classes of drugs, the analgesics, stimulants and depressants. Dr. T. Cicero (Department of Psychiatry, Washington University, St. Louis, MO) chairs this committee, and I am the Biological Coordinator.

There are two university-based groups involved with the DEC's evaluation of the analgesic-types of drugs, and three which evaluate the stimulants and depressants. The analgesics are explored in the Department of Pharmacology and Toxicology at the Medical College of Virginia, Virginia Commonwealth University, Richmond, VA (Drs. M. D. Aceto, E. R. Bowman, L. S. Harris, and E. L. May), and the University of Michigan Medical School in Ann Arbor, MI (Drs. J. H. Woods, F. Medzihradsky, C. B. Smith, G. D. Winger, C. P. France, and S. S. Negus). These groups use different methodologies to discern the physical dependence potential and abuse liability of presumed analgesics. The stimulant-depressant testing groups are based in the University of Michigan Medical School (Drs. G. D. Winger and J. H. Woods), the University of Chicago Medical School (Drs. W. L. Woolverton, B. W. Massey, and M. A. Nader), and the Medical College of Virginia (Drs. G. A. Patrick, L. J. Powell, and R. M. Kirby). All of these groups receive their main financial support from the National Institute on Drug Abuse (NIDA) for this work. The Chairman of the DEC serves to implement the NIDA "center" grant for the stimulant-depressant testing groups.

Each of the testing groups have a representative on the DEC, and there are, usually, one or two scientists from the Board of Directors of the CPDD who are invited to participate in the annual meeting of the DEC. At that meeting we discuss and evaluate our work on those drugs which have been released for publication. The DEC offers to pharmaceutical industry, universities, and governmental organizations such as NIDA, the Drug Enforcement Agency, and the World Health Organization, the impartial, scientific evaluation of drugs with the potential for abuse problems which might have an impact on public health.

THE DETERMINATION OF THE PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY OF ANALGESICS

New compounds are evaluated concurrently at the Medical College of Virginia (MCV) and the University of Michigan (UM).

The following assays are carried out on analgesics at MCV (about 0.7 grams of a compound with morphine-like potency is sufficient for a few of these procedures, such as the antinociceptive assays in mice, and the single dose suppression and, if warranted, precipitated withdrawal studies in monkeys):

1) **Antinociceptive and narcotic antagonist assessment** - determined through the phenylquinone, tail-flick, hot plate, and tail-flick antagonism vs. morphine assays in mice. Apparent pA_2 values have been obtained on compounds of interest using the mouse tail-flick assay.

2) **Substitution and primary physical dependence** using rat infusion assays.

3) **Single dose suppression** and, if warranted, **precipitated withdrawal,** as well as **primary physical dependence** studies in the rhesus monkey.

Other studies on analgesics are carried out at UM. Some, or all of these studies are carried out if needed, and if a sufficient supply of the drug is available.

1) **Opioid receptor binding** - These studies are carried out at two levels. The binding affinity of the tested compound in displacing [^{3}H]-etorphine from opioid receptors in membranes from rat brain cerebrum is determined. When warranted, the compound can be further characterized by assessing its binding selectivity at the μ (using [^{3}H]-DAMGO), δ (using [^{3}H]-DPDPE), and κ receptor (using [^{3}H]-U69,593) in monkey brain cortex.

2) **Mouse vas deferens** - The effect of ligands on particular opioid receptors is studied in the electrically stimulated mouse vas deferens preparation. In this preparation, concentrations of a drug ranging between 10^{-10} and 10^{-5} M are tested to determine an EC_{50} for the drug, and a maximum response for inhibition of the twitch is reported. ICI-174864, a δ receptor agonist, is used to determine whether a shift occurs in the dose-response curve. Naltrexone and norbinaltorphimine (nor-BNI, a κ antagonist) are also used to see whether the ligand has interacted with individual receptor types. The compound is then examined in this preparation as an opioid antagonist, and its effect on the actions of sufentanil (a μ agonist), U50,488 (a κ agonist), and DSLET (a δ agonist) are examined. In this manner, the actions of a ligand, both as a possible agonist and/or antagonist, is examined for its interaction with the three main opioid receptor types.

3) **Self-administration** - Analgesic compounds may be evaluated for their potential reinforcing effects in rhesus monkeys experienced in intravenous opioid self-administration under fixed ratio schedules. Several doses of each test compound are evaluated for their capacity to maintain responding in each of three monkeys. Test drugs must be soluble in water to be evaluated for reinforcing effects.

4) **Drug discrimination** assays in normal rhesus monkeys discriminating between saline and a prototypic μ or κ opioid agonist, and in morphine-treated monkeys discriminating between saline and naltrexone.

5) **Analgesic studies in rhesus monkeys** or rats using a warm water tail-withdrawal assay.

6) **Respiratory function** studies in unanesthetized rhesus monkeys breathing 5% CO_2 in air.

THE DETERMINATION OF THE PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY OF STIMULANTS AND DEPRESSANTS

The DEC, CPDD, presently offers evaluation of compounds in the stimulant or depressant classes by use of the following methodology.

1) Initial experiments to provide **potency estimates** and, also, the **physical dependence potential** of the examined compound are undertaken at MCV. The procedures can include:

a) An assessment of **activity** in an inverted screen test and spontaneous locomotor activity in mice;

b) Assessment of **physical dependence potential by substitution** in pentobarbital-dependent rats using continuous intraperitoneal infusion;

c) **Primary physical dependence determination** in rats, by infusion.

2) **Self-administration** studies are carried out at UM. Rhesus monkeys are trained to respond to a fixed ratio 10, time out 10, schedule of intravenous methohexifal (0.1 mg/kg/inj) delivery. Test drugs are substituted for the barbiturate on a periodic basis. A range of doses of each test drug is studied in each of three monkeys. Drugs must be water-soluble to be evaluated in this procedure.

3) **Drug discrimination** studies are obtained at the University of Chicago. The discriminative stimulus properties of drugs are determined in rhesus monkeys trained to discriminate pentobarbital or d-amphetamine from saline. Benzodiazepines can be distinguished from other depressants, they are blocked by Ro 15-1788. The amphetamines are blocked by raclopride.

4) Testing in baboons (under the direction of Drs. Roland Griffiths and Joseph V. Brady, Johns Hopkins University) may be carried out for particular compounds, when necessary.

The amount needed for these assays is dependent on the potency of the compound. We generally request about 35 grams for evaluation of a stimulant or depressant, but the required amount is highly dependent on potency. For more potent compounds, 10 grams may be sufficient. With an initial supply of 2.0 grams, we can determine the potency of the compound and calculate the additional quantity needed.

INTERRELATIONSHIP BETWEEN THE DRUG EVALUATION COMMITTEE AND THE NIDA MEDICATIONS DEVELOPMENT DIVISION

A group at SRI, Int., under the direction of Dr. L. Toll, has been engaged by NIDA's Medication Development Division to examine potential analgesics in various binding assays (μ ([^{3}H]-DAMGO), δ ([^{3}H]-DPDPE-CI), κ_1 ([^{3}H]-U69,593), κ_2, κ_3 ([^{3}H]-NalBzoH), (σ ([^{3}H]-3PPP), PCP ([^{3}H]-MK801)), and in the guinea pig

ileum (GPI) and mouse vas deferens (VD) preparations. In the GPI, the μ activity of ligands is tested using CTAP, and the κ activity with nor-BNI. The dose-response of ligands is examined in the presence of naltrindole in the VD to determine δ-activity. The SRI group also evaluates stimulants. Their compounds come from university groups or are requested from pharmaceutical industry. Occasionally, drugs are tested by both NIDA and CPDD. Several members of the DEC, CPDD, are involved on the NIDA panel which discusses the SRI work.

There appears to be little overlap between the testing procedures of the two groups. We do not often examine specific subtypes of opioid receptors, nor do we test for σ and PCP activity, and we do not use the GPI assay. Drugs with interesting properties can be evaluated using some or all of the testing procedures of the DEC, CPDD, and through the Medications Development Division, NIDA.

CPDD DATA ONLINE

As I mentioned in my previous report (Jacobson 1992) NIDA's Medications Development Division has successfully achieved the production of an impressive, clearly usable computerized database for drugs of abuse through a contract with the Biometric Research Institute, Inc., in Arlington, VA (under the direction of Dr. Gene Barnett). The Medications Development database which is now in its final testing phase is being maintained on a microVAX 3300 computer at ERC BioServices Corp. (a subcontractor), in Gaithersburg, MD. It incorporates two software packages, the Oracle database program, which contains biological data, and MACCS from Molecular Design Ltd., which contains the structural information on a drug.

Members of DEC have been involved in this program since its inception. In fact, for several years prior to NIDA's involvement, members of the DEC considered various possibilities for forming a computerized database on drugs of abuse examined under CPDD auspices. Our exploration was limited by both funding and the available technology at that time. It should be noted that the development of a extensive, usable database is costly, and we are indebted to NIDA's Medications Development Division for having the wisdom and tenacity to pursue and successfully obtain this database.

The Medications Development database includes. all of the DEC, CPDD, data which have been printed in the various NIDA Research Monographs (information from 1979 to the present). The easy retrieval of a combination of pharmacological data, receptor binding, behavioral studies, pharmacokinetics and chemical structures of drugs of abuse will undoubtedly play a major role in the future study of drugs of abuse by scientists involved with this area of research.

STATISTICS

The number of compounds which have been sent to the analgesic testing groups for evaluation from 5/1/91 to 4/30/92 are close to the mean of those sent over the years 1980-1991, and certainly well within the standard deviation of the mean calculated for those 12 years. Similarly, the number of reports from UM and MCV (87, from the evaluation of 49 drugs - see Aceto *et al.* 1993, Woods *et al.* 1993) is close to the mean number for the last 12 years. The source of the drugs is, as

usual, divided between pharmaceutical industry, academia, governmental institutions, and non-profit organizations. The percentage of compounds received from pharmaceutical industry is, again this year, below the mean of 15%. The standard deviation of the mean is, however, considerable. Thus, submission from pharmaceutical industry (10% of the total number) was similar to that of last year, and below that of 1987-1988, 1982-1983, and the years preceding 1981. With the exception of those years, the number of samples from industrial sources is fairly typical of the current trend.

We have received about half of our total number of compounds from universities and non-profit organizations over the past twelve years. This year, the percentage of compounds from those sources increased to 70%. It should be noted that an extraordinarily large number of compounds came from one non-profit institution. Lastly, we usually obtain about 21% of our samples from NIH and CPDD (the latter representing those samples sent to test the system). This year, 20% of our examined samples originated from those sources. In general, this was a reasonably normal year for the analgesics.

Although the data on four compounds evaluated by the Stimulant/Depressant testing groups of the DEC have been released for discussion this year (see below), it should be noted that only one new compound was received from 5/1/91 to 4/30/92 for evaluation by these groups. However, I have been told that several drugs will soon be submitted from industrial sources, and one drug will be sent from NIDA on behalf of the World Health Organization. As I have previously mentioned, the Stimulant/Depressant testing groups of the DEC work under a NIDA center grant, and research is meant to be a major part of their activity. Several research publications have resulted from this work, and several others are being prepared.

SURVEY OF COMPOUNDS EVALUATED AS ANALGESICS

Tables 1-10 summarizes the work on potential analgesics. The 4,5-epoxymorphinans are shown in table 1. Both NIH 10585 and 10685 were described last year (Jacobson 1992, Aceto *et al.* 1992, Woods *et al.* 1992). The work on those compounds was completed this year, and all of the data are shown in the table. NIH 10701 and 10702 are potent narcotic antagonists and were prepared as precursors to potential imaging agents for SPECT (Single Photon Emission Computed Tomography) scanning (de Costa *et al.* 1992). The corresponding radiolabelled compounds might be useful for the determination of normal and abnormal opioid (μ and κ) receptor populations in the brains of conscious humans.

Table 2 includes the completion of our work on LAAM (levo-alpha-acetylmethadol), and work on relatively inactive (+)-isomers of N-benzyl substituted morphinans.

Table 3 contains the (+)- and (-)-isomers of the N-benzylbenzomorphans. Unexpectedly, some of these, like the N-benzyl substituted morphinans, show weak antagonist activity in the VD assay. The data on N-H and N-alkyl substituted benzomorphans shown in table 3 add to those collected on these types of compounds last year (Jacobson 1992, Aceto *et* al. 1992, Woods *et al.* 1992). These compounds were prepared by Dr. E. L. May (Medical College of Virginia, VCU, Richmond, VA) and will be the subject of a comprehensive paper

on N-alkyl substituted benzomorphans which will be submitted to J. Med. Chem. It might be noted that some of the (+)-enantiomers of these compounds are among the most potent σ ligands known (Mattson and Jacobson 1992).

Table 4 includes some structurally unusual phenylpiperidines. NIH 10689 appears to have interesting biological properties. Although devoid of significant opioid activity in binding and the VD, it showed κ-agonist and μ-antagonist activity in drug discrimination. It could not be easily characterized by the assays used.

A considerable number of new fentanyl analogues are noted in tables 5 - 7. Their potency varies considerably, from morphine-like to several orders of magnitude more potent than morphine. All of them appeared to have the physical dependence potential of morphine; all but one completely suppressed morphine abstinence in morphine-dependent monkeys in the SDS assay, and NIH 10724, which only showed partial suppression, completely substituted for alfentanil in drug discrimination. Although a few of them showed anomalous results in the mouse vas deferens preparation (e.g., NIH 10723, 10731) and their potency varied, they were generally quite similar in their display of morphine-like physical dependence potential in the SDS or DD assays.

The three compounds grouped in table 8 bear a structural resemblance to κ-opioids. None of these compounds displayed much antinociceptive activity and they were generally inactive in the other assays.

A second group of miscellaneous compounds (from a structural viewpoint) are listed in table 9. Three of them (NIH 10670, 10705, and 10709) are among the most potent known σ-receptor ligands. σ-Receptors have been noted to be nonopioid, nondopaminergic sites which exhibit high affinity for haloperidol, DTG, (+)-PPP, and SKF-10,047 (Rothman et *al.* 1991). The three compounds tested do not exhibit appreciable antinociceptive activity, do not appear to bind to opioid receptors, and do not suppress morphine abstinence in the SDS assay. The NIH 10700 in table 9 is one of the most potent known PCP-like ligands, acting as a non-competitive antagonist in the NMDA/glutamate receptor system. It appears to have some antinociceptive activity and some affinity for opioid receptors.

Lastly, the three anxiolytics shown in table 10 were examined to see whether they displayed opioid-like physical dependence potential. Of these, only NIH 10687 partially suppressed morphine abstinence in the SDS assay. The signs indicating partial suppression were not necessarily indicative of interaction through opioid receptors.

ABBREVIATIONS USED IN TABLES 1 - 10

Rounded numbers are used in the tables. For precise values, and details of the procedures see Aceto *et al.* 1993 and Woods et *al.* 1993.

1) **MOUSE ED50/AD50:** Antinociceptive Assays (sc injection)
Confidence limits are listed in the MCV report (Aceto *et al.* 1993).

HP = hot plate (morphine ED_{50} = 0.8 (0.3-1.8)

PPQ = phenylquinone (morphine ED_{50} = 0.23 (0.20-0.25))

TF = tail-flick (morphine ED_{50} = 5.8 (5.7-5.9))

TFA = tail-flick antagonism vs. morphine (naltrexone AD_{50} = 0.007 (0.002-0.02); naloxone AD_{50} = 0.035 (0.01-0.093)).

I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

2) IN VITRO (Data from UM, Woods et *al.* 1993)

RBH = binding affinity in rat cerebrum membranes (displacement of 0.5 nM [3H]etorphine) in the presence of 150mM NaCl (morphine EC_{50} = 23.6).

NE = no effect.

NOTE: Contemporary EC_{50} data cannot be directly compared with those from some previous reports (Jacobson 1984, and preceding years) in which -Na values were quoted.

VD = electrically stimulated mouse vas deferens EC_{50} values, rounded to one significant figure.

Agonist activity is stated using "E" followed by a negative number: E = 10^{-x} M, where x = the negative number, thus: 1 E-3 = 1 x 10^{-3} or 0.001 M (1 mM), 1E-6 = 1 μM, and 1 E-9 = 1nM.

SE = slight effect on twitch

NE = No significant agonist or antagonist effect

ANT = Antagonist activity. Selective antagonist activity at μ, δ, and/or κ receptors is noted in parentheses. The antagonist effect may or may not be competitive.

Compounds which suppress the twitch and are not antagonized by naltrexone or other narcotic antagonists are said to be non-opioid agonists (e.g., clonidine can suppress the twitch, but is not antagonized by naltrexone. It is a non-opioid agonist). Compounds which bind with reasonable affinity in the RBH assay and do not suppress the twitch in the VD may have narcotic antagonist properties. The opioid receptor at which the drug exerts its antagonist effect is determined by testing various concentrations of the drug to induce a blockade (antagonism) of the suppression of the twitch in the VD preparation caused by sufentanil (μ), DSLET (δ), or U50,488 (κ) (for these data see Woods *et al.* 1993).

3) IN VIVO: in the rhesus monkey (from MCV, Aceto *et al.* 1993; prior to 1988 from MCV or UM).

SDS = single-dose-suppression

NS = no suppression

CS = complete suppression

PS = partial suppression

(Parenthesized numbers = dose range studied, in mg/kg)

Other Studies (noted in the footnotes to the tables)

A) In Rat - **RI** = rat continuous infusion (data from MCV)

1) SM = substitution for morphine
   NS = no substitution for morphine
   CS = complete substitution
   PS = partial substitution

2) **PPD** = primary physical dependence

B) In Rhesus Monkey:

1) **PPt-W** = studies in non-withdrawn monkeys (data from MCV)
   PW = precipitated-withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N].
   SP = slight precipitation
   NP = no precipitation

2) **ND** = studies using non-dependent monkeys (data from MCV)
   M-like = morphine-like effect.

3) **PPD** = primary physical dependence (data from MCV)

4) **SA** or SI = self-administration or self-injection (data from UM)
   NE = no effect
   High = codeine-like
   IN = intermediate between saline and codeine
   SE = slight effect

5) **DD** = drug discrimination (data from UM)
   NE = no effect
   CS = complete substitution

6) **MA** = monkey analgesia (data from UM)

7) **RF** = respiratory function (data from UM)

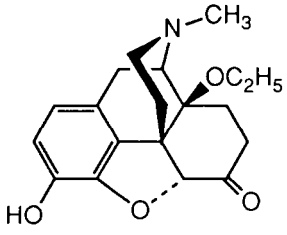
C) In Vitro (data from UM)

BIND - binding affinity using monkey brain cortex membranes (selectivity for μ, κ, and δ opioid receptors using [^{3}H]-sufentanil, [^{3}H]-DPDPE and [^{3}H]-1169,593, respectively).

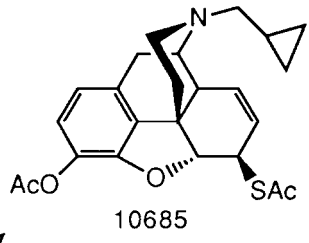
Previous Reports

Previous work on a compound is noted using the year listed in the monograph title (e.g., work cited as "1991" indicates that the work was included in "Problems of Drug Dependence 1991", which was published in 1992). Note that the monograph's publication date may be one year after the titled year of the monograph. Complete details of the original work on a compound can be found in the Annual Report of either Aceto *et al.* or Woods *et al.*

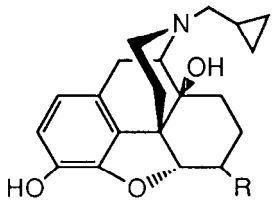
TABLE 1. 4,5-EPOXYMORPHINANS[a]



10585



10685

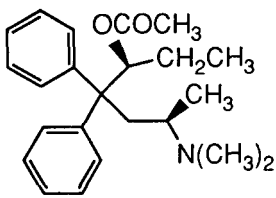


10701: R=β-I
10702: R=α-I

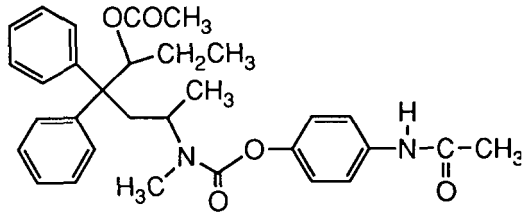
	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10585	-	0.0003	0.001	I	2.3nM[b]	2E-8[A][b]	CS(0.03-0.06)[c]
10685	4.6[b]	0.01[b,d]	2.8[b,d]	I[b,e]	7nM[f,g]	2E-8[A][h]	NS(1.5,6)[b,i,j]
10701	I	I	I	0.08	5.2nM	ANT[k]	NS(0.015,0.06)[l]
10702	I	I	I	0.04	2.1nM	ANT[m]	NS(0.005.0.02)[n]

a) See text for explanation of column headings and abbreviations.
b) Previously reported (1991).
c) 100 x more potent than morphine.
d) High dose of naloxone needed for antagonism.
e) No dose-effect (50% at 30 and 80 mg/kg).
f) **BIND:** μ = 1 nM; δ = 13 nM; κ = 0.8 nM.
g) **DD:** Potent naltrexone-like effect; **SA:** Failed to maintain responding; MA: Strong analgesic, blocked by quadazocine. Compound has κ-agonist and μ-antagonist activity, similar to cyclazocine in monkeys.
h) Antagonist at μ, δ, κ receptors.
i) Agonist-antagonist (appeared to exacerbate withdrawal). Some dopaminergic activity.
j) **RI** - SM: PS; **RI** - PPD: low physical dependence potential - κ opioid action predominant.
k) Non-selective.
l) **PPt-W:** PW.
m) Selective at μ-opioid receptors.
n) Precipitated withdrawal in SDS assay.

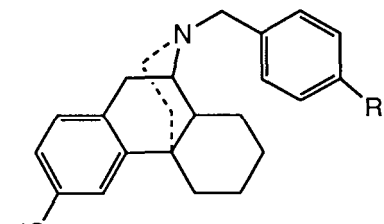
TABLE 2. DIPHENYLMETHANES AND MORPHINANS [a]



10679: LAAM



10699

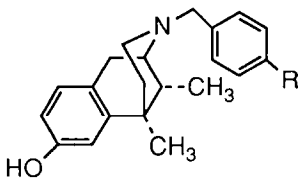


10736: (+) R=OCH_3
10737: (+) R=OH

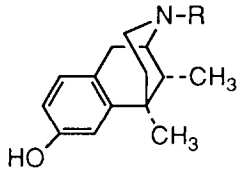
	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10679 & 4539	-	0.4[b]	7.2[b]	Ib	388nM[b,c]	9E-7[A][b]	CS(0.5,2)[b,d,e]
10699	I	I	I	I	>6µM	_f	NS(16)
10736	I	9.9	I	I	>6µM	ANT[g]	-
10737	I	I	I	I	>6µM	ANT[h]	-

a) See text for explanation of column headings and abbreviations.
b) Previously reported - 1991.
c) **BIND** [b]: µ = 34 nM, κ = 2.3 µM, δ = 3.6 µM.
d) Onset slower, duration longer than morphine, equivalent potency.
e) **DD:** failed to substitute for µ- or κ-agonists or naltrexone; RF: depression, antagonized by naltrexone and quadazocine; **SA:** less than, or equivalent to, alfentanil; MA: long-lasting, prevented by quadazocine. Probably µ-agonist with a slow onset.
f) Not tested - insoluble.
g) Low potency µ and δ antagonist.
h) Low potency κ antagonist.

TABLE 3. 6,7-BENZOMORPHANS[a]



10686: (-) R=OCH_3
10691: (+) R=OCH_3
10692: (-) R=OH
10694: (+) R=OH

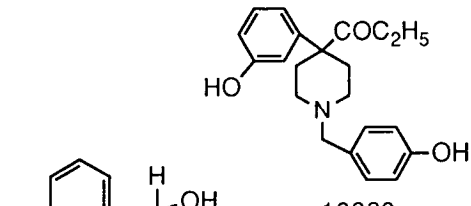


10696: (-) R=H
10695: (+) R=H
10721: (±) R=$(CH_2)_7CH_3$
10697: (-) R=$(CH_2)_7CH_3$
10698: (+) R=$(CH_2)_7CH_3$
10729: (-) R=$(CH_2)_8CH_3$
10730: (+) R=$(CH_2)_8CH_3$

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	PPQ	TF	TFA	RBH	VD	SDS
10686	I	I	21.1	I	7.0 μM[b]	ANT[b,c]	-
10691	I	I	I	I	6.1 μM[b]	ANT[b,d]	-
10692	I	I	I	I	>6 μM	5E-7[A]	-
10694	I	I	I	I	>6 μM[b]	ANT[b,e]	-
10695	I	I	I	I	939nM[f]	4E-5	
10696	I	I	I	I	939nM[g]	4E-5	
10697	5.4	0.5	10.0	I	226nM	ANT[h]	-
10698	11.1	7.8	I	I	3.4 μM	ANT[i]	-
10721	3.6	2.9	8.0	I	675nM[j]	NE[k](10μM)	-
10729	I[l]	I[l]	I[l]	I[l]	1.9μM	NE	NS(5,15)[l]
10730	I[l]	I[l]	I[l]	I[l]	5.4μM	NE[m]	NS(3,15)[l]

a) See text for explanation of column headings and abbreviations.
b) Previously reported - 1991.
c) Very weak antagonist, with some κ selectivity.
d) μ, δ, and κ antagonist; insurmountable at κ, not simple competitive at μ,δ opioid receptors.
e) Antagonist only at high concentrations; slight non-opioid actions.
f) **BIND:** μ = 4 μM.
g) **BIND:** μ = 130 nM δ = 642 nM, κ =299 nM.
h) Non-typical μ and κ agonist, weak μ antagonist.
i) Weak at μ and κ.
j) BIND: μ= 280 nM, δ = 330 nM, κ = 280nM.
k) Low potency μ antagonist.
l) Lack of activity may be due to insolubility.
m) Low potency δ and κ antagonist

TABLE 4. PHENYLPIPERIDINES[a]



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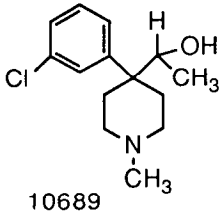

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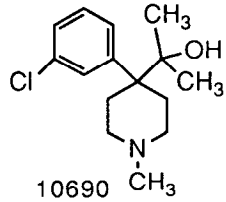

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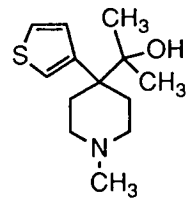
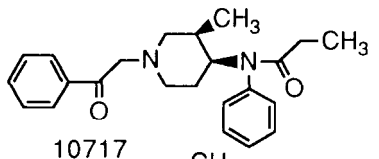


10688

NIH #	MOUSE ED50/AD50 HP	PPQ	TF	TFA	IN VITRO RBH	VD	MONKEY SDS
10680	-	I[b]	I[b]	I[b]	2.6µM ANT[c]		NS(2,8)[b]
10688	I	5.4	I	I	10.3µM SE[d]		PS(4,24)[e,f]
10689	I	2.7	I	I	>6µM[g]	7.6E-8(27)[g]	NS(4,16)[h]
10690	I	3.0	I	I	>6µM[g]	5.3E-8(30)[g]	NS(3,12)[i]

a) See text for explanation of column headings and abbreviations.
b) Previously reported - 1991.
c) Weak µ (insurmountable) and δ antagonist.
d) Unusual partial agonist with doubtful opioid action.
e) **RI (SM:** NS, but behavioral suppression; and **PPD:** PS): Doubtful µ-like dependence potential.
f) **DD** - κ agonist effects (>5.6 mg/kg), no µ agonist or antagonist activity; **MA** - 100% effect (10 mg/kg, 50°, attenuated by quadazocine); **RF** - decreased function (attenuated by quadazocine); **SA** - limited reinforcing capacity.
g) Devoid of significant opioid activity.
h) Opioid activity not definitely characterized by: **DD** - κ agonist and µ antagonist in some monkeys, no µ agonist effects; **MA** - modest (1-10 mg/kg) temperature dependent analgesia antagonized by quadazocine, toxic at 32 mg/kg; **RF** - decreased function not clearly altered by quadazocine; **SA** - maintained rates between saline and alfentanil.
i) No significant opioid effect from: **DD** - no opioid agonist effects, substituted for naltrexone in 1/3 monkeys; **MA** - temperature-dependent analgesia not antagonized by quadazocine; **RF** - modest or no effect; **SA** - no reinforcing effects.

TABLE 5. RACEMIC FENTANYL-LIKE COMPOUNDS[a]



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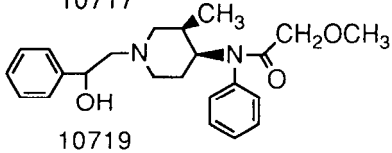
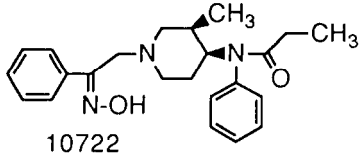


10719



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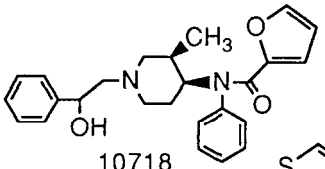

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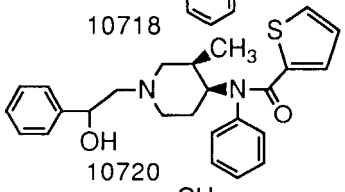

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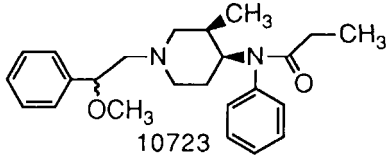


10723

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10717	0.03	0.008	0.03[b]	I	470nM	3.7E-9[A][c]	CS(0.04,0.16)
10718	4E-4	3.9E-4	7E-4[d]	I	17nM	2.5E-9[A][e]	CS(5-20E-4)[d]
10719	4E-4	5E-5	8E-4[f]	I	17nM	3E-10[A][g]	CS(3-6E-3)[f]
10720	0.002	0.003	4E-3[h]	I	97nM	3.5E-9[A][i]	CS(25,100E-4][j]
10722	3.0	0.2	12.4	I	7.3μM	NE[k]	CS(0.5-1.0)
10723	0.02	0.009	0.01[l]	I	40nM	1.9E-6[NA][m]	CS(15-60E-3)[n]

a) See text for explanation of column headings and abbreviations.

b) N (AD_{50}) vs ED_{50} = 0.02.

c) Unusual - naltrexone antagonism insurmountable, nor-BNI less effective than with normal κ agonists.

d) N (AD_{50}) vs ED_{50} = 7.5E-3. (8000 x M in TF; 6000 x M in SDS).

e) Also some κ activity.

f) 7000 x M (6000 x M in SDS).

g) μ and δ agonist.

h) N (AD_{50}) vs ED_{50} = 0.007 (very low).

i) Also κ and possibly δ activity.

j) 1000 x M.

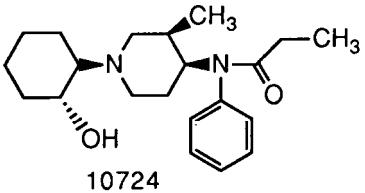
k) No significant agonist or antagonist activity.

l) N (AD_{50}) vs ED_{80} = 0.1.

m) Biphasic response, non-opioid. (On replication - possible opioid component to higher affinity but not lower affinity actions).

n) 100 x M in SDS assay. **MA** - full analgesic response (0.056, 0.1 mg/kg); **DD** - NE (morphine-treated monkeys), reversed naltrexone-lever responding morphine-abstinent monkeys); **RF** - depressed function.

TABLE 6. RACEMIC FENTANYL-LIKE COMPOUNDS (CONTINUED)[a]



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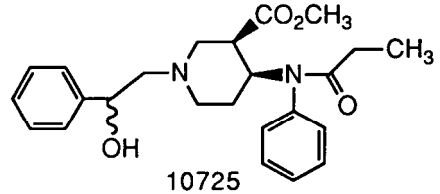
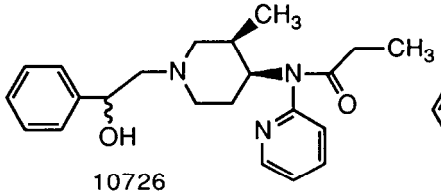
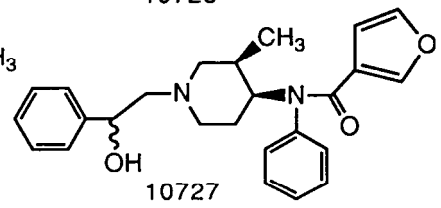


10725



10726



10727

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	H P	P P Q	TF	TFA	RBH	VD	SDS
10724	0.4	0.05	0.6[b]	I	1.2μM	1.8μM[A][c]	PS(0.3,1.2)[d]
10725	0.01	0.009	0.02[b]	I	64nM	449nM[A][e]	CS(0.025)[f]
10726	2E-4	1.5E-4	4E-4[b]	I[g]	25nM	9E-8[A][h]	CS(2.5E-4)[i]
10727	4E-3	9.1E-4	2E-3[j]	I	4.8nM	200nM[A][k]	CS(2E-3)[l]

a) See text for explanation of column headings and abbreviations.

b) N (AD_{50}) vs ED_{80} = 0.02.

c) Weak, non-selective, partial agonist.

d) 2.5 x M in SDS assay. **MA** - full analgesic response (0.056, 0.1 mg/kg); **DD** - CS (for alfentanil, but not ketocyclazocine), reversed naltrexone-lever responding (morphine-abstinent monkeys); **RF** - depressed function.

e) Complex biphasic action (also, 58μM); possible opioid component to higher and lower affinity actions. Complicated low potency agonist.

f) 100 x M in SDS assay. **MA** - full analgesic response (0.056, 0.1 mg/kg); **DD** - CS (for alfentanil), reversed naltrexone-lever responding (morphine-abstinent monkeys); **RF** - depressed function.

g) Toxic at 10 mg/kg (2/6).

h) Selective μ antagonist, δ agonist.

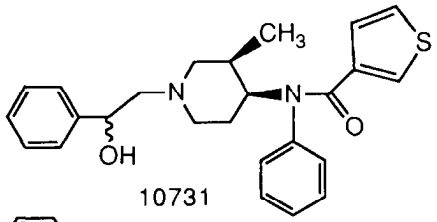
i) *ca.* 12000 x M.

j) N (AD_{50}) vs ED_{80} = 0.05.

k) Complex biphasic action. (also, 19μM); possible opioid component to higher, not lower affinity component. Complicated low potency agonist.

l) 1500 x M in SDS assay. **DD** - reversed naltrexone-lever responding (morphine-abstinent monkeys); **RF** - depressed function.

TABLE 7. RACEMIC FENTANYL-LIKE COMPOUNDS (CONTINUED)[a]



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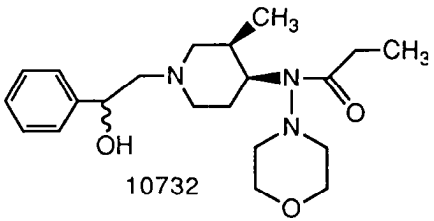

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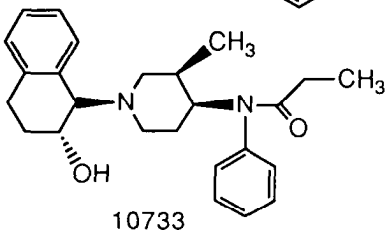

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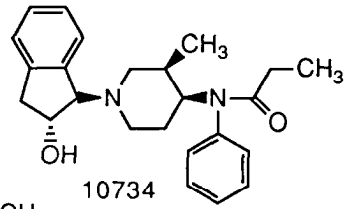
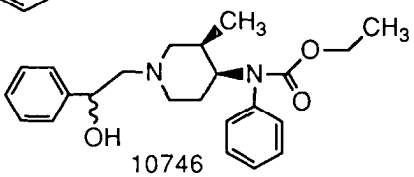


10734

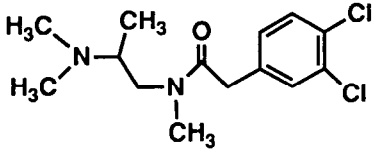


10746

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10731	4E-3	1E-3	3E-3[b]	I	7.3nm	2.6E-7[NA][c]	CS(1-4E-3)[d]
10732	0.6	0.3	0.7[e]	I	3µM	15.7µM[f]	CS(0.25,1.0)[g]
10733	4.8	3.3	8.9	I	420nM	9E-10,2E-6[h]	CS(2,8)[i]
10734	6.8	3.2	6.5	I	7.9µM	NE[j]	CS(2.5,10)
10746	3E-3	1E-3	5E-3[k]	I	20nM	1.9E-9[A][l]	CS(1-8E-3)[m]

a) See text for explanation of column headings and abbreviations.
b) N (AD_{50}) vs ED_{80} = 0.02.
c) Non-opioid.
d) *ca.* 750 x M.
e) N (AD_{50}) vs ED_{80} = 0.09.
f) Small shift by µ and δ antagonists; possibly not mediated by opioid receptors.
g) *ca.* 12 x M.
h) Complex, biphasic; also κ, not δ, agonist.
i) µ-Agonist profile, *ca.* 0.4 x M.
j) No agonist or antagonist activity.
k) N (AD_{50}) vs ED_{80} = 0.01.
l) Selective for µ opioid receptors.
m) Potent µ-agonist, 7500 x M.

TABLE 8. MISCELLANEOUS - POTENTIAL KAPPA RECEPTOR OPIOIDS[a]



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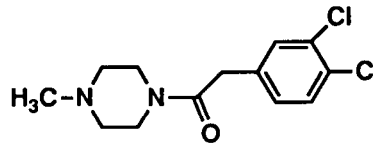

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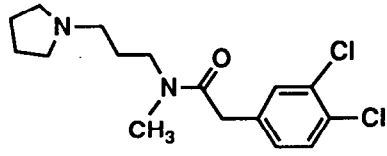
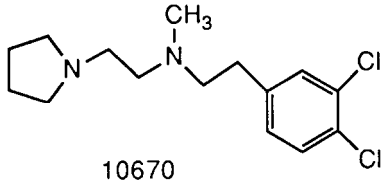


10706

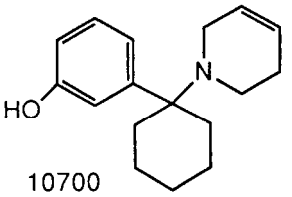
		MOUSE ED50/AD50			IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10703	I	13.4	I	I	>6µM	49µM[b]	NS(1.5,6)[C]
10704	6.3	11.3	I	I	>6µM	8.4E-7[d]	NS(3,12)[c]
10706	I	I	I	I	>6µM	NE	NS(3,12)[e]

a) See text for explanation of column headings and abbreviations.
b) Possibly some κ or mixed µ and κ activity.
c) Side-effects noted.
d) Biphasic.
e) Non-opioid exacerbation of withdrawal.

TABLE 9. MISCELLANEOUS - POTENT SIGMA AND PCP LIGANDS[a]



10670



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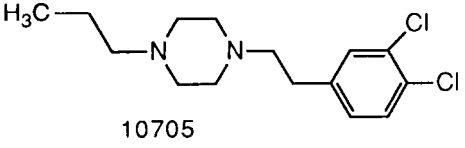

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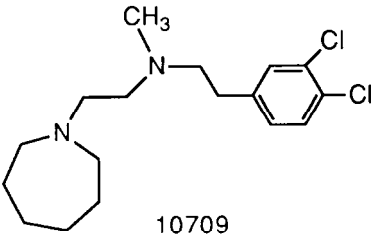
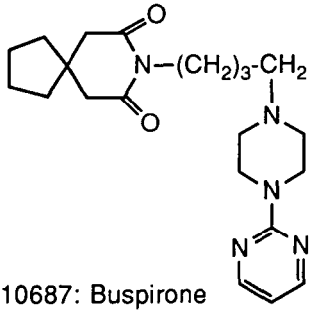


10709

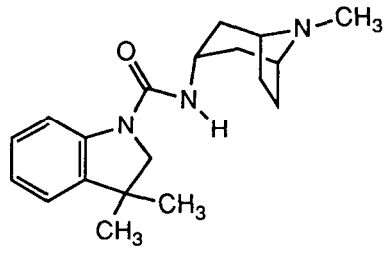
	MOUSE ED50/AD50					IN VITRO	MONKEY
NIH #	HP	PPQ	TF	TFA	RBH	VD	SDS
10670[b]	-	I	I	I	>6µm[c]	2.2E-8[NA][c]	NS(1.5,6)
10700[d]	I[e]	0.3[e]	4.8[e,f]	I[e]	619nM	ANT[g]	-
10705[b]	I	10.6	I	I	>6µM	NE	NS(2,8)[h]
10709[i]	I	4.0	I	I	>6µM	ANT[j]	NS(2,10)

a) See text for explanation of column headings and abbreviations.
b) Very potent σ-ligand.
c) No significant opioid activity.
d) Among the most potent PCP-like ligands.
e) Previously reported - 1991.
f) Straub tail, ataxia, convulsions.
g) Weak, non-selective narcotic antagonist.
h) Exacerbates withdrawal. Side-effects - vomiting, rapid respiration, etc.
i) One of the most potent known σ-ligands.
j) Low potency, not simple competitive.

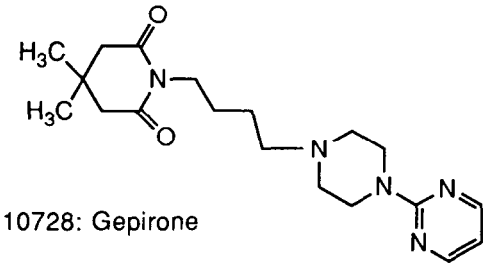
TABLE 10. MISCELLANEOUS - ANXIOLYTICS[a]



10687: Buspirone



10710, CPDD 0037



10728: Gepirone

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	TF	TFA	RBH	VD	SDS
10687	I[b]	14.6[b,c]	I[b]	I[b]	-	-	PS(0.2-0.8)[b,d,e]
10710[f]	I	I	I	I	-	-	NS(2,8)[d,g]
10728	-	-	-	-	-	-	NS(0.5,2)[h]

a) See text for explanation of column headings and abbreviations.
b) Previously reported - 1991.
c) N (AD_{50}) vs ED_{80} = I at 1 and 10 mg/kg.
d) **PPTW -** NP.
e) **RI - PPD:** none; **PPD with cocaine:** buspirone dose-dependently prevented stereotypy and weight loss associated with cocaine.
f) See CPDD 0037 in Table 11 for the evaluation of this compound by the stimulant/depressant testing group.
g) May exacerbate withdrawal; **PPTW - NP(3,12); RI - PD:** low or none.
h) Side-effects noted (rapid respiration, aggressiveness, tremors, disorientation).

STIMULANT/DEPRESSANT DRUG TESTING

One new compound was received for evaluation this year (5/1/91 to 4/30/92). The report by Woolverton *et al.* (1993) will include the detailed evaluation of four compounds which have been released for publication, CPDD 0021, 0034, 0036 and 0037. CPDD 0036 was requested for comparison purposes, and CPDD 0037 was submitted through NIDA's Medications Development Division. The molecular structures of these four compounds, all of which were obtained from pharmaceutical industry, are shown in table 11. The data collected on these compounds by the Stimulant/Depressant testing groups in the Drug Evaluation Committee are summarized below and in Table 11.

3-(3-Dimethylaminopropyl)-3-(mmethoxyphenyl)-4,4-dimethyl-2,6- -piperidinedione hydrochloride (CPDD 0021)

This compound did not share pentobarbital's discriminative stimulus effects in monkeys, nor did it display reinforcing properties It is unlikely to have pentobarbital-like subjective effects in humans. The compound was toxic at a high dose in rodents and a monkey.

N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide tartrate (Zolpidem tartrate, CPDD 0034)

Zolpidem is a hypnotic noted to be a selective benzodiazepine receptor agonist (Merck Index). The compound, perhaps because of its poor solubility, was found to partially substitute for pentobarbital in dependent rats, and withdrawal was mild or negligible. It acted as a reinforcer in methohexital-trained monkeys and, from drug discrimination studies, its subjective effects were predicted to be similar to pentobarbital.

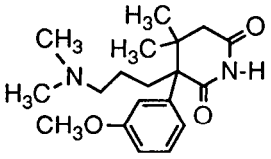
(+)-10,11-Dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (Dizocilpine, MK801, CPDD 0036)

Dizocilpine is known to be one of the most potent PCP-like compounds. It acts as a non-competitive antagonist in the NMDA-glutamate receptor system, blocking the flow of calcium ions through ion channels. Surprisingly, the drug did not show rate-maintaining effects in ketamine-trained monkeys with behaviorally-active doses, nor did it produce discriminative stimulus effects similar to pentobarbital or *d*-amphetamine.

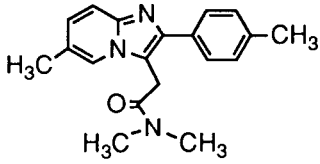
endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxamide (CPDD 0037)

This drug, known to be a potent 5-HT_3 antagonist, did not appear to act as a reinforcer in methohexital-trained monkeys, nor did it produce discriminative stimulus effects similar to pentobarbital or d-amphetamine. From these results, CPDD 0037 would not be predicted to produce pentobarbital-like or amphetamine-like subjective effects in man.

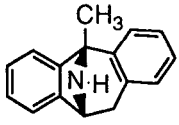
TABLE 11. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



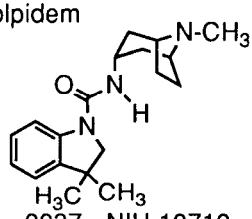
0021



0034: Zolpidem



0036: Dizocilpine (MK801)



0037, NIH 10710

CPDD#	SLA[a]	IS[b]	PD-S[c]	SA[d]	DD[e]
0021	0.21[f]	0.339	NO[h]	NO[i]	NO[j]
0034	DEPRESSION[k]	DEPRESSION[k]	PARTIAL[l]	YES[m]	YES
0036	ERRATIC[n]	NO[o]	SLIGHT[p]	NO[q]	NO[r]
0037[s]	DEPRESSION	DEPRESSION	YES[t]	NO[r]	NO[u]

a) Spontaneous locomotor activity (mouse).
b) Inverted screen assay (mouse).
c) Physical dependence - substitution for pentobarbital (rat infusion).
d) Self-administration (monkey).
e) Drug discrimination (intragastric administration, monkey).
f) Potency relative to pentobarbital (5-15 min.).
g) Potency relative to pentobarbital (20 min.); toxic at 200 mg/kg.
h) Did not substitute for pentobarbital to prevent weight loss on withdrawal.
i) Lethal effect at 60 mg/kg.
j) Does not share discriminative stimulus effects with pentobarbital.
k) Slightly more potent than pentobarbital, longer duration of activity.
l) Substitutes partially for pentobarbital; mild to negligible withdrawal.
m) In sodium methohexital-trained monkeys.
n) Mild effect. Not dose-related.
o) Moderate depression at 20 mg/kg.
p) Unlikely to produce dependence of depressant type.
q) In ketamine-trained monkeys; not reinforcing, but long duration of action.
r) Little effect in methohexital-trained monkeys.
s) See NIH 10710, in Table 10, for evaluation in analgesic assays.
t) Partial suppression of barbiturate dependence.
u) Does not share discriminative stimulus effects with damphetamine or pentobarbital.

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DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1992)

M. D. ACETO; E. R. BOWMAN; L. S. HARRIS; AND E. L. MAY

All compounds, except buspirone, HCl, cocaine. HCl, gepirone, HCl, and morphine SO_4 were supplied by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. The identities of all the compounds, except those indicated above, were unknown to us when they were originally submitted. These studies were conducted under the auspices of the Drug Evaluation Committee of the College on Problems of Drug Dependence.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine.SO_4 every 6 h. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 h and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-h observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ±SEM was calculated and the data illustrated in figure form.

Precipitated- Withdrawal (PPT- W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 h after the last dose of morphine. These animals were not in withdrawal. Naloxone,HCl (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with antagonist or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink

normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 h. Occasionally, when deemed necessary, as with cocaine, infusions were given *via* the right jugular vein.

Substitution-for-Morphine (SM) Test. The rats received morphine SO_4 (50 mg/kg/24 h on the first day, 100 mg/kg/24 h on the second day, and 200 mg/kg/24 h from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 h at 6, 24, 48, 72 and/or 96 h after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED_{50}'s were calculated by using computerized probit analysis.

Tail-Flick (TF) and (TF vs *M) Assays.* The procedure and modifications were described D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 s under control conditions. Mice were injected with drug or vehicle and tested 20 m later. In the assay for antagonism of the antinociceptive effect, the potential antagonists were administered 10 m before the agonist, and evaluation occurred 20 m later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drugs and 10 m later received 2.0 mg/kg ip of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten minutes after the PPQ injection, the total number of stretches per group were counted over a l-m period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 s or more, but no more than 30 s beyond the control time.

Calculation of Apparent pA_2 Using the tail-flick assay, the apparent pA_2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, N.Y., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. Dose-response lines for antinociception were plotted using at least 4 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED50s were estimated according to the method of Litchfield

and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratios (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-1) was plotted against the negative logarithm of the molar dose of the antagonist. At lease four logs (x-1) were plotted. The pA_1 values for the antagonist were calculated from the point of intersection of the regression line with the abscissa.

Table 1

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	1 8 (12-26)	1.7 (1.0-2.5)	- - - -
Cyclazocine	17% at 1.0[a]	0.03 (0.020-0.78)	0.01 (0.005-0.03)	- - - -
Nalorphine•HCl	None at 10.0	2.6 (0.7-10.0)	0.6 (0.03-1.44)	- - - -
Naloxone• HCl	None at 10.0	0.04 (0.01-0.09)	No Activity	- - - -
Naltrexone•HCl	None at 10.0	0.007 (.002-0.02)	No Activity	- - - -
Morphine•SO_4[b]	0.73 (0.35- 1.53)	Inactive	0.4 (0.2-0.8)	3.1 (1.5-6.4)
Codeine•PO_4	- - -	Inactive	- - - (0.39-16.8)	6.4 (0.39-16.8)
Meperidine•HCl	- - -	Inactive	- - -	4.6 (1.8-11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time.
[b]Submitted recently as an unknown.

Compound NIH	Chemical Name or Generic Class	MOUSE				RAT		MONKEY		
		TF	TF vs M	PPQ	HP	SM PPD		SDS	PPt-W	PPD
0001 Morphine		+[b]								
8211 Cocaine•HCl	Azabicyclooctane						Special[A]			
9276 Sufentanil		+[b]								
9470 U-50,488	Benzeneacetamide		+[b]							
10365 Nalmefene	14-Substituted Morphine	+[b]								
10443	14-Substituted Morphine	+[c]								
10585	Dihydromorphone	+	+	+						
10647 Mirfentanil	4-Aminopiperidine	+[b,c]								
10670	Pyrrolidinylethylamine	+	+	+				+		
10672	Benzofuranoacetamide	+[b]								
10685	6-Thiocetylheroin	+[d]				+	+			
10686	6,7-Benzomorphan	+[d]	+	+	+					
10687 Buspirone	Piperazine	+					+			
10688	4-(3-Thienyl)piperidine	+	+	+	+	+	+	+		
10689	4-(3-Chlorophenyl)piperidine	+	+	+	+			+		
10690	4-(3-Chlorophenyl)piperidine	+	+	+	+			+		
10691	6,7-Benzomorphan	+	+	+	+					
10692	6,7-Benzomorphan	+	+	+	+					
10694	6,7-Benzomorphan	+	+	+	+					
10695	(+)-Normetazocine	+	+	+	+					
10696	(-)-Normetazocine	+	+	+	+					
10697	6,7-Benzomorphan	+	+	+	+					
10698	6,7-Benzomorphan	+	+	+	+					
10699	Diphenylmethane	+	+	+	+			+		
10701	4,5-epoxymorphinan	+	+	+	+			+	+	
10702	4,5-epoxymorphinan	+	+	+	+			+		
10703	N-Phenylacetylethylamine	+	+	+	+			+		
10704	N-Phenylacetylpiperazine	+	+	+	+			+		

SUMMARY OF NEW DATA (cont.)

Compound NIH		Chemical Name or Generic Class	MOUSE TF	TF vs M	PPQ	HP	RAT SM PPD	MONKEY SDS	PPt-W	PPD
10705		N-Phenylethylpiperazine	+	+	+	+		+		
10706		Pyrrolinylethylamide	+	+	+	+		+		
10709		Homopiperidinylethylamine	+	+	+	+		+		
10710		Dimethylindole	+	+	+	+	+	+	+	
10717		4-Piperidylphenylamide		+	+	+		+		
10718		4-Piperidylphenylamide	+[d]	+	+	+		+		
10719		4Piperidylphenylamide	+[d]	+	+	+		+		
10720		4Piperidylphenylamide	+[d]	+	+	+		+		
10721		6,7-Benzomorphan	++	+	+					
10722		4Piperidylphenylamide	+	+	+	+		+		
10723		4-Piperidylphenylamide	+[d]	+	+	+		+		
10724		4Piperidylphenylamide	+[d]	+	+	+				
10725		4-Piperidylphenylamide	+	+	+	+		+		
10726		4Piperidylphenylamide	+[d]	+	+	+		+		
10727		4-Piperidylphenylamide	+[d]	+	+	+		+		
10728	Gepirone•HCl	Dialkyl glutaramide						+		
10729		6,7-Benzomorphan	+	+	+	+		+		
10730		6,7-Benzomorphan	+	+	+	+		+		
10731		4-Piperidylphenylamide	+[d]	+	+	+		+		
10732		4-Piperidylphenylamide	+[d]	+	+	+		+		
10733		4-Piperidylphenylamide	+	+	+	+		+		
10734		4-Piperidylphenylamide	+	+	+	+		+		
10736		3-Hydroxymorphinan	+	+	+	+				
10737		3-Hydroxymorphinan	+	+	+	+				
10746		4-Piperidylphenylcarbamate	+[d]	+	+	+		+		

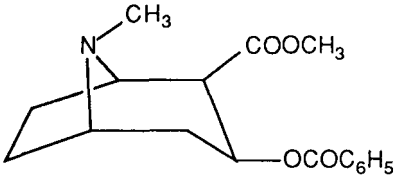
[a]Special rat infusion pharmacokinetic study: Cocaine-Buspirone Interaction, bpA_2 determinations using mouse TF, [c]CCAM, naloxone, and nalmefene prevention and reversal of ED80 of Buprenorphine in mouse TF, [d]Special Study: Naloxone vs ED80 in TF test.

pA_2s are useful for classifying drugs and receptors (e.g. Schild, 1947, Aceto et al., 1969 and Tallarida et al., 1979). A discussion and interpretation of the results can be found in an abstract in this monograph (Aceto, et al.).

Summary table of apparent pA_2 results using mouse tail-flick assay

TREATMENT	SCHILD PLOT		CONSTRAINED PLOT
Antagonist/Agonist	pA2 (95 % C.L.)--Slope		pA2 (95 % C.L)
A. Naloxone/Sufentanil	7.0 (6.9-7.1)	1.0	7.0 (6.9-7.0)
B. Naloxone/Morphine	7.2 (7.0-7.4)	1.2	7.3 (7.1-7.6)
C. Naloxone/Mirfentanil	7.6 (7.3-8.0)	0.7	7.2 (6.9-7.5)
D. Naloxone/U- 50,488	6.6 (6.3-6.9)	1.1	6.6 (6.3-7.0)
E. Naloxone/NIH 10672	6.1 (5.6-6.6)	1.2	6.2 (5.9-6.5)
F. Nalmefene/Morphine	8.0 (7.6-8.3)	1.1	8.0 (7.7-8.3)

NIH 8211, Cocaine•HCl



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 1% at 1.0, 9% at 10.0 and 11% at 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 2.83 (0.97 - 8.28)[a]

[a]Reported previously

[a]See NIDA Research Monograph 105:646,1990.

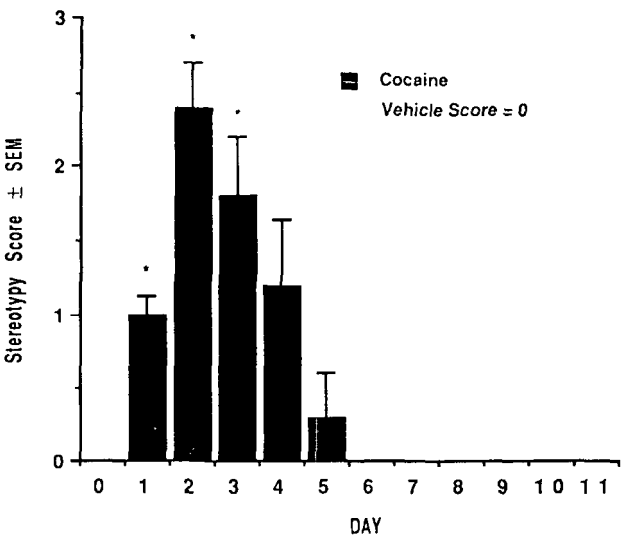
RAT CONTINUOUS INFUSION

Special Tolerance Pharmacokinetic Study

Despite the fact that high doses of cocaine are abused chronically, relatively little is known regarding the development of tolerance and/or sensitization under these circumstances. Therefore, male Sprague-Dawley rats were infused continuously i.v. for 10 days, at a rate of 150 mg/kg/day (0.1 mg/kg/m) with cocaine hydrochloride. Body weight, food and water consumption, urine and fecal excretion, as well as blood pressure, heart rate and stereotypic behavior were monitored daily. Blood samples were also drawn daily so that plasma could be analyzed for cocaine and benzoylecgonine (BEG) by gas chromatography/mass spectrometry. Severe, body-weight loss on days 1

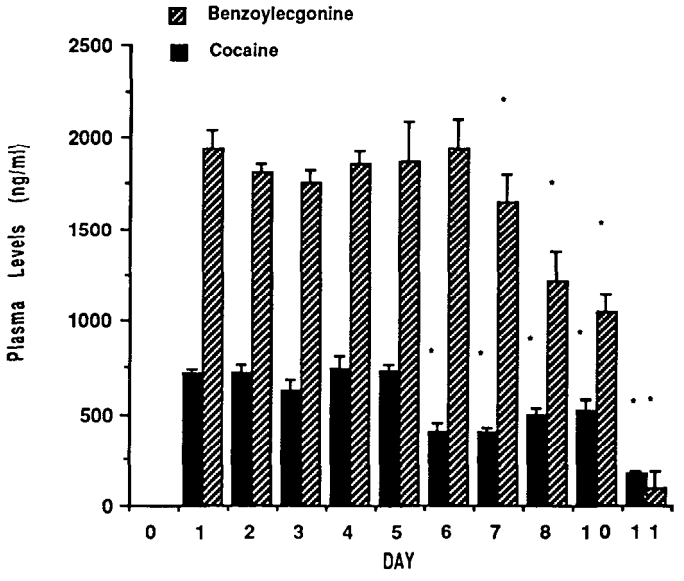
through 4 was followed by a gradual return to pre-drug levels. In addition, cocaine's effects on food and water consumption and urine and fecal excretion, which were maximal by day 2, were imperceptible by day 5. Complete tolerance developed rapidly to the remarkable rise in blood pressure noted on the first day. However, tolerance did not develop to the cocaine-induced increase in heart rate. A profound decrease in heart rate was noted in some animals, which was interpreted to be cardiotoxicity, since these animals subsequently died. On the other hand, sensitization or intensification of behavioral stereotypy occurred during the first 2 days followed by complete tolerance to this effect by day 5 (see Fig. 1 - Cocaine Stereotypy).

Figure 1 - Cocaine Stereotypy



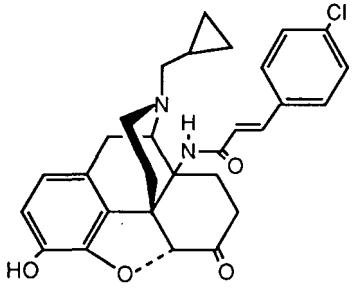
No withdrawal phenomena were noted 24 h after cocaine was abruptly withdrawn. Plasma concentrations of cocaine rose rapidly during the first day and remained elevated at a constant level until day 5. Then, a sharp decline in plasma levels occurred at day 6 which remained depressed for the duration of the infusion. Plasma levels of BEG also rose strikingly to much higher levels than cocaine during the first day and remained stable until day 6, followed by a steady decline. The cocaine infusion was discontinued on day 10. Twenty-four hours after the abrupt withdrawal of cocaine, significant amounts were still present in plasma. BEG was also present in plasma but at concentrations lower than those of cocaine (see Fig. 2 - Cocaine and BEG Plasma Levels).

Figure 2 - Cocaine and BEG Plasma Levels



Since sensitization and tolerance to the pharmacological effects preceded changes in plasma levels of cocaine and did not develop uniformly for all endpoints, it was concluded that functional tolerance was primarily responsible. However, dispositional tolerance also occurred as suggested by the decreased cocaine plasma concentrations beginning on day 5. For full details, see Johansson, et al., Eur. J. Drug Metab. & Pharamacokin. 1992 (in press).

NIH 10443 (14β-(p-Chlorocinnamoylamino)-7,8-dihydro-N-cyclopropylmethylnormorphinone mesylate (CCAM)



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - 0.12 (0.07 - 0.23)
3) PPQ - 23% at 3, 34% at 10.0, 69% at 30.0 and 54% at 60.0
4) HP - Inactive at 20.0

NIH 10443 (14β-(p-Chlorocinnamoylamino)-7,8-dihydro-N-cycloproylmethylnormorphinone mesylate (CCAM). . . continued

MONKEY DATA[a]
(SDS)

[a]See NIDA monograph 81:507, 1987.

Special Study: CCAM, naloxone and nalmefene prevention and reversal of ED80 of buprenorphine in the TF assay.

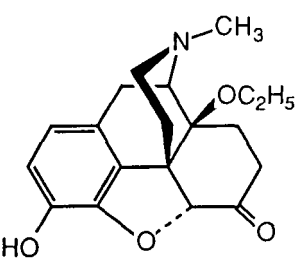
CCAM, an extraordinarily long-acting opioid antagonist (Aceto, et al., Arzneimittel Forschung, 39, 570, 1989) was studied for its ability to block the antinociceptive action of buprenorphine (BU) using the mouse tail-flick assay. The results were compared with those obtained with naloxone (NOX) and nalmefene (NME). They are summarized in the table below as AD50's (95% C. L.). All doses are expressed as mg/kg s.c.

MPE 0
AD50's of CCAM, NOX or NME given before or after BU

Opioid Antagonist	Before AD50 of BU	After AD50 of BU
CCAM	1.0 (0.3-3.2)	0.8 (0.3-2.4)
NOX	0.15 (0.06-0.36)	0.0% at 10.0
NME	0.02 (0.007-0.06)	15% at 10.0

It is obvious that CCAM was equally effective in preventing or reversing analgesia whereas NOX and NME were effective only when given before BU. Thus, CCAM has the unique ability to reverse BU's antinociceptive effects. In addition, in time-course studies, CCAM blocked Bu's action when given 72 h before BU. The mechanism of action is unknown. However, CCAM like BU may be quite lipid soluble or it may be tightly bound to the mu opioid receptor. These studies suggest many pharmacotherapeutic uses for CCAM.

NIH 10585 14-Ethoxydihydromorphinone



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

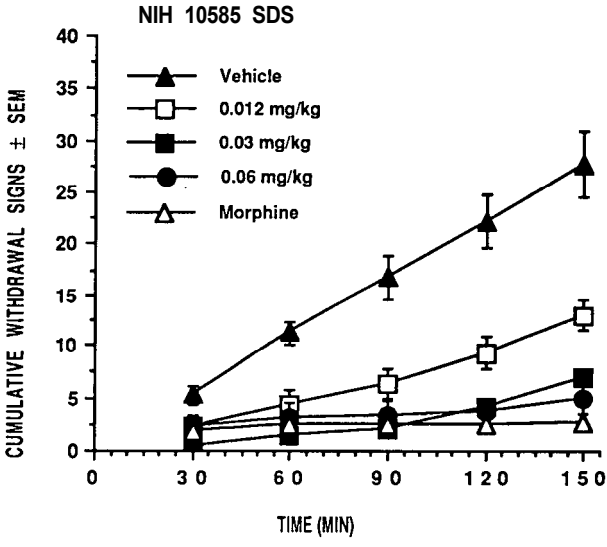
1) TF - 0.001 (0.0004 - 0.002)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.0003 (0.00001 - 0.0007)[a]

[a]Vehicle - few drops lactic acid in water

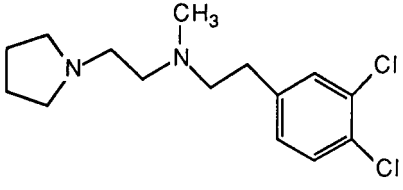
MONKEY DATA
(SDS)

NIH 10585 substituted completely for morphine; the action was dose-related. The drug appeared to be 100 x more potent than the positive control, morphine. Other signs associated with acute exposure to morphine were also noted namely, scratching, rubbing face and "cataleptic-like" stance. Vehicle contained one drop of H_3PO_4 in 10 ml of water.

NIH 10585 14-Ethoxydihydromorphinone...continued



NIH 10670 N-[3,4-dichlorophenylethyl]-N-methyl-2-(1-pyrolidinyl)ethylamine dihydrobromide



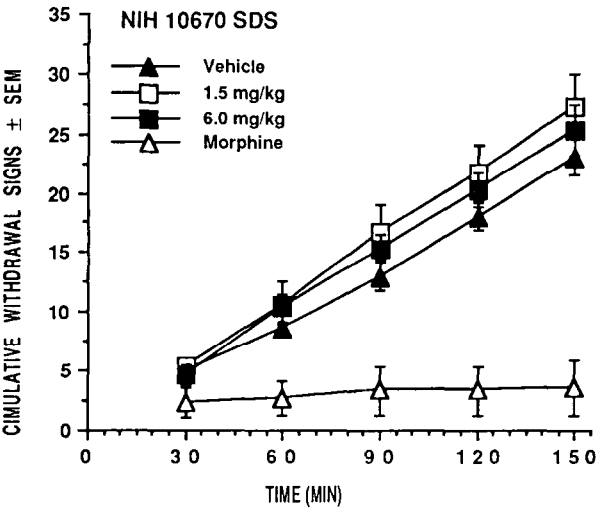
MOUSE MOUSE DATA-ED50-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0 and 30.0
3) PPQ - 11% at 3.0, 25% at 10.0, 42% at 30.0 and 53% at 60.0

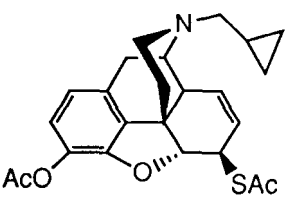
MONKEY DATA
(SDS)

As shown in the graph, NIH 10670 neither substituted for morphine nor exacerbated withdrawal at doses of 1.5 and 6.0 mg/kg.

NIH 10670 N-[3,4-dichlorophenylethyl]-N-methyl-2-(1-pyrrolidinyl)ethylamine dihydrobromide



NIH 10685 (-)-3-Acetyl-6β-(acetylthio)-N-(cyclopropylmethyl)normorphine



MOUSE DATA-ED50 OR AD50 mg/kg (95% C.L.) or % change

1) TF - 2.8 (0.9 - 9.1)[a]
2) TF vs. M - 28% at 1.0, 18% and 24% at 10.0; 52% and 76% at 30; 71% at 60; and 51% at 80[a,b]
3) PPQ - 0.01 (0.002 - 0.04)[a]
4) HP - 4.6 (1.4 - 15.4)[a]

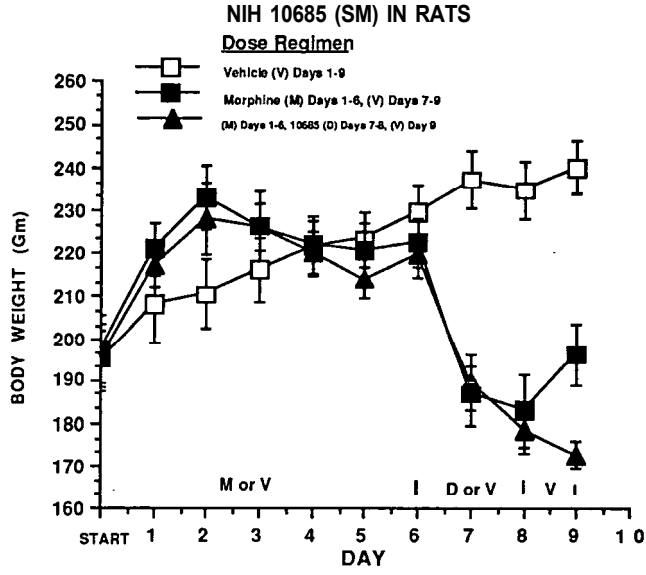
[a]See CPDD Monograph (in press, 1991)
[b]Some of the doses were re-tested.

Special Study: Naloxone vs ED_{80} of 10685 in TF, AD_{50} - 1.2 (0.3 - 4.1)

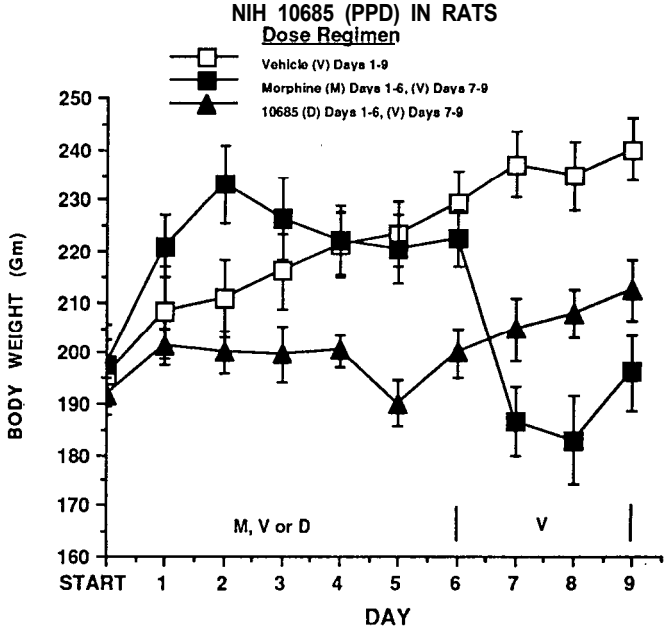
RAT CONTINUOUS INFUSION

A. (SM) When substituted for morphine on days 7 and 8, NIH 10685, at a dose of 160 mg/kg/day, this compound did not prevent the drastic loss of body weight associated with morphine withdrawal (see fig 1). Regarding behavior, the drug suppressed the withdrawal signs designated wet-dog shakes, rubbing and chewing; however, the animals were squealing and showed some aggressiveness as noted in the morphine controls. See table for other experimental details,

NIH 10685 (-)-3-Acetyl-6 β-(acetylthio)-N-(cyclopropylmethyl)normorphine
. . . continued



B. (PPD) In the primary-physical-dependence study, the dose regimen used suppressed normal, body-weight gain. However, when drug was discontinued on day 6, no weight loss was observed. In fact, the animals gained weight. Regarding behavioral-withdrawal signs, minimal activity was observed. This compound does not produce a high level of physical dependence.



NIH 10685 (-)-3-Acetyl-6β-((acetylthio)-N-(cyclopropylmethyl)normorphine
. . . continued

Table: Primary-Physical-Dependence (PPD) and Substitution for Morphine (SM) Studies With NIH 10685 in Continuously-Infused Rats

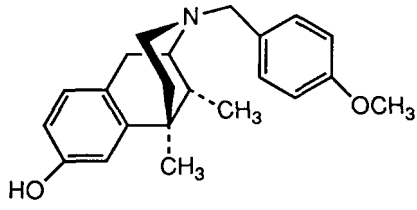
Treatment (I.P.)	Hours in Withdrawal (Day)		
	24 (Day 7)	48 (Day 8)	72 (Day 9)
	Mean Number of Withdrawal Signs[a]		
1. Vehicle Controls[d]	0.3	0.3	1.3
2. Morphine Controls[e]	11.8[b]	14.8[b]	7.3
3. NIH 10685-(PPD)[f]	3.2[c]	2.6[c]	2.4
4. NIH 10685-(SM)[g]	1.5	2.3[b,c]	12.8[b]

[a]Hypersensitivity, squeaking, aggression, wet-dog shakes, rubbing and chewing;
[b]One-tailed Mann-Whitney U test, p = 0.05 or less compared with water controls;
[c]One-tailed Mann-Whitney U test, p = 0.05 or less compared with morphine controls;
[d]Sterile distilled H_2O-8 ml/24 h. N=3;
[e]Dose regimen of morphine SO_4, 50 mg/kg on day I, 100 mg/kg on day 2,200 mg/kg on days 3-6. Then, vehicle on days 7-9. N =4;
[f]Dose regimen of NIH 10685,25 mg/kg on days 1-2,40 mg/kg on day 3,80 mg/kg on day 4, 160 mg/kg on days 5-6. Then, vehicle on days 7-9, N=5;
[g]Morphine SO_4 Infusion, days 1-6 as above, then, NIH 10685, at 160 mg/kg, on days 7 and 8, and H_2O, as above, on day 9. N = 4.

Remarks:

The data suggest some mu agonist/antagonist activity. However, the mu physical dependence liability is considered low. The predominate opioid action appears to be kappa.

NIH 10686 (-)-5,9α·-Dimethyl-2'-hydroxy-2-(4-methoxybenzyl)-6,7-benzomorphin hydrobromide

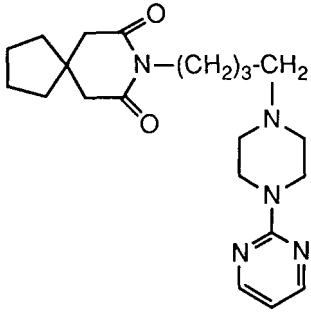


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 21.1 (10.4 - 42.7)[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0% at 1.0, 3% at 10.0, 43% at 30.0 and 73% at 60.0[a,b,c]
4) HP - 0% at 1.0, 25% at 10.0 and 13% at 30.0[a,b,c]

[a]10% DMSO in water
[b]Clonic convulsions at 60.0
[c]Vehicle - 13% activity

NIH 10687 Buspirone



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - 0% at 1.0 and 19.0% at 30.0
3) PPQ - 14.6 (4.6 - 46.1)
4) HP - Inactive at 1.0. 10.0 and 30.0

Special Study: Naloxone vs ED80 of Buspirone in PPQ. Inactive at 1.0 and 10.0.

MONKEY DATA[a]

[a]See NIDA Research Monograph, 119, 1992. Attenuated withdrawal and did not precipiate abstinence.

RAT CONTINUOUS INFUSION

(PPD and Special Cocaine Interaction Study)

Long-term cocaine stimulation is associated with progressive augmentation of behavioral effects in laboratory animals which may be related to types of psychopathology associated with chronic use of cocaine in humans. We decided to investigate the effects of buspirone, a remarkable anxiolytic with little abuse liability on cocaine-induced stereotyped behavior in the rat.

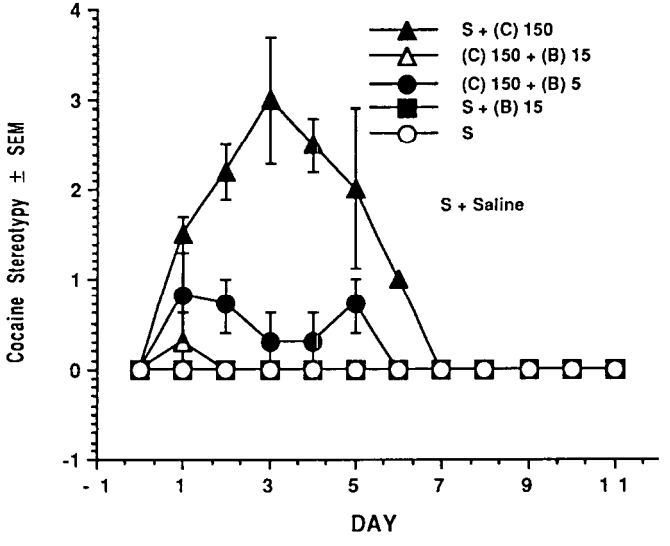
Methods

Briefly, unanesthetized male rats were infused continuously via a jugular cannula connected to an infusion pump with 1) sterile saline (vehicle), 2) cocaine 150 mg/kg/day, 3) buspirone 15 mg/kg/day + cocaine 150 mg/kg/day, 4), buspirone 15 mg/kg/day, 5) buspirone 5 mg/kg/day, and 6) buspirone 5 mg/kg/day and cocaine 150 mg/kg/day and observed for stereotyped behavior. (Magos, Eur. J. Pharmacol. 6, 200, 1969) and overt signs throughout the infusion and for 4 days after abrupt withdrawal.

Results and Discussion

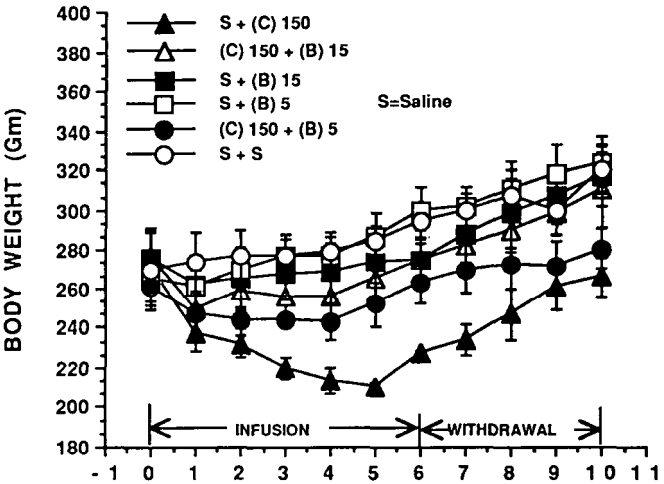
When buspirone was given along with cocaine, i.v., it dose-dependently prevented the emergence of stereotyped behaviors associated with cocaine per se (see Fig. Cocaine-buspirone stereotypy). Neither saline nor buspirone-control rats showed any stereotyped behavior. In addition, no behavioral evidence for physical dependence was observed.

Figure 1. Cocaine (C)-Buspirone (B) Stereotypy



Buspirone, in combination with cocaine, also dose-dependently prevented the drastic weight loss caused by cocaine. (depicted in Fig. Cocaine-buspirone-body weight). Buspirone-control rats at the high dose showed a slight loss of body weight during drug administration. Recovery was evident 2 days after abrupt withdrawal. The saline controls gained weight throughout the entire study.

Figure 2. Cocaine-Buspirone Body Weight



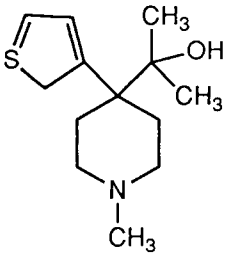
Two rats receiving the high dose of buspirone and cocaine were observed standing on their hind legs during the infusion and during abrupt withdrawal. In addition, one buspirone control rat behaved similarly. One rat receiving the low dose of buspirone and cocaine was found dead 48 h after the start of the experiment. Two of 6 rats in the cocaine-vehicle group developed autophagia after 96 h on cocaine. These animals were euthanized to prevent needless suffering. Finally, two other rats on cocaine and vehicle were found dead at 96 and 120 h after the start of drug infusion.

Comments

These results are remarkable because they demonstrate that buspirone blocked the development of stereotyped behavior and mortality associated with the chronic administration of cocaine. Based on the lack of overt behavioral and other signs, physical dependence did not develop to any of the drugs or drug combinations. These results suggest that buspirone may be very useful in the pharmacotherapy of cocaine and/or stimulant toxicity and abuse.

Equally important, the drug attenuated withdrawal in morphine-dependent monkeys. Thus, buspirone may also be of value in the treatment of opioid abuse.

NIH 10688 α,α,1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride



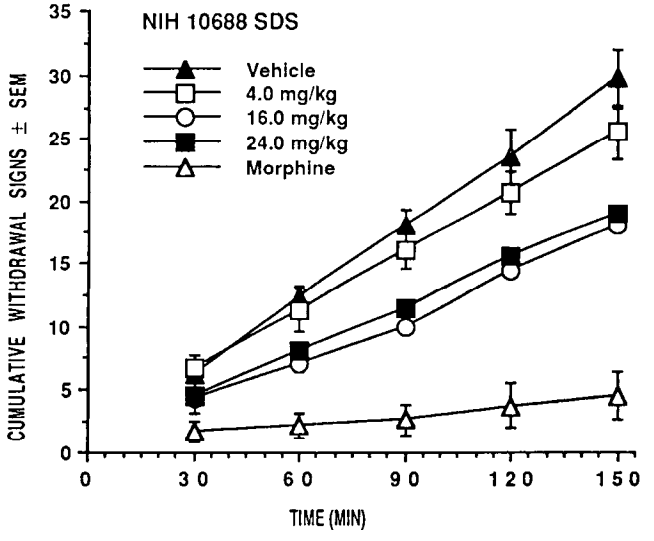
MOUSE DATA - ED50 OR AD50, mg/kg (95% C.L. or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 5.4 (2.1 - 14.1)
4) HP - Inactive at 1.0, 10.0 and 30.0

MONKEY DATA

SDS

At doses of 4, 16 and 24 mg/kg (see fig.), NIH 10688 did not substitute for morphine or exacerbate withdrawal. The attenuation in withdrawal at doses of 16 and 24 mg/kg is due mainly to a reduction in the incidence of signs designated wet-dog shakes and retching.



RAT INFUSION

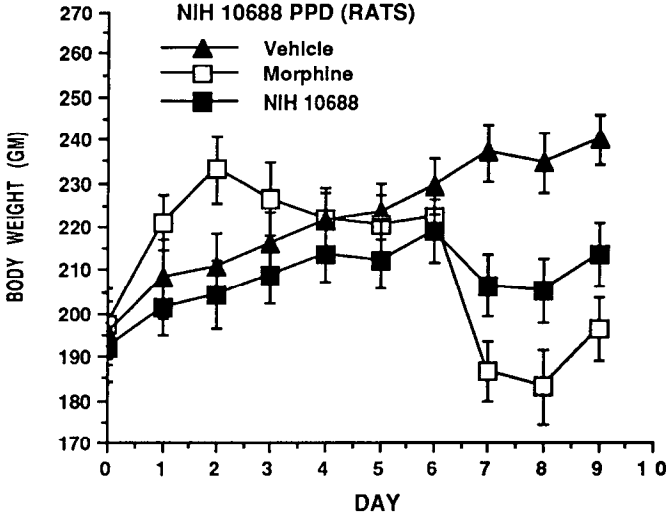
A. (SM)

At 200 mg/kg day, NIH 10688 did not substitute for morphine on days 7 and 8 as evidenced by the inability of this drug to prevent body-weight loss normally observed when morphine is abruptly withdrawn. Some evidence for behavioral suppression of withdrawal signs is apparent on days 7 and 8. See table for particulars.

NIH 10688 α,α,.1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride (continued)

B. (PPD)

The dose regimen 25 mg/kg/day on the 1st day, 50 mg/kg/day on the second day, 100 mg/kg/day on day 3 and 200 mg/kg/day on days 4,5 and 6 produced some evidence for opioid-like physical dependence liability after withdrawal (days 7, 8, and 9) regarding weight loss (see fig.). Behaviorally, the animals showed some statistically significant increases in withdrawal signs when compared to vehicle controls.



NIH 10688 α,α,1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride (continued)

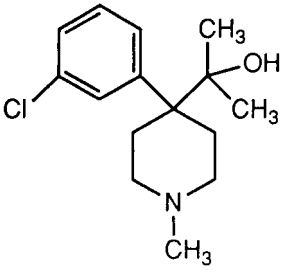
Table: Primary Physical Dependence (PPD) and Substitution for Morphine (SM) Studies With NIH 10688 in Continuously-Infused Rats

Treatment (I.P.)	Hours in Withdrawal (Day)		
	24 (Day 7)	48 (Day 8)	72 (Day 9)
	Mean Number of Withdrawal Signs[a]		
1. Vehicle Controls[d]	0.3	0.3	1.3
2. Morphine Controls[e]	11.8[b]	14.8[b]	7.3
3. NIH 10688 (PPD)[f]	5.6	3.0[c]	4.8
4. NIH 10688 (SM)[g]	4.8[b]	7.8[b]	9.8

[a]Hypersensitivity, squeaking, aggression, wet-dog shakes, rubbing and chewing; bone-tailed Mann-Whitney U test, p = 0.05 or less compared with water controls; cone-tailed Mann-Whitney U test, p = 0.05 or less compared with morphine controls;
[d]Sterile distilled H_2O-8 ml/24 h on days 1-9. N = 3;
[e]Dose regimen of morphine•SO_4, 50 mg/kg on day 1, 100 mg/kg on day 2,200 mg/kg on days 3-6. Then, vehicle days 7-9. N = 4.
[f]Dose regimen of NIH 10688,25 mg/kg on day 1,50 mg/kg on day 2,100 mg/kg on day 3,200 mg/kg on days 4-6. Then, vehicle on days 7-9. N = 5;
[g]Morphine•SO_4 Infusion, days 1-6 as above, then, NIH 10688,200 mg/kg, on days 7 and 8, and H_2O, as above, on day 9. N = 4.

Comment: This is an unusual compound. Although most of the results of the acute experiments are not remarkable, chronic studies in rats indicate a mu and kappa opioid-like physical-dependence liability. The dopaminergic (D) system may also be involced

NIH 10689 α,α,1-Trimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride



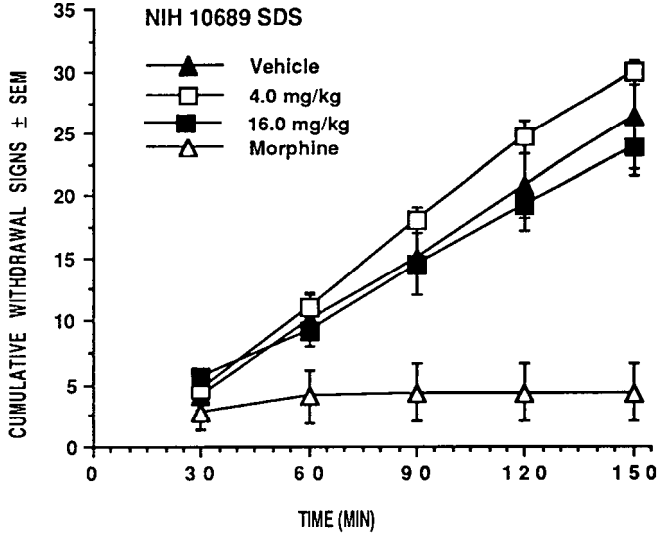
MOUSE DATA - ED50 OR AD50, mg/kg (95% C.L. or % change)

1) TP - 4% at 10.0, 9% at 10.0 and 9% at 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 2.7 (0.7 - 9.7)
4) HP - 13% at 1.0 and 10.0 and 25% at 30.0

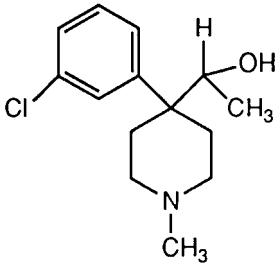
NIH 10689 α,α,1-Trimethyl-4-(3-chlorophenyl)-4-piperidiol hydrochloride (continued)

MONKEY DATA
(SDS)

As shown in the accompanying figure, NIH 10689 neither substituted for morphine nor exacerbated withdrawal at doses of 4 and 16 mg/kg.



NIH 10690 α,1-Dimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride



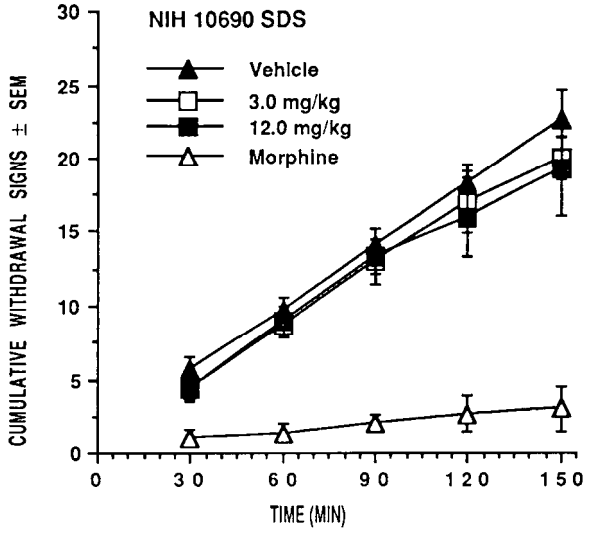
MOUSE DATA-ED50 OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - 11% at 1.0, 10% at 10.0 and 14% at 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 3.0 (0.8 - 10.9)
4) HP - 13% at 10.0, 50% at 30.0 and 38% at 60.0

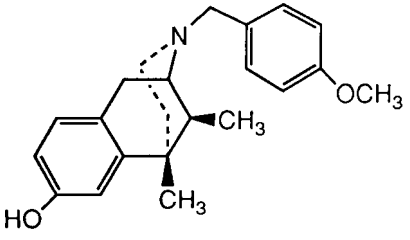
MONKEY DATA
(SDS)

NIH 10690 neither substituted for morphine nor exacerbated withdrawal (see fig.) at 3.0 and 12.0 mg/kg. Two monkeys showed signs designated as searching eye movements, chewing and licking lips.

NIH 10690 α,1-Dimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride (continued)



NIH 10691 (+)-5,9α-Dimethyl-2'-hydroxy-2-(4-methoxybenzyl)-6,7-benzomorphan hydrobromide

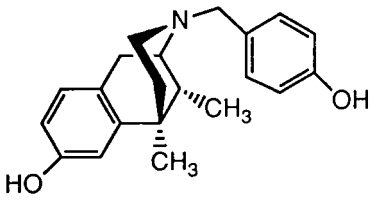


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 15% at 1.0, Inactive at 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 14% at 0.3, 31% at 1.0, 39% at 3.0 and 10.0 and 47% at 30.0[a]
4) HP - 0% at 1.0, 13% at 10.0 and 30.0[a,b]

[a]2% DMSO in water
[b]Vehicle - 13% activity

NIH 10692 (-)-5,9α-Dimethyl-T-hydroxy-2-(4-hydroxybenzyl)-6,7-benzomorphan hemioxalate

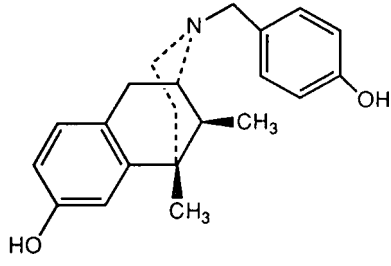


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 12% at 1.0, Inactive at 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - Inactive at 1.0, 10.0 and 30.0[a]
4) HP - 25% at 1.0, 0% at 10.0 and 13% at 30.0[a,b]

[a]5% DMSO in water
[b]Vehicle - 13% activity

NIH 10694 (+)-5,9α-Dimethyl-2'-hydroxy-2-(4-hydroxybenzyl)-6,7-benzomorphan hemioxalate

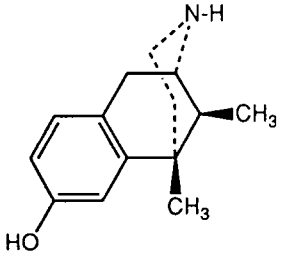


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 1% at 1.0, 13% at 10.0 and 11% at 30.0[a,b]
2) TF vs. M - Inactive at 1.0, 26% at 10.0 and 30.0[a]
3) PPQ - 14% at 1.0, Inactive at 10.0 and 30.0[a]
4) HP - Inactive at 1.0 and 10.0, 25% at 30.0[a,c]

[a]10% DMSO in water
[b]Vehicle - 6% activity
[c]Vehicle - 13% activity

NIH 10695 (+)-N-Normetazocine

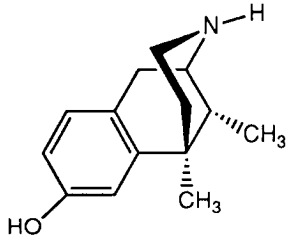


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 3% at 1.0, 14% at 10.0 and 27% at 30.0[a,b]
2) TF vs. M - Inactive at 1.0 and 10.0[a,c]
3) PPQ - 14% at 1.0 and 23% at 10.0[c,d]
4) HP - 0% at 1.0, 13% at 10.0[a,e]

[a]Vehicle - phosphoric acid and water
[b]2/6 mice died at 30.0
[c]4/6 mice died at 30.0
[d]4/6 mice died at 30
[e]5/6 mice died at 30.0

NIH 10696 (-)-N-Normetazocine

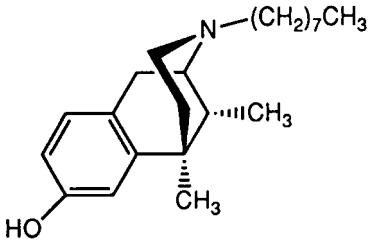


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 6% at 1.0, 11% at 10.0 and 13% at 30.0[a,b]
2) TF vs. M - 23% at 1.0, 3% at 10.0 and 14% at 30.0[a]
3) PPQ - 14% at 1.0 and 10.0 and 66% at 30.0"
4) HP - 25% at 1.0, 0% at 10.0 and 38% at 30.0[a.c]

[a]Vehicle - phosphoric acid, then, water
[b]Vehicle - 7% activity
[c]Vehicle - 13% activity

NIH 10697 (-)-5,9α-Dimethyl-2'-hydroxy-2-*n*-octyl-6,7-benzomorphan hydrochloride

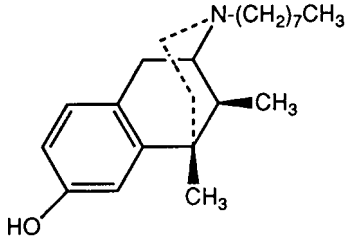


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 10.0 (4.3 - 23.2)[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,b]
3) PPQ - 0.5 (0.2 - 1.5)[a,c]
4) HP - 5.4 (3.4 - 8.6)[a,d]

[a]Vehicle - 50% DMSO in water
[b]Vehicle - inactive
[c]Vehicle - 47% inhibition
[d]Vehicle - 25% inhibition

NIH 10698 (+)-5,9α-Dimethyl-2'-hydroxy-2- *n*-octyl-6,7-benzomorphan hydrochloride

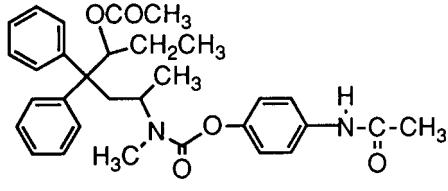


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0 and 10.0, 14% at 30.0[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 7.8 (1.2 - 49.5)[a,b]
4) HP - 11.1 (3.1 - 40.3)[a,c]

[a]Vehicle - 40% DMSO in water
[b]Vetticle - inactive
[c]Vehicle - 25% activity

NIH 10699 N-[(2S,5S)-5-Acetoxy-4,4-diphenyl hept-Zyl]-N-methyl-O (4-N-acetamidophenyl) carbamate



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

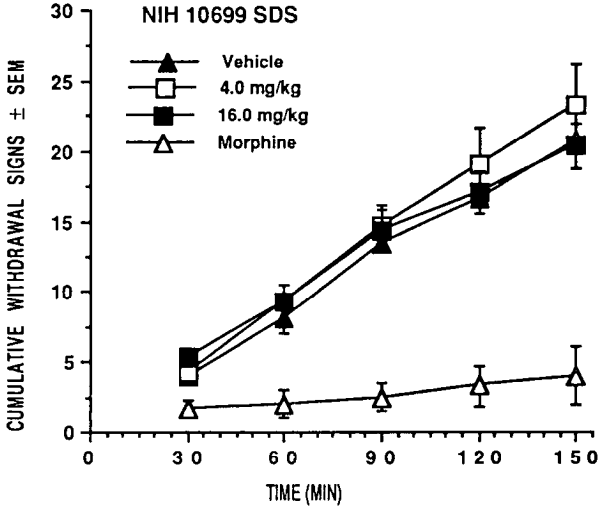
1) TF - Inactive at 1.0 and 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,d]
3) PPQ - Inactive at 1.0, 31% at 3.0, 37% at 10.0 and 46% at 30.0
4) HP - Inactive at 1.0, 10.0 and 30.0

[a]Vehicle - 20% Tween 80 in water

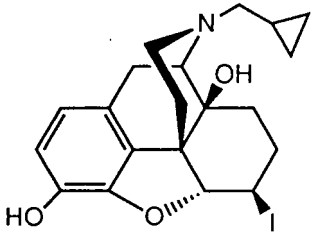
NIH 10699 N-[(2S,5S)-5-Acetoxy-4,4-diphenyl hept-2-yl]-N-methyl-O (4-N-acetamidophenyl) carbamate (continued)

MONKEY DATA
SDS

NIH 10699 neither substituted for morphine nor exacerbated withdrawal up to 16 mg/kg (see Fig. NIH 10699 SDS). Vehicle was 20% Tween 80 in water.



NIH 10701 6β-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5 α-epoxymorphinan oxalate



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

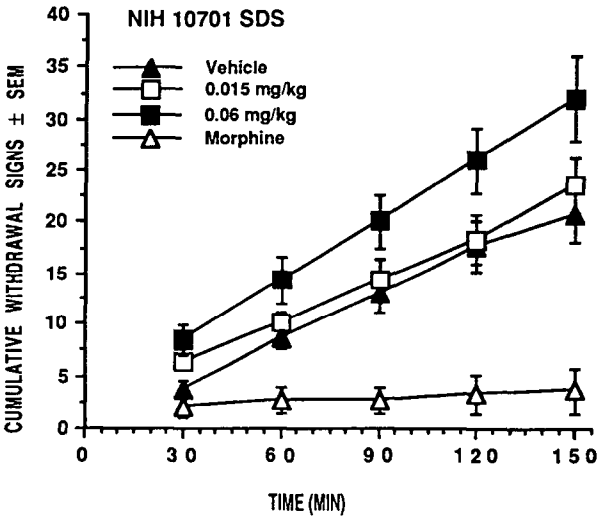
1) TF-0% at 1.0, 17% at 10 and 15% at 30.0
2) TF vs. M - 0.08 (0.03 - 0.22)
3) PPQ - Inactive at 1.0, 10.0 and 20.0, 86% at 30.0[a]
4) HP - 13% at 1.0, 38% at 3.0 and 63% at 10.0 and 30.0

[a]ataxia and jumping

MONKEY DATA
A. (SDS)

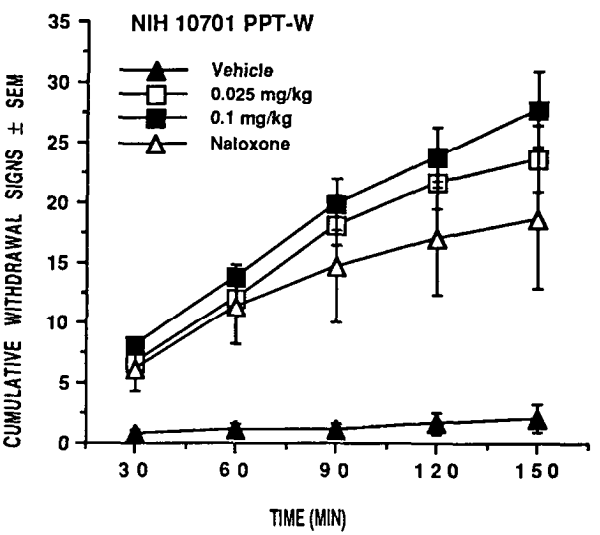
This compound did not substitute for morphine at doses of 0.015 and 0.06 mg/kg. Instead, it exacerbated withdrawal in a dose-dependent manner (see Fig. NIH 10701 SDS).

NIH 10701 6β-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5α-epoxymorphinan oxalate . . . continued

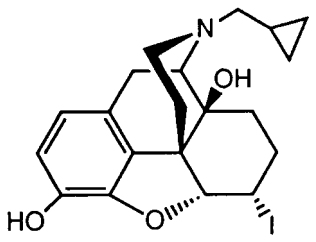


B. (PPt-W)

NIH 10701 promptly precipitated withdrawal. The action was dose dependent. This drug behaved approximately as did the positive control, naloxone.



NIH 10702 6α-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5α-epoxymorphin~ oxalate

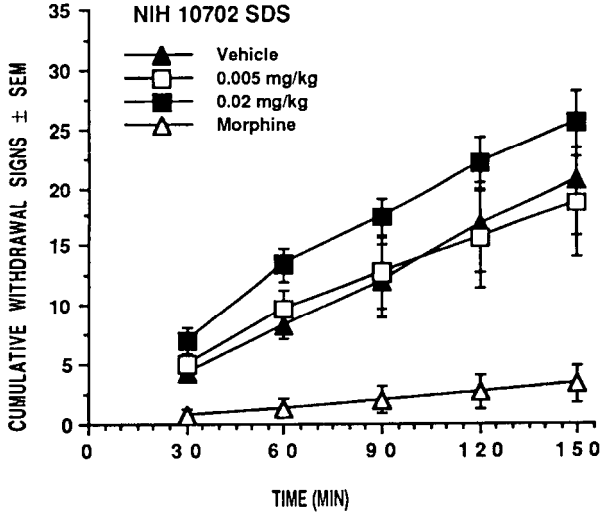


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

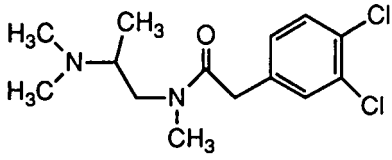
1) TF - Inactive at 1.0. 10.0 and 30.0
2) TF vs. M - 0.04 (0.02 - 0.09)
3) PPQ - Inactive at 1.0, 10.0 and 30.0
4) HP - 13% at 1.0 and 30.0 and 0% at 10.0

MONKEY DATA
(SDS)

At doses of 0.02 and 0.005 mg/kg, NIH 10702 did not substitute for morphine. Instead, as shown in the accompanying figure (NIH 10702-SDS), the compound appeared to exacerbate withdrawal.



NIH 10703 N-[3,4-Dichlorophenyl)acetyl]-N,2-dimethyl-2-(N',N'-dimethylamino)-ethylamine oxalate

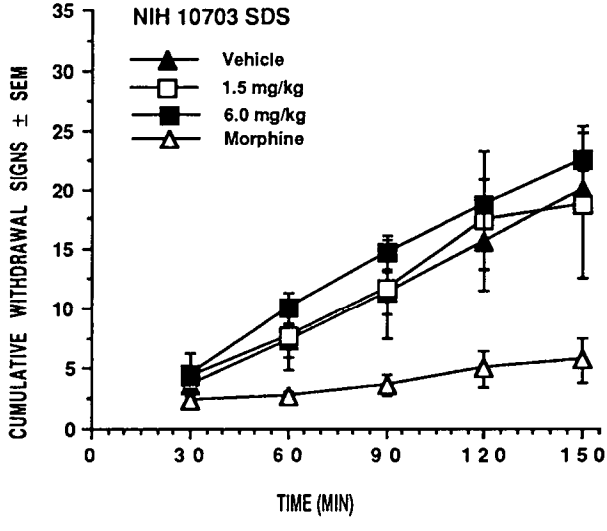


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L) or % change

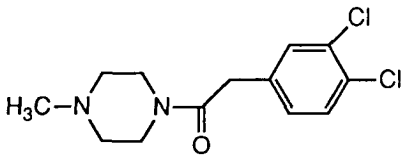
1) TF - 13% at 1.0, 1 0% at 10.0 and 11% at 30,00
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 13.4 (5.0 - 36.0)
4) HP - 13% at 1.0, 0% at 3.0, 50% at 10.0 and 63% at 30.0

MONKEY DATA
(SDS)

As shown in the illustration, NIH 10703 did not substitute for morphine nor did it precipitate withdrawal at doses of 1.5 and 6.0 mg/kg. One monkey receiving the higher dose appeared disoriented 45 m after receiving drug. Head bobbing, and frequent retching were also noted in another monkey at the higher dose. At the lower dose, bruxism was noted in one animal.



NIH 10704 N-Methyl-N-(3,4-dichlorophenylacetyl]piperazine



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

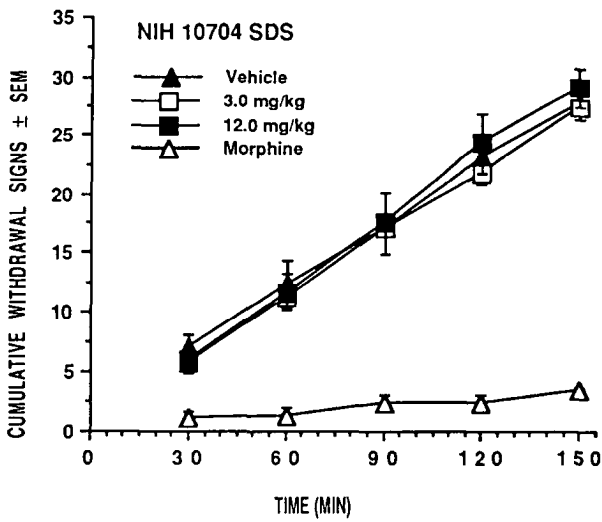
1) TF - 21% at 1.0, 15% at 3.0, 30% at 10.0 and 4% at 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 11.3 (3.8 - 33.9)[a]
4) HP - 6.3 (4.0 - 10.0)[a]

[a]Vehicle - phosphoric acid and water

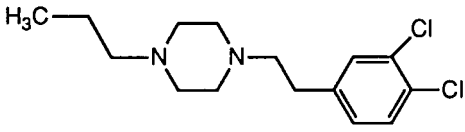
MONKEY DATA

(SDS)

At doses of 3 and 12 mg/kg, NIH 10704 neither substituted for morphine nor exacerbated withdrawal (see graph indicated). The incidence of retching, vomtting, wet-dog shakes and restlessness was much greater in the animals receiving the higher dose. This is not evident in the accompanying illustration because any one sign is scored only once per 0.5h-interval. Thus, frequency is not indicated.



NIH 10705 N-(*n*-Propyl)-N'-(3,4-dichlorophenylethyl)piperazine dihydrobromide



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

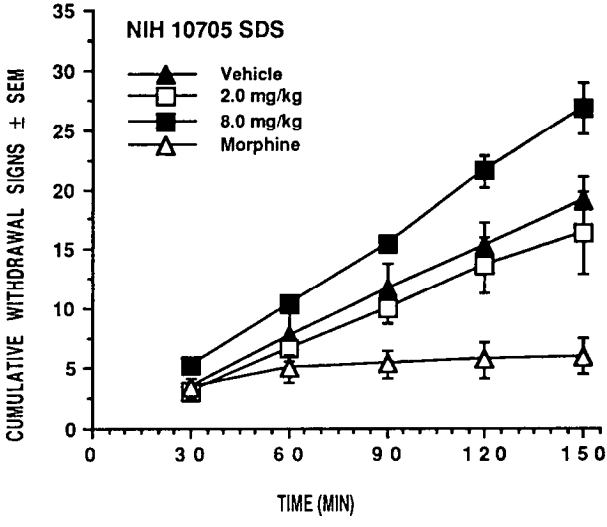
1) TF - Inactive at 1.0 and 10.0, 13% at

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 10.6 (4.0 - 28.5)
4) HP - Inactive at 1 and 10.0, 15% at 30.0

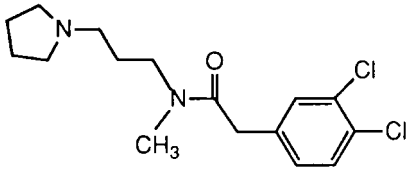
MONKEY DATA

(SDS)

In a preliminary study, NIH 10705 produced profuse vomiting and rapid respiration. Two doses of morphine were required to terminate this action. In the SDS study, as shown in the fig., NIH 10705 did not substitute for morphine; it exacerbated withdrawal at the higher dose. In addition, frequent retching, and oral signs such as chewing and licking were observed in 2 monkeys.



NIH 10706 N-(3,4-Dichlorophenylacetyl)-N-methyl-3-(1-pyrrolidinyl)propylamine fumarate

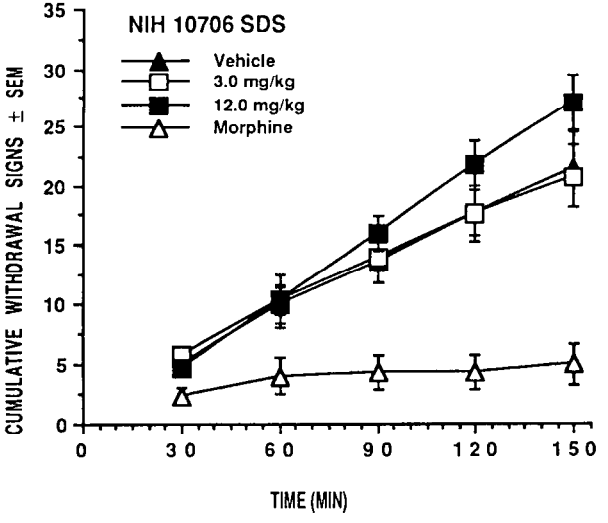


MOUSE DATA-ED50 OR AD50, mg/kg

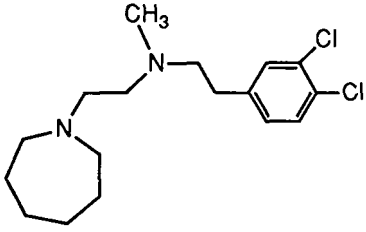
1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPG - 23% at 1.0, 25% at 3.0, 17% at 10.0 and 51% at 30.0
4) HP - 13% at 1.0 and 10.0 and 50% at 30.0

MONKEY DATA
(SDS)

As shown in the graph, NIH 10706 did not substitute for morphine at doses of 3.0 and 12.0 mg/kg. Instead, the compound appeared to exacerbate withdrawal at the higher dose. However, the higher score is due primarily to an increase in the signs designated wet-dog shakes and retching. Finally, at the higher dose, one monkey appeared more aggressive than usual. These results suggest that the exacerbation of withdrawal was not due to mu-opioid, antagonist properties.



NIH 10709 N-[2-(3,4-Dichlorophenylethyl)-N-methyl-2-(1-homopiperiidinyl)]-ethylamine dihydrochloride



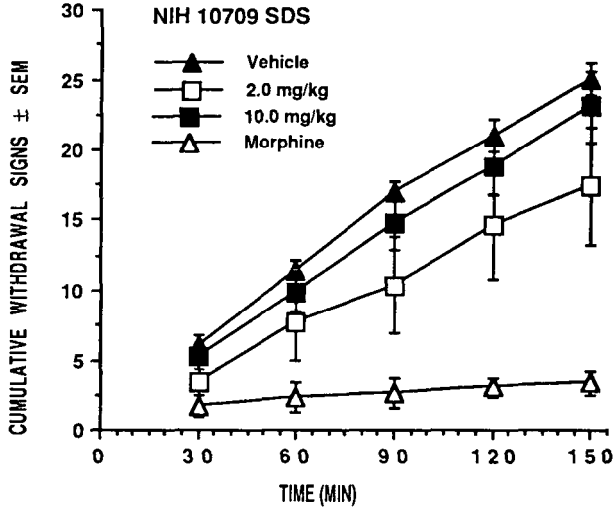
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0 and 10.0, 12% at 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 4.0 (1.1 - 14.4)[a]
4) HP - 13% at 1.0 and 10.0, 38% at 20.0 and 50.0% at 30.0[a]

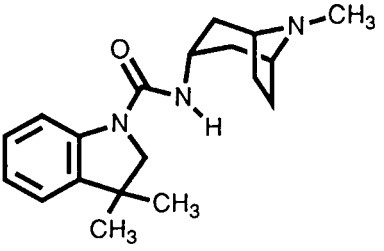
[a]One drop of H_3PO_4 and water.

MONKEY DATA
(SDS)

NIH 10709 neither substituted for morphine nor exacerbated withdrawal (see fig.). The apparent attenuation of withdrawal at 2.0 mg/kg reflects mainly a lack of response to the signs designated rigid abdominal muscle and vocalization when abdomen palpated in one animal.



NIH 10710 *endo*-N-(8-Methyl-9-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxyamide hydrochloride



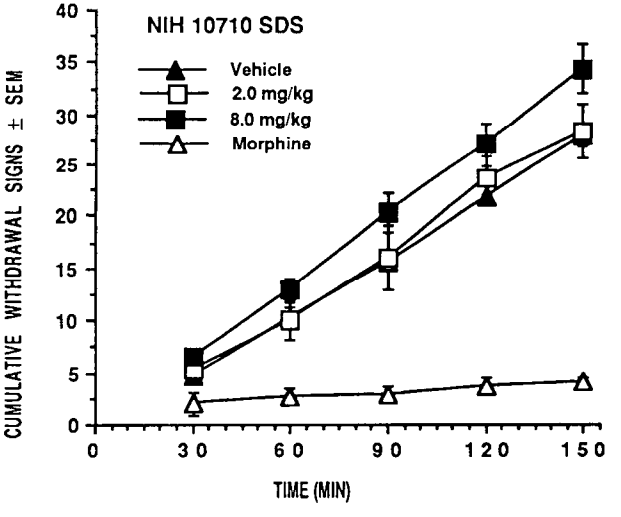
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TP vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 10% at 1.0 and 10.0 and 17% at 30.0
4) HP - Inactive at 1.0, 10.0 and 30.0

MONKEY DATA

A. (SDS)

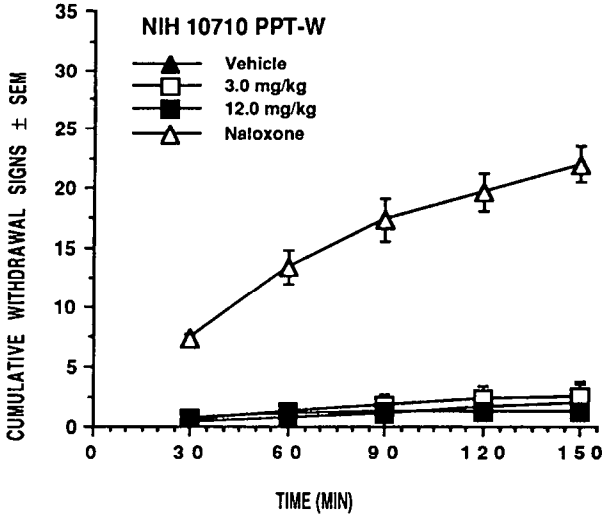
NIH 10710 did not substitute for morphine at 2.0 and 8.0 mg/kg. It may have exacerbated withdrawal.



NIH 10710 *endo*-N-(8-Methyl-9-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxyamide hydrochloride . . . continued

B. (PPt-W)

As shown in this accompanying illustration, at doses of 3 and 12 mg/kg, NIH 10710 did not precipitate withdrawal.



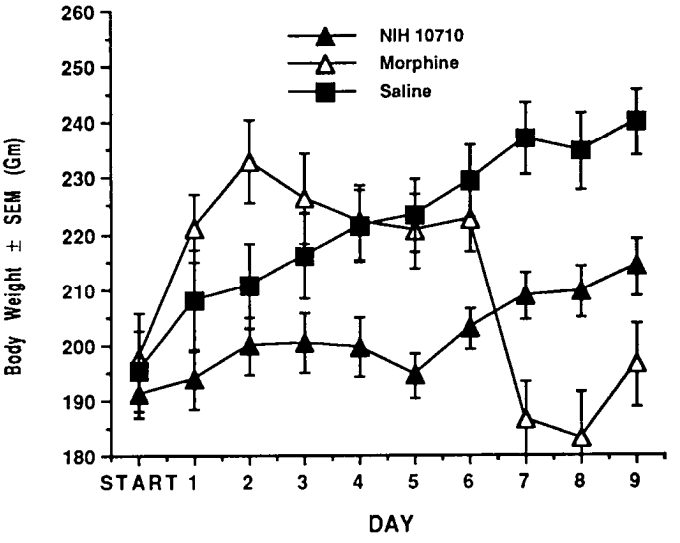
RAT INFUSION

(PPD)

After continuous administration of doses of 25 mg/kg on days 1 and 2,50 mg/kg on day 3, 100 mg/kg on day 4 and 200 mg/kg on days 5 and 6, no body weight loss (see fig. 1) or behavioral signs of withdrawal were noted 24 (Day 7), 48 (Day 8) or 72 h (Day 9) after NIH 10710 was abruptly withdrawn. The statistically significant value calculated on day 8 (48 h) was due predominantly to the signs designated wet-dog shakes and rubbing. See table for additional details.

NIH 10710 *endo*-N-(8-Methyl-9-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxyamide hydrochloride . . . continued

Figure 1. Body Weight



Rat Infusion - New Data

Table: Primary Physical Dependence (PPD) Study with NIH 10710 in Continuously-Infused Rats

Treatment (I.P.)	Hours in Withdrawal (Day)		
	24 (day 7)	48 (day 8)	72 (day 9)
	Mean Number of Withdrawal Signs[a]		
1. Vehicle Controls[d]	0.3	0.3	1.3
2. Morphine Controls[e]	11.8[b]	14.8[b]	7.3
3. NIH 10710 (PPD)[b]	1.8[c]	5.0[b]	1.0[c]

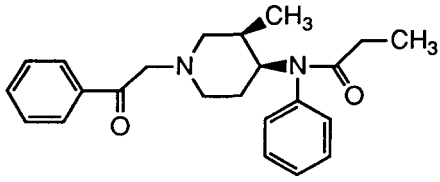
[a]Hypersensitivity, squeaking, aggression, wet-dog shakes, rubbing and chewing;
hone-tailed Mann-Whitney U test, p = 0.05 or less compared with water controls;
[c]One-tailed Mann-Whitney U test, p = 0.05 or less compared with morphine controls;
[d]Sterile distilled H_2O-8 ml/24 h on days 1-9. N = 3;
[e]Dose regimen of morphine SO_4, 50 mg/kg on day 1,100 mg/kg on day 2,200 mg/kg on days 3-6. Then, vehicle on days 7-9. N = 4;
[f]Dose regimen of NIH 10710, 25 mg/kg on days 1-2.50 mg/kg on day 3, 100 mg/kg on day 4,200 mg/kg on days 5-6. Then, vehicle on days 7-9. N = 5;

NIH 10710 *endo*-N-(8-Methyl-9-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxyamide hydrochloride . . . continued

Comment

The profile of activity indicates that NIH 10710 is relatively free of opioid-like physical dependence activity.

NIH 10717 (±)-*cis*-N-[3-Methyl-1-(2-oxo-2-phenylethyl)-4-piperidyl]-N-phenylpropranamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.03 (0.01 - 0.07)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.008 (0.002 - 0.03)
4) HP -0.03 (0.01 - 0.06)

[a]Straub tall and increased locomotor activity at 1.0.

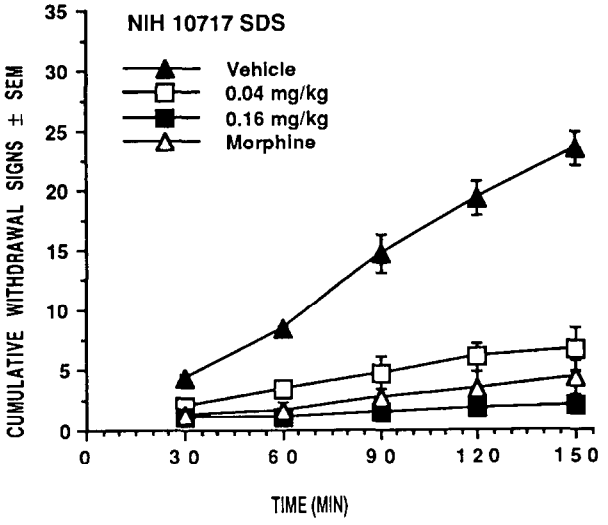
Special Study: Naloxone vs ED80 of NIH 10717 in TF gave an AD50 of 0.02 (0.01 = 0.0.5)

MONKEY DATA

(SDS)

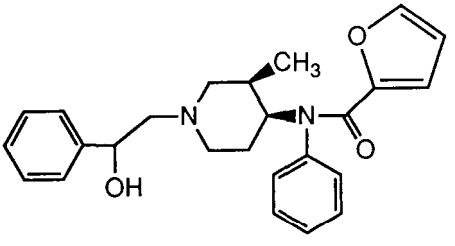
As depicted in the illustration designated NIH 10717 SDS, this compound substituted completely for morphine at doses of 0.04 and 0.16 mg/kg. Onset and offset of action were similar to morphine's. At the higher dose, opioid behavioral signs and other signs were noted. They were ataxia, body and jaw sag, drowsiness, eyelid ptosis, slowing, scratching, chewing, rubbing face, retracted testicles and persistent penile erection.

NIH 10717 (±)-*cis*-N-[3-Methyl-1-(2-oxo-2-phenylethyl)-4-piperidyl]-N-phenylpropranamide hydrochloride. . . continued



Comment: The data on NIH 10717 suggests a mu-opioid profile of activity. The drug is about 100 x mote potent than morphine.

NIH 10718 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-furanamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 7 x 10^{-4} (3.7 x10^{-4} - 1.5 x 10^{-3})[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 3.9 x 10" (1.6 x 10^{-4} - 9.4 x 10^{-4})[a,b]
4) HP - 4.0 x 10^{-4} (1.7 x 10^{-4} - 1.0 x 10^{-3})[a,b]

[a]Vehicle 10% DMSO in water
[b]Straub tail starting at 0.01 mg/kg

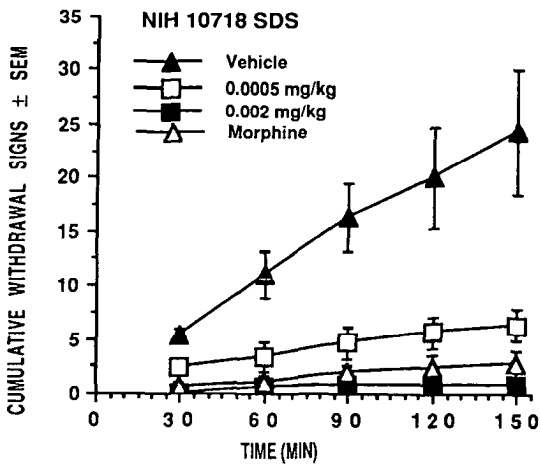
Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10718 in TF = 7.5 x 10^{-3} (2.0 x 10^{-3} - 2.5 x 10^{-2})

NIH 10718 (±)-*cis*-N-[1-(2-Hyd.roxy-2-phenylethyl)-3-methyl-4-piperidyI]-N-phenyl-2-furanamide hydrochloride. . . continued

MONKEY DATA

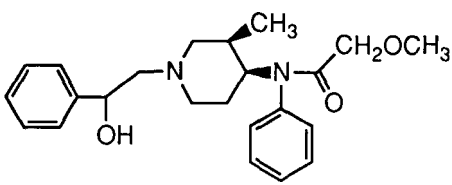
SDS

NIH 10718 dose dependently substituted completely for morphine (see fig.). The onset of action was prompt and some monkeys receiving the higher dose did not require the noon injection of morphine. Some jaw and body sag, ataxia, scratching and slowing were noted in animals receiving the higher dose. The estimated potency is 6000 x morphine.



Comment: NIH 10718 is an extremely potent mu agonist.

NIH 10719 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-pipetidyl]-N-phenyl-2-methoxyacetamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 8 x 10^{-4} (3 x 10^{-4} - 2 x 10^{-3})
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 5 x 10^{-5} (2 x 10^{-5} - 1 x 10^{-4})
4) HP - 4 x 10^{-4} (2 x 10^{-4} - 9 x 10^{-4})

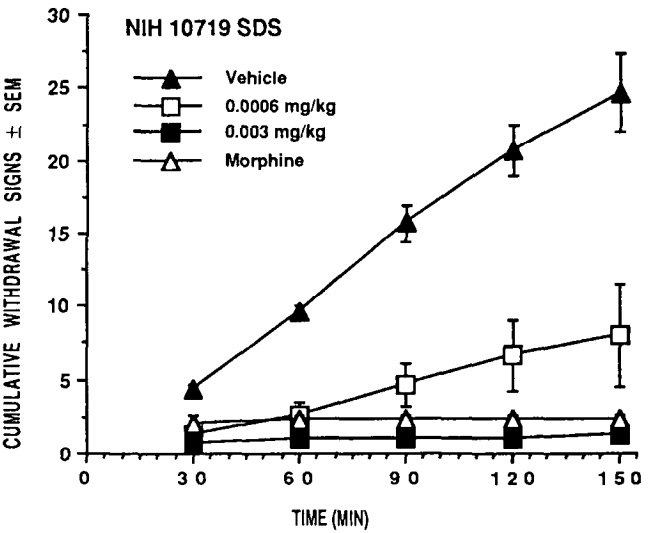
Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10719 in TF = 0.03 (0.02 - 0.04)

NIH 107 19 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-methoxyacetamide hydrochloride . . . continued

MONKEY DATA

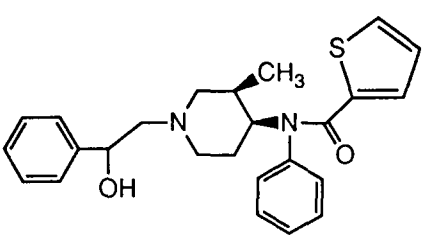
SDS

NIH 10719 dose-dependently substituted completely for morphine. At the higher dose, namely 0.003 mg/kg s.c., this compound also produced a wide variety of overt opioid signs; namely, jaw and body sag, scratching, slowing, rubbing face and eyelid ptosis. Onset of action was rapid and duration was approximately 2.5 h. Potency estimate was approximately 5000 x morphine.



Comment: NIH 10719 appeared to be a potent mu agonist.

NIH 10720 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-thiophenecarboxamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.004 (0.002-0.01)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,b]
3) PPQ - 0.003 (0.001 - 0.006)[a]
4) HP - 0.002 (0.0005 - 0.005)[a]

[a]Two drops of H_3PO_4 and water.
[b]One of 6 died at 30.0 mg/kg.

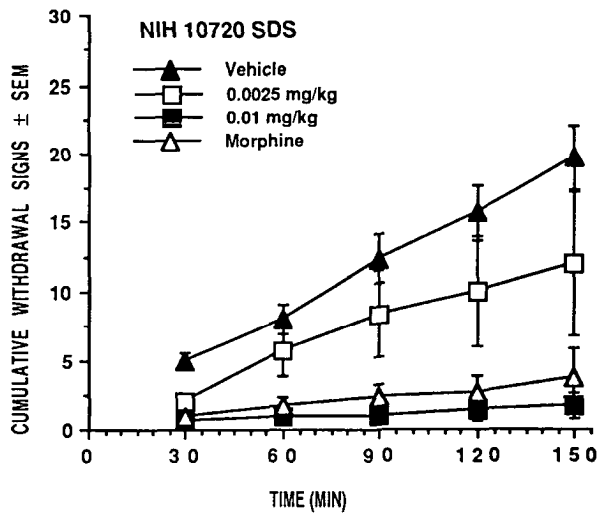
NIH 10720 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-thiophenecarboxamide hydrochloride. . . continued

Special Study: Naloxone AD50 vs ED80 of NIH 10720 in TP = 0.007 (0.003 - 0.02)

MONKEY DATA

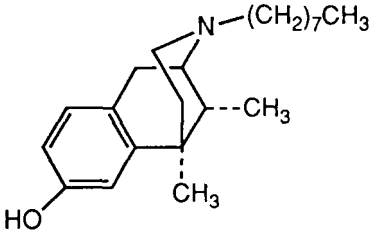
(SDS)

As shown in the accompanying figure, NIH 10720 dose-dependently substituted completely for morphine. In addition, at the higher dose, the signs designated jaw sag, rubbing face, scratching and eyelid ptosis were seen. Onset of action was prompt. Offset was about 2.5 hs. Potency estimate is 1000 X morphine.



Comment: The data suggest that NIH 10720 is a potent mu agonist (1000 x morphine).

NIH 10721 (±)-5,9α-Dimethyl-2'-hydroxy-2-*n*-octyl-6,7-benzomorphan hydrochloride

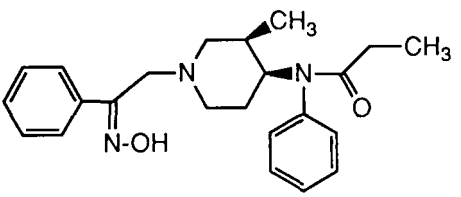


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 8.0 (3.8 - 17.0)[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 2.9 (1.2 - 6.7)[a]
4) HP - 3.6 (1.2 - 10.9)[a,c]

[a]Vehicle - 20% DMSO, 10% propylene glycol in water.
[b]Mice would not move at 30.0.
[c]Mice appeared sedated at 30.0.

NIH 10722 (±)-*cis*-N-[3-Methyl-1-(2-iminohydroxy-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide



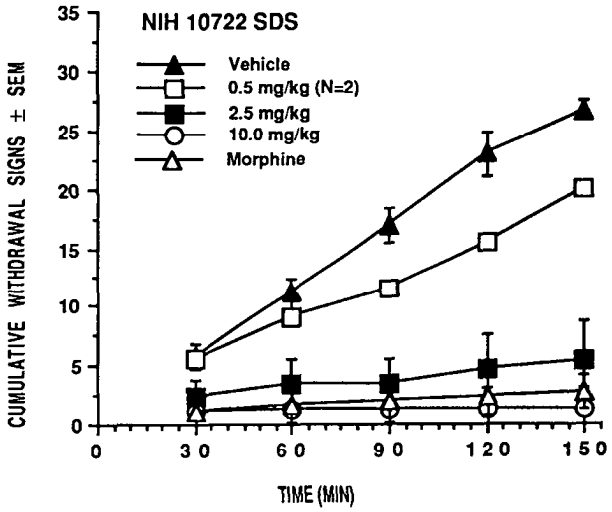
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 12.4 (4.4 - 35.2)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.2 (0.07 - 0.4)
4) HP - 3.0 (1.0 - 8.7)

MONKEY DATA
(SDS)

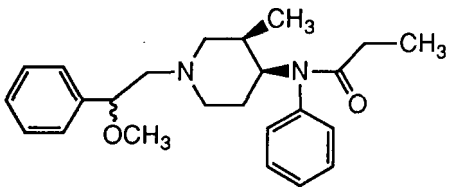
As shown, below, NIH 10722 acted promptly and substituted completely for morphine for about 2.5 h. The action was dose dependent. At the highest dose, some jaw and body sag, scratching, and rubbing face were noted. Finally, this compound appeared to be as potent as morphine.

NIH 10722 (±)-*cis*-N-[3-Methyl-l-(2-iminohydroxy-2-phenylethyl)-4-piperil]-N-phenylpropanamide . . . continued



Comment: This compound appeared to be a typical mu agonist as potent as morphine.

NIH 10723 (±)-*cis*-N-[1-(2-Methoxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.01 (0.006 - 0.03)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.009 (0.003 - 0.027)
4) HP - 0.02 (0.01 - 0.04)[a,b]

[a]One of 6 mice died.
[b]Straub tails noted at doses of 0.01 mg/kg or higher also increased locomotor activity noted at 0 mg/kg.

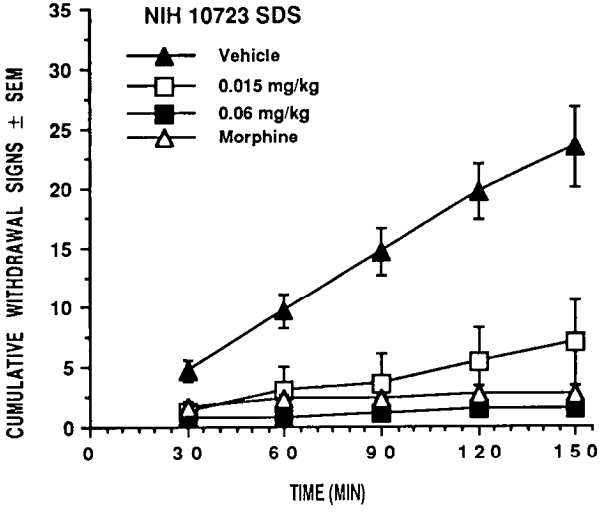
Special Study: Naloxone vs ED80 of NIH 10723, AD50 = 0.1 (0.04 - 0.3)

MONKEY DATA
(SDS)

NIH 10723 substituted completely for morphine in, morphine-dependent monkeys (see fig. NIH 10723 SDS). Onset and offset of action were similar to those of morphine.

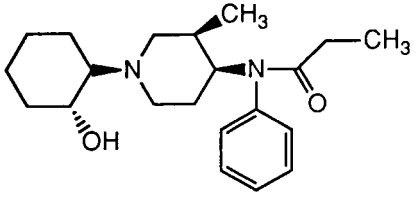
NIH 10723 (±)-*cis*-N-[1-(2-Methoxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpro-panamide hydrochloride . . . continued

Potency estimated at 100 x morphine. In addition, at the higher dose overt signs normally seen after higher doses of mu and/or kappa agonists were observed. They were ataxia, body and jaw sag, drowsiness, eyelid ptosis, scratching, slowed respiratory rate and rubbing face.



Comment: NIH 10723 has mu opioid and possibly kappa opioid activity.

NIH 10724 (±)-*cis*-N-[1-(*trans*-2-Hydroxycyclohexyl)-3-methyl-4-piperidyll-N-phenylpropanamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.6 (0.4 - 1.0)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.05 (0.03 - 0.09)
4) HP - 0.4 (0.2 - 0.7)[a]

[a]Straub tail and increased locomotion at 1.0

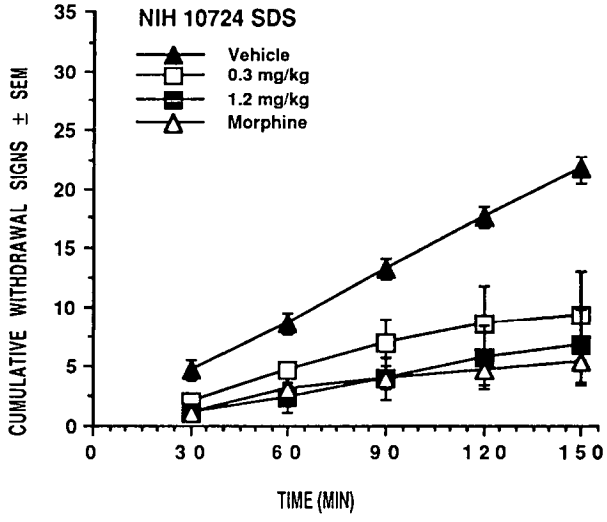
Special Study: Naloxone AD50 vs ED80 of NIH 10724 in TF = 0.1 (0.04 - 0.25)

NIH 10724 (±)-*cis*-N-[1-(tram-2-Hydroxycyclohexyl)-3-methyl-4-piperid-N-phenylpropanamide hydrochloride . . . continued

MONKEY DATA

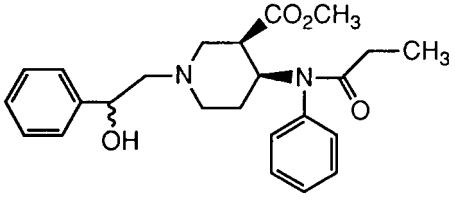
(SDS)

NIH 10724 nearly substituted for morphine. However, the drug did not completely suppress wet-dog shakes and restlessness. The action was prompt, dose-related and of shorter duration than that of morphine. At the higher dose, jaw and body sag and scratching were noted. Potency estimate is 2.5 x that of morphine.



Comment: The compound behaved as a mu/kappa agonist.

NIH 10725 (+)-*cis*-N-[3-Carbomethoxy-l-(2-hydroxy-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.02 (0.01 - 0.05)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.009 (0.004 - 0.02)
4) HP - 0.01 (0.004 - 0.03)

[a]Four of 6 died at 30.0 mg/kg

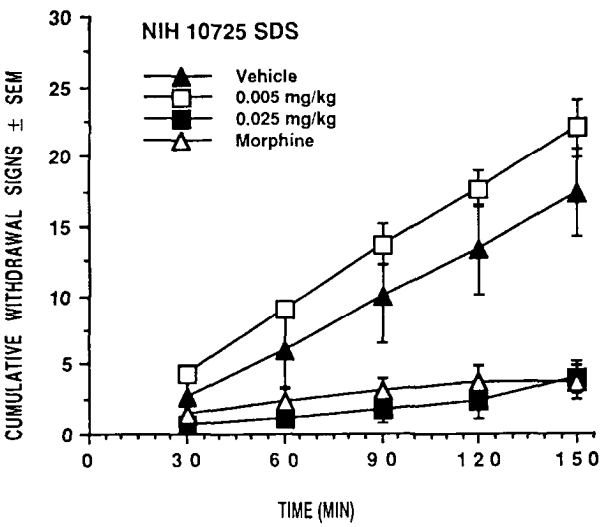
Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10725 in TF = 0.1 (0.04 - 0.2)

NIH 10725 (+)-*cis*-N-[3-Carbomethoxy-l-(2-hydroxy-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide hydrochloride . . . continued

MONKEY DATA

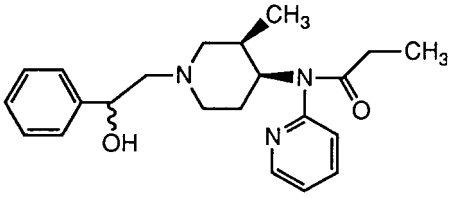
(SDS)

This compound substituted completely for morphine at 0.025 mg/kg (see fig.). The drug acted promptly and duration of action was at least 2.5 h. Potency estimated at 100 x morphine. The results at 0.005 mg/kg are more apparent than real. The apparent exacerbation of withdrawal reflects a relatively weak vehicle response.



Comment: NIH 10725 has mu agonist and possibly kappa-agonist opioid properties.

NIH 10726 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-(2-pyridinyl)propanamide hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

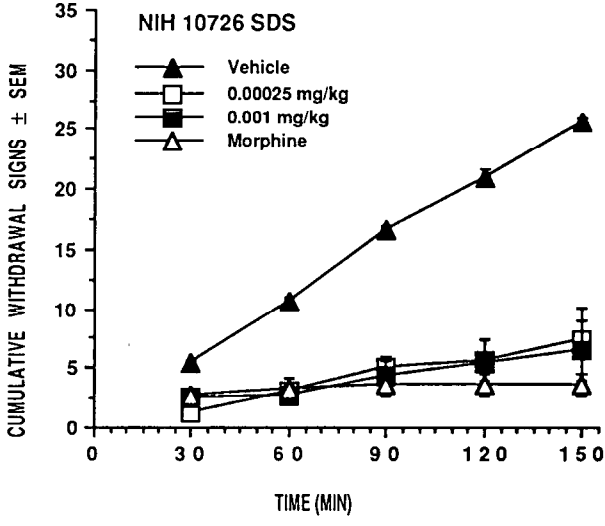
1) TF - 3.6 x 10" (2.0×10^{-4} - 6.0×10^{-3})
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 1.5×10^{-4} (6.7×10^{-5} - 3.2×10^{-4})
4) HP - 2.0×10^{-4} (1.0×10^{-4} - 4.0×10^{-4})

[a]2 of 6 mice died at 10.0 mg./kg and all 6 died at 30.0 before testing could commence.

Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10726 = 0.02 (0.006 - 0.07)

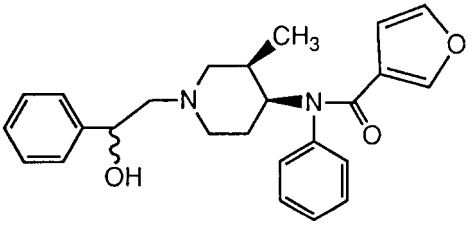
MONKEY DATA
(SDS)

NIH 10726 substituted completely for morphine at doses as low as 2.5×10^{-4}. The drug acted promptly; its duration of action may be somewhat longer than that of morphine since some of the monkeys did not require the usual injection at noon. Its potency is estimated as 12,000 x that of morphine (see fig. designated NIH 10726 SDS).



Comment: The data indicate that NIH 10726 is a very potent mu agonist.

NIH 10727 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-3-furanamide hydrochloride



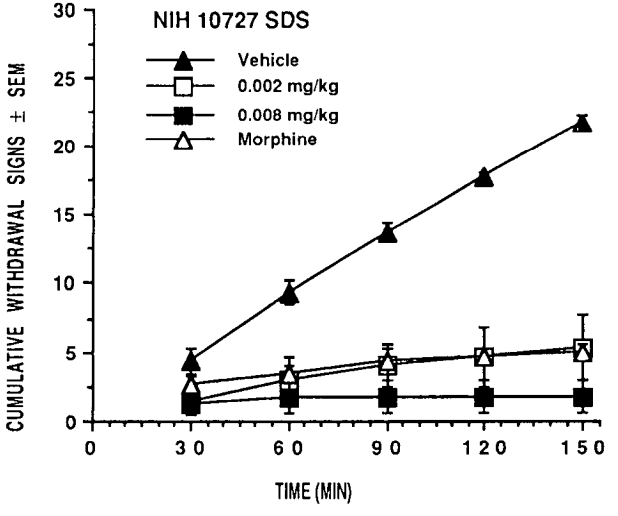
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.002 (0.001 - 0.004)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 9.1 x 10^{-4} (3.9 x 10^{-4} - 2.1 x 10^{-3})
4) HP - 0.004 (0.002 - 0.01)

Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10727 = 0.05 (0.03 - 0.09)

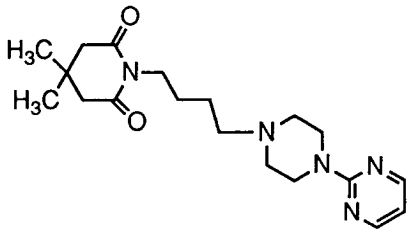
MONKEY DATA
(SDS)

NIH 10727 completely substituted for morphine at doses as low as 0.002 mg/kg (see fig.). At the highest dose (0.008 mg/kg), the signs jaw and body sag and scratching were noted. Some of the monkeys did not require morphine at noon. Onset of action was prompt and duration longer than that of morphine. Potency estimate is 1,500 times morphine.



Comment: The profile of activity suggested that NIH 10727 was a potent mu agonist.

NIH 10728 Gepirone hydrochloride



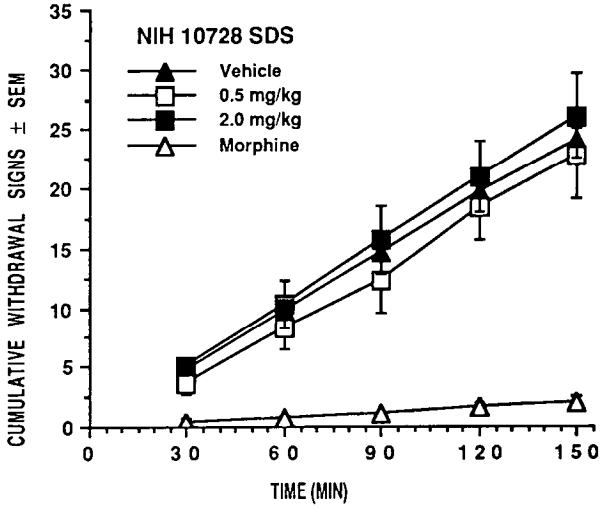
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - [a]
2) TF vs. M- [a]
3) PPQ - [a]
4) HP - [a]

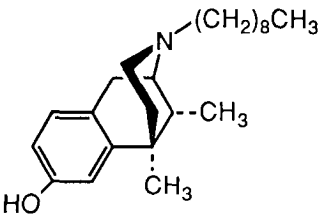
[a]Not tested

MONKEY DATA
(SDS)

We recently demonstated that buspirone, a nonbenzodiazepine anxiolytic, attenuated withdrawal in rhesus monkeys maximally dependent on morphine (Bowman and Aceto, FASEB J., 5, A497, 1991). In order to test the commonality of this action for this class of drugs, gepirone, a dialkyl glutarimide analog of buspirone, was tested. Gepirone even at a dose which produced psychomotor slowing and ataxia, was totally inactive (see Fig NIH 10728 SDS). This, lack of correspondence between buspirone and gepirone suggests that buspirone has actions or combinations of actions not shared by gepirone. Since the two drugs have similar actions on 5HTIA receptors, it seems unlikely that this property per se underlies buspirone's action in dependent monkeys. In addition, since buspirone, unlike gepirone, has certain actions on dopamine receptors, this system, at least in part, may play a role.



NIH 10729 (-)-5,9α-Dimethyl-2'-hydroxy-2- *n*-nonyl-6,7-benzomorphan hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0% at 1.0, 10% at 10.0 and 19% at 30.0. Vehicle 15% activity[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 49% at 1.0, 54% at 10.0 and 10% at 30. Vehicle showed 31% activity[a]
4) HP - 0% at 1.0, 13% at 10.0 and 25% at 30.0. Vehicle showed 13% activity"

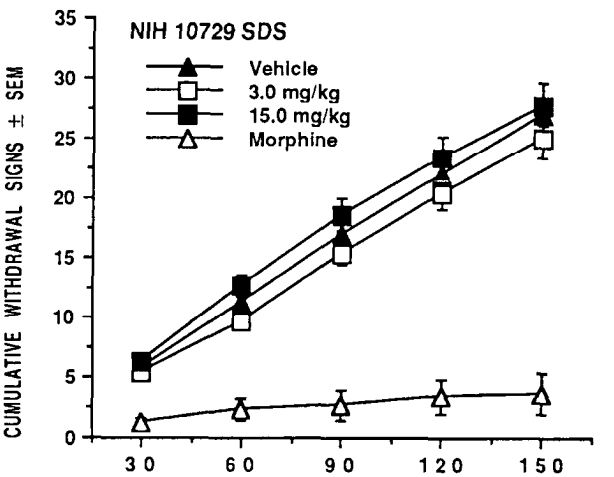
[a]Vehicle was 40% DMSO, 25% propylene glycol and water.

MONKEY DATA

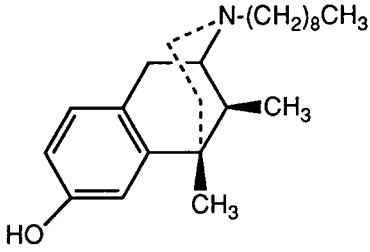
(SDS)

As shown in the accompanying figure, at doses of 5 and 15 mg/kg, NIH 10729 neither substituted for morphine nor exacerbated withdrawal. Vehicle was 2.5% gum tragacanth in water.

Comment: The drug is devoid of activity in the antinociceptive tests in mice and as an opioid agonist or antagonist in the monkey. Low solubility may account for the apparent inactivity.



NIH 10730 (+)-5,9α-Dimethyl-2'-hydroxy-2-*n*-nonyl-6,7-benzomorphan hydrochloride



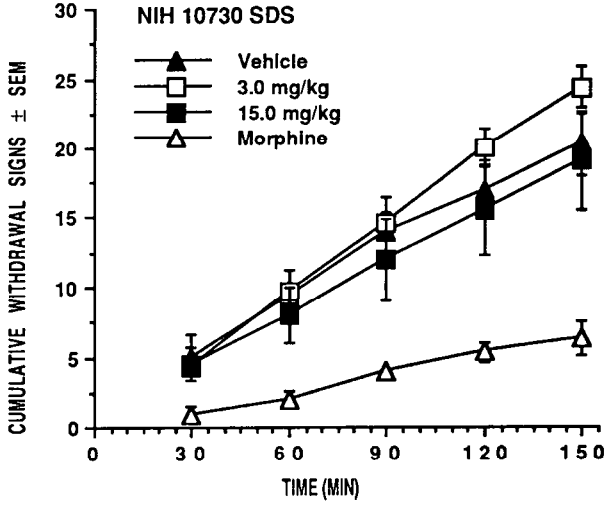
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 9% at 1.0, 14% at 10.0 and 29% at 30.0[a]
4) HP - 13% at 30.0; 25% at 10; and 13% at 1.0. Vehicle 25% activity.

[a]Vehicle - 40% DMSO and 25% propylene glycol and H_2O.

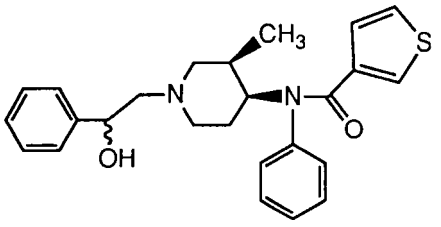
MONKEY DATA
(SDS)

As shown in the figure NIH 10730 SDS, the drug neither substituted for morphine nor exacerbated withdrawal at doses of 3 and 15 mg/kg. Vehicle was 2.5% gum tragacanth in water.



Comment: NIH 10730 appeared to be devoid of antinociceptive properties and did not Comment: behave as a mu agonist or antagonist in abruptly withdrawn, morphine-dependent monkeys. Solubility may have been a factor regarding the lack of biological activity.

NIH 10731 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl)]-N-phenyl-3-thiophenecarboxamide hydrochloride



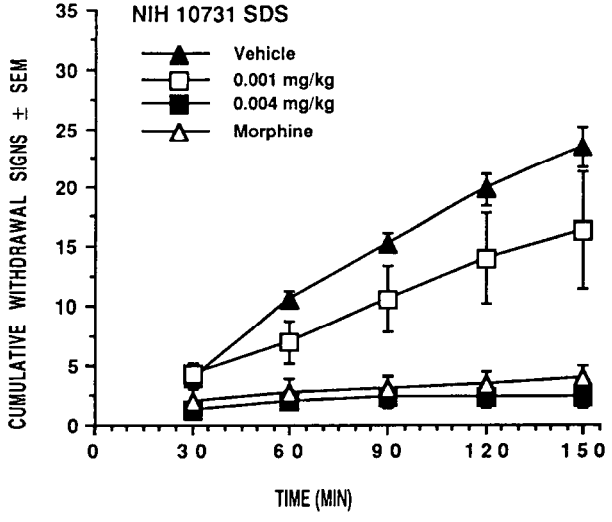
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.003 (0.001 - 0.008)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 1.0 x 10^{-3} (5.5 x 10^{-4} - 3.0 x 10^{-3})
4) HP - 0.004 (0.003 - 0.005)

Special Study: Naloxone AD_{50} vs ED_{80} of 10731 in TF = 0.02 (0.006 - 0.03)

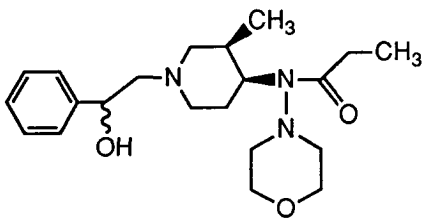
MONKEY DATA
(SDS)

As shown in the illustrated results, NIH 10731 dose-dependently substituted completely for morphine. The drug acted promptly and its duration of action was at least as long as that of the reference control, morphine. This substance is believed to be about 750 times more potent than morphine.



Comment: The results indicate that NIH 10731 is a potent mu agonist.

NIH 10732 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl)]-N-(4-morpholinyl)propanamide hydrochloride



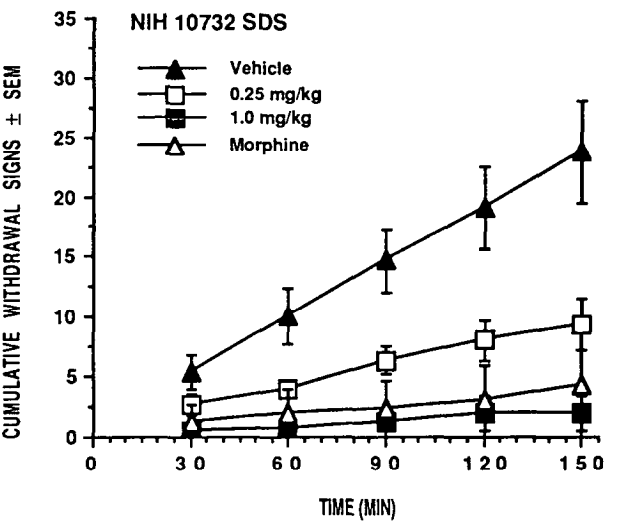
MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.7 (0.3 - 1.6)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.3 (0.01 - 1.0)
4) HP - 0.6 (0.3 - 1.0)

Special Study: Naloxone AD50 vs ED80 of 10732 in TF = 0.09 (0.03 - 0.24)

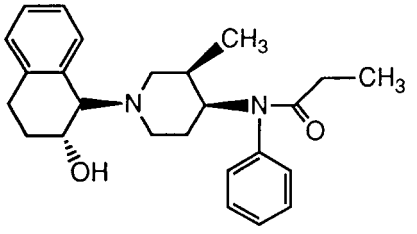
MONKEY DATA
(SDS)

NIH 10732 substituted completely for morphine (see fig.). The action was dose-dependent, of rapid onset and with a duration of action longer than that of morphine. The monkeys did not require the noon injection of morphine. Some jaw sag and scratching were noted in the monkeys receiving the higher dose. The drug is estimated to be about 12 times more potent than morphine.



Comment: NIH 10732 is an opioid with mu properties.

NIH 10733 (±)-*cis*-N-[1-(1-*trans*-2-Hydroxy-1,2,3,4-tetrahydronapthyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride

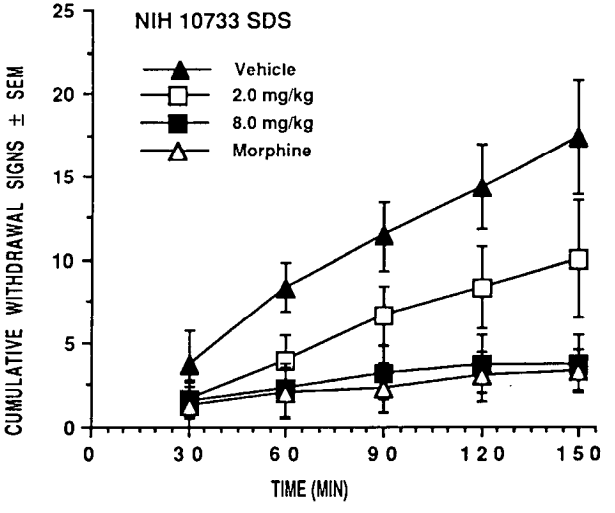


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 8.9 (2.5 - 30.2)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 3.3 (1.1 - 9.4)
4) HP - 4.8 (3.3 - 6.8)

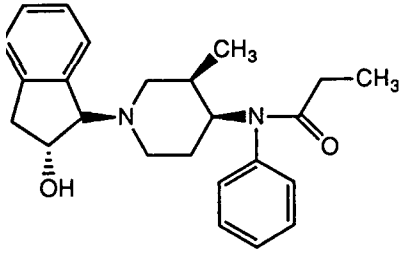
MONKEY DATA
SDS

NIH 10733 dose-dependently substituted completely for morphine. The action was prompt and of at least a 2.5 h duration (see fig.). Some jaw and body sag and scratching were noted at the higher dose. The drug is about 1/3 to 1/2 as potent as morphine.



Comment: This drug displayed a profile of activity reminiscent of mu agonists.

NIH 10734 (±)-*cis*-N-[1-(1-(*trans*-2-Hydroxy-1-indanyl)-3-methyl-4-piperidyl)]-N-phenylpropanamide hydrochloride

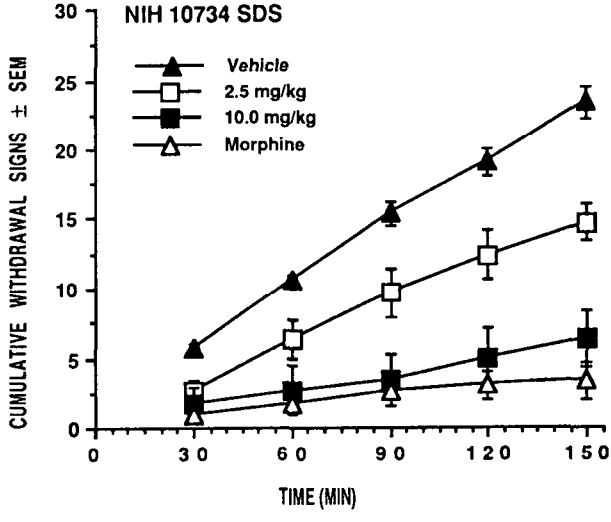


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 6.5 (3.0 - 14.0)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ- 3.2 (1.2 - 8.9)
4) HP - 6.8 (2.9 - 16.1)

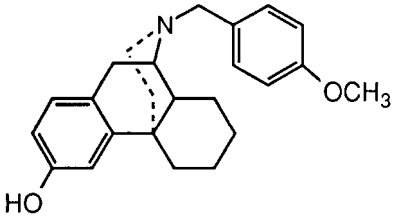
MONKEY DATA
(SDS)

NIH 10734 dose-dependently substituted completely for morphine. Onset of action was rapid Offset was longer than that of morphine. The monkeys, especially those receiving the higher dose, did not require the noon injection of morphine. The drug is considered to be about 1/3 as potent as morphine at peak effect.



Comment: NIH 10734 shows a profile of activity typical of mu agonists.

NIH 10736 (+)-3-Hydroxy-N-(4-methoxybenzyl)morphinan hydrobromide

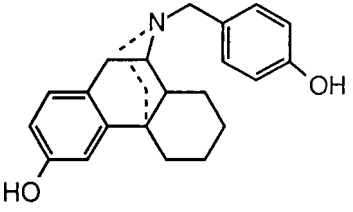


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 9.9 (3.8 - 25.9)[a]
4) HP - Inactive at 1, 13% at 10 and 13% at 30[a]

[a]5% DMSO, 10% Propylene glycol in water

NIH 10737 (+)-3-Hydroxy-N-(4-hydroxybenzyl)morphinan hydrobromide

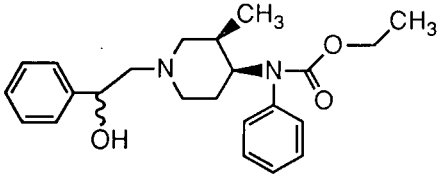


MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 26% at 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 20 % at 1.0, 31% at 10.0 and 29% at 30.0[a]
4) HP - 13% at 1.0, 0% 10.0 and 13% at 30.0[a]

[a]5% DMSO aqueous solution

NIH 10746 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidinyl]-N-phenylcarbamic acid ethyl ester hydrochloride



MOUSE DATA-ED50 OR AD50, mg/kg (95% C.L.) or % change

1) TF - 0.005 (0.002 - 0.01)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.001 (0.0005 - 0.002)
4) HP - 0.003 (0.001 - 0.008)

[a]Straub tail, ataxia, increased locomotion

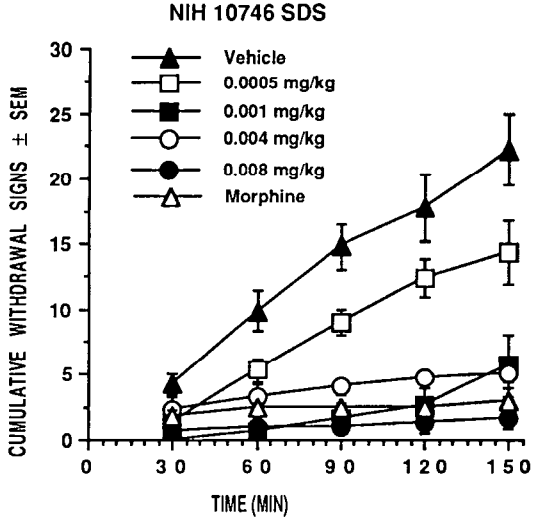
Special Study: Naloxone AD_{50} vs ED_{80} of NIH 10746 in TF = 0.01 (0.006 - 0.03)

NIH 10746 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidinyl]-N-phenylcarbamic acid ethyl ester hydrochloride. . . continued

MONKEY DATA

(SDS)

As shown in the data illustrated below (NIH 10746 SDS), this compound dose-relatedly substituted completely for morphine. The onset and offset of action were similar to those of the reference control. Potency estimate is 7500 x morphine. Jaw and body sag and scratching were noted at the higher dose.



Comment: The profile of activity of NIH 10746 is consistent with that of a potent mu agonist.

ACKNOWLEDGEMENTS

This study was supported by a contract (#271-90-7200) from the National Institute on Drug Abuse, Dr. David Johnson, Contract Officer. We also acknowledge the expert assistance of Susan M. Tucker and Chistopher C. Cull and Larry Hughes. Special thanks to Laura Johnson for her help in the preparation of this manuscript using the Macintosh IIci.

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EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY, 1992

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This report contains information on opioid abuse liability evaluations on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained can involve both *in vitro* evaluation in opioid binding assays and smooth muscle (largely, mouse *vas deferens)* preparations. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. Each of these assays is described below. Usually when limited information is provided (e.g., *in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities, government laboratories, and international organizations are submitted to Dr. Jacobson.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. After the evaluation is complete and the report submitted to Dr. Jacobson, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported to the Drug Evaluation Committee.

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in isolation chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection

before the start of the cycle. Each cycle lasts 15min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. sessions consist of between two and six discrete, 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively (*i.e.,* fixed-ratio 5) the lever appropriate for the solution administered during

the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.,* irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.,* alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (i.e., precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (i.e., withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

DEPENDENCE EVALUATION IN RHESUS MONKEYS

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting) by Deneau and Seevers (1963) and by Villarreal (1973).

ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the

thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40° C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.,* alfentanil) or κ (e.g., U-50,488) opioid agonist.

RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 101/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V,) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the inter-injection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (e.g., alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce a five-sec intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a ten-min timeout condition is in effect, during which responses have no scheduled consequence and neither light is illuminated. Each of the two daily sessions consist of 13 injections or 130 min, whichever occurs first. Other details of the procedure and initial findings with a variety of narcotics are given in previous reports (*e.g.,* Woods, 1977; 1980).

Doses of the drugs are typically described in terms of mg/kg/ injection (inj). Duplicate observations of codeine (0.32 mg/kg/inj) and of saline are obtained for each monkey. A saline substitution is conducted before and after the series of observations on a test drug; the control rates of codeine- reinforced responding are obtained by a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; each symbol is the mean of duplicate observations for a given dose in each monkey. The closed circles indicate the averaged data for observations on the subset of monkeys used to study each drug under each of the experimental conditions. In all cases, the rates of responding given are those calculated during only the fixed-ratio portion of each session.

DISPLACEMENT OF RADIOLABELED LIGAND BINDING

Details of the binding assay based on the displacement of ^{3}H-etorphine in rat brain membranes have been described previously (Medzihradsky et al., 1984). Briefly, aliquots of a membrane preparation from rat cerebrum are incubated with ^{3}H-etorphine in the presence of 150 mM NaCI, and in the presence of different concentrations of the drug under investigation. Specific, i.e., opioid-receptor-related interaction of ^{3}H-etorphine is determined as the difference in binding obtained in the absence and presence of an appropriate excess of unlabeled etorphine. The potency of the drugs in displacing the specific binding of ^{3}H-etorphine is determined from log-probit plots of the data. See Table I for representative results with different opioids.

To enhance the characterization of novel opioids, we are also investigating their selectivity in binding to μ-, δ-, and κ--opioid receptors in membranes from monkey brain cortex. Thus, we are now providing EC_{50} values of the tested compounds in displacing the following radiolabeled opioid ligands:

etorphine (nonselective, reflects opioid character),
sufentanil or Tyr-D-Ala-Gly-(Me)Phe-Gly-ol (DAMGO); (μ selective),
[D-Pen^{2}-D-Pen^{5}]enkephalin (DPDPE; δ selective),
U-69,593 (κ selective).

Using the receptor-specific assays, we have described the selectivity of various established opioids in brain membranes of different species (Clark et al., 1988). The selection of *monkey brain* as the tissue for the selective binding assays strengthens the correlation between this *in vitro* assessment and the behavioral evaluation of the tested compounds.

In the ANNUAL REPORT, the results of the selective binding assays are listed under "Binding in monkey brain cortex". See Table II for representative results with different opioids in rat and monkey brain.

Based on ligand binding, a method was recently developed for the determination of lipophilicity of opioids (Medzihradsky *et al.,* 1992). The procedure offers the routine determination of the octanol-water partition coefficients, requires submilligram amounts of the compounds, and yields accuracy that is comparable to other, less sensitive and

TABLE I

EC_{50}'s of representative opioids for displacement of 0.5 nM ^{3}H-etorphine from rat brain membrane, and inhibition of the twitch of the mouse vas deferens preparation.

Compound	BINDING* EC_{50} (nM)	MVD
DPDPE	---	5.52
U50,488	---	6.29
Fentanyl	3 6 . 2	37.1
DAMGO	23.9	81.3
Etorphine	0.37	0.0068
(-)Cyclazocine	0.53	11.9
Naltrexone	0.63	---
Bremazocine	1.42	0.29
UM 1071R**	1.55	
Sufentanil	1.60	4.43
(-)SKF 10047	3.93	
Ethylketazocine	6.60	11.6
Ketazocine	14.1	1.18
Morphine	23.6	395
DSLET	43.0	1.71
Dextrorphan	< 6000	1010

*In the presence of 150 mM NaCl.

**1R-5R-9R-2"R-5.9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphanhydrochloride

more cumbersome methods of quantitation. Considering the significance of lipophilicity in the function of opioids, the lipid/water partition coefficient should be a valuable biochemical determinant in the preclinical evaluation of opioids (Medzihradsky, 1987).

TABLE II

Inhibition of radiolabeled sufentanil, DPDPE and U69,593 binding in rat and monkey brain. In membranes from rat cerebrum and monkey brain cortex, the inhibition of specific equilibrium binding of 0.5 UM [^{3}H]sufentanil, 1.5 nM [^{3}H]DPDPE and 1.5 nM [^{3}H]UG9,593 by five different concentrations of the listed compounds was investigated in the presence of 1.50 mM NaCl (modified from Clark et al., 1988).

Compound	EC_{50} (nM) [^{3}H]Sufentanil	[^{3}H]DPDPE	[3H]U69,593
Rat cerebrum			
DAMGO	13.2	690	
Sufentanil	1.25	45.0	
Morphine	31.4	422	
β-FNA	6.99	43.9	
β-CNA	1.29	7.48	
Naloxone	6.37	14.3	
Etorphine	0.60	1.13	
Buprenorphine	1.07	1.12	
Bremazocine	1.79	1.12	
Superfit	576	16.5	
DSLET*	121	1.05	
ICI-174,864	58900	59.0	
DPDPE	7720	6.44	
U50,488	7230	13100	
U69,593	38000	13400	
Monkey cortex			
Sufentanil	1.18	81.1	> 10000
DPDPE	18900	4.21	> 10000
U69,593	10700	17000	8.41

* (D-Ser^2,Leu^5)-enkephalin-Thr^6

Within our goal to enhance the molecular characterization of novel opioids (Medzihradsky, 1987) we have established functional assays for assessing receptor-effector interactions, reflecting receptor coupling to regulatory G protein and adenylate cyclase, respectively.

The methods are based on the stimulation of brain GTPase and inhibition of adenylate cyclase by opioid agonists, processes blocked by antagonists (Clark and Medzihradsky, 1987; Carter and Medzihradsky, 1992). We are presently evaluating the quantitative responses of partial and irreversible agonists in these assays.

ISOLATED, ELECTRICALLY-STIMULATED MOUSE *VAS DEFERENS* PREPARATION

The development of new, highly selective antagonists such as the reversible, noncompetitive κ receptor antagonist norbinaltorphimine (Smith et al., 1989) and the competitive δ receptor antagonist ICI-174864 have made possible the evaluation of selectivity of opioid agonists and antagonists by use of the mouse *vas deferens* preparation. Male, albino ICR mice, weighing between 25 and 30 g, are used. The mice are decapitated, the *vasa deferentia* removed, and 1.5 cm segments are suspended in organ baths which contain 30 ml of a modified Kreb's physiological buffer. The buffer contains the following (mM): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; $MgSO_4$, 1.19; KH_2PO_4, 1.19; glucose, 11; $NaHCO_3$, 25; pargyline HCl, 0.3; and disodium edetate, 0.03. The buffer is saturated with 95% O_2 - 5% CO_2 and kept at 37° C. The segments are attached to strain gauge transducers and suspended between two platinum electrodes. After a 30-min equilibration period, the segments are stimulated once every 10 sec with pairs of pulses of 2 msec duration, 1 msec apart and at supramaximal voltage. See Table III for potencies of representative agonists.

The following antagonists are studied: naltrexone HCl, ICI- 174864 [N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH] and norbinaltorphimine. The antagonists are added to the organ baths 15 minutes before the determination of cumulative concentration-effect relationships for the various agonists. See Table III for the potencies of different competitive antagonists studied in relation to prototypic agonists. EC_{50}'s are calculated by probit analysis, and pA_2 values are determined to assess relative potencies of antagonists.

All drugs which are submitted for evaluation are studied in the following manner: 1) the submitted drug is tested on the *vas deferens* preparation in the absence and in the presence of a concentration of naltrexone sufficient to block μ, κ and δ receptors. 2) If the submitted drug inhibits the twitch and its actions are blocked by naltrexone, it is evaluated further in the absence and presence of ICI-174864 and norbinaltorphimine used in concentrations at which these antagonists are selective for δ and κ receptors, respectively. 3) If the submitted drug is a partial agonist or devoid of agonistic activity at opioid receptors, it is evaluated further as an antagonist against the following agonists: sufentanil

TABLE III

Potencies of antagonists assessed in the mouse vas deferens

	pA_2 values* determined with three agonists		
	Sufentanil (μ)	U50,488 (κ)	DSLET (δ)
Antagonist			
Naltrexone	8.76	7.74	7.41
Naloxone	7.99	6.90	7.35
Cyprodime**	7.41	6.15	5.98
Nalbuphine	7.23	6.31	5.76
Naltrindole	7.71	7.38	9.44
ICI-174.864	<5.00	<5.00	7.90

*The pA_2 value is the negative logarithm of the molar concentration of antagonist necessary to shift the agonist concentration-effect curve to the right by a factor of 2-fold.

(μ selective), DSLET (δ selective) and U50,488 (κ selective). If the submitted drug has antagonistic activity against any or all of the receptor-selective agonists or upon any of the other preparations used in the Drug Evaluation Unit, the type of antagonism (competitive, noncompetitive, irreversible) is determined. For further details of the procedure and for a description of experiments in which β-funaltrexamine was used see Smith (1986). Drugs studied in the preparation prior to 1987 were evaluated with the protocol reported in the 1985 Annual Report.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year, and the individual tests which were performed are shown in Table IV. Also shown are dates of Reports to the Biological Coordinator, Dr. A. E. Jacobson, in which results are reported.

TABLE IV

SUMMARY OF TESTS PERFORMED

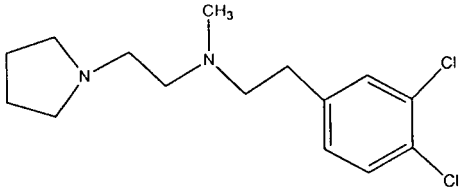
NIH	CHEMICAL CLASS OR GENERIC NAME	SA	MVD	BIND	DD	ANLG	RSP	REPORT
10670	Phenethylnmine	-	+	+	-	-	-	06/06/90
10679	Acetylmethadol (LAAM)	+	+	+	+	+	+	07/10/90
10680	Norketobemidone	-	+	+	-	-	-	07/10/90
10685	Morphine	+	1991	1991	1991	1991	1991	07/10/90
10688	Piperidine methanol	+	+	+	+	+	+	11/20/90 07/10/91
10689	Piperidine methanol	+	+	+	+	+	+	11/20/90 07/10/91
10690	Piperidine methanol	+	+	+	+	+	+	11/20/90 07/10/91
10692	6,7-Benzomorphan	-	+	+	-	-	-	09/05/91
10695	Normetazocine	-	+	+	-	-	-	08/26/91
10696	Normetazocine	-	+	+	-	-	-	08/26/91
10697	6,7-Benzomorphan	-	+	+	-	-	-	07/12/91
10698	6,7-Benzomorphan	-	+	+	-	-	-	07/10/91
10699	Complex carbamate	-	+	+	-	-	-	01/03/92
10700	Dehydropiperidine	-	+	+	-	-	-	07/10/90
10701	Epoxymorphinan	-	+	+	-	-	-	07/10/91
10702	Epoxymorphinan	-	+	+	-	-	-	07/10/91
10703	Phenylethylamine	-	+	+	-	-	-	07/10/91
10704	Phenylacetylpiperazine	-	+	+ MBC	-	-	-	07/10/91
10705	Phenylelhylpiperozine	-	+	+	-	-	-	08/26/91
10706	Propylamine	-	+	+	-	-	-	08/26191
10709	Phenylethylamine	-	+	+	-	-	-	02/28/92

Table IV (continued)

NIH	CHEMICAL CLASS OR GENERIC NAME	SA	MVD	BIND	DD	ANLG	RSP	REPORT*
10717	Phenylpropanimide	-	+	+	-	-	-	01/03/92
10718	Phenylfuramide	-	+	+	-	-	-	01/03/92
10719	Phenylacetamide	-	+	+	-	-	-	01/03/92
10720	Phenylthiozide	-	+	+	-	-	-	01/03/91
10721	6,7-Benzomorphan	-	+	+ MBC	-	-	-	02/20/92
10722	Phenylpropanamide	-	-	+	-	-	-	02/03/92
10723	Phenylpropanamide	-	+	+ MBC	-	-	-	02/20/92
10724	Phenylpropanamide	-	+	+	-	-	-	02/03/92
10725	Phenylpropanamide	-	-	-	+	+	+	07/12/91
10726	Phenylpropanamide	-	+	+	-	-	-	02/03/92
10727	Phenylfuramide	-	-	-	+	-	+	07/12/91
10729	6,7-Benzomorphan	-	+	+	-	-	-	02/20/92
10730	6,7-Benzomorphan	-	+	+	-	-	-	02/20/92
10731	Phenylthiozide	-	+	+	-	-	-	02/03/92
10732	Phenylpropanamide	-	+	+	-	-	-	02/03/92
10733	Phenylpropanamide	-	+	+	-	-	-	02/03/92
10734	Phenylpropanamide	-	+	+	-	-	-	02/10/92
10736	Morphinan	-	+	+	-	-	-	03/23/92
10737	Morphinan	-	+	+	-	-	-	03/23/92
10746	Phenylpropanamide	-	+	+	-	--	-	02/04/92

+ Dale report was submitted to CPDD Biological Coordinator.
MBC = Monkey Brain Cortex

NIH 10670 N-[3,4-Dichlorophenylethyl]-N-methyl-2-(1-pyrrolidinyl)ethylamine dihydrobromide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

7.5 inhibition at 6 μM in the presence of 150 mM NaCl.

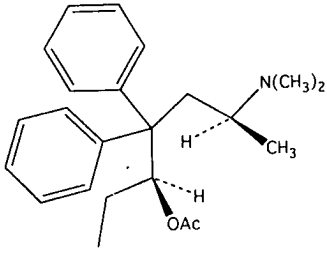
MOUSE *VAS DEFERENS* PREPARATION

NIH 10670 was studied upon the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 10^{-9} M to 3 x 10^{-6} M. It caused a partial inhibition of the twitch of the *vas deferens.* The EC_{50} for NIH 10670 was 2.20 x 10^{-8} M ± 0.83, and the maximum response was a 23.5 ± 1.3% inhibition of the twitch (n = 3). Naltrexone, 10^{-7} M, had no appreciable effect upon the NIH 10670 concentration-effect curve. In the presence of naltrexone, the EC, was 2.89 ± 10^{-8} M (a 1.3-fold shift), and the maximum response was a 16.5 ± 6.2% inhibition of the twitch (n = 3). NIH 10670 did not act as an antagonist at μ, κ, or δ opioid receptors.

SUMMARY

NIH 10670 was without significant opioid activity in either preparation.

NIH 10679 (-)-α-Acetylmethadol hydrochloride



For the *in vitro* results of NIH 10679, see the 1991 Annual Report.

DISCRIMINATIVE STIMULUS EFFECTS IN RHESUS MONKEYS

NIH 10679 was studied in rhesus monkeys for its discriminative stimulus effects. NIH 10679 had relatively modest or, under some conditions, no effects when studied using cumulative dosing procedures (*i.e.,* when increasing doses were administered every 15 or every 30 minutes). For example, up to a cumulative dose of 3.2 mg/kg, NIH 10679 failed to substitute for the opioid, μ agonist alfentanil, failed to substitute for the opioid κ agonist ethylketocyclazocine, failed to substitute for the opioid antagonist naltrexone (i.e., precipitate withdrawal) in morphine-treated subjects, failed to attenuate (-)-α-naltrexone lever responding (i.e., withdrawal) in morphine-abstinent subjects, and failed to exert analgesic effects in a warm-water tail withdrawal procedure. A cumulative dose of 10.0 mg/kg of NIH 10679 was studied for its effects on respiration (see below)

NIH 10679 Acetylmethadol hydrochloride

continued...

and upon observing the subject in the home cage after termination of the experiment, it became clear that this compound had profound behavioral effects (see below); however, these effects had a delayed onset of action. Consequently, additional studies were conducted under selected conditions to characterize the time course of effects of NIH 10679.

RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

Using a cumulative dosing procedure NIH 10679 was administered up to a maximum dose of 10.0 mg/kg; NIH 10679 decreased in a dose-related manner both ventilatory frequency (f) and ventilatory volume (V_T) in a monkey breathing air or 5% CO_2 in air (left and right panels, respectively, Figure 1). For example, at the largest dose studied f was decreased to less than 60% of control and V_T was decreased to less than 70% of control in the presence of 5% CO_2. Additional injections of NIH 10679 were not given; however, the

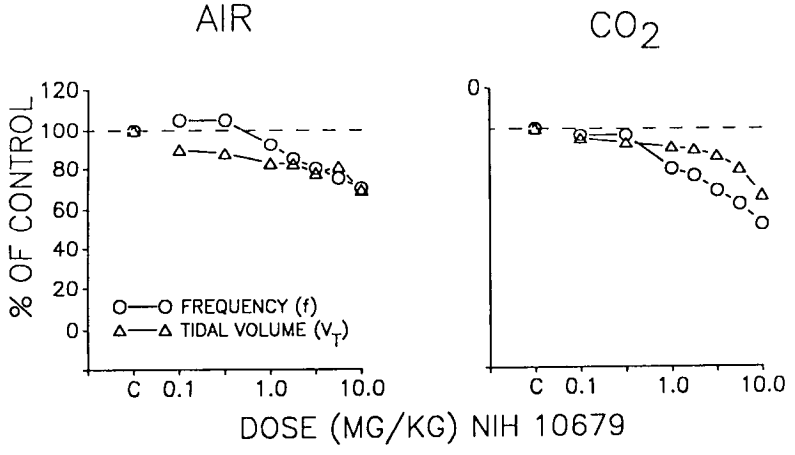


Fig. 1 Effects of NIH 10679 on ventilatory frequency (f; O) and ventilatory volume (V_T; Δ) in a monkey breathing air (left panel) or 5% CO_2) (right panel). *Ordinates:* effect, expressed as a percentage off and V-r under control conditions. *Abscissae:* dose in mg/kg body weight.

effects of 10.0 mg/kg of NIH 10679 were studied for a short time after the normal 30-minute test cycle. By 35 minutes after administration of 10.0 mg/kg of NIH 10679, overall respiratory function (i.e., minute volume; V_c) was decreased to 34% of control in the presence of 5% CO_2. At this time the only other observable effect was profuse

continued...

salivation; however, 75 minutes after administration of 10.0 mg/kg of NIH 10679 the subject showed pronounced muscle relaxation, frequent and prolonged eye closure, and a markedly decreased frequency of respiration. As the subject's condition appeared to be deteriorating, particularly with regard to respiratory function, 0.7 mg/kg of each of the opioid antagonists naltrexone and quadazocine were administered s.c. Within 5 minutes of administration of quadazocine and naltrexone the subject was standing upright, eyes were open, respiratory function appeared normal, although salivation was still profuse. For the next several hours salivation was observed, although other effects of NIH 10679 were not evident.

ANALGESIA STUDIES IN RHESUS MONKEYS

Single doses of NIH 10679 were studied for their analgesic effects under conditions in which tail withdrawal latencies from warm water (50 or 55° C) were assessed every 30 minutes for 6.5 hours and also at 24 and 48 hours after administration of NIH 10679. Whereas a dose of 0.32 mg/kg of NIH 10679 failed to exert any analgesic effects under the conditions studied (circles, Figure 2), a 10-fold larger dose produced the maximum

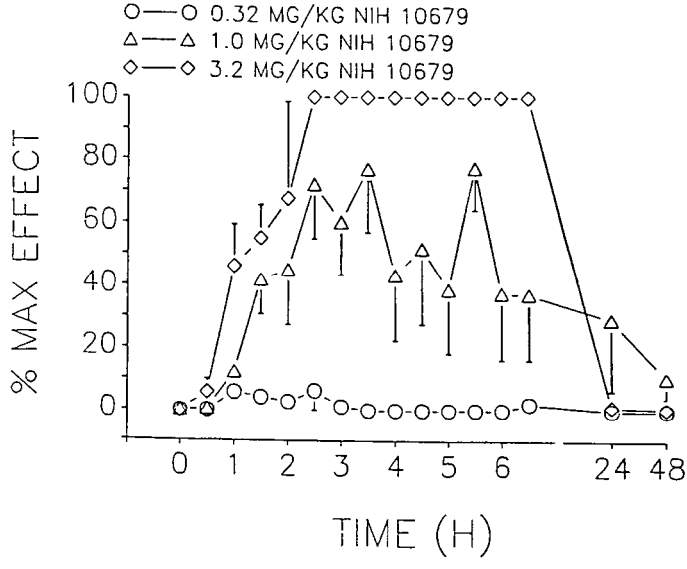


Fig. 2 Time course of anlagesic effects of NIH 10679 (0.32, 1.0, or 3.2 mg/kg) with a 50° C stimulus. *Ordinate:* analgesic effects expressed as a percentage of the maximum possible effect (*i.e.,* 20 sec latency). *Abscissae:* time (hr) after administration of NIH 10679.

possible effect with a 50° C stimulus. A maximum effect was obtained with 3.2 mg/kg of NIH 10679 2.5 hours after drug administration and this analgesic effect was still evident 6.5 hours after drug administration. However, there were no longer any effects of this dose of NIH 10679 24 or 48 hours after s.c. injection. With a 55° C stimulus, 3.2 mg/kg of NIH 10679 produced 53% of the maximum possible effect (not shown) 4 hours after drug administration and this maximum lasted only for 1 hour. An intermediate dose of NIH 10679 (1.0 mg/kg) produced intermediate analgesic effects with a 50° C stimulus (triangles, Figure 2) and produced no apparent analgesic effects with the 55° C stimulus (not shown).

Pretreatment with a dose of 1.0 mg/kg of the opioid antagonist quadazocine attenuated the analgesic effects of NIH 10679 (Figure 3). In the presence of quadazocine a dose of 1.0 mg/kg of NIH 10679 produced only 19% of the maximum possible effect 2 hours after drug administration; under control conditions this dose produced 45% of the maximum possible effect 2 hours after drug administration.

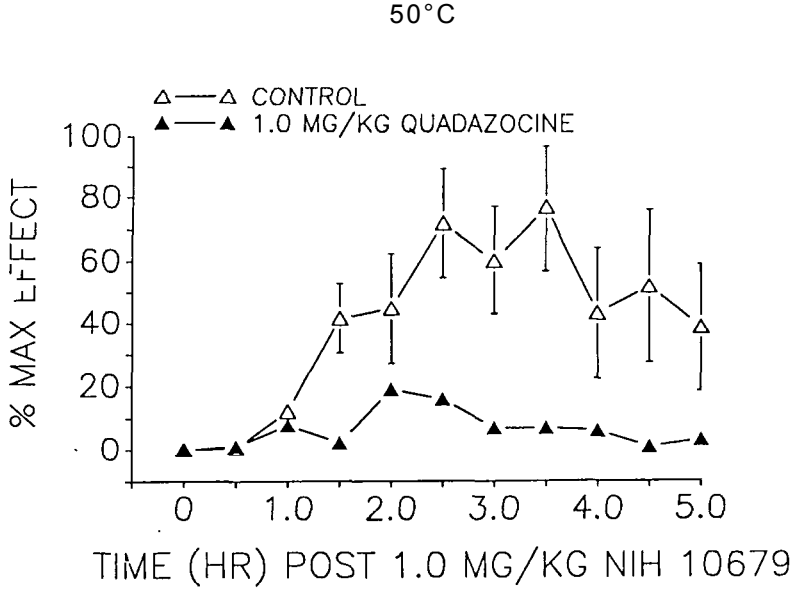


Fig 3 Antagonism of analgesic effects of 1.0 mg/kg of NIH 10679 (△) by a dose of 1.0 mg/kg of quadazocine (▲). See Fig 2 for other details.

NIH 10679 (-)-α-Acetylmethadol hydrochloride

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SELF-ADMINISTRATION STUDIES IN RHESUS MONKEYS

The reinforcing effects of NIH 10679 were evaluated in three monkeys experienced in responding and receiving intravenous infusions of alfentanil. Doses of from 0.0003 to 0.3 mg/kg/inj NIH 10679 were evaluated. In two monkeys, a range of from 0.0003 to 0.01 mg/kg/inj was evaluated during one session, a range of from 0.001 to 0.03 mg/kg/inj was evaluated during another session, and a range of from 0.003 to 0.1 mg/kg/inj was evaluated during a third session. Because the maximum rate of responding was not clearly determined across these dose ranges, one of these monkeys received a range of from 0.01 to 0.3 mg/kg/inj. Although this monkey appeared minimally sedated one hour after the session, at 2.5 hours after the session, he was found comatose in his cage. He appeared cyanotic and rate of respiration was deeply depressed. Naltrexone (1 mg/kg) was administered and the monkey revived and recovered. Because of this toxic effect, the third monkey was evaluated only acrfoss a range of 0.0003 to 0.1 mg/kg/inj.

NTH 10679 maintained rates of responding that were less than rates maintained by alfentanil in two monkeys, and maintained rates of responding that were as high as those maintained by alfentanil in the third monkey.

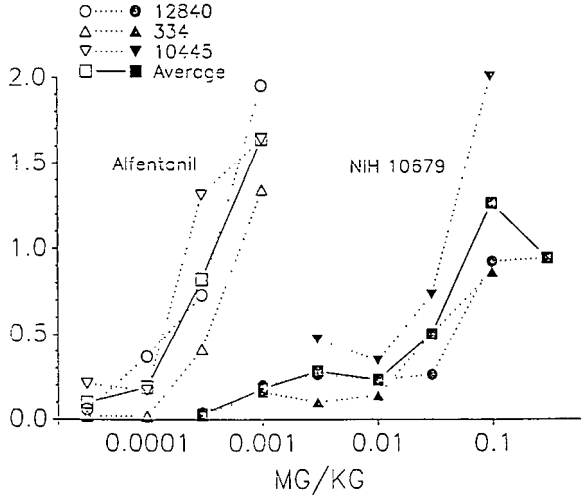


Fig 4 The data from individual monkeys are indicated by each animal's identification number and the distinctive symbols. The closed squares indicate average rates of responding maintained by alfentanil in the sessions immediately preceding those in which NIH 10679 was substituted. The open squares are the average of these data. The open symbols are the data obtained with NIH 10679. The closed squares are the average of these data.

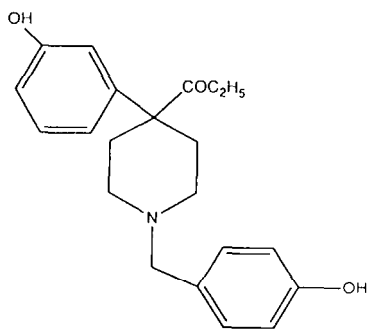
NIH 10679 (-)-α-Acetylmethadol hydrochloride

continued...

SUMMARY

NIH 10679's discriminative effects were not well characterized by the observations described above. NIH 10679 produced respiratory depression that was antagonized by narcotic antagonists. NIH 10679 produced a long-lasting analgesia that was prevented by co-administration of quadazocine. It produced a reinforcing effect that was almost as efficacious as alfentanil and 100 times less potent. NIH 10679 is probably a μ agonist, although it was not definitely characterized by these observations. Its maximum effect is reached slowly.

NIH 10680 N-(4-Hydroxybenzyl)-N-norketobemidone hydrobromide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 2558 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

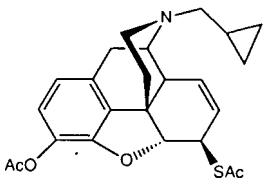
Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
DSLET	6.48	1.13 ± 0.06	6.57 ± 0.38	6

No agonist activity up to 3 μM at which concentration the twitch was increased in both control preparations and in the presence of 100 nM naltrexone. NIH 10680 was a weak δ receptor antagonist and a weak, unsurmountable antagonist at μ receptors. At a concentration of 30 μM it caused a 3.92-fold shift to the right in the U-50,488 concentration effect curve.

SUMMARY

NIH 10680 had low potency in displacing etorphine in the binding assay. It had *no* agonist actions up to 3 μM; while it was a δ receptor antagonist with a pA_2 of 6.48.

NIH 10685 (-)-3-Acetyl-6β-(acetylthio)-N-(cyclopropylmethyl)normorphine



SELF-ADMINISTRATION STUDIES IN RHESUS MONKEYS

Doses of from 0.00003 to 0.01 mg/kg/inj NIH 10685 were evaluated. NIH 10685 maintained rates of responding that were less than rates maintained by 0.001 mg/kg/inj alfentanil in all three monkeys. The drug appeared to have virtually no capacity to maintain drug-contingent responding. Figure 1 is a graphic representation of the data described.

SUMMARY

The *in vitro* evaluations, the drug discrimination, analgesia and respiratory studies on NIH 10685 were reported in the 1991 Annual Report. In the self-administration paradigm NIH 10685 failed to maintain significant self-injection responding over a significant range of doses.

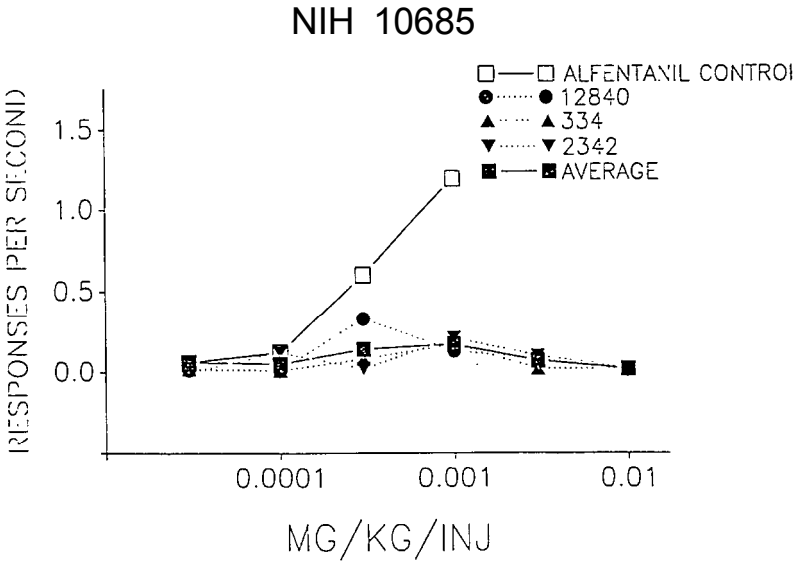


Fig 1 The data from individual monkeys are indicated by each animal's identification number and the distinctive symbols. The open symbols indicate rates of responding maintained by alfentanil in the sessions immediately preceding those in which NIH 10685 was substituted. The open squares are the average of these data. The closed symbols are the data obtained with NIH 10685. The closed squares are the average of these data.

NIH 10685 (-)-3-Acetyl-6β-(acetylthio)-N-(cyclopropylmethyl)normorphine

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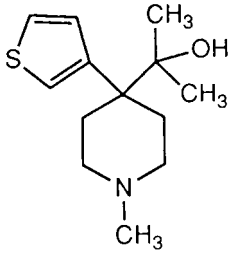
NIH 10685 appears to have affinity for each of the receptor types assessed *in vitro* and it shows agonist and antagonist activity in the *vas deferens.* It had κ-*agonist* and μ-antagonist activity in drug discrimination assays. The evidence and the corraborative analgesic and reinforcing effects lead us to suggest that in rhesus monkeys NIH 10685 has κ-agonist and μ-antagonist activity reminiscent of cyclazocine.

NIH 10688 α,α,1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 10303 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	10421.0 ± 1196.6	83.4 ± 4.3		9
Naltrexone (100 nM)	954.0 ± 34.2	30.1 ± 3.0	0.1	3
ICI-174864 (100 nM)	9660.6 ± 1486.4	74.8 ± 8.6	0.9	3
Nor-BNI (10 nM)	14332.0 ± 5144.6	64.2 ± 7.3	1.3	3

DRUG DISCRIMINATION STUDIFS IN RHESUS MONKEYS

NIH 10688 was studied in rhesus monkeys for its discriminative stimulus effects. In one subject discriminating between saline and 0.032 mg/kg of the opioid κ agonist ethylketocyclazocine, NIH 10688 substituted completely for ethylketocyclazocine at a dose of 5.6 mg/kg; in a second subject NIH 10688 substituted for ethylketocyclazocine only at a dose (10.0 mg/kg) that also decreased response rates to less than 10% of the control

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response rate (not shown). Up to a dose of 10.0 mg/kg NIH 10688 did not reliably substitute for the opioid μ agonist alfentanil in a separate group of subjects discriminating between saline and 0.056 mg/kg of alfentanil. In morphine-treated (3.2 mg/kg/day) monkeys discriminating between 0.032 mg/kg of naltrexone and saline, NIH 10688 failed to substitute for naltrexone (precipitate withdrawal) up to a dose of 10.0 mg/kg (not shown). When saline is substituted for the daily injection of morphine in monkeys discriminating between naltrexone and saline, subjects respond on the naltrexone lever; this naltrexone-lever responding is reversed by morphine-like opioids (e.g., alfentanil) and appears to be related to opioid withdrawal. NIH 10688 failed to attenuate naltrexone-lever responding in morphine-abstinent monkeys up to a dose of 10.0 mg/kg. Thus, with regard to discriminative stimulus effects, NlH had no apparent μ agonist nor μ antagonist activity but did appear to have κ agonist effects at doses of 5.6 mg/kg and larger.

ANALGESIA STUDIES IN RHESUS MONKEYS

NIH 10688 also was studied for its effects on the latency of monkeys to remove their tails from warm water. Up to the largest dose that could be administered, 10.0 mg/kg, NIH produced analgesic effects that were 100% and 79% of the maximum possible effect (i.e., 20-sec latency) for 50 and for 55" C, respectively (closed symbols, Figure 1). Large

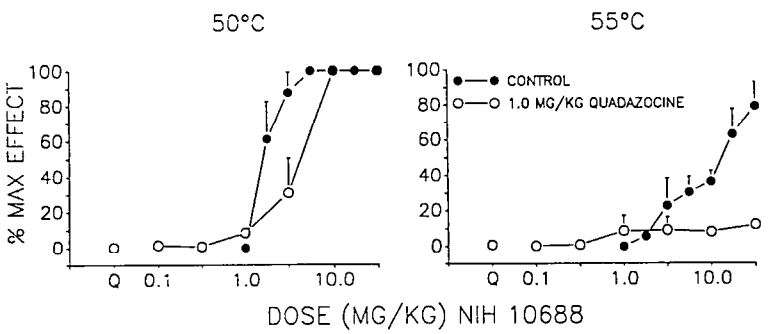

Fig 1 Effects of NIH 10688 on tail withdrawal latencies from 50° C (left panel) and 55° C (right panel) water. Closed symbols represent the effects of NIH 10688 administered alone and open symbols represent the effects of NIH 10688 administered 30 min after administration of 1.0 mg/kg of the opioid antagonist quadazocine.

doses of NIH 10688 also produced pupil dilation; no salivation was apparent. The analgesic effects of NIH 10688 were attenuated by pretreatment with 1.0 mg/kg of the opioid antagonist quadazocine (open symbols, Figure 1). For example, the analgesic effects of 32.0 mg/kg of NIH 10688 observed with 55° C water under control conditions were attenuated completely by quadazocine (compare open and closed symbols, right panel, Figure 1).

NIH 10688 $\alpha,\alpha,$.1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride

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RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The effects of NIH 10688 on respiratory function were studied in a monkey breathing air or 5% CO_2 in air (Figure 2). NIH 10688 produced dose-related decreases both in ventilatory frequency (f, left panel) and in ventilatory volume (V_T, right panel) in the presence of 5 % CO_2; qualitatively similar results were obtained under air only conditions (data not shown). At the largest dose studied, 32.0 mg/kg, NIH 10688 decreased f to 80% and 63% of control, respectively, in air and in 5% CO_2 in air; at the same dose, V_T was decreased to 24% and 63% of control, respectively, in air and in 5% CO_2 in air. Decreases in respiratory function produced by NIH 10688 were attenuated by pretreatment with 1.0 mg/kg of quadazocine. For example, decreases in V_T were attenuated completely by quadazocine (compare open and closed symbols, right panel, Figure 2).

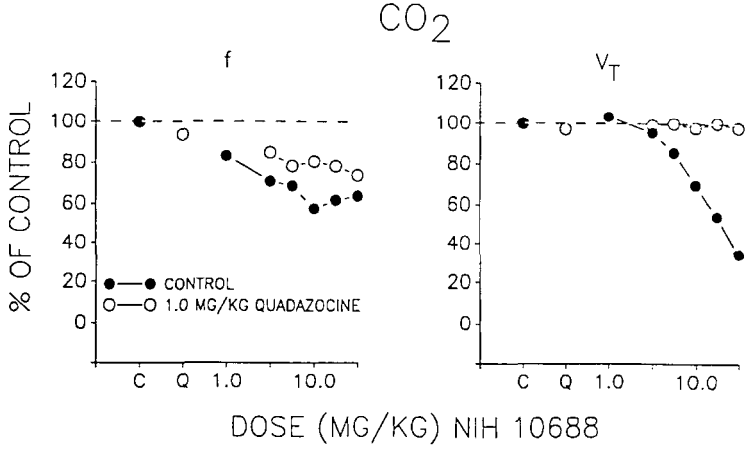

Fig 2 Effects of NIH 10688 on respiratory function in a monkey breathing 5 % CO_2 in air (similar results were obtained under air only conditions). The effects of NIH 10688 on respiratory frequency (f) and on tidal volume (V_T) are shown for control conditions (●) and for a study in which this monkey received 1.0 mg/kg of quadazocine 30 min prior to the first injection of NIH 10688 (O).

SELF-ADMINISTRATION STUDIES IN RHESUS MONKEYS

The reinforcing effects of NIH 10688 were evaluated in three monkeys experienced in responding and receiving intravenous infusions of alfentanil. Doses from 0.003 to 1.0 mg/kg/inj NIH 10688 were evaluated. NIH 10688 maintained rates of responding that were less than rates maintained by 0.001 mg/kg/inj alfentanil in all three monkeys. Rates of responding were not as low on average as those maintained by 0.0001 mg/kg/inj

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alfentanil, however, suggesting a limited reinforcing capacity of NIH 10688. Although there was a slight tendency for rates of responding to increase as dose/injection increased, we did not evaluate doses above 1 mg/kg because we were warned about potential toxicity if more than 10 mg/kg were delivered acutely.

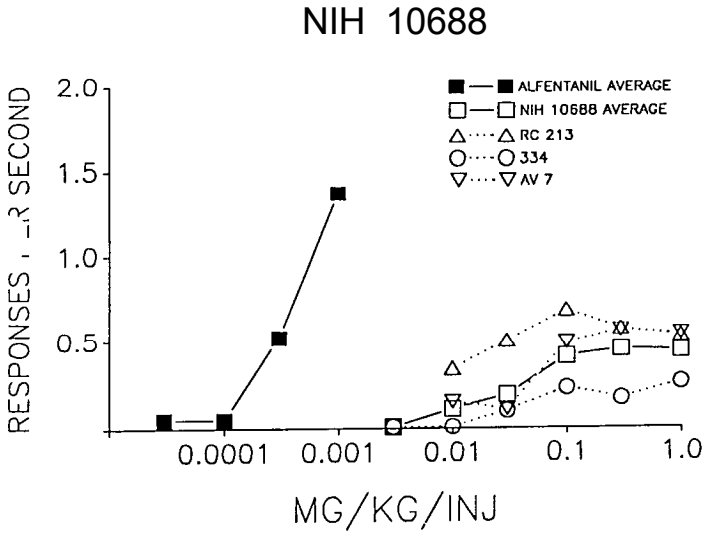


Fig 3 The data from individual monkeys are indicated by each animal's identification number and the distinctive symbols. The closed squares indicate average rates of responding maintained by alfentanil in the sessions immediately preceding those in which NIH 10688 was substituted. The open symbols are the data obtained with NIH 10688. The open squares are the average of these data.

SUMMARY

NIH 10688 had low potencies in the binding and smooth muscle preparations. Naltrexone decreased the maximum response to this drug, but did not shift the concentration-effect curve to the right. Neither ICI 174864 nor binaltorphimine significantly altered responses to this drug. NIH 10688 did not antagonize the actions of sufentanil, DSLET or U-50,488 in concentrations up to 50 μM. It is doubtful that this drug is an opioid in these preparations.

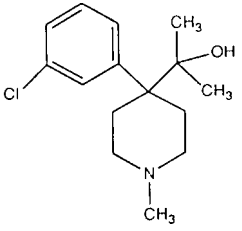
The *in vivo* data also suggest that NIH 10688 is not potent, but seems to have opioid activity that is not readily interpretable in relation to known standards of reference. It has some κ discriminative effects at high doses (5.6 - 10.0 mg/kg); its discriminative effects are not nalorphine-like in that there does not appear to be a narcotic antagonist component of action since it failed to substitute for naltrexone in morphine-treated monkeys. NIH

NIH 10688 α,α,1-Trimethyl-4-(3-thienyl)-4-piperidinemethanol hydrochloride

continued..

10688 had analgesic effects (10 mg/kg) that were reversed by large doses of quadazocine, suggestive of κ activity. It would, however, be unprecedented to find that a κ agonist was self-injected in this procedure, and NIH 10688 produced a modest self-injection rate at doses of 0.1-1.0 mg/kg/inj. Thus, all the evidence taken together, NIH 10688 has a very unusual profile of action. Since it shows a profile that differs from standards of reference, we should be cautious in the prediction of liability of abuse. However, it would certainly seem reasonable to assume that NIH 10688's abuse liability would be as low as nalbuphine or lower.

NIH 10689 α,α,1-Trimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6,000 nM (26% inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10689 was studied upon the isolated, electrically stimulated mouse vas deferens preparation in concentrations that ranged from 10^{-9} M to 3 x 10^{-6} M. Concentrations between 10^{-8} M and 3 x 10^{-6} M caused a small inhibition of the twitch. The EC_{50} for the inhibitory actions of NIH 10689 was 7.53 x 10^{-8} ± 2.67, and the maximum response was a 27.5 ± 1.8% inhibition of the twitch (n=3). Naltrexone did not significantly block the inhibitory actions of this drug. In the presence of naltrexone, 10^{-7} M, the EC_{50} for NIH 10689 was 2.61 x 10^{-8} M ± 0.48, and the maximum response was an 18.4 ± 5.0% inhibition of the twitch (n=3). When evaluated as an antagonist, NIH 10689 in a concentration of 10 μM caused a 1.5-fold shift to the right in the sufentanil concentration-effect curve, a 1.61-fold shift in the DSLET concentration-effect curve, and no shift at all in the U-50,488 concentration-effect curve.

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

NIH 10689 was studied in rhesus monkeys for its discriminative stimulus effects. Up to a dose of 17.8 mg/kg, NIH 10689 did not substitute for alfentanil in monkeys discriminating between 0.056 mg/kg of the opioid μ agonist alfentanil and saline. In one monkey discriminating between saline and 0.032 mg/kg of the opioid κ agonist ethylketocyclazocine NIH 10689 substituted completely for ethylketocyclazocine at a dose of 5.6 mg/kg; this subject did not respond after administration of a larger dose (10.0

continued...

mg/kg) of NIH 10689. A second subject did not respond after administration of doses of NIH 10689 larger than 1.78 mg/kg and up to that dose NIH 10689 failed to substitute for ethylketocyclazocine. In morphine-treated (3.2 mg/kg/day) monkeys discriminating between 0.032 mg/kg of naltrexone and saline, NIH 10689 substituted for naltrexone in one subject on two occasions; in a second subject NIH 10689 failed to substitute for naltrexone up to a dose of 5.6 mg/kg. When saline is substituted for the daily injection of morphine in monkeys discriminating NIH between naltrexone and saline, subjects respond on the naltrexone lever; this naltrexone-lever responding is reversed by morphine-like opioids (e.g., alfentanil) and appears to be related to opioid withdrawal. Up to a dose of 5.6 mg/kg NIH 10689 failed to attenuate naltrexone lever responding in morphine-abstinent monkeys. Thus, with regard to discriminative stimulus effects NIH 10689 produced mixed results: κ agonist and μ antagonist effects, but only in some of the subjects, and no μ agonist effects.

ANALGESIA STUDIES IN RHESUS MONKEYS

NIH 10689 was also studied for its effects on the latency of monkeys to remove their tails from warm water. In a single subject, NIH 10689 produced 100% of the maximum analgesic response (i.e., 20-second latency) with 50° C water at a dose of 17.8 mg/kg; only a dose of 32.0 mg/kg produced an analgesic effect (56% of the maximum) with 55" C water. Two hours after injection of 32.0 mg/kg of NIH 10689 this subject appeared to

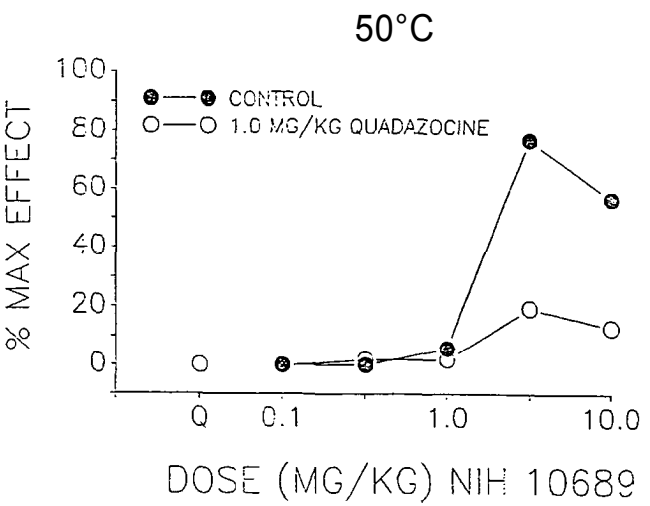


Fig 1 The effects of NIH 10689 on tail withdrawal latency from 50° C water under control conditions (●) and in the presence of 1.0 mg/kg of quadazocine (○).

NIH 10689 α,α,.1-Trimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride

continued...

be convulsing and these convulsions were not visibly altered by administration of 1.0 mg/kg of naltrexone nor by administration of diazepam. The subject died approximately 3 hours after administration of 17.8 mg/kg of NIH 10689.

In a second subject NIH 10689 was studied up to a cumulative dose of 10.0 mg/kg. Doses of NIH 10689 larger than 1.0 mg/kg produced >50% of the maximum possible effect with 50° C water (closed symbols, Figure 1) and had no effect with 55° C. water (not shown). This analgesic effect of NIH 10689 was attenuated markedly by pretreatment with a dose of 1.0 mg/kg of the opioid antagonist quadazocine (open symbols, Figure 1).

RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The effects of NIH 10689 on respiratory function were studied in a monkey breathing air or 5% CO_2 in air. Up to a dose of 10.0 mg/kg, NIH 10689 produced modest decreases (<30%) in ventilatory frequency (f) and in ventilatory volume (V^T). Decreases in respiratory function produced by NIH 10689 were not clearly altered by pretreatment with 1.0 mg/kg of the opioid antagonist quadazocine (not shown).

SELF-ADMINISTRATION STUDIES IN RHESUS MONKEYS

Doses of from 0.0003 to 0.3 mg/kg/inj NIH 10689 were evaluated. NIH 10689 maintained rates of responding that were less than rates maintained by 0.001 mg/kg/inj alfentanil in all three monkeys. Rates were higher than those maintained by 0.0001 mg/kg/alfentanil, however, and on average, there was a peak rate of responding at dose of 0.0003 mg/kg/inj, monkey #AV 7 showed peak rates at 0.03 mg/kg/inj, and monkey # RC 213 showed peak rates at 0.1 mg/kg/inj.

SUMMARY

NIH 10689 was devoid of significant opioid activity in both the smooth muscle and binding assays. NIH 10689 produced variable results in the drug discrimination assays. Doses of 1.0-10.0 mg/kg produced a modest, temperature-dependent analgesia that was antagonized by quadazocine in one monkey. One monkey died following the administration of 32 mg/kg which produced convulsions. In self-injection studies, NIH 10689 maintained rates above those of saline and below those of alfentanil. There were large individual differences in potency of NIH 10689 across subjects. Taken together, the evidence suggests NIH 10689 has opioid activity that has not been definitely characterized by these assays. The compound produced a toxic response and variability in response across different monkeys.

NIH 10689 α,α,1-Trimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride

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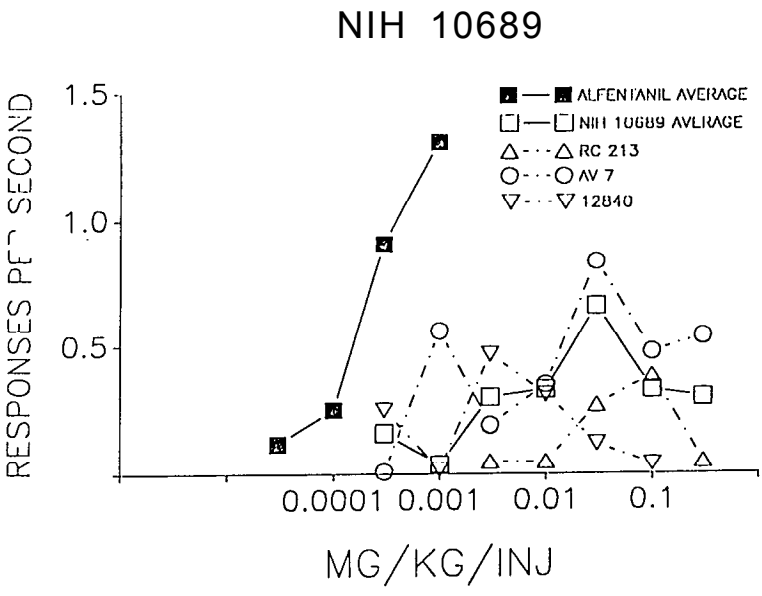
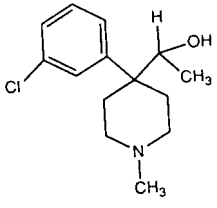


Fig 2 The data from individual monkeys are indicated by each animal's identification number and the distinctive symbols. The closed squares indicate average rates of responding maintained by alfentanil in the sessions immediately preceeding those in which NIH 10689 was substituted. The open symbols are the data obtained with NIH 10689. The open squares are the average of these data.

NIH 10690 α,1-Dimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6,000 nM (19 % inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10690 was studied upon the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations that ranged from 10^{-8} M to 3 x 10^{-5} M. Concentrations between 10^{-7} M and 3 x 10^{-5} M caused a small inhibition of the twitch. The EC_{50} for the inhibitory actions of NIH 10690 was 5.31 x 10^{-7} ± 0.58, and the maximum response was a 29.9 ± 6.1% inhibition of the twitch (n=3). Naltrexone did not significantly block the

inhibitory actions of this drug. In the presence of naltrexone, 10^{-7} M, the EC_{50} for NIH 10690 was 2.41 x 10^{-7} M ± 1.0, and the maximum response was an 18.4 ± 5.0% inhibition of the twitch (n=3). When evaluated as an antagonist, NIH 10690 in a concentration of 100 μM caused a 3.42-fold shift to the right in the sufentanil concentration-effect curve, a 2.83-fold shift in the DSLET concentration-effect curve, but no shift at all in the U-50,488 concentration-effect curve.

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

Up to a dose of 10.0 or 17.8 mg/kg, NIH 10690 failed to substitute for the opioid μ agonist alfentanil or for the opioid κ agonist ethylketocyclazocine in monkeys discriminating between saline and one of these selective opioid agonists (not shown). However, NIH 10690 substituted for naltrexone in one of three morphine-treated (3.2 mg/kg/day) monkeys discriminating between 0.032 mg/kg of naltrexone and saline. When saline is substituted for the daily injection of morphine in monkeys discriminating between naltrexone and saline, subjects respond on the naltrexone lever; this naltrexone-lever responding is reversed by morphine-like opioids (e.g., alfentanil) and appears to be related to opioid withdrawal. NIH 10690 failed to attenuate naltrexone lever responding in morphine-abstinent monkeys. Thus, with regard to discriminative stimulus effects, NIH 10690 had no apparent opioid agonist effects but did substitute for the opioid antagonist naltrexone in one subject.

ANALGESIA STUDIES IN RHESUS MONKEYS

NIH 10690 was studied for its effects on the latency of monkeys to remove their tails from warm water. Up to the largest dose administered, 32.0 mg/kg, NIH 10690 produced dose-related increases in the latency for monkeys to remove their tails from warm water (Figure 1). A dose of 10.0 mg/kg of NIH 10690 produced the maximum possible effect (20-sec latency) with 50° C water; this dose of NIH 10690 had no effect with 55° C water. However, a dose of' 32.0 mg/kg of NIH 10690 produced 65% of the maximum possible effect with 55° C water. The apparent analgesic effects of NIH 10690 were not antagonized by pretreatment with the opioid antagonist quadazocine (not shown). For example, under control conditions the smallest dose of NIH 10690 to produce a full effect at 50° C was 10.0 mg/kg and in the presence of 1.0 mg/kg of quadazocine the smallest dose to produce a full effect at 50° C was also 10.0 mg/kg (not shown).

RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The effects of NIH 10690 on respiratory function were studied in a monkey breathing air or 5% CO_2 in air (left and right panels, respectively, Figure 2). Up to a dose of 10.0 mg/kg, NIH 10690 produced very modest decreases in ventilatory frequency (f, circles) and little or no change in ventilatory volume (VT triangles).

NIH 10690 α,1-Dimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride

continued...

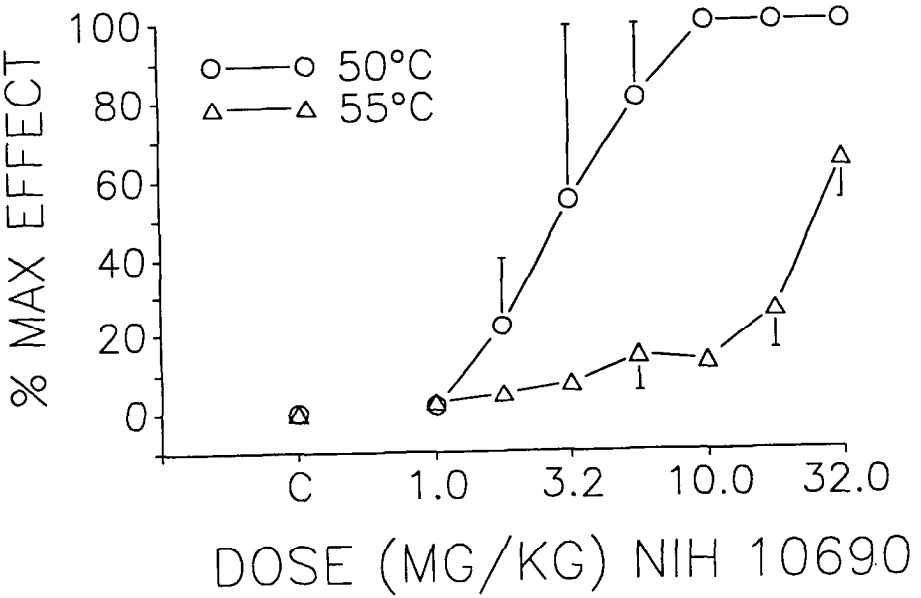


Fig 1 Effects of NIH 10690 on tail withdrawal latencies from 50° and 55° C water.

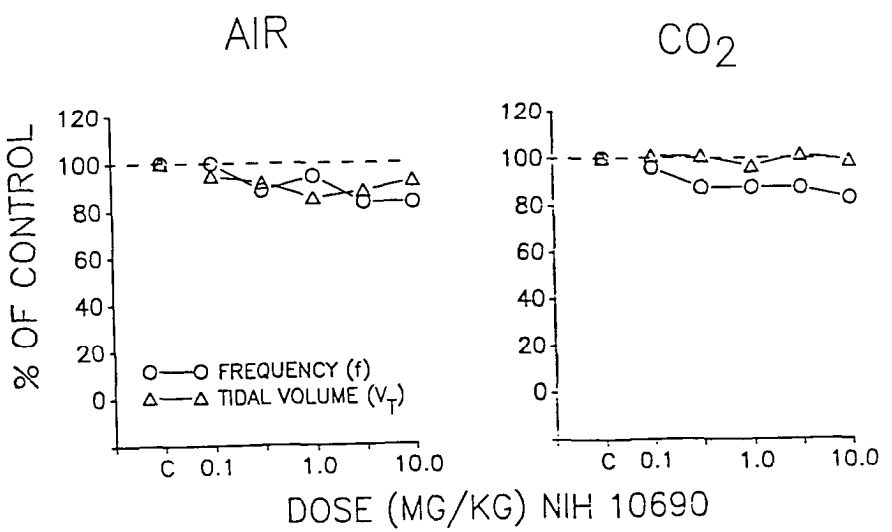


Fig 2 Effects of NIH 10690 on ventilatory frequency (O) and on ventilatory volume (Δ) in a monkey breathing air (left panel) or 5% CO_2 in air (right panel).

NIH 10690 α,β1-Dimethyl-4-(3-chlorophenyl)-4-piperidinemethanol hydrochloride

continued...

SELF-ADMINISTRATION STUDIES IN RHESUS MONKEYS

Doses of from 0.003 to 1.0 mg/kg/inj NIH 10690 were evaluated. NIH 10690 maintained rates of responding that were well below rates maintained by 0.001 alfentanil, and not significantly above the criterion rate when saline is substituted in this procedure. There was little inter-subject variability in rates of drug maintained responding; the data suggest that NIH 10690 has no reinforcing effect at the tested doses in this paradigm.

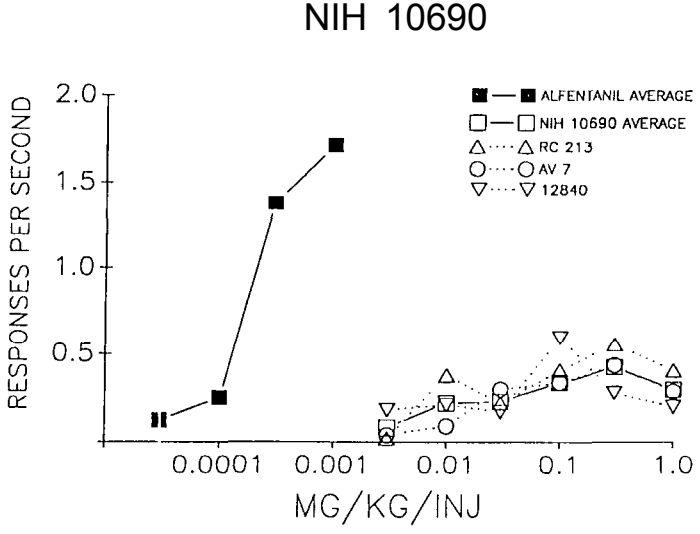
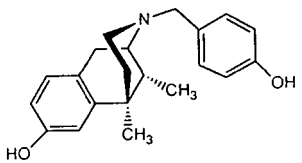


Fig 3 The data from individual monkeys are indicated by each animal's identification number and the distinctive symbols. The closed squares indicate average rates of responding maintained by alfentanil in the sessions immediately preceeding those in which NIH 10690 was substituted. The open symbols are the data obtained with NIH 10690. The open squares are the average of these data.

SUMMARY

NIH 10690 is devoid of significant opioid activity in the mouse *vas deferens* and binding assays. The *in vivo* data confirm this prior report. At analgesic doses, NIH 10690 fails to induce discriminative effects equivalent to naltrexone in morphine-dependent monkeys. At doses that would be expected to maintain self-injection responding, based on the relative potencies of opioids, NIH 10690 failed to maintain self-injection responding. NIH 10690 produced a significant, temperature-dependent analgesia that was not antagonized by a large dose of quadazocine. The nonopioid drug classes that induce analgesia in this procedure are excitatory amino acid antagonists (NMDA-type) and α-adrenergic agonists (clonidine-type). Haloperidol-like compounds will produce a modest effect at very large doses.

NIH 10692 (-)-5,9α-Dimethyl-2'-hydroxy-2-(4-hydroxybenzyl)-6,7-benzomorphan hemioxalate



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6,000 nM (37% inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

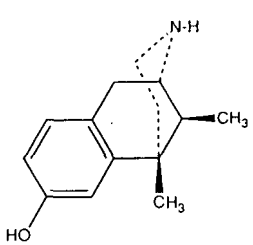
Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	504.7 ± 83.1	80.1 ± 4.7		9
Naltrexone (100 nM)	3470.1 ± 1609.2	65.8 ± 17.5	6.9	3
ICI-174864 (100 nM)	471.5 ± 46.8	85.2 ± 4.0	0.9	3
Nor-BNI (10 nM)	244.0 ± 90.9	18.8 ± 4.6	0.5	3

Note: Solubility - 3 mM in 16% DMSO.

SUMMARY

NIH 10692 had a very low affinity for the etorphine site, but it inhibited the contractions of the *vas deferens.* The inhibition was antagonized by naltrexone and by nor-BNI. The interaction between nor-BNI and NIH 10692 was similar to that found with nor-BNI and U50,488.

NIH 10695 (+)-N-Normetazocine



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 939 nM in the presence of NaCl.

NIH 10695 (+)-N-Normetazocine

continued...

MONKEY BRAIN CORTEX BINDING

This finding was obtained in displacing the specific equilibrium binding of (a) 0.5 nM [^{3}H]DAGO (μ-selective assay), (b) 1.5 nM [^{3}H]DPDPE (δ-specific assay), and in 1.5 nM [^{3}H]U69,593 (κ-selective assay) in membranes from monkey brain cortex suspended in 50 mM Tris.HCl buffer (pH 7.4) containing 150 mM NaCl. EC_{50}'s (nM) are as follows:

(a)	μ-receptor	4111
(b)	δ-receptor	24% inhibition at 6 μM
(c)	κ-receptor	40% inhibition at 6 μM

MOUSE *VAS DEFERENS* PREPARATION

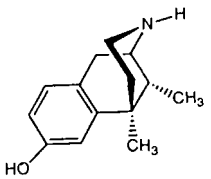
Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	42078.0 ± 4970.1	84.8 ± 2.5		9
Naltrexone (100 nM)	94339.0 ± 29640.0	70.0 ± 12.7	2.2	3
ICI 174864 (100 nM)	72774.0 ± 5372.9	74.2 ± 5.4	1.7	3
Nor-BNI (100 nM)	41872.0 ± 3616.8	92.9 ± 4.5	1.0	3

At the highest concentration studied, 100 μM, NIH 10695 did not produce a maximum response on the mouse *vas deferens* preparation. Thus, the EC_{50}'s are not accurate and over-estimate the relative potency of this drug. NIH 10695 appears to be a very weak agonist on the mouse *vas deferens* preparation which might have some activity at δ opioid receptors.

SUMMARY

NIH 10695 is a very weak compound in both preparations. There is a slight suggestion of δ agonist activity in the *vas deferens*.

NIH 10696 (-)-N-Normetazocine



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 939 nM in presence of 150 mM NaCl.

MONKEY BRAIN CORTEX BINDING

This finding was obtained in displacing the specific equilibrium binding of (a) 0.5 nM [^{3}H]DAGO (μ-selective assay), (b) 1.5 nM [^{3}H]DPDPE (δ-specific assay), and in 1.5 nM [^{3}H]U69,593 (κ-selective assay) in membranes from monkey brain cortex suspended in 50 mM Tris.HCl buffer (pH 7.4) containing 150 mM NaCl. EC_{50}'s (nM) are as follows:

(a)	μ-receptor	130
(b)	δ-receptor	642
(c)	κ-receptor	299

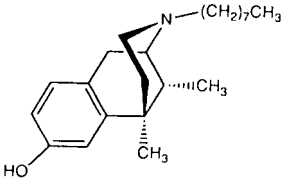
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift	n
Control	4447.80 ± 640.3	100		9
Naltrexone (100 nM)	57850.0 ± 14241.0	91.2 ± 4.8	12.9	3
Nor-BNI (0.1 nM)	8700.7 ± 2642.7	95.4 ± 0.5	1.9	3
ICI 174864 (100 nM)	3285.6 ± 423.9	98.1 ± 1.9	0.7	3

SUMMARY

NIH 10696 was a weak μ agonist in the *vas deferem*. It was a slightly selective μ ligand in the monkey brain.

NIH 10697 (-)-5,9α-Dimethyl-2'-hydroxy-2- *n*-octyl-6,7-benzomorphan hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 226 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

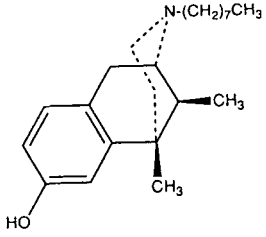
Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil	6.46	1.71 ± 0.28	6.77 ± 0.62	6
DSLET	<5.50			
U50,488	<5.50			

Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	1589.5 ± 335.4	100		9
Naltrexone (100 nM)	63.0 ± 3.5	15.5 ± 2.3	0.04	3
ICI 174864 (100 nM)	2208.7 ± 614.0	100	1.4	3
Nor-BNl (10 nM)	147.7 ± 16.1	34.8 ± 9.0	0.1	3

SUMMARY

NlH 10697 had only modest affinity in both preparations. In the *vas deferens* NIH 10697 was a weak μ opioid receptor antagonist. Because of agonist activity, concentrations higher than 3 μM could not be evaluated. It has significant agonist activity on the mouse *vas deferens* which is blocked by both naltrexone and nor-binaltorphimine. This pattern of agonist activity is unusual.

NIH 10698 (+)-5,9α-Dimethyl-2'-hydroxy-2-*n*-octyl-6,7-benzomorphan hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 3444 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

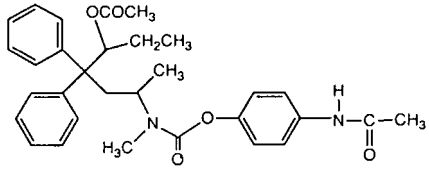
Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil	5.65	1.36 ± 0.04	5.70 ± 0.47	6
DSLET	<5.50			
U50,488	5.99	0.85 ± 0.01	5.91 ± 0.28	6

NOTE: For the *vas deferens,* the compound was dissolved in 15 % ethanol. It had no agonist actions in concentrations up to 2 μM.

SUMMARY

NIH 10698 had low potency in both preparations. In the *vas deferens,* it was an antagonist against μ and κ agonists.

NIH 10699 N-[(2S,5S)-4-Acetyoxy-4,4-diphenylhept-2yl]-N-methyl-O-(4-N-acetamidophenyl)carbamate



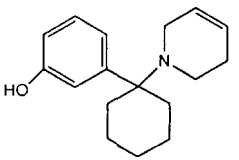
DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of >6000 nM (27% at 6 μM) in presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10699 was insoluble in all media normally compatible with studies on the mouse *vas deferens* preparation.

NIH 10700 1-[1-(2-Hydroxyphenyl)cyclohexyl]-3,4-dihydropiperidine hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 619 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

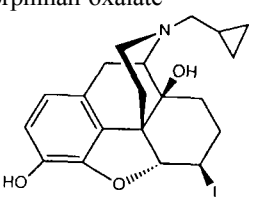
Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil	5.75	0.94 ± 0.08	5.72 ± 0.22	8
DSLET	5.79	1.07 ± 0.11	5.81 ± 0.36	6
U50,488	5.48	0.71 ± 0.15	5.49 ± 0.25	6

No agonist activity was found up to concentrations of 10 μM.

SUMMARY

NIH 10700 was a weak, nonselective narcotic antagonist.

NIH 10701 6β-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5 α-epoxymorphinan oxalate



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 5.2 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil	7.30	1.87 ± 0.35	7,98 ± 0.70	6
DSLET	7.71	1.04 ± 0.07	7.76 ± 0.35	6
U50,488	8.01	1.06 ± 0.16	8.15 ± 0.36	6

No agonist activity up to concentrations of 10 μM.

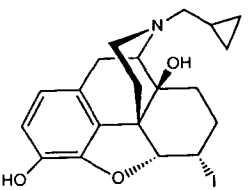
NIH 10701 6β-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5α-epoxymorphinan oxalate

continued...

SUMMARY

NIH 10701 is a fairly potent, nonselective opioid antagonist.

NIH 10702 6α-Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5α-1-epoxymorphinan oxalate



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 2.1 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

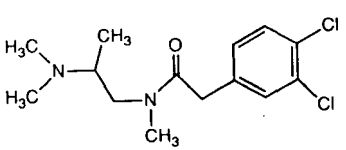
Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil	8.52	1.02 ± 0.16	8.53 ± 0.34	6
DSLET	7.95	1.00 ± 0.13	7.95 ± 0.33	6
U50,488	8.26	0.49 ± 0.08	8.25 ± 0.18	6

There was no agonist activity up to 10 μM.

SUMMARY

NIH 10702 is a fairly potent antagonist with modest μ-selectivity.

NIH 10703 N-[(3,4-Dichlorophenyl)acetyl]-N,2-dimethyl-2-(N'N'-dimethy-lamino) ethylamine oxalate



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of >6,000 nM (3.7% inhibition at 6 μM) in the presence of 150 mM NaCl.

NIH 10703 N-[(3,4-Dichlorophenyl)acetyl]-N,2-dimethyl-2-(N',N'-dimethy-lamino) ethylamine oxalate

continued...

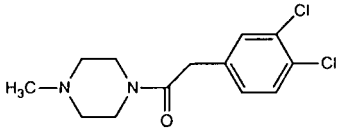
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift	n
Control	48.9 ± 10.7	100		9
Naltrexone (100 nM)	98.9 ± 31.0	100	2.0	3
Nor-BNI (0.1 nM)	147.4 ± 18.7	100	3.0	3
ICI 174864 (100 nM)	62.3 ± 23.3	100	1.3	3

SUMMARY

NIH 10703 had low potency in both preparations. Its inhibition of the *vas deferens* twitch was antagonized to a modest extent by naltrexone and norBN1. Thus, it might have some κ (or mixed μ·κ)) opioid activity *in vivo* (unless it has much higher affinity for another receptor system [nonopioid]).

NIH 10704 N-Methyl-N'-(3,4-dichlorophenylacetyl)piperazine



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6000 nM (3.9% inhibition at 6 μM) in the presence of NaCl.

NIH 10704 N-Methyl-N'-(3,4-dichlorophenylacetyl)piperazine

continued...

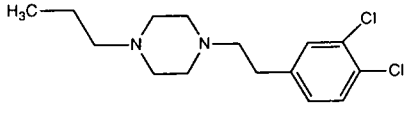
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	836.0 ± 510.0	100		5
Naltrexone (100 nM)	1045.0 ± 590.0	100	1.2	3
ICI 174864 (100 nM)	4080.4 ± 3357.0	100	4.9	2

SUMMARY

NIH 10704 was very weak in both *in vitro* assays. The concentration effect curve in the *vas deferens* was biphasic and the lower limb of the curve appeared to be shifted by both naltrexone and ICI-174864.

NIH 10705 N-(*n*-Propyl)-N'-(3,4-dichlorophenylethyl)piperazine dihydrobromide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6000 nM (14% inhibition at 6 μM) in the presence of 150 mM NaCl.

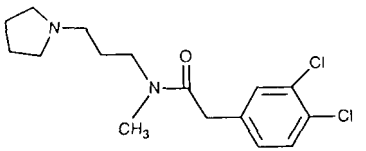
MOUSE *VAS DEFERENS* PREPARATION

NIH 10705 was devoid of agonist activity on the isolated, electrically stimulated mouse *vas deferens* preparation. This drug, in concentrations up to and including 30 μM, did not block the agonist actions of sufentanil (μ), DSLET (δ) or D50,488 (κ). Thus, NIH 10705 does not have opioid activity on the mouse *vas deferens* preparation.

SUMMARY

NIH 10705 had no significant opioid activity in either preparation.

NIH 10706 N-(3,4-Dichlorophenylacetyl)-N-methyl-3-(1-pyrrolidinyl) propylamine fumarate



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6,000 nM (4% inhibition at 6 μM) in presence of 150 mM NaCl.

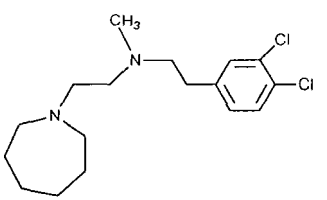
MOUSE *VAS DEFERENS* PREPARATION

NIH 10706 had slight agonist activity on the isolated, electrically stimulated mouse *vas deferens* preparation which was not blocked by naltrexone, ICI 174864 or nor-binaltorphimine. The maximum inhibition of the twitch was approximately 30%. This drug, in concentrations up to and including 30 µM, did not block the agonist actions of sufentanil (μ), DSLET (δ) or U50,488 (κ). Thus, NIH 10706 does not have opioid activity on the mouse *vas deferens* preparation.

SUMMARY

NIH 10706 had no significant opioid activity in either preparation.

NIH 10709 N-[2-(3,4-Dichlorophenyl)ethyl-N-methyl-2-(1-homo-piperidinyl)etyl-amine dihydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETO-RPHINE BINDING

EC_{50} of > 6000 nM (6.3 % inhibition at 6 μM) in presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil (μ)	6.10	1.42 ± 0.67	6.35	6
DSLET (δ)	5.79	1.50 ± 0.14	6.10 ± 0.67	6
U50,488 (κ)	5.99	2.92 ± 0.91	6.93 ± 1.35	6

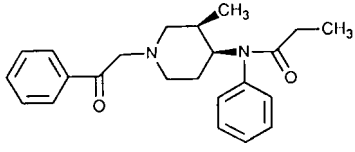
NIH 10709 N-[2-(3,4-Dichlorophenyl)ethyl-N-methyl-2-(1-homo-piperidinyl)etylamine dihydrochloride

continued...

SUMMARY

NIH 10709 had quite low potency in both *in vitro* assays. In the *vas deferens* it was atypical in that the slopes of the Schild plots were quite high, suggesting that the antagonism was not simply competitive in nature.

NIH 10717 (±)-*cis*-N-[3-Methyl-1-(2-oxo-2-phenylethyl)4-piperidyl]-N-phenyl-propanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 470 nM in the presence of 150 mM NaCl.

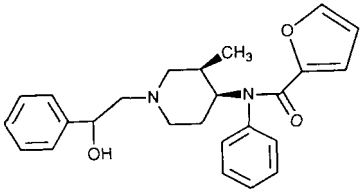
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	36.8 ± 6.7	87.0 ± 4.5		9
Naltrexone (100 nM)	11.6 ± 5.8	17.4 ± 2.3	0.3	3
ICI-174,864 (100 nM)	68.9 ± 14.0	61.3 ± 11.4	1.9	3
Nor-BNI (10 nM)	114.9 ± 93.8	90.4 ± 9.6	3.1	3

SUMMARY

NlH 10717 was less potent than morphine in the binding assay. On the mouse *vas deferens,* it was an agonist slightly more potent than morphine. NIH 10717 was unusual in that naltrexone caused an insurmountable antagonism of its inhibitory actions. ICI 174864 caused a shift to the right in its concentration-effect curve, although this shift was considerably different than those seen when norbinaltrophimine blocks the action of selective κ opioid receptor agonists.

NIH 10718 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-furamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 17 nM in presence of 150 mM NaCl.

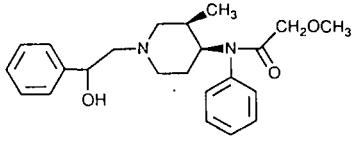
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	24.6 ± 7.0	93.9 ± 3.2		9
Naltrexone (100 nM)	92.4 ± 28.4	96.0 ± 2.0	3.8	3
ICI-174864 (100 nM)	12.2 ± 2.7	100	0.5	3
Nor-BNI (10 nM)	67.9 ± 23.9	89.5 ± 6.3	2.8	3

SUMMARY

NIH 10718 was about 10 times more potent than morphine in the binding assay. On the mouse *vas deferens* preparation, NIH 10718 was an agonist slightly more potent than morphine. It was antagonized by naltrexone and norbinaltorphimine, but not by ICI-174864. This suggests that it had some activity at κ opioid receptors.

NIH 10719 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-methoxyacetamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 17 nM in presence of 150 mM NaCl.

NIH 10719 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-methoxyacetamide hydrochloride

continued...

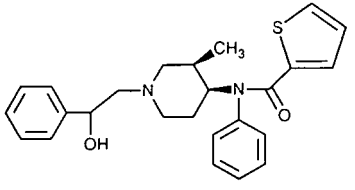
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	0.32 ± 0.01	100		9
Naltrexone (100 nM)	278.3 ± 114.3	100	879.6	3
ICI-174864 (100 nM)	4.16 ± 1.21	100	13.1	3
Nor-BNI (10 nM)	0.50 ± 0.16	100	1.6	3

SUMMARY

NIH 10719 was about as potent as morphine in the binding assay. On the mouse *vas deferens* preparation, NIH 10719 was a fairly potent agonist. The concentration-effect curve was shifted markedly by naltrexone and by ICI-174864 (a δ receptor-selective antagonist). Thus, NIH 10719 appeared to be an agonist at μ and δ receptors.

NIH 10720 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-thiophenecarboxamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 96.8 nM in the presence of 150 mM NaCl.

NIH 10720 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-2-thiophenecarboxamide hydrochloride

continued...

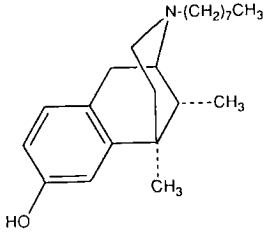
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift	n
Control	3.54 ± 1.60	97.2 ± 1.6		9
Naltrexone (100 nM)	238.3 ± 153.3	100.0	67.3	3
ICI-174864 (100 nM)	17.0 ± 13.7	100.00	4.8	3
Nor-BNl (10 nM)	146.1 ± 79.7	64.6 ± 6.2	39.7	3

SUMMARY

NIH 10720 had activity in both preparations. It was more potent in the *vas deferens.* In the *vas deferens,* it was an agonist with activity at κ opioid receptors, and was similar in potency to U50,488. It was antagonized markedly by naltrexone and norbinaltorphimine. ICI-174864 also caused a slight rightward shift in the concentration-effect curve. Although this drug had significant activity at κ receptors, activity at other types of opioid receptors cannot be ruled out.

NIH 10721 (±)-5,9|α-Dimethyl-2'-hydroxy-2-*n*-octyl-6,7-benzomorphan hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 675 nM in the presence of 150 mM NaCl.

NIH 10721 (+)-5,9α-Dimethyl-2'-hydroxy-2-*n*-octyl-6,7-benzomorphan hydrochloride

continued...

MONKEY BRAIN CORTEX BINDING

This finding was obtained in displacing the specific equilibrium binding of (1) 0.5 nM [^{3}H]DAGO (p-selective assay), (b) 1.5 nM [^{3}H]DPDPE (δ-selective assay), and 1.5 nM [^{3}H]U69,593 (κ-*selective* assay) in membranes from monkey brain cortex suspended in 50 mM Tis.HCl buffer (pH 7.4) containing 150 mM NaCl. The EC50's for NIH 10678 in monkey brain are:

(1)	μ-receptor:	280 nM
(2)	δ-receptor:	330 nM
(3)	κ-receptor:	280 nM

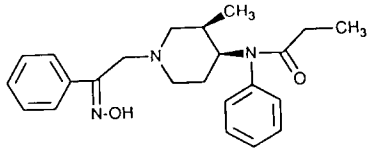
MOUSE VAS DEFERENS PREPARATION

NIH 10721 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 10 μM had no appreciable effect on this preparation. At a concentration of 30 μM, NIH 10721 completely inhibited the twitch, an effect that was not blocked by 100 nM naltrexone. When tested as an antagonist NIH 10721 (10 μM) caused a 5.92-fold shift to the right in the sufentanil concentration-effect curve. Because of the low potency of this drug as a μ opioid receptor selective antagonist, pA_2 values could not be determined. NIH 10721, 10 μM, did not affect responses of the *vas deferens* to DSLET, a δ opioid receptor agonist, or to U50,488, a κ opioid receptor agonist. Thus, NIH 10721 appears to be a μ-opioid receptor antagonist of very low potency and to be devoid of opioid-agonist activity on the mouse *vas deferens* preparation.

SUMMARY

NIH 10721 was not potent in any of the preparations. It was a low potency, μ-antagonist in the *vas deferens*.

NIH 10722 (±)-*cis*-N-[3-Methyl-1-(2-iminohydroxy-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 7.3 μM in the presence of 150 mM NaCl.

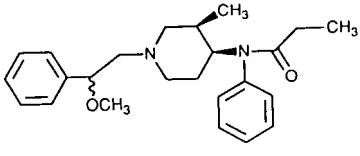
MOUSE *VAS DEFERENS* PREPARATION

NIH 10722 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 100 μM. Concentrations up to 300 nM had no appreciable effect on this preparation. Concentrations of 1 μM and greater caused marked increases in the magnitude of the twitch. When tested as an antagonist at a concentration of 100 μM, NIH 10722 did not block the inhibitory actions of sufentanil, a μ opioid receptor selective agonist, DSLET, a δ opioid receptor agonist, or U50,488, a κ opioid receptor agonist. Thus, NIH 10722 is devoid of significant opioid agonist or antagonist activity on the mouse *vas deferens* preparation.

SUMMARY

NIH 10722 had no significant opioid activity activity in either preparation.

NIH 10723 (±)-*cis*-N-[1-(2-Methoxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 40 nM in presence of 150 mM NaCl.

NIH 10723 (±)-*cis*-N-[1-(2-Methoxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride

continued...

MOUSE *VAS DEFERENS* PREPARATION

HIGHER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	852.7 ± 185.6	48.1 ± 7.5		10
Naltrexone (100 nM)	1202.2 ± 312.4	51.3 ± 13.4	1.4	4
ICI-174864 (100 nM)	1009.9 ± 614.5	26.3 ± 8.0	1.2	3
Nor-BNI (10 nM)	752.1 ± 351.1	47.6 ± 7.5	0.9	3

LOWER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	29.6 ± 8.4	100		10
Naltrexone (100 nM)	26.4 ± 6.1	100	0.9	4
ICI-174864 (100 nM)	25.6 ± 7.6	100	0.9	3
Nor-BNI (10 nM)	25.4 ± 0.8	100	0.9	3

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

In morphine-treated monkeys, NIH 10723 failed to substitute for naltrexone; in morphine-abstinent (withdrawn) monkeys, NIH 10723 reversed naltrexone-lever responding at doses of 0.01-0.0178 mg/kg.

ANALGESIA STUDIES IN RHESUS MONKEYS

NIH 10723 produced dose-related increases in the latency for monkeys to remove their tails from warm water and a full analgesic response (*i.e.,* 20-sec latency at 50° and 55°

NIH 10723 (±)-*cis*N-[1-(2-Methoxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride

continued..

C at doses of 0.056 mg/kg and 0.1 mg/kg, respectively.

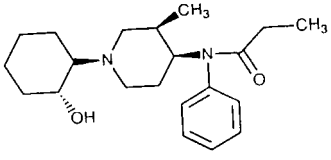
RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

NIH 10723 decreased in a dose-related manner both frequency of respiratory (f) and tidal volume (V_T) in air and in CO_2. At the largest dose studied, 0.1 mg/kg, f and V_T were decreased to 56.5% and 72.3%, respectively, of control in 5% CO_2.

SUMMARY

NIH 10723 was more potent in the binding assay than morphine in displacing etorphine. Its actions in the *vas deferens* were complex and perhaps nonopioid. It had a number of opioid effects in common with morphine, but NIH 10723 was more potent.

NIH 10724 (+)-*cis*-N-[1-(trans-2-Hydroxycyclohexyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 1219 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift	n
Control	1.83 ± 0.42	78.6 ± 7.9		9
Naltrexone (100 nM)		0.0		3
ICI-174864 (100 nM)	5.81 ± 3.79	72.5 ± 15.4	3.2	3
Nor-BNI (10 nM)	18.15 ± 14.70	39.8 ± 10.0	9.9	3

NIH 10724 (±)-*cis*N-[1-(*trans*-2-Hydroxycyclohexyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride

continued...

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

In a single subject, NIH 10724 failed to substitute for ethylketocyclazocine up to a dose that eliminated responding, 0.32 mg/kg. Up to a dose of 1.0 mg/kg, NIH 10724 also failed to substitute for naltrexone in morphine-treated monkeys; however, at a dose of 0.32 mg/kg, this compound reversed completely naltrexone-lever responding in morphine-abstinent monkeys. NIH 10724 also substituted completely for alfentanil in a single subject at doses of 1.78 mg/kg and larger.

ANALGESIA STUDIES IN RHESUS MONKEYS

Although at the 50° C stimulus intensity this compound produced a full analgesic response at a dose of 0.178 mg/kg, up to a dose of 1.0 mg/kg, analgesic effect at the 55° C stimulus was less than 26% of the maximum possible effect.

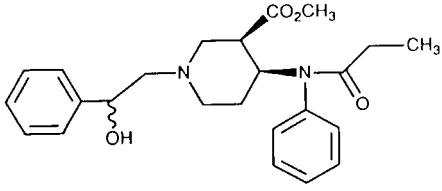
RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

In the single subject in which the respiratory effects of NIH 10724 were assessed, there was a decrease in both f and V_T in air and in CO_2 with overall maximum decreases in respiration to 55-74% of control.

SUMMARY

NIH 10724 had low potency in the binding and *vas deferens* assays. It was a partial agonist on the mouse *vas deferens* preparation. Concentrations above 100 μM increased the magnitude of the twitch markedly. Naltrexone completely blocked all responses to NIH 10724, and ICI-174864, a δ opioid receptor antagonist, and norbinaltorphimine, a κ opioid receptor antagonist, partially blocked the effects of NIH 10724. In a concentration of 100 nM, NIH 10724 had no effect upon responses of the *vas deferens* preparation to DSLET, a δ opioid receptor agonist, U-50,488, a κ receptor agonist, or sufentanil, a μ receptor agonist. Thus, NIH 10724 appears to be a partial, nonselective opioid receptor agonist of low potency in the *vas deferens.* In the *in vivo* assays, NIH 10724 had some morphine-like, agonist effects in that it reversed the discriminative stimulus effects of naltrexone and had analgesic and respiratory depressant effects. The characterization will be incomplete without antagonist studies in combination with NIH 10724.

NIH 10725 (±)-*cis*-N-[3-Carbomethoxy-1-(2-hydroxy-2-phenylethyl)-4-piperidyl]-N-phenyl propanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 64 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10725 is one of a series of drugs that have very similar actions in that they cause a biphasic inhibition of the twitch of the isolated, electrically stimulated mouse *vas deferens* preparation. If one assumes that the higher affinity inhibitory action of this drug is maximal at a concentration of 10 μM and that the lower affinity inhibitory action does not start until this concentration is achieved, it is possible to calculate EC_{50}'s for both phases of the inhibitory action of NIH 10725 in control experiments and in the presence of various receptor-selective antagonists.

HIGHER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	448.9 ± 140.6	48.6 ± 6.8		9
Naltrexone (100 nM)	847.0 ± 364.4	39.1 ± 5.7	1.9	3
ICI-174864 (100 nM)	568.5 ± 152.0	22.5 ± 9.2	1.3	3
Nor-BNI (10 nM)	277.1 ± 77.7	22.0 ± 4.7	0.6	3

NIH 10725 (±)-*cis*-N-[3-Carbomethoxy-1-(2-hydroxy-2-phenylethyl)-4-piperidyll-N-phenylpropanamide hydrochloride

continued...

LOWER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	58.5 ± 11.0	100		9
Naltrexone (100 nM)	49.6 ± 5.3	100	0.8	3
ICI-174864 (100 nM)	100.5 ± 10.2	75.2 ± 24.8	1.7	3
Nor-BNI (10 nM)	107.2 ± 19.7	100	1.8	3

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

NIH 10725 failed to substitute for naltrexone in a morphine-treated monkey; however, in morphine-abstinent monkeys, this compound reversed completely naltrexone-lever responding at a dose of 0.0032-0.01 mg/kg. Moreover, NIH 10725 substituted completely for the alfentanil discriminative stimulus at a dose of 0.0032 mg/kg.

ANALGESIA STUDIES IN RHESUS MONKEYS

In the analgesia assay, NIH 10725 produced a maximum analgesic response at 50° and 55° C at doses of 0.056 mg/kg and 0.1 mg/kg, respectively.

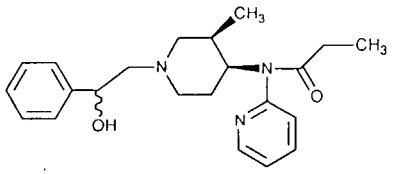
RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

Up to a dose of 0.32 mg/kg, NIH 10725 decreased in a dose-related manner both f and V_T in air and in CO_2; a dose of 0.1 mg/kg produced apnea, an effect readily reversed by administration of 1.0 mg/kg of naltrexone.

SUMMARY

NIH 10725 had complex actions in the mouse *vas deferens.* It was a potent, morphine-like agonist in the behavioral preparations.

NIH 10726 (+)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-(2-pyridinyl) propanamide dihydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 24.7 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	91.34 ± 30.24	99.6 ± 0.4		9
Naltrexone (100 nM)	910.0 ± 507.8	99.3 ± 0.7	10.0	3
ICI-174864 (100 nM)	454.60 ± 84.36	100.0	5.0	3
Nor-BNI (10 nM)	72.23 ± 53.96	100.0	0.8	3

DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS

In the two subjects studied, NIH 10726 reversed naltrexone-lever responding in morphine-abstinent monkeys at doses between 0.000178 and 0.001 mg/kg.

RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The respiratory effects of this compound were studied in a single subject; doses of 0.0001-0.01 mg/kg produced dose-related decreases in respiratory function. At the largest dose studied, 0.01 mg/kg, NIH 10726 decreased f to 46-82% of control in air and CO_2 and decreased V_T to 32% of control under both conditions.

SUMMARY

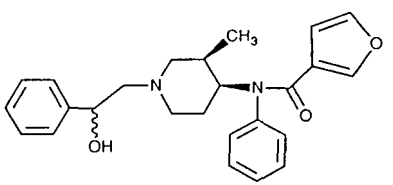
NIH 10726 was active in both *in vitro* assays. In the mouse *vas deferens* it was an unusual mixed agonist-antagonist. It was fairly potent in inhibiting the twitch of this preparation, and its inhibitory actions were antagonized by naltrexone and ICI-174864, a δ-selective opioid receptor antagonist, which suggests that this drug has some affinity for δ opioid receptors. It also acted as a selective antagonist. Its pA_2 value for antagonism of sufentanil, a μ opioid receptor agonist, was 8.20 ± 0.09 (λ = 1.18, n=8). Because of its agonist properties, the highest concentration that could be evaluated as an antagonist

NIH 10726 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-(2-pyrridinyl) propanamide dihydrochloride

continued...

was 100 nM. This concentration of NIH 10726 had no effect upon responses to either DSLET, a b-selective opioid receptor agonist, or U-50,488, a κ-selective opioid receptor agonist. Thus, NIH 10726 appeared to be a selective, fairly potent μ receptor antagonist and a fairly potent, selective δ receptor agonist. NIH 10726 was partially characterized in the *in vivo* assays. It appeared to have potent p-agonist effects (*i.e.,* reversal of naltrexone discriminative effects and respiratory depression).

NIH 10727 (+)- *cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-3-furanamide dihydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 4.8 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10727 is one of a series of drugs that have very similar actions in that they cause a biphasic inhibition of the twitch of the isolated, electrically stimulated mouse *vas deferens* preparation. If one assumes that the higher affinity inhibitory action of this drug is maximal at a concentration of 10 μM and that the lower affinity inhibitory action does not start until this concentration is achieved, it is possible to calculate EC_{50}'s for both phases of the inhibitory action of NIH 10727 in control experiments and in the presence of various receptor-selective antagonists.

HIGHER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	200.4 ± 66.6	47.0 ± 8.3		9
Naltrexone (100 nM)	325.9 ± 177.7	55.6 ± 12.9	1.6	3
ICI-174864 (100 nM)	349.6 ± 32.8	22.1 ± 5.2	1.7	3
Nor-BNI (10 nM)	518.9 ± 266.7	14.0 ± 2.9	2.6	3

NIH 10727 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-3-furanamide dihydrochloride

continued...

LOWER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	19.1 ± 1.2	98.7 ± 1.3		9
Naltrexone (100 nM)	7.5 ± 2.8	100	0.4	3
ICI-174864 (100 nM)	17.5 ± 2.1	100	0.9	3
Nor-BNI (10 nM)	33.1 ± 6.8	100	1.7	3

DRUG DISCRIMMATION STUDIES IN RHESUS MONKEYS

NIH 10727 reversed naltrexone-lever responding in morphine-abstinent monkeys at doses between 0.00032 and 0.001 mg/kg.

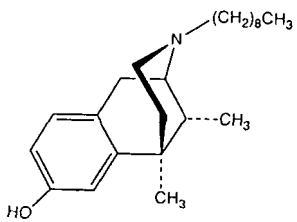
RESPIRATORY FUNCTION STUDIES IN RHESUS MONKEYS

The respiratory effects of this compound were studied in a single subject; doses of 0.0001-0.0032 mg/kg produced dose-related decreases in respiratory function; maximum decreases obtained with a dose of 0.0032 mg/kg were 83-89% of control. Administration of a larger dose of NIH 10727, 0.01 mg/kg, produced apnea which was readily reversed by administration of 1.0 mg/kg naltrexone.

SUMMARY

NIH 10727 had high potencies in each of the *in vitro* assays; its actions in the *vas deferens* were complex. NIH 10727 was partially characterized in behavioral studies, appearing to be a potent μ agonist.

NIH 10729 (-)-5,9α-Dimethyl-2'-hydroxy-2- *n*-nonyl-6,7-benzomorhan hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 1953 nM in the presence of 150 mM NaCl.

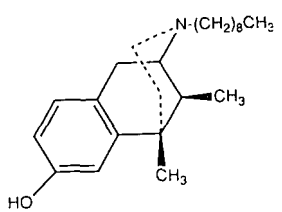
MOUSE *VAS DEFERENS* PREPARATION

NIH 10729 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 3 μM had no appreciable effect on this preparation. At a concentration of 10 μM, NIH 10729 almost completely suppressed the twitch. This response was not altered in the presence of naltrexone, 100 nM. When tested as an antagonist at a concentration of 3 μM, NIH 10729 did not block the inhibitory actions of sufentanil, a μ-opioid receptor agonist, DSLET, a δ-opioid receptor agonist, or U50,488, a κ-opioid receptor agonist.

SUMMARY

NIH 10729 displaced etorphine at high concentrations and it was devoid of opioid activity in the *vas deferens* preparation.

NIH 10730 (+)-5,9α-Dimethyl-2'-hydroxy-2- *n*-nonyl-6,7-benzomorphan hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 5390 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10730 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 1 μM had no appreciable effect on this preparation. At a concentration of 3 μM, NIH 10730 markedly increased the magnitude of the twitch. At a concentration of 10 μM, NIH 10730 initially increased the magnitude of the twitch, then subsequently inhibited the twitch completely. This response was not altered in the presence of naltrexone, 100 nM. When tested as an antagonist NIH 10730 (3 μM) did not block the inhibitory actions of

NIH 10730 (+)-5,9α·-Dimethyl-2'-hydroxy-2-n-nonyl-6,7-benzomorhan hydrochloride

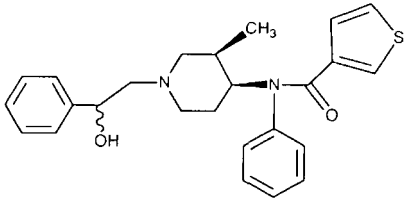
continued...

sufentanil, a μ-opioid agonist. NIH 10730 caused a 2.0-fold shift to the right in the concentration-effect curve for DSLET, a δ opioid receptor agonist, and a 3.1-fold shift to the right in the concentration-effect curve for U50,488, a κ opioid receptor agonist.

SUMMARY

NIH 10730 displaced etorphine only at high concentrations. It appeared to be devoid of opioid agonist activity, but appeared to be an antagonist of very low potency on the mouse *vas deferens* preparation.

NIH 10731 (±)- *cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-3-thiophenecarboxamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 7.3 nM in the presence of 150 mM NaCl

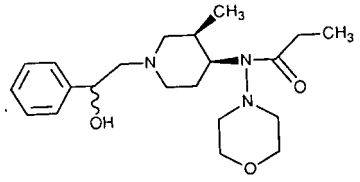
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	259.2 ± 82.7	67.5 ± 3.3		9
Naltrexone (100 nM)	117.3 ± 48.9	98.4 ± 1.6	0.5	3
ICI-174864 (100 nM)	460.0 ± 76.4	36.9 ± 1.3	1.8	3
Nor-BNI (10 nM)	318.2 ± 125.1	51.4 ± 9.9	1.2	3

SUMMARY

NIH 10731 was unusual in that it had a reasonable potency in the binding assay, but was not active as an opioid in the mouse *vas deferens* preparation.

NIH 10732 (±)-*cis* -N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-(4-morpholinyl)propanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 3069 nM in the presence of 150 mM NaCl.

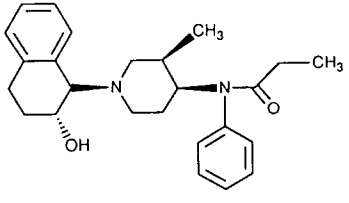
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	15.67 ± 7.78	100.0		9
Naltrexone (100 nM)	29.50 ± 4.94	100.0	1.9	3
ICI- 174864 (100 nM)	27.71 ± 13.22	100.0	1.8	3
Nor-BNI (10 nM)	1.42 ± 0.43	100.0	0.1	3

SUMMARY

NIH 10732 was of low potency in both assays. In the mouse *vas deferens* preparation, it was not clear that the actions of this drug were mediated by opioid receptors. Naltrexone and ICI-174864, a δ receptor antagonist, caused very small shifts to the right in the NIH 10732 concentration-effect curves. NIH 10732, in a concentration of 10 μM, did not antagonist the actions of sufentanil, a μ receptor agonist, DSLET, a δ receptor agonist, or U-50,488, a κ receptor agonist.

NIH 10733 (±)-*cis*-N-[1-(1-(truns-2-Hydroxy-1,2,3,4-tetrahydro)napthyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 420 nM in the presence of 150 mM NaCl.

NIH 10733 (±)- *cis* -N-[1-(1-(*trans*-2-Hydroxy-1,2,3,4-tetrahydro)napthyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride

continued...

MOUSE *VAS DEFERENS* PREPARATION

HIGHER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	0.90 ± 0.30	52.1 ± 6.0		9
Naltrexone (100 nM)	0.98 ± 0.47	27.1 ± 5.6	1.1	3
ICI-174,864 (100 nM)	0.77 ± 0.26	40.8 ± 5.6	0.9	3
Nor-BNI (10 nM)	1.53 ± 0.69	23.9 ± 4.1	1.7	3

LOWER AFFINITY INHIBITORY ACTIONS

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.98 ± 0.81	95.8 ± 2.1		9
Naltrexone (10 nM)	22.6 ± 1.8	100	11.4	3
ICI-174,864 (100 nM)	3.04 ± 1.34	100	1.5	3
Nor-BNI (10 nM)	6.24 ± 2.42	100	3.2	3

SUMMARY

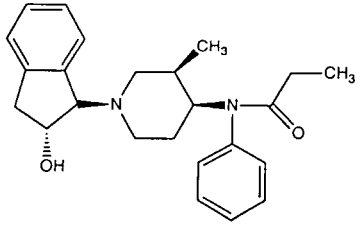
NIH 10733 was moderately potent in the binding assay in displacing etorphine. It was an agonist on the mouse *vas deferens* preparation. It produced an inhibitory action associated with a biphasic concentration-effect curve. It was fairly potent, with concentrations as low as 0.03 nM causing an inhibition of the twitch. Naltrexone and norbinaltorphimine reduced the magnitude of the responses produced by the lower concentrations of the drug, but did not shift this limb of the concentration-effect curve. Both naltrexone and

NIH 10733 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenyl-propanamide hydrochloride

continued...

norbinaltorphimine caused shifts to the right in the portion of the concentration effect curve associated with higher concentrations of NIH 10733. ICI-174864, a δ opioid receptor antagonist, did not significantly alter either portion of this complex concentration-effect relationship.

NIH 10734 (±)-*cis*-N-[1-(1-(truns-2-Hydroxy)indanyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 7882 nM in the presence of 150 mM NaCl.

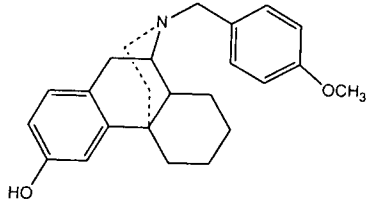
MOUSE *VAS DEFERENS* PREPARATION

NIH 10734 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 100 μM. Concentrations up to 300 nM had no appreciable effect on this preparation. Concentrations of 1 μM and greater caused marked increases in the magnitude of the twitch. When tested as an antagonist at a concentration of 100 μM, NIH 10734 did not block the inhibitory actions of sufentanil, a μ opioid receptor selective agonist, DSLET, a δ opioid receptor agonist, or U50,488, a κ opioid receptor agonist. Thus, NIH 10734 is devoid of significant opioid agonist or antagonist activity on the mouse *vas deferens* preparation.

SUMMARY

NIH 10734 had no significant opioid activity activity in either preparation.

NIH 10736 (+)-3-Hydroxy-N-(4-methoxybenzyl)morphinan hydrobromide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6000 nM (41% inhibition at 6 (μM) in the presence of 150 mM NaCI.

NM 10736 (+)-3-Hydroxy-N-(4-methoxybenzyl)morphinan hydrobromide

continued...

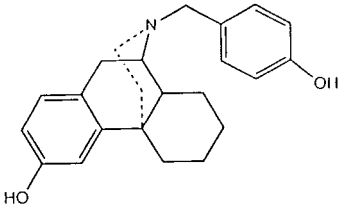
MOUSE *VAS DEFERENS* PREPARATION

NIH 10736 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 1 μM had no appreciable effect on this preparation. At concentrations of 3 μM and 10 μM, NIH 10736 markedly increased the magnitude of the twitch. This response was not altered in the presence of 100 nM naltrexone. When tested as an antagonist NIH 10736 (10 μM) did not block the inhibitory actions of U50,488, a κ opioid receptor agonist. NIH 10736 caused a 9.8-fold shift to the right in the concentration effect curve for DSLET, a δ opioid receptor agonist, and a 5.9-fold shift to the right in the concentration-effect curve for sufentanil, a μ opioid receptor agonist. Because of the low potency of this drug, pA_2 values were not determined.

SUMMARY

NIH 10736 was not potent in either assay. It may be a very low potency antagonist in the *vas deferens* of some opioid effects.

NIH 10737 (+)-3-Hydroxy-N-(4-hydroxybenzyl)morphinan hydrobromide



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of > 6,000 nM (10% at 6 µM) in the presence of 150 mM NaCI.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10737 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 1 μM had no appreciable effect on this preparation. At concentrations of 3 μM and 10 μM, NIH 10737 markedly increased the magnitude of the twitch. This response was not altered in the presence of 100 nM naltrexone. When tested as an antagonist NIH 10737 (10 μM) did not block the inhibitory actions of sufentanil, a μ opioid receptor selective agonist or DSLET, a δ opioid receptor agonist. NIH 10737 caused an 8.3-fold shift to the right in the concentration-effect curve for U50,488, a κ opioid receptor agonist. Because of the low potency of this drug, pA_2 values were not determined.

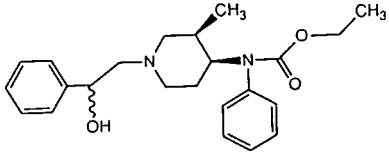
NIH 10737 (+)-3-Hydroxy-N-(4hydroxybenzyl)morphinan hydrobromide

continued...

SUMMARY

NlH 10737 was not potent in either assay; it may be an antagonist of some some opioid effects at high concentrations in the *vas deferens.*

NIH 10746 (±)- *cis* -N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylcarbamic acid ethyl ester hydrochloride



DISPLACEMENT OF SPECIFIC [^{3}H]ETORPHINE BINDING

EC_{50} of 20.4 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.89 ± 0.26	100		9
Naltrexone (100 nM)	157.4 ± 37.5	100	83.5	3
ICI-174864 (100 nM)	2.73 ± 1.04	100	1.4	3
Nor-BNI (10 nM)	3.39 ± 0.74	100	1.8	3

SUMMARY

NIH 10746 was potent in both preparations; slightly more so in the *vas deferens* preparation where it was selective for μ opioid receptors.

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ACKNOWLEDCEMENTS:

Grant DA 00254 - National Institute on Drug Abuse and College on Problems of Drug Dependence

AFFILIATION:

The Drug Abuse Basic Research Program, Departments of Pharmacology, Psychology and Biological Chemistry. University of Michigan, Ann Arbor, MI

PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUG (1992)

W. L. WOOLVERTON; M. A. NADER; G. WINGER; J. H. WOODS; G. A. PATRICK AND L. S. HARRIS

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately ten years. The groups include laboratories at the University of Chicago (Nader, Woolverton), The University of Michigan (Winger, Woods), Virginia Commonwealth University (Patrick, Harris), and NIH (Jacobson). The group is part of the Drug Evaluation Committee, chaired by Ted Cicero, of the College on Problems of Drug Dependence (CPDD) and is supported by both CPDD and NIDA. One of the purposes of the group is to evaluate new compounds generally classified as either stimulants or depressants for their abuse liability and dependence potential. Compounds are received, coded and distributed by Dr. Jacobson for blind testing in the various laboratories. They are evaluated for discriminative stimulus effects (UC), reinforcing effects (UM), and capacity to produce physiological dependence (VCU). This report includes the results of the evaluation of the following compounds: CPDD-0021,-0034 (zolpidem),-0036 (dizocilpine; MK-801), and-0037 (BRL-46470A).

METHODS

Reinforcing Effects in Rhesus Monkeys

The reinforcing effects of test compounds were evaluated in a substitution self-administration procedure with methohexital serving as the baseline drug. Rhesus monkeys were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. The catheter passed subcutaneously from the site of the incision to the mid-scapular region, where it exited the monkey and continued, through a hollow restraining arm, to the outside rear of the cage.

The restraint and catheter protection device has been described in detail by Deneau et al., (1969). Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. Each monkey wore a tubular stainless steel harness that protected the exit site of the catheter and allowed relatively unrestricted movements within the cage. A Teflon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection for animals who tended to locate and pull their catheters. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage

where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the case. Across the top of the stimulus panel, 2.5 cm apart, were three circles, 2.5 cm in diameter, covered with translucent plastic and capable of being illuminated from behind by 5 W colored bulbs. The two side lights could be illuminated red and the center light could be illuminated green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by 10-15 gms of force. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairfield, VT) software and located in an adjoining room.

Monkeys were adapted to restraining arms for a week or more, then an intravenous catheter was implanted and the animals were given the opportunity to respond to receive drug. Evaluation of drugs with depressant properties was carried out in monkeys trained to self-administer sodium methohexital. For these monkeys, at the beginning of each session, a red light was illuminated over one of two levers in each monkey's cage and 10 responses (fixed-ratio 10; FR 10) on that lever resulted in a 5-second infusion of 0.1 mg/kg/sodium methohexital, followed by a 10-second time-out during which all stimulus lights were extinguished and responding had no programmed consequence. During an infusion, the red lever light was extinguished and the center green light was illuminated for the duration of the infusion. Experimental sessions were limited to 210 min or until a maximum of 200 injections were delivered. No monkey ever received 200 injection of methohexital. Two sessions were scheduled each day, separated by a least four hours. On approximately half the baseline sessions, the monkeys were exposed to response-contingent saline. When there was a clear and consistent differential response between saline and methohexital, a dose of the test compound was substituted for one session. All conditions were similar to training sessions except the maximum number of injections of the test compound was limited to 150/session. Each dose was tested twice in each monkey.

Monkeys scheduled to evaluate the potential reinforcing effects of CPDD-0036, an NMDA antagonist, had been trained to self-administer ketamine under a schedule much like that described by Winger et al. (1989). In this paradigm, the onset of the red stimulus light signalled the availability of one of four doses of intravenously delivered ketamine. Drug delivery was contingent on 30 responses on the response lever (FR30) and was followed by a 45 sec time out period (TO45). Up to 20 infusions of a given dose were permitted, or 25 min of access to each dose, whichever came first. When one of these limits had been reached, a 210 min time-out period occurred during which all stimulus lights were extinguished and responses had no programmed consequences. When the red stimulus light was again illuminated, another dose of ketamine was delivered following completion of the FR30 TO45 response requirement. Over a 130 min session, four doses of ketamine was made available. These doses were selected to produce a monotonically increasing function between rate of response and dose per injection of ketamine.

CPDD-0021 and -0037 were dissolved in distilled water, CPDD-33 was dissolved in a vehicle of propylene glycol 15%, ethanol 10%, Tween 80 20% in distilled water, CPDD-0036 was dissolved in propylene glycol 40%, ethanol 10% in distilled water.

Discriminative Stimulus Effects in Rhesus Monkeys

The subjects were two female and five male rhesus monkeys that weighed between 6.5 and 12.1 kg. All monkeys had extensive experience with the present drug discrimination procedure. They were housed individually in stainless steel cages in which water was continuously available. They were fed 100 to 150 g of monkey chow after each session and were given a chewable vitamin tablet 3 days/week. During experimental sessions the monkeys were seated in a Plas-Lab restraining chair and placed in a wooden cubicle (175 cm high x 85 cm wide x 65 cm deep) containing two response lovers mounted 100 cm above the floor. A 40 w white house light was mounted on the ceiling. The monkey's feet were placed into shoes, the bottoms of which were fitted with brass plates which could deliver electric shocks. Programming and recording of experimental events were accomplished by an Aim 65 microprocessor located in an adjacent room.

The monkeys had been trained previously to discriminate d-amphetamine (AMPH: 7737, 7739, 8515) or pentobarbital (PB: 8106, 8236, 7976, 8814) from saline in a two-lever, discrete-trial shock avoidance procedure similar to the one described by Holtzman (1982). One hour after an intragastric infusion (via naso-gastric tube) of the training drug (0.56- 1.0 mg/kg AMPH or 10 mg/kg PB) or saline. the houselights and lever lights were illuminated (trial) and responding on one lever (designated the correct lever) avoided electric shock and extinguished the lights. Responding on the incorrect lever started a 2 second change-over delay during which correct lever responding had no consequence. If a correct lever response was not made within 5 seconds of onset of the lights, an electric shock (250 msec duration, 7 mA intensity) was delivered; if a correct response was made within 2 sec after the first shock (escape), the trial was terminated, otherwise, a second shock automatically ended a trial. Two consecutive trials with escape failures automatically ended the session. Trials were separated by a 30-s TO. The session lasted for 30 trials or 20 min, whichever came fist. The correct lever was determined by the infusion that was administered before the session. For three monkeys, the right lever was correct after drug infusion and the left lever was correct after saline infusions. This condition was reversed for the other four monkeys.

Monkeys were considered to be stable in the discrimination when more than 90% of the trials were completed on the correct lever on at least seven out of eight consecutive sessions. At this point, testing was begun with the training drugs and the test drugs. Two S-day sequences alternated drug, vehicle and test sessions so that the fist test session was preceded by two training sessions, one with saline and one with drug pretreatment and the second test session of the sequence was preceded by either vehicle or drug pretreatment. In the event that the criterion for stimulus control was not met during the training sessions, the training sequence was continued. During test sessions, both levers were operational, i.e., shock could be avoided by responding on either lever.

Saline, at least three doses of the training drug, and three doses of each test drug, in addition to the test drug vehicle, were evaluated under the test conditions for each monkey. The percentage of trials that were completed on the drug lever is presented for each test session. In addition, the average time between the onset of a trial and a lever press (average latency) was calculated for each test session. Because these test compounds were evaluated blind without any dose-response information, initial test doses were done in an ascending

order from 0.1 mg/kg to doses that either significantly increased latency to respond or resulted in at least 90% drug-appropriate responding. Out of concern for the monkeys, doses greater than 30 mg/kg were not tested. If a dose substituted for a training drug, that dose and doses higher and lower were tested again, in a random order.

PB and the test drugs were prepared immediately before testing, while a stock solution of AMPH was prepared each week. PB (40 mg/ml) and AMPH (5 mg/ml) were dissolved in saline. CPDD-0021, -0034 and -0036 were dissolved in water. CPDD-0037 was dissoved in saline.

Physical Dependence (Substitution) in Rats and Potency Estimation in Mice

Male Sprague-Dawley rats (Dominion Labs, Dublin, VA) initially weighing 200-225 g were individually housed in stainless steel cages with food and water available ad lib. They were used in the infusion and substitution experiments. CF-1 mice (Dominion Labs, Dublin VA) weighing 25-30 g were housed in plastic cages with food and water *ad lib*. The mice were used in initial studies for potency estimation. All animals were acclimated to the animal facility for several days prior to use in any study.

Rats were surgically prepared with an intraperitoneal cannula (PE90) while under methoxyflurane anesthesia. All rats were allowed several days to recover from surgery prior to being placed into an infusion harness. Acclimation to the infusion system occurred for three days during which the rats were continuously infused with 0.9% saline. This was followed by the continuous infusion of either saline (control) or pentobarbital sodium for 12 consecutive days using an escalating dosing schedule (Yutrzenka et al. 1985). At the end of the infusion period most rats were receiving pentobarbital at a dose of 900-1000 mg/kg/24 hours. Body weight was monitored daily during the drug infusion period.

Following the final day of pentobarbital infusion, a 24-hour substitution period commenced during which pentobarbital-dependent rats were infused with either saline, vehicle, or test drug. This was followed by a 24-hour drug withdrawal period during which all rats received saline.

Every two hours for the first 12 hours and again at 24 hours of each period, rats were assigned a withdrawal score based on the degree of expression of several behavioral responses and signs. In addition, body weight was determined at 0, 8, and 24 hours of each period. Scores were assigned by two observers who were blind to the drug treatment. Investigators were blind to the identity of the compounds until all data were collected and analyzed (Yutrzenka et al. 1989).

Preliminary studies to ascertain potency of the test compounds, relative to pentobarbital were conducted in mice. Drug-treated mice were assayed using the inverted screen test (Coughenour et al. 1977) and alteration of spontaneous locomotor activity. At least three doses of each drug, with at least six mice per dose, were used to determine dose-response curves. Vehicle-treated mice served as controls and were assayed concurrently with drug-treated mice.

The inverted screen test was conducted at 20, 30, 60, and 120 minutes following drug administration. The ED_{50} dose, which was determined to be the dose at which one-half of the treated mice failed to right themselves within the 60 second time period, was computed for each time period. Spontaneous locomotor activity was determined using a single beam photocell which bisected a plastic

cage containing two mice. Movement of the mice disrupted the beam and a "count" of activity was recorded. Following drug administration, activity was recorded at 5-15 min, 35-50 min, 65-95 min, and 125-185 min. The ED_{50} dose was determined to be that dose which reduced spontaneous locomotor activity to one-half that recorded for concurrently tested vehicle-treated control mice. Potency ratios of each test drug relative to pentobarbital were determined at time of peak activity and when, in addition, the vehicle effect was no longer evident.

Pentobarbital sodium was dissolved in distilled water made isotonic with sodium chloride. CPDD-0021 and -0037 were dissolved in water. CPDD-0034 was dissolved in propylene glycol (16%), ethanol (4%). CPDD-0036 was dissolved in propylene glycol (40%), ethanol (10%) and water.

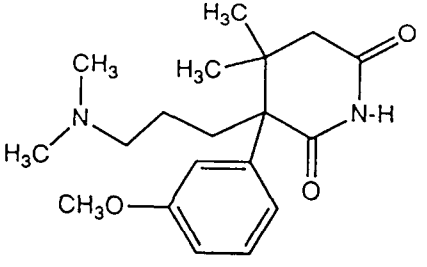
Withdrawal scores for each treatment group were compared to the control by use of the Mann-Whitney U-test. Alterations in body weight was tested for significance by use of t-tests. ED_{50} values and 95% confidence intervals in the inverted screen test and locomotor activity measure were also determined (Litchfield and Wilcoxon, 1949).

RESULTS

CPDD-0021

3-(3-Dimethylaminopropyl)-3-3(3-methoxyphenyl)-4,4-dimethyl-2,6-piperidinedione hydrochloride

MOLECULAR STRUCTURE



Reinforcing Effects in Rhesus Monkeys

Two doses of CPDD-002 1 (1.0 and 3.2 mg/kg/inj) were evaluated in three monkeys while the highest dose (10 mg/kg/inj) was tested in only two monkeys. CPDD-0021 did not maintain respondmg above levels seen with saline in any monkey at any of the doses tested. At the highest dose of 10 mg/kg/inj, monkey 833 was observed soon after she had self-administered eight injections. She was lying on the bottom of her cage, her eyes were wide open, and she did not appear sedated. She sat up and appeared normal within 10 minutes of this observation; she took no further injections in this session. The next time she was exposed to the dose, she took six injections and was found dead in her cage a few minutes after the sixth injection. Monkey 583C self-administered 11 and 12 infusions at this dose of CPDD-0021 (10 mg/kg/inj) on the two occasions it

was made available to her. Her behavior was not monitored, and we do not know if the drug produced any behavioral change in this monkey.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD-0021 (3.0-30 mg/kg) did not occasion any pentobarbital- or amphetamine-appropriate responding in any monkey. There were no systematic effects on response latency.

Physical Dependence (Substitution) in Rats and Potency Estimation in Mice

(1) Potency estimation

Table 1. Potency of CPDD-0021

	Time after Treatment (min)			
	Inverted Screen Test		Locomotor Activity	
	20	30	5-15	35-90
ED-50 (mg/kg/i.p.)	54.2 (26.4-112)	130 (112-152)	118 (39-354)	139
Relative Potency*	0.33	0.19	0.21	

*Relative to pentobarbital at the same time.

CPDD-0021 suppressed spontaneous locomotor activity and impaired performance on the inverted screen task. It was approximately one-fifth to one-third as potent as pentobarbital. Its effects were largely dissipated within 60 minutes at non-lethal doses (Table 1). Notably, a dose of 200 mg/kg was lethal to one-third of mice treated, while 300 mg/kg quickly killed all mice given that dose.

Due to the inherent toxicity of CPDD-0021 and the lack of certainty about whether or not the pentobarbital infusion would convey tolerance to the toxicity, the doses of the compound that were substituted for pentobarbital were less than equi-sedative doses. In previous studies with depressant agents when a similar situation occurred, such doses have effectively substituted for pentobarbital in preventing signs of abstinence.

When CPDD-0021 was substituted for pentobarbital, there were no alteration in the course of overt barbiturate withdrawal signs. However, this observation is not definitive in this case, because the signs in saline-substituted rats were unusually mild. That is, the abstinence syndrome based on overt signs was so mild that significant suppression of it would be difficult to demonstrate. Reasons for this result are not apparent.

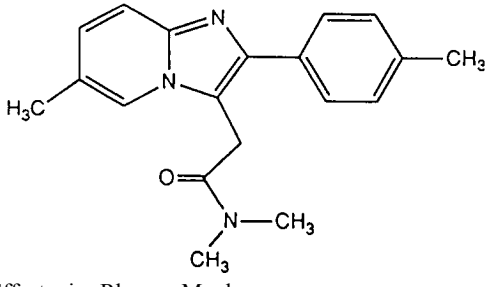
When CPDD-0021 was discontinued and saline was substituted, there was no increased incidence of signs of withdrawal. This, again, suggests that the compound did not substtute for pentobarbital. Rats that were withdrawn from pentobarbital after 13 days of infusion did exhibit a pattern of elevated incidence of withdrawal signs, albeit the withdrawal was milder than is seen customarily.

Changes occurring during withdrawal in the more objective measure of body weight were both more typical and more conclusive. The loss of body weight in pentobarbital-abstinent (saline-substituted) rats, 6% loss at 24 hr into withdrawal, was still less than is typically observed (around 10%). However, that was a significantly greater loss of weight than occurred in rats which continued to receive pentobarbital. The loss of body weight in rats receiving CPDD-0021 in place of pentobarbital was not significantly different from saline-substituted rats. Therefore, CPDD-0021 did not substitute for pentobarbital to prevent weight loss associated with abstinence.

CPDD-0034 (zolpidem)

N,N,6-Trimethyl-2-(4-methylphenyl-imidazo[1,2-a]pyridine-3-acetamide tartrate [Zolpidem tartrate]

MOLECULAR STRUCTURE



Reinforcing Effects in Rhesus Monkeys

Four to five doses of CPDD-0034 were evaluated in three monkeys. Each of the three monkeys was tested at least twice at each dose. CPDD-0034 was a reinforcer in each of the three monkeys (Figure 1).

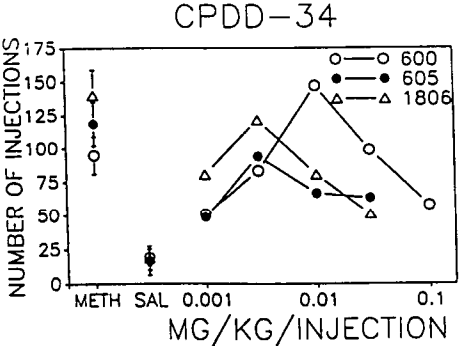


Figure 1. Self-administration of CPDD-0034 by rhesus monkeys. The points shown at METH are the average number of injections taken of 0.1 mg/kg/inj sodium methohexital on the sessions just preceding each substitution of CPDD-0034. These averages are shown for the individual monkeys as indicated by the legend. Similar data are shown for saline availability over the point indicated by SAL. Data shown for CPDD-0034 are averaged across at least two observations for each monkey.

Each of the monkeys self-administered more injections of CPDD-0034 than of saline, and one monkey (600) self-administered more injections of CPDD-0034 than of 0.1 mg/kg/inj methohexital. The other two monkeys self-administered nearly equal amounts of one dose of CPDD-0034 as of 0.1 mg/kg/inj methohexital. A dose of 0.003 mg/kg/inj of CPDD-34 maintained the most behavior in these latter two monkeys; whereas a dose of 0.01 mg/kg/inj CPDD-34 maintained the most behavior in monkey 600.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD-0034 completely substituted for pentobarbital in all four monkeys (Figure 2). There was considerable individual variability in sensitivity, with complete substitution in one monkey at 1.0 mg/kg and two other monkeys at 30 mg/kg. There were substantial increases in response latency at 30 mg/kg. In monkey 8814, CPDD-0034 substituted for pentobarbital on one occasion at 3.0 mg/kg but not in a second test. At doses of 3.0 mg/kg and higher, latency to respond was increased in this monkey and shocks were received.

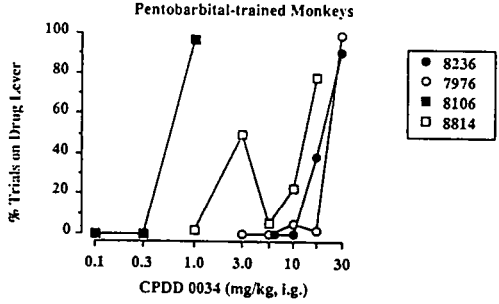


Figure 2. Discriminative stimulus effects of CPDD-0034 in rhesus monkeys trained to discriminate pentobarbital from saline. Each point represents the percentage of trials in a test session that were completed on the drug lever. Generally, each point is the mean of two determinations and this is always the case for points that are above 80%.

Physical Dependence (Substitution) in Rats and Potency Estimation in Mice

(1) Potency estimation

Table 2. Effects of CPDD-0034 on Spontaneous Locomotor Activity

	Time after Treatment			
Dose (mg/kg)	5-15	35-50	65-95	125-185
2.5	22[a]	86	82	100
5	8	94	91	80
20	8	72	83	100
30	2	61		76
40	1			

[a]Values expressed as percent of control activity of concomitantly tested, vehicle-treated mice.

CPDD-0034 produced a dose-related depression of activity at 5-15 min and a lesser depression at 35-50 min after treatment (Table 2). Performance on the inverted screen task was affected from 20 to 30 mm post-treatment, with an ED_{50} of 9.5 mg/kg (95% c.l., 4.3-21.1). Both effects had dissipated by 60 min after drug administration.

CPDD-0034 appeared to be slightly more potent than pentobarbital in these preliminary tests. Since its high degree of solubility in water permitted dosing equal to the final pentobarbital dose, that dose (500 mg/kg/day) and a lower dose (250 mg/kg/day) were substituted for pentobarbital in chronically infused rats (n=7 and 3, respectively).

The withdrawal syndrome in vehicle-substituted rats was atypically mild, making assessment of suppression of signs more difficult. When CPDD-0034 was substituted for pentobarbital, the higher dose caused a slight reduction in the overt signs of barbiturate withdrawal (Figure 3). The suppression by the higher dose of CPDD-0034 was significant only between 6 and 10 hours, and the lower dose produced no significant suppression of signs. When CPDD-0034 was discontinued and saline was substituted, there was no increase in signs suggestive of a withdrawal syndrome.

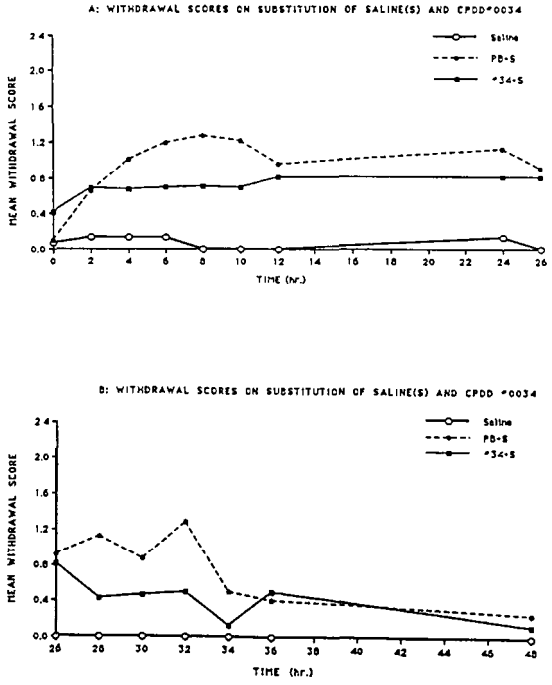


Figure 3. Mean withdrawal score of control rats and pentobarbital dependent rats during (A) zolpidem (CPDD-0034) or vehicle substitution (Day 13) and (B) saline substitution (Day 14). Zolpidem was infused in doses of 500 ma/kg - 24 hrs (n=7) and 250 mg/kg - 24 hrs (n = 3, data not shown).

The pattern of changes in body weight during substitution and withdrawal were of interest. The loss of weight associated with barbiturate withdrawal was almost completely prevented by both doses of CPDD-0034 (Figure 4). Interestingly, when CPDD-0034 was discontinued, there was very little loss of weight associated with that abstinence.

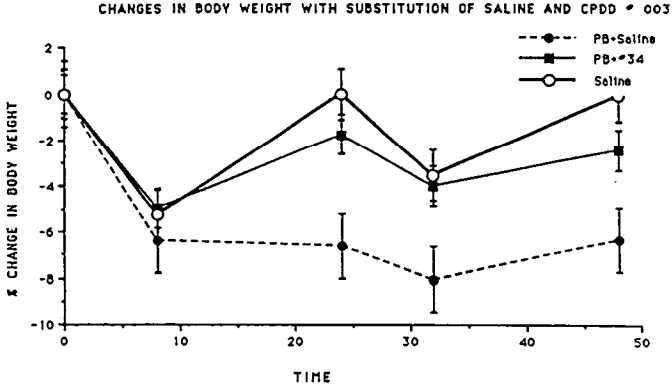
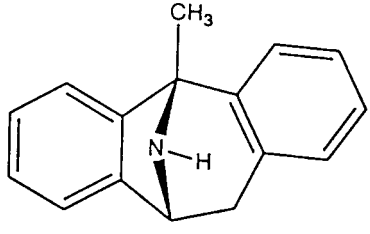


Figure 4. Change in body weight of control rats and pentobarbital-dependent rats during substitution of zolpidem or vehicle (0 to 24 hr. substitution phase) and during substitution of saline (24 to 48 hr. withdrawal phase). Pentobarbital-dependent rats infused with either vehicle or zolpidem (CPDD-0034) at 500 mg/kg - 24 hr (n=7).

CPDD-0036 (dizocilpine; MK-801)

(+)-10,11-Dihydro-5-methyl-5H-dibenzo[*a,d*]cyclohepten-5,10-imine hydrochloride (Dizocilpine)

MOLECULAR STRUCTURE



Reinforcing Effects in Rhesus Monkeys

Ketamine (0.01-0.3 mg/kg/inj) maintained dose-related increases in rates of lever pressing with a maximum (1.8 res/sec) at 0.1 mg.kg.inj. CPDD-0036 (0.00003-0.03 mg/kg/inj) failed to maintain responding above saline levels at any dose. That sufficiently high doses of CPDD-0036 were tested was evident from the fact that ketamine-maintained responding was disrupted (i.e., rates were increased) in sessions four hours after sessions of CPDD-0036 availability. This finding also suggests that CPDD-0036 has a long duration of action.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD-0036 (3.0-30 mg/kg) occasioned no pentobarbital-appropriate responding and a maximum of 3% d-amphetamine-appropriate responding in in one of three monkeys tested. There were no systematic effects on response latency.

Physical Dependence (Substitution) in Rats and Potency Estimation in Mice

Table 3. Effects of CPDD-0036 on Spontaneous Locomotor Activity

	Time interval after treatment (mm)			
	5-15	35-50	65-95	125-185
Dose (mg/kg)				
10	49*	228	70	77
20	88	45	27	175
40	138	117	102	163
66	106	80	193	732

*Values expressed as % of activity of vehicle-treated (control) mice.

The effects of CPDD-0036 on locomotor activity were quite erratic (Table 3). Both depression and stimulation of activity were observed but neither effect was strongly dose-related nor did they follow a regular time course. The most consistent effect observed was moderate depression at 20 mg/kg which persisted for approximately 95 mm. Performance in the inverted screen task was also mildly affected, but the effect was not dose-related. All four doses tested produced between 16% and 42% effect for the first 30 min after treatment, but the effect was virtually completely dissipated by 60 min.

Due to the lack of good potency estimates and solubility limitations of CPDD-0036, the daily doses selected for infusion were a dose approaching the limits of solubility in the propylene glycol-ethanol-water vehicle (200 mg/kg, obtained with mild heating and stirring) and one-half that dose (100 mg/kg).

Substitution of CPDD-0036 produced a slight suppression of withdrawal signs between 6 and 10 hr into the substitution phase, but the suppression was significant only at 10 hr (Figure 5). Following discontinuation of the substitution (withdrawal phase), there was one time point at which signs of withdrawal increased in the rats treated with the 100 mg/kg dose. Neither dose of CPDD-0036 significantly affected the changes in body weight associated with barbiturate abstinence, nor did significant loss of weight occur when infusion of the drug was discontinued.

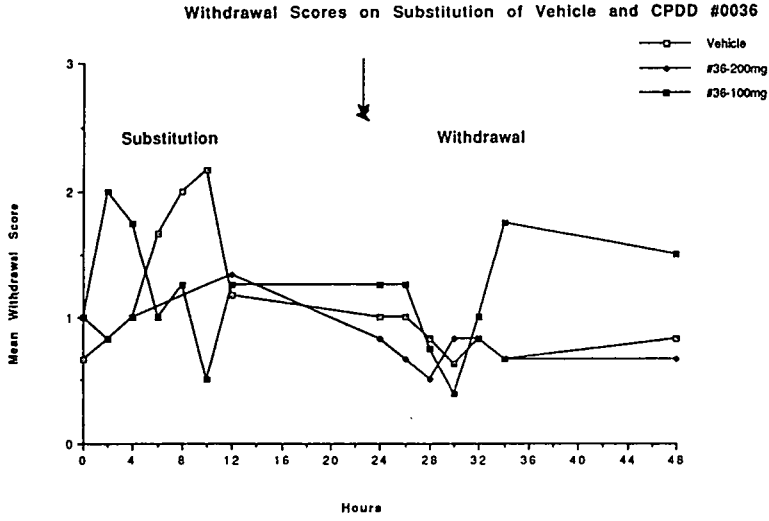
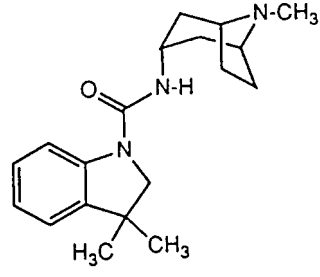


Figure 5. Mean withdrawal score of control rats and pentobarbital-dependent rats during substitution of dizocilpine (CPDD-0036) or vehicle (0 to 24 hr) and during substitution of saline (24 to 48 hr.-withdrawal phase). Dizocilpine was infused in doses of 100 and 200 mg/kg - 24 hr (n-3 to 5).

CPDD-0037 (BRL-46470A)

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole- 1 -carboxamide hydrochloride

MOLECULAR STRUCTURE



Reinforcing Effects in Rhesus Monkeys

Five doses of CPDD-0037 were evaluated in the three monkeys. Each of the three monkeys was tested at least twice at each dose. CPDD-0037 maintained rates of responding that were higher than those maintained by saline in only one monkey and at only one dose (0.03 mg/kg/inj). Even in this monkey at this dose, the number of injections taken was much below the number of methohexital injections taken.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD-0037 (3.0-30 mg/kg) occasioned no pentobarbital-appropriate responding and a maximum of 10% d-amphetamine-appropriate responding in one of three monkeys tested. There were no systematic effects on response latency.

Physical Dependence (Substitution) in Rats and Potency Estimation in Mice

Table 4. Effects of CPDD-0037 on Spontaneous Locomotor Activity

	Time interval after treatment (min)			
	5-15	35-50	65-95	125-185
Dose (mg/kg)				
10	206*	207	85	127
40	51	55	37	27
120	21	15	64	56
240**	6	1	1	11
ED_{50} (mg/kg) (95% CL)	50.4 (16.7-152)	49.6 (16.1-152)	39.6 (10.0-156)	

*Values expressed as % of activity of vehicle-treated (control) mice.

**One of 6 mice died at this dose.

The effects of CPDD-0037 on locomotor activity were consistently depressant-like at doses of 40 mg/kg and above (Table 4). The depressant effect was dose-related, although confidence limits were large. The effect persisted for more than 3 hours. Performance in the inverted screen task was also affected at doses of 40 to 240 mg/kg, and the effect was strongly dose-related at early testing times. At 30 min after treatment the ED-50 and 95% confidence limits in this test were 82.4 mg/kg (37.2-183). The effect was greatly diminished by 60 min, except for the highest dose which significantly affected performance for up to 4 hr.

CPDD-0037 was infused into pentobarbital-dependent rats at dosages of 500 and 1000 mg/kg/24 hr. The higher dose was slightly less potent than the highest dose of pentobarbital administered, but it was uncertain that higher doses could be safely administered, based on the lethality observed in the acute study and the lack of certainty concerning cross-tolerance between the compound and pentobarbital.

Substitution of CPDD-0037 produced a slight and sometimes significant suppression of withdrawal signs between 6 and 24 hr into the substitution phase, and the suppression was greater at the higher dose (Figure 6). Some rats were notably sedated on gross observation. Following discontinuation of the substitution (withdrawal phase), there was no evidence of increased signs of withdrawal. In contrast, withdrawal signs were decreased in the rats related with both doses. The lower dose of CPDD-0037 significantly reduced the loss in body weight associated with barbiturate abstinence, whereas the higher dose did not (Figure 7). Both doses were followed by a slight loss of body weight when infusion of the drug was discontinued.

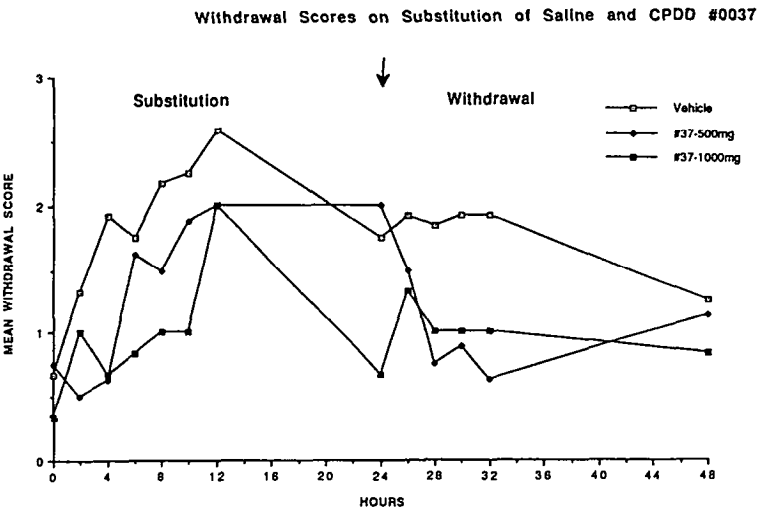


Figure 6. Mean withdrawal score of control rats and pentobarbital-dependent rats during substitution of (CPDD-0037) or vehicle (0 to 24 hr) and during substitution of saline (24 to 48 hr. withdrawal phase). CPDD-0037 was infused in doses of 500 and 1000 mg/kg - 24 hr (n= 3 to 5).

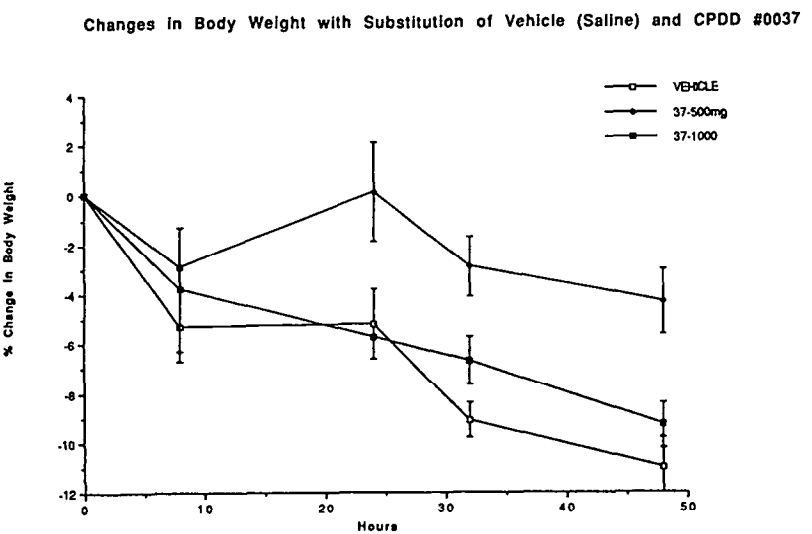


Figure 7. Change in body weight of pentobarbital-dependent rats during substitution of vehicle or CPDD-0037 (0 to 24 hr. substitution phase) and substitution of saline (24 to 48 hr, withdrawal phase). CPDD-0037 was infused in doses of 500 and 1000 mg/kg - 24 hr (n= 3 to 5).

CONCLUSIONS

CPDD-0021 did not have reinforcing effects nor did it have pentobarbital- or d-amphetamine-like discriminative stimulus effects in rhesus monkeys. CPDD-0021 did have locomotor effects in mice that were typical of central nervous system depressant drugs with a potency approximately one-third to one-fifth that of pentobarbital. However, CPDD-0021 at doses up to 500 mg/kg/day did not significantly alter the course of pentobarbital withdrawal signs in rats. Notably, the compound was lethal in one monkey at a dose of 60 mg/kg. In mice its lethal dose was only two to five times its locomotor depressant and ataxic doses. These results suggest that although CPDD-0021 may have some behavioral effects typical of CNS depressant effects, it is unlikely to have barbiturate-like abuse or dependence potential. The acute toxicity of the compound appears to be significant.

CPDD-0034 was a positive reinforcer in all of the monkeys tested. In addition, it had pentobarbital-like discriminative stimulus effects in all four monkeys. CPDD-0034 had acute locomotor effects that resembled those of pentobarbital. Its potency in producing these effects was slightly greater than pentobarbital, and its duration of action was longer. The compound substituted partially for pentobarbital in dependent rats, and withdrawal from CPDD-0034 appeared to be mild, perhaps negligible. These findings are similar to those reported by Griffiths et al. (1992) in baboons and suggest that CPDD-0034 has abuse and dependence potential of the barbiturate type.

CPDD-0036 did not serve as a positive reinforcer in ketamine-maintained monkeys nor did it have pentobarbital- or d-amphetamine-like discriminative stimulus effect. The compound had acute effects on locomotor activity that were not typical of either CNS stimulant or depressant drugs. CPDD-0036 did not significantly affect barbiturate withdrawal nor did it appear to cause notable signs of abstinence. These results suggest that although CPDD-0036 is unlikely to have abuse potential or barbiturate or amphetamine-like discriminative stimulus effects. Moreover, it is unlikely to have barbiturate-like dependence potential.

CPDD-0037 did not have reinforcing effects nor did it have pentobarbital- or amphetamine-like discriminative stimulus effect in rhesus monkeys. CPDD-0037 had acute locomotor effects that resembled those of pentobarbital, although the dose-response curves were rather shallow in slope. The compound produced a partial suppression of barbiturate dependence, and dependence upon it would be expected to be mild. Since CPDD-0037 is a 5HT3 antagonist (BRL 46470A) these results suggest that 5-HT3 antagonists are unlikely to have barbiturate or amphetamine-like abuse potential and may have some utility in the relief of barbiturate withdrawal. This result is consistent with the findings of Costall et al. (1990) suggesting that 5-HT3 antagonists may reverse withdrawal signs following repeated administration of other drugs.

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NIH Publication No. 93-3505
Printed 1993