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Neurobiology of Behavioral Control in Drug Abuse

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Preface

Advances in complex research fields are frequently driven by new technologies developed within the field, or in a neighboring field, to which the connections are not immediately obvious. Drug abuse is a complex problem with significant social, psychological, and biomedical components, and researchers are constantly pressed to develop new and better methodologies for prevention and treatment of drug abuse. The Idea for this review evolved from a research retreat held 8 years ago, during which hypotheses on the demand side of the etiology of drug abuse in general were discussed and specific questions on drug action on the brain, that might only be effectively studied through the application of advanced technologies, were first explored. Now that these advanced technologies are realities and it is possible to visualize specific neurochemical entities, such as opiate, dopamine, serotonin, and other receptors, in the living human brain, the time is ripe for an examination of their potential for advancing our understanding of the neurobiology of behavioral control in the drug-abusing population.

This research monograph is a summary of discussions of invited experts who participated in a 2-day Technical Review meeting held at the National Institutes of Health campus in Bethesda, Maryland, on October 3-4, 1985.

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Introduction

Stephen Szara

At a meeting in 1977 of a Task Force on Research on Drug Abuse, the concept of self-control was identified by many of our expert consultants as a central issue in drug abuse:

> The self-control concept in drug abuse research should be of high priority, since it integrates a number of concepts (Joseph Brady).
>
> Looking for commonalities across various substances of abuse may be an oversimplified notion. The self-control concept may be the only commonality (Charles R. Schuster).
>
> Getting rid of drug-using behavior is dependent on the successful establishment of a substitute behavior. Drug abuse may be seen as a disorder of effective self-control (Gene Smith).
>
> Peptides and neurotransmitter amines may affect self-image, feeling states, or even self-control; we just have to find ways of measuring It (William Martin).

Some of the consultants actually suggested general guidelines for research:

> The endorphin story is very important and should be followed up in human studies (Charles P. O'Brien).
>
> To pin down disorders of self-control in drug abuse patients, we should follow the natural history of recovery and find out what accounts for their success (Gene Smith).
>
> Basic research is not necessarily biochemistry, pharmacology, or anatomy; it is behavior that can

> also be considered basic itself. We need good objective measures of present status so that we can measure change (Peter Dews).

Scanning the drug abuse literature for evidence of research activities on this parameter, I was struck by the relative paucity of papers in the drug abuse context. Digging into the psychosocial literature, however, I was impressed with the numerous studies that focused on the apparently narrow issue of "locus of control," as measured by a single dimensional scale devised by Julian Rotter, to assess the external/internal attitudes for control of life events (Rotter 1966; Rotter 1975). At least two books (Lefcourt 1976; Perlmutter and Monty 1979) and hundreds of papers have been published on this topic in various journals.

Some papers on alcoholism have dealt with subjective feelings of losing control as a central feature of this disease (Rohsenow and O'Leary 1978; Abbot 1984), and I found a few papers reporting on some measure of control as playing a role in other drug abuse situations (Langrod et al. 1983; Craig 1979).

There have been a number of questions raised in the psychological literature as to the validity of the Rotter scale of locus of control, and other psychological variables, such as sensation seeking, have been suggested as crucial in getting involved with drugs.

However, a major question can be raised, If self-control is such an important issue in drug abuse, considering the fact that drugs, including alcohol, are chemicals acting at the chemical level on the brain, is there a relationship that can be identified and explored so that we can gain a better understanding of what is going on with drugs and the brain? Based on this, could we find better ways of helping addicts to return to normal life or find ways to prevent people from becoming addicted in the first place?

There is an enormous gap between the receptors, the points in the brain where drugs presumably act, and issues at the conceptual level, such as self-control, sensation seeking, etc. How do we deal with this gap in a scientific manner? Paul Willner argues (Willner 1984) that coming to grips with this question is the central issue of psychopharmacology and proposes at least four explanatory domains needed to bridge the conceptual gap between the biochemical and subjective levels:' the biochemical, physiological, cognitive, and subjective. He suggested that we think in terms of a computer analogy, according to which these four domains roughly correspond to two levels of hardware and two levels of software: components and wiring at the hardware level and programming and editing at the software level. The four levels may be generally described as follows:

1. **Hardware level.** This means the elementary active operating components, such as transistors, gates, flip flops, memory registers, etc. in computers. In the brain these would correspond to neurons, cortical columns, strfatal patches, islands, etc.

2. **Connectivity between the components.** In the computer, connectivity between transistors defines their interactions and forms the basis for higher level action. In the brain, the connectivity pattern among the functional units is extremely complex with multiple feedback loops forming intricate patterns.

3. **Program level.** In computers the programs may reside in a plugged-in module or have to be loaded in by the user. In animals and humans the situation is much more complex. Fixed action patterns (FAP) are recognized by ethologists in animals as genetically determined programs for action, and some of these are suspected to have survived the evolutionary process although there are some doubts as to whether they are operational in man. In humans, much of the "programning" occurs at the psychosocial and cultural levels as part of the lifetime learning process.

4. **Editing level.** Here the analogy between brain and computer breaks down. We don't have an equivalent feature in computers of fntentfonality, consciousness, and emotions, just to mention a few of the subjective phenomena that are of obvious significance for human behavior.

I would like to avoid getting bogged down in philosophical discussion of these issues. Rather, I would like to focus on a relatively narrow aspect of human functioning that would hopefully be researchable. What I am proposing is to explore the possible causal relationships between molecular events in the brain, as revealed by Positron Emission Tomography (PET) scanning, and some high-level symbolic action, for example holding a specific belief of locus of control that appears to play a major role in the decision processes involved in substance abuse.

Bridging the enormous gap that this represents has been attempted before (Zuckerman 1984). This Technical Review asked the participants to take a look at the newly emerging potentials of high technology in visualizing functional states of specific receptors in the living human brain and explore some concrete hypotheses relevant to drug abuse that may be resolved using this technology.

We know from preliminary research that PET-scanning techniques can visualize receptors in the human brain *in vivo* (Wagner et al. 1983; Frost et al. 1985). and that locus of control measures are available and have been useful in assessing some aspects of

substance abuse behavior (Langrod et al. 1983; Craig 1979). Animal data suggest that some brain transmitters and/or receptors are affected by awareness of the availability of "control" (Smith et al. 1982; Drugan et al. 1981).

The following questions were addressed at the Technical Review:

- What kind of specific hypotheses may be formulated that would be of interest to drug abuse research and that could be tested using the newly available methodologies?

- Are these methodologies sufficiently sensitive and specific to obtain reliable measures at the biochemical/receptor level, the clinical/psychological level, and the behavioral/instrumental level?

- What kind of subject population may be most suitable: a nondrug-using sample from the general population; current drug users in treatment; some other diagnostic category of patients; or all of the above?

- What would be the most appropriate experimental design to carry out these studies?

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Basic Research Strategies for Imaging Neurotransmitter Systems

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INTRODUCTION

The advent of powerful new imaging techniques, such as positron emission tomography (PET) scanning and magnetic resonance imaging, has raised the possibility of evaluating metabolic functions in the brains of intact humans. Substantial advances have already been made in PET scanning, especially in studying 2-deoxyglucose uptake. PET scanning has also been employed to image neurotrans-mftter receptors such as dopamine, opiate, and benzodiazepfne receptors. Magnetic resonance imaging has thus far been restricted to studies of protons, permitting the visualization of anatomical structures but not studies of metabolism. In the not too distant future, magnetic resonance imaging is likely to be employed for phosphorus, so that energy metabolism, such as the disposition of ATP, will be imaged.

The major limitation of PET scanning is technological. Positron-emitting isotopes have a very short half-life, so the synthesis of appropriate ligands must be done at the site of the PET scanning operation. Additionally, the cost of a cyclotron and the PET scanning camera equipment is considerable. In some instances, one might be able to accomplish similar objectives utilizing lfgands such as iodine-123, which can be detected by single proton emission tomography, utilizing equipment that is already available in most academic medical centers.

Thus, at the present time one can image almost any ligand provided it can be synthesized with the appropriate isotope. For the information to be useful, the ligand must interact only with the desf red target site. Thus, if one wished to image opiate receptors, morphine would be unsuitable. While morphine does indeed bind to opiate receptors, at pharmacologically effective doses about 80 percent of the morphine in the brain is not bound to opiate receptors, but occurs at adventitious locations. Accordingly, a sophisticated understanding of the relevant neurochemical system is necessary to develop appropriate ligands. Sophistication is also required in determining which systems may be of greatest

interest for imaging and can be approached with available technology.

The types of neurochemfcal systems that have been explored or that may be explored in the future can be placed in several categories. The first has to do with comprehensive metabolic function as exemplified by studies with 2-deoxyglucose. As a neuron fires more frequently, 2-deoxyglucose consumption increases. It appears that neurons, rather than glia, account for the bulk of 2-deoxyglucose uptake. There have been many demonstrations of 2-deoxyglucose uptake varying with the functional state of neuronal groupings. Investigators have begun to approach studies of protein synthesis by PET scanning. As already mentioned, phosphorus disposition might be evaluated by magnetic resonance.

In this essay, we will not deal with general metabolic markers for imaging. Instead, we will limit our attention to studies of neurotransmitter disposition at three levels. One involves labelling neurotransmftter receptors. A second involves labellfng neurotransmitter-specific neurons. Yet a third has to do with studies of second messenger systems for neurotransmftters.

NEUROTRANSMITTER RECEPTORS

Neurotransmitters come in different varieties, including amines, amino acids, and peptides. At the present time, well over 50 distinct neurotransmftter candidates are known, and the total number may be substantially higher. Generally, there are several subtypes of receptors for each neurotransmftter. Thus, the multiplicity of potential receptors to be imaged is considerable. Why would one want to image any neurotransmftter receptor? One can determine the detailed localization of the receptor in animal studies far more efficiently than in humans. In humans, one presumably would be Interested prfmarfly in alterations associated with specific disease states. The second possfbflfty has to do with changes relating to drug treatment.

What might one be seeking in studies of neurotransmitter receptors in disease states and following drug admfnfstratian? Presumably, one would be looking for some sort of alteratlon. Two types of changes can be potentially detected by fmaging. If the affinfty of the receptor for its ligand changes, then the amount of a tracer dose of the lfgand that binds would be altered. For instance, if a given disease state is associated with an alteration in the protein structures of the receptor, so that its affinity for ligands is decreased to one-tenth its original affinity, then, with a tracer dose of radioactive drug, one would probably observe much less binding. More straightforward would be changes in actual numbers of receptors. These would be detected with tracer doses of ligand, as well as with saturatfng doses. Distinguishing between alterations in affinity or receptor number might be possible by utilizing different doses of the radioactive ligand in imaging studies. Changes in receptor <u>number</u> would be apparent by altered ligand binding of similar magnitude, regardless of the

dose of radioactive ligand. Altered receptor affinity would be apparent in terms of changes in ligand binding only with low ligand concentrations.

Conceivably, certain brain disorders are related to changes in numbers of receptors. The limited investigations that have been done thus far in postmortem brain have not been particularly promising. Thus, though dopamine is thought to be involved in schizophrenia, any changes in levels of dopamine receptors in postmortem schizophrenic brain are thought to be related more to drug treatment than to the disease process (MacKay et al. 1982). Numbers of various receptors are changed in Huntington's disease (Penney and Young 1982; Whitehouse et al. 1985), but this is not surprising considering the vast deterioration of neurons, especially in the corpus strfatum. The same could be said for reports of alterations in receptor number in Alzheimer's disease.

Might there be changes in receptor number with varying physiological state? In other words, would extreme and prolonged stress alter number of receptors? If one anticipates such changes in receptors to arise from an altered rate of receptor synthesis, then the likelihood of detecting alterations would depend on the rate of turnover of the receptors. Receptors are membrane proteins which do not turn over at a very rapid rate. However, rapid changes in apparent numbers of receptors are associated with conformational alterations in the receptor protein; these alterations change ligand binding. We know that GABA stimulates benzodiazepine receptor binding by allosteric effects that enhance the affinity of the benzodiazepine receptor for drugs (Olsen 1981). These types of changes may be the receptor-binding alterations most likely to correlate with changes in total brain function. For instance, if a drug-induced change in brain activity led to increased firing of GABA neurons, the release of GABA might increase the affinity of benzodiazepine receptors, which would be apparent in augmented levels of ligand binding.

There is yet another way in which transient changes in neuronal firing might alter apparent numbers of receptors. This has to do with receptor occupancy by transmitter. The conventional model of neurotransmitter action assumes that interaction with receptors is followed by a rapid dissociation of the neurotransmitter, leaving the receptor vacant for occupancy by the transmitter associated with the next nerve impulse. On the other hand, there is abundant evidence that, under some circumstances, transmitters bind with very high affinity to receptors, so that dissociation is slow. This is usually the case in receptor desensitization. Many studies with different neurotransmftters suggest that a major mechanism of desensitization involves tight binding of the transmitter to its receptor. Also, high-affinity binding of transmitter to receptor occurs in the "active" state of certain receptors, as has been best exemplified for catecholamines at beta adrenergic and dopamine receptors (DeLean et al. 1980; Leff et al. 1985).

If a transmitter binds tightly to its receptor, then imaging with a radioactive ligand may indicate an apparent decrease in receptor number. On the other hand, if one administered a drug that displaced the tightly bound transmitter from its receptor, there would be an apparent increase in receptor number. Examples of this phenomenon derive from studies of opiate receptors. In our earliest investigations of opiate receptor binding following opiate administration, we found apparent increases in receptor number (Pert et al. 1973). The properties of these increases were quite similar to increases observed if one merely incubated brain membranes in buffer solutions (Pasternak et al. 1975). In these latter studies, the increase in receptor binding was associated with the release into the buffer solution of a small peptide molecule with affinity for opiate receptors. Accordingly, we suspect that a certain amount of enkephalin is normally tightly bound to opiate receptors in a noncovalent fashion. Drug treatment of intact animals or incubating brain membranes at 37°C releases the bound enkephalin, increasing the apparent number of opiate receptors.

One might speculate that altered physiological states associated with increased firing of enkephalin neurons would lead to greater receptor occupancy of tightly bound enkephalin, with an associated decrease in apparent number of opiate receptors. Such changes have been detected in studies wherein rats were forced to swim; there was an associated apparent decrease in opiate receptor number (Seeger et al. 1984).

NEURONS CONTAINING SPECIFIC TRANSMITTERS

No well-known disease state is "caused" by demonstrated changes in receptor number, though we do know of conditions associated with degeneration of neurotransmitter-specific neurons. In Alzheimer's disease, there is a relatively selective deterioration of cholinergic- and somatostatin-containing neurons. Similarly, in Parkinson's disease, degeneration of the nigrostriatal dopamine pathway appears to be responsible for the major symptoms. Imaging techniques have already been applied to dopamine neurons. ^{18}F-DOPA is administered to humans; decarboxylation to ^{18}F-dopamine takes place selectively in dopamine neurons, which can thus be imaged. This technique has been employed to demonstrate a loss of dopamine neurons in patients with idiopathic Parkinson's disease and may detect early stages in the loss of dopamfne neurons, not yet associated with clinical symptoms of Parkinson's disease. One cannot predict by any conventional means who will be likely to develop idiopathic Parkinson's disease, since this condition is not genetically determined and has no known environmental cause. MPTP (1-methyl-4-thenyl-1,2,3,6-tetrahydropyridine) is a Parkinsonism-inducing neurotoxin occurring as a contaminant of synthetic opiates sold illicitly as designer drugs. Some individuals who self-administered MPTP-containing preparations developed an abrupt onset of Parkinsonism with demonstration of dopamine neuronal degeneration at autopsy. However, the great bulk of 500 or more individuals who have received MPTP appear to be devoid of neurological symptoms. Are any of these individuals at risk to

develop Parkinsonism? In normal subjects, dopamine neurons deteriorate with age, so that by the age of 70 most normal people have only about half of the dopamine neurons they had in young adulthood. With a loss of 70 to 80 percent of dopamine neurons, one obtains clinical symptoms of Parkinsonism. Conceivably, asymptomatic MPTP users have a limited loss of dopamfne neurons, but, as they grow older, the normal age-related loss of dopamine neurons would bring them to the threshold where Parkinson's disease would become apparent. In four MPTP users with no neurological symptoms, Calne et al. (1985) have demonstrated a loss of dopamfne neurons by PET scanning with ^{18}F-DOPA. Presumably, this or similar techniques could now be employed in patients with very slight neurological abnormalities suggestive of Parkinson's disease to provide a differential diagnosis.

How else might one image neurotransmitter-containing neurons? Conceivably, the precursor strategy might be applicable to other neuronal populations. For instance, 5-hydroxytryptophan might be converted to serotonin selectively by serotonin neurons. However, the enzyme that carries out this transformation is enzymologically identical to DOPA decarboxylase , so that most of the enzymatic conversion may take place in dopamine neurons. Choline, the precursor of acetylcholfne, is involved in many other biochemical pathways, so it may not be a suitable precursor for the imaging of acetylcholfne neurons. The same is likely to hold true for glutamic acid, the precursor of GABA. Other amino acid transmitters, such as glycine or glutamic and aspartic acids, are even more difficult to approach, because they are involved in so many metabolic processes.

One approach to labelling transmitter-specific neurons takes advantage of selective uptake mechanisms. Most amino acids and amine neurotransmitters are inactivated by reuptake pumps. One can regard the site where the transmitter is recognized on the neuronal membrane prior to uptake as an "uptake receptor." Such uptake receptors have been labelled in biochemical binding studies for various transmitters. Serotonin uptake sites have been labelled with antidepressant drugs such as ^{3}H-imipramine, ^{3}H-paroxetfne, and ^{3}H-citalopram. Uptake receptors for norepinephrine neurons have been labelled with the antidepressant ^{3}H-desfpramfne (Lee et al. 1982) and the appetite suppressant ^{3}H-mazindol (Javitch et al. 1984). In binding Studies, dopamine neuronal uptake sites have been labelled with ^{3}H-matindol, which has similar affinity for dopamfne and norepinephrine uptake sites. The high-affinity choline uptake system providing the precursor pool of choline for acetylcholine synthesis has an uptake receptor that can be labelled with ^{3}H-hemicholinium, a potent inhibitor of the high-affinity choline uptake process.

Might it be possible to image these neuronal systems in humans with lfgands similar to the ones employed in biochemical binding experiments? The considerations involved in assessing feasibility are similar to those associated with labelling postsynaptic neurotransmitter receptors. Thus, at the tracer concentration of the

ligand employed, the great majority of the radioactive drug would have to be associated with the uptake receptor being investigated. Receptor occupancy is related to the affinity of the ligand for the binding site. Dopamine and serotonin receptors have been imaged by PET scanning utilizing derivatives of spiperone with a dissociation constant of about 10^{-10}M. The opiate that has been employed for PET imaging ^{11}C-carfentanil, has a similar affinity for opiate receptors. In intact rats, ^{3}H-diprenorphine, whose dissociation constant for opiate receptors is approximately 10^{-10}M, occupies 85 percent or more of opiate receptors in the brain after intravenous-administration. By contrast, ^{3}H-naloxone, with a KD of about $2x10^{-9}$M, occupies only about 30 percent of receptors under similar conditions. All the drugs that have been employed as ligands to label uptake receptors have affinities for uptake sites similar to that of naloxone, or even less affinity. This would argue against their suitability for imaging purposes. However, the number of uptake receptors in most cases is substantially greater than the number of postsynaptic neurotransmitter receptors. Conceivably, a large number of binding sites may make up for lesser affinity.

SECOND MESSENGERS

In our earlier discussion of neurotransmitter receptors, we were dealing largely with the recognition site of the receptor. Equally important are the second messengers, which communicate to the interior of the cell recognition information. Second messengers are dynamic and may more likely show changes with varying physiological and pathological states than do the receptor recognition sites. One might not anticipate major changes in biosynthesis of second messenger proteins. However, most of the regulation of second messenger proteins involves allosteric alterations, which could cause marked and rapid alterations in apparent receptor number. *In vitro* biochemical studies suggest this possibility. What are some of the second messengers that might be explored? The two major second messenger systems for neurotransmitters are the cyclic AMP system and the phosphoinositide cycle. The phosphoinositide cycle has only been recently elucidated but appears to be involved in conveying messages for numerous neurotransmitters including acetylcholine, serotonin, norepinephrine, and substance P, as well as a variety of hormones and general mediators such as thrombin and even mitogenic growth factors.

The phosphoinositide cycle involves the triggering by receptor recognition of the breakdown of phosphatidylinositol-bis-phosphate into inositol triphosphate (IP-3) and diacylglycerol. IP-3 acts upon receptor sites on the endoplasmic reticulum to release calcium within the cell. Diacylglycerol stimulates protein kinase C by enhancing its sensitivity to the stimulatory effects of calcium. The phorbol ester tumor promoters bind with nanomolar affinity to protein kinase C. Indeed, what was thought first to be the phorbol ester receptor appears to be the enzyme kinase C. In this way, protein kinase C may be regarded as the third messenger in the phosphoinositide system.

Protein kinase C can be labelled in binding studies with radioactive phorbol esters. Autoradiographic maps reveal a discrete localization of neuronal systems containing protein kinase C (Worley et al., in press). This presumably provides a map of those synaptic systems that make use of protein kinase C as a messenger. Protein kinase C is extremely dynamic. It exists in soluble and membrane-bound forms. Increases in intracellular calcium trigger a movement of the cytoplasmic enzyme to a membrane-bound state, which appears to be the active form of the enzyme. We have found that stressful stimuli, such as needle injections into the brain or stress associated with the agonal state, cause ten- to fiftyfold increases in membrane-associated kinase C. The development of appropriate ligands for imaging protein kinase C might provide a dynamic reflection of synaptic activity in a number of neuronal systems. Phorbol esters have high affinity for protein kinase C, though not as high as that of spiperone for dopamine and serotonin receptors. On the other hand, the number of protein kinase C molecules in the brain is more than 100 times that of serotonin or dopamine receptors, a circumstance that might facilitate imaging.

The cyclic AMP-forming system possesses a number of components. Neurotransmitter recognition at receptors triggers an association of the receptor recognition proteins with ATP-binding protein. This "G" or "N" protein interacts with the catalytic unit of adenylate cyclase to cause a conversion of ATP to cyclic AMP. Some neurotransmitters stimulate cyclic AMP formation while others inhibit. There appear to be distinct stimulatory and inhibitory G proteins. Cholera toxin binds with fairly high affinity to the stimulatory protein, and pertussis toxin binds to the inhibitory protein. Conceivably, modified forms of cholera and pertussis toxins might be used for imaging. Of course, these two toxins would not pass the brain blood barrier without substantial modification.

Another approach to the adenylate cyclase system might be to image the catalytic unit of the enzyme, utilizing a derivative of forskolin. Forskolin is a plant derivative that potently stimulates adenylate cyclase. ^{3}H-forskolin binds to the enzyme with nanomolar affinity. As with protein kinase C, the number of forskolin binding sites is substantially greater than the number of neurotransmitter postsynaptic receptors. Conceivably, some derivative of forskolin would be useful for imaging the cyclic AMP system.

In summary, the possibility of imaging neurotransmitter-containing neurons via their uptake sites, postsynaptic receptor recognition proteins, or second messenger proteins is very real. The limitations at present are not conceptual but merely technological and within the grasp of presently existing technology. The possibility of detecting alterations in brain function as a result of changes in physiological status, drug treatment, or pathology offers promise for application in the not too distant future.

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Measurement of Neurotransmitter Receptors by Positron Emission Tomography: Focus on the Opiate Receptor

J. James Frost

APPLICATION OF POSITRON EMISSION TOMOGRAPHY TO NEURORECEPTORS

The impetus for developing noninvasive methods to image and quantify neuroreceptors by positron emission tomography (PET) was twofold: (1) the recognition that many widely used psychoactive drugs exert their actions through binding to neuroreceptors, and (2) the observation that neuroreceptors are altered (in number or affinity) in some psychiatric and neurodegenerative disorders, when measured by postmortem methods. For example, haloperidol, a neuroleptic drug widely used in the treatment of schizophrenia, exerts its action predominantly by binding to the dopamine receptor and inhibiting dopamfnergic neurotransmission (Creese et al. 1975; Seeman et al. 1975). Postmortem measurements of dopamine receptors in the caudate nucleus of schizophrenics demonstrate an increase in the number of dopamine receptors, giving rise to the hypothesis that schizophrenia is a disorder resulting from an excess of dopamine receptors (Seeman et al. 1984; Owen et al. 1978). Development of a method to measure dopamine receptors in vivo would clearly be useful in confirming or refuting this hypothesis, as well as providing a basis for rational drug therapy and possible subclassification of schizophrenia based on dopamine receptor concentration. Such a method would also have obvious application to other neuropsychiatric disorders in which receptor number or affinity is altered.

POSITRON-EMITTING ISOTOPES

Positron emission tomography is a sophisticated method of measuring the distribution of positron-emitting isotopes in the brain or other body regions (Phelps and Mazziotta 1985; Ter-Pogossian et al. 1982). The principle of radioactivity detection is based on the simultaneous detection of two 511-keV gamma rays emitted 180° apart by a circular ray of opposed detectors. The registration of only coincident gamma rays by detectors 180° opposed results in (1) an approved spatial localization of the decaying isotope, and (2) a simpler correction for gamma ray attenuation when compared to methods utilizing the detection of single gamma rays. The

existence of positron-emitting isotopes of several elements of biological interest makes PET even more suitable for imaging biological systems. These isotopes include carbon-11 (half-life=20 minutes), oxygen-15 (half-life=2 minutes), nitrogen-13 (half-life=10 minutes), and fluorine-18 (half-life=110 minutes). When these isotopes are incorporated into appropriate molecules, biochemical processes that correspond to the labelled molecule can be measured. Using this principle, it is possible to noninvasively measure regional cerebral oxygen utilization using ^{15}O-O_2. regional cerebral glucose utilization using ^{18}F-fluorodeoxyglucose, regional cerebral blood flow using ^{15}O-H_2O, regional cerebral blood volume using ^{15}O-CO, etc. (Phelps et al. 1979; Reivich et al. 1979; Phelps et al. 1982; Reivich et al. 1982; Frachowiak et al. 1980; Mintun et al. 1984b; Grubb et al. 1978; Raichle et al. 1983). When using such methods, the importance of tracer kinetic models for quantitative estimation of metabolic or other parameters cannot be overemphasized; without such mathematical models, quantitative interpretation of the PET images would not be possible (Phelps et al. 1982).

RECEPTOR IMAGING

In the case of receptor imaging, the situation is much the same as described above. One challenge of developing methods for imaging and quantifying neuroreceptors by PET is in identifying appropriate drugs or ligands to be labelled. Studies carried out over several years provided the first insights into some of the properties a compound must have if the distribution of radioactivity in the brain was to correspond closely to the distribution of a neuroreceptor following intravenous administration (Klemm et al. 1979; Kuhar et al. 1978; Kuhar et al. 1976; Laduron et al. 1978; Laduron and Leyson 1977; Hollt et al. 1977; Pert et al. 1975; Yamamura et al. 1974). For the method to be successful, a high degree of receptor-specific binding and a low degree of nonspecific or background binding in the brain had to be achieved at some time following injection. For the ratio of specific/nonspecific binding (or total/nonspecific binding) to be high, it became apparent that drugs with dissociation constants on the order of 1 nM or less were necessary. Under these conditions, ratios of specific/nonspecific binding as high as 10 could be achieved within a few hours following injection, making the methods amenable to PET, using positron emitting isotopes with relatively long half-lives, such as ^{11}C or ^{18}F The higher the ratio of specific/nonspecific binding for a given labelled drug, the more accurately changes can be distinguished in in vivo receptor binding (other parameters being constant). This increased accuracy has obvious implications for the detection and quantitation of neuroreceptor alterations in disease. A high receptor affinity appears to be an important property of a ligand if prolonged in vivo receptor binding is to be achieved, although other parameters may be of importance (Frost and Wagner 1984).

In some cases, a labelled drug with a high affinity may not be suitable for in vivo receptor labelling because of the high degree

of nonspecific or background binding. The nonspecific binding is difficult to predict prior to *in vivo* studies, since the relationship between the drug's physiochemical properties and drug distribution, metabolism, excretion, and permeability is complex (Frost and Wagner 1984). The choice of labelled drugs for PET studies is therefore currently based on the study of labelled compounds in animal models by direct tissue dissection methods. To synthesize labelled drugs is often expensive and laborious, and of questionable value when their usefulness is in doubt. An improved understanding of the relationship between structure and specific- and nonspecific-binding kinetics could improve the identification of drugs for labelling neurotransmitter receptors *in vivo*. This identification is important since the number of potentially useful unlabelled drugs far exceeds the number of labelled drugs. Table 1 shows a series of labelled drugs identified for use in PET studies of neuroreceptors.

TABLE 1. *Partial list of drugs labelled with positron-emitting radionuclides for in vivo neuroreceptor studies*

Labelled Drug	Neuroreceptor
^{11}C-carfentanil	opiate
^{11}C-diprenorphine	
^{18}F-acetylcyclofoxy	
^{11}C-methylspiperone	dopamine-2 and serotonin
^{18}F-methylspiperone	
^{18}F-spiperone	
^{75}Br, ^{76}Br-bromospiperone	
^{11}C-raclopride	dopamine-2
^{11}C-SCH-23,390	dopamine-1
^{11}C-ketanserin	serotonin-2
^{11}C-methylketanserin	
^{11}C-methyl bromo LSD	
^{11}C-dexetimide	muscarinic cholinergic
^{11}C-quinuclidyn benzilate	
^{11}C-scopolamine	
^{11}C-Ro 15-1788	benzodiazepine
^{11}C-suriclone	

OPIATE RECEPTORS

We have utilized ^{11}C-carfentanil, a potent opiate agonist, to image opiate receptors *in vivo* in humans (Frost et al. 1985; Dannals et al. 1985). Carfentanil has a potency approximately

8,000 times that of morphine in the rat, with a correspondingly high receptor affinity (Van Daele et al. 1976). Additionally, the effect of sodium on carfentanil binding is small compared to most opiate agonists, making carfentanil attractive for in vivo binding studies (Stahl et al. 1977; Frost and Wagner 1984). The dissociation constant of carfentanil for mu opiate receptors measured in the rat brain at 37°C is 0.051 nM (Frost et al. 1985). Carfentanil binds to delta and kappa opiate receptors under similar conditions with a 90- and 250-fold higher dissociation constant. Therefore, ^{11}C-carfentanil is expected to be highly selective for mu opiate receptors in vivo.

HUMAN STUDIES

Human studies using ^{11}C-carfentanil were carried out using PET following the injection of approximately 7 µg (20 mCi) ^{11}C-carfentanil alone, and following the administration of 1 mg/kg naloxone (figure 1). Images obtained immediately following injec-^{11}C-carfentanil showed homogeneous and approximately equal binding throughout the grey matter structures of the brain, with and without naloxone (Frost et al. 1985). When ^{11}C-carfentanil was administered alone, the radioactivity in structures known to be rich in opiate receptors such as the thalamus and basal ganglia increased with time, whereas the radioactivity decreased in the occipital cortex, a structure with very few opiate receptors (Kuhar et al. 1973). The ratio of radioactivity when carfentanil was given alone to that in the presence of naloxone increased until 30 minutes after injection, then remained relatively constant for up to 60 minutes in the caudate nucleus, thalamus, and amygdala (data not shown). This value is equivalent to the ratio of total/nonspecific binding discussed previously. In the amygdala. the ratio of total/nonspecific binding is approximately 7. This measured ratio is an underestimate of the actual total/nonspecific binding ratio, due to the finite spatial resolution of the Neuro ECAT PET scanner (Hoffman et al. 1983). When the corrections in this effect are made, approximately 90 percent of the radioactivity in the amygdala is estimated to be specifically bound to receptors. In the caudate nucleus and thalamus, the percent of specific binding is somewhat less.

Figure 1 shows images from the two ^{11}C-carfentanil studies for the period 30 to 60 minutes after injection. The three imaging planes are 32 mm apart with a slice thickness of approximately 16 mm. The highest radioactivity concentrations are seen in the amygdala, thalamus, and basal ganglia. Intermediate radioactivity levels are observed in the frontal, parietal, and temporal cortex, the cerebellum, and the hippocampus. Low levels of radioactivity are observed in the occipital cortex, white matter regions, and primary sensory cortex. This distribution closely corresponds to the known distribution of human mu opiate receptors (Kuhar et al. 1973).

The images in the bottom row of figure 1 are obtained using ^{11}C-carfentanil, following pretreatment with 1 mg/kg naloxone. In

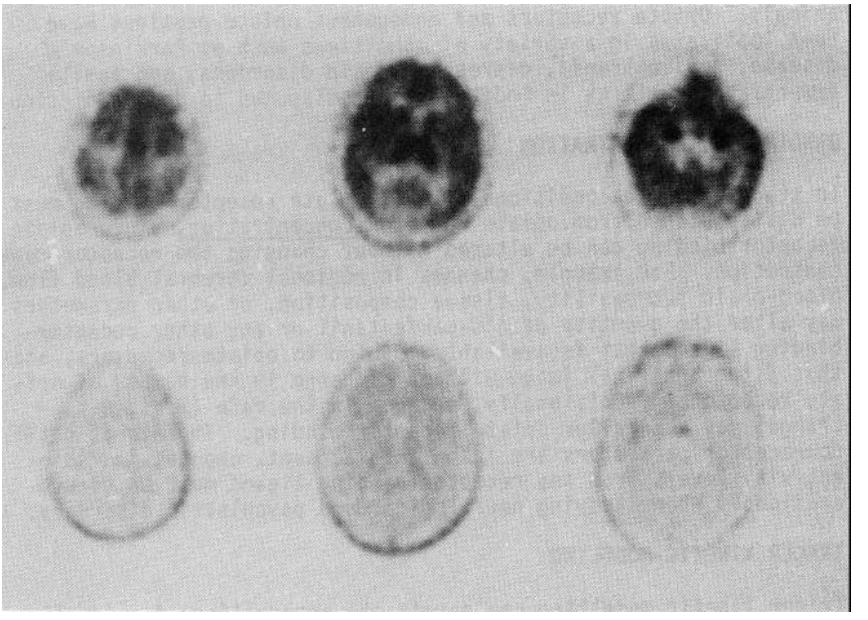

FIGURE 1. *Localization of opiate receptors in man using ^{11}C-carfentanil*

NOTE: The Images in the top row were obtained using the Neuro ECAT from 30 to 60 minutes after IV administration of 20 mCI ^{11}C-carfentanil, 7 µg. The three Images were localized using x-ray CT at approximately 7.2, 4, and 0.8 cm above the canthomeatal Iine. Images in the bottom row were acquired at the same time, following IV administration of the opiate antagonist naloxone, 1 mg/kg. and the same dose of ^{11}C-carfentanil used in the first study. The brightness of each image is normalized for the injected activity, the acquisition time, and radioactive decay. A preferential accumulation of activity is seen in areas known to contain high concentrations of opiate receptors, such as the thalamus, basal gangIia, amygdala. and cerebral cortex (particularly the cingulate cortex). Conversely, low activity is seen where opiate receptors exist in low concentrations, such as the occipital cortex, the postcentral gyrus, and the cerebellum. The Images in the bottom row demonstrate the low level of nonreceptor binding in the brain. Binding is not inhibited In the skull or venous sinuses.

these images, a low and homogeneous concentration of radioactivity is seen throughout the brain, due to competitive binding of naloxone and ^{11}C-carfentanil at opiate receptors. The radioactivity was not significantly affected in the skin and skull or the venous sinuses, consistent with the absence of opiate receptors in these regions.

The ability to measure opiate receptor binding by PET in humans will permit exploration of questions that cannot be addressed in animals. Opiate receptors and endogenous opiate peptides have been implicated in a variety of conditions such as Parkinson's disease, schizophrenia, depression, pain disorders, and senile dementia, as well as in individuals predisposed to drug addiction.

BINDING VS. CONCENTRATION

In studying these conditions by PET, opiate receptor binding must be distinguished from opiate receptor concentration, since opiate receptor binding can be altered without changing the receptor concentration. For example, changes in regional cerebral blood flow, blood-brain permeability,tissue composition, or other parameters may alter the quantity of ^{11}C-carfentanil or any other receptor-binding ligand that is available to bind to opiate receptors, and thus alter the final image without a change in the number of opiate receptors. Additionally, changes in the rate (e.g., a K_D change) may also alter opiate receptor binding. Therefore, until nonreceptor parameters are taken into account, changes in radioactivity levels from any receptor-binding ligand must be viewed cautiously when studying neurological and psychiatric disorders.

TRACER KINETIC MODELING

Tracer kinetic modelling can permit the unravelling of a complex process in vivo, so that the number of binding sites or rate constants can be estimated if parameters such as the arterial concentration of the tracer, regional cerebral blood flow, regional cerebral blood volume, and other parameters are known (Phelps et al. 1982; Mintun et al. 1984b). Using such approaches, it has been possible to determine quantitative estimates of important biological processes such as regional cerebral blood flow, regional cerebral glucose utilization, and regional cerebral oxygen utilization. Similar methods can also, in principle, be applied to receptor binding in vivo as measured by PET.

A primary piece of independent information, which is necessary to apply such techniques, is the tracer concentration as a function of time in the arterial plasma. Most, if not all, of the labelled drugs that have been used for receptor imaging are metabolized in vivo. For example, we have measured the metabolism of ^{11}C-carfentanil in human plasma during PET scan studies. At 10, 30, and 60 minutes after injection, the fraction of the total plasma radioactivity represented by ^{11}C-carfentanil is approximately 85, 45, and 25 percent, respectively. In addition, greater metabolism of ^{11}C-carfentanil was observed following pretreatment with 1 mg/kg

naloxone. Using this information, the true kinetics of ^{11}C-carfentanil in the plasma can be computed and used with tracer kinetic models. Additional issues to be addressed are the ability of metabolites to enter the brain and the receptor-binding potential of metabolites. Although metabolites can be measured directly using chromatographic methods, the process is laborious and not easily translatable to routine clinical studies. Following a rigorous approach to tracer kinetic modelling, with the accurate estimation of all involved rate processes, it should become possible to simplify the methods where appropriate.

AREAS OF INVESTIGATION

In studying opiate receptor binding or binding to other receptor types in vivo by PET, three fundamental areas of investigation can be identified. First, it is of great interest to identify and characterize changes in receptors as a function of disease and aging. In this respect, it is of interest to obtain quantitative estimates of receptor concentration and the rate constants for receptor binding, which then can be compared to values obtained in normal populations. This approach may lead to an improved biochemical characterization of neurological and psychiatric disorders, an ability to identify disease subtypes, and a rational approach to drug therapy.

Second, in some receptor systems, it may be possible to detect changes in receptor binding following alterations in receptor occupancy by endogenous neurotransmitters. For example, it has been recently demonstrated that the stress of swimming reduces apparent opiate receptor binding in vivo, presumably by releasing enkephalin, which then occupies receptors (Seeger et al. 1984). Using this approach, the physiologic role of the opiate system could be elucidated by PET scanning, usfng control-test paradigms following stressful or painful stimuli. This approach could also be used to study opiate addiction and withdrawal.

Third, changes in opiate receptor occupancy following the administration of exogenous drugs can also be detected, as was demonstrated for naloxone in the case of opiate receptor binding. Drug therapy is currently monitored when possible by following the plasma drug level, although, in many cases, the plasma level does not closely mirror the therapeutic response. Ideally, the effective concentration of the drug at the receptor site with which it interacts would be monitored. For example, it has been demonstrated by PET that approximately 85 to 90 percent of dopamine-2 receptors in the putamen of schizophrenic patients are occupied by conventionally used antipsychotic doses of neuroleptic drugs (Farde et al. 1986). Similar studies are in progress using ^{11}C-carfentanil to assess changes in opiate receptor occupancy and the correlation of those changes with behavioral and subjective changes in chronic-pain patients receiving morphine and related drugs, narcotic addicts, and former addicts receiving methadone or naltrexone.

SUMMARY

In summary, it is now possible to image the distribution of several neurotransmitter receptors by PET. When quantitative estimates of receptor number and affinity can be made, it will be important to study (1) changes in receptor number or affinity as a function of disease, (2) changes in receptor occupancy by endogenous neurotransmitters, and (3) changes in receptor occupancy and correlation with behavior during drug treatment.

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The Personality Structure of Heroin Addicts

Robert J. Craig

INTRODUCTION

When a search of the literature for data that other clinicians and researchers found in the area of personality characteristics of drug abusers failed to uncover such a body of material, I decided to produce it myself. My investigation culminated in several research reviews (Craig 1979a; Craig 1979b; Craig 1982a; Craig 1982b).

My first review uncovered 98 articles from 1925 to 1975, and my second review found an additional 47 articles from 1976 to 1979. Clearly, research in this area was burgeoning with interest. This is even more noteworthy when you understand that I included in these reviews only articles that were empirical and that administered some type of assessment instrument. Clinical articles and those based on opinion were not included in my review.

Given the steady volume of papers published on the personality characteristics of drug addicts since then, another review was warranted. (Within the last 5 years, another 50 papers have appeared in scientific journals.) I wanted to produce more of an integration and knowledge summary than my earlier work; when my task was finished, I had produced a 75-page paper (Craig 1985b). When Dr. Szara from NIDA said he wanted someone to discuss what is known about the personality characteristics of drug addicts, in my hand was the very paper I needed.

What follows is a distillation of this 75-page effort, adjusted for the needs of this technical review.

METHODOLOGY

The methodology for this paper was simple but tedious. A literature search was conducted for any empirical study that used a psychological test or scale with heroin addicts (HAs). Among heroin addicts we include clients who abused any opiates, such as heroin, methadone, codeine, Talwin, etc., but the overwhelming

emphasis in the literature has been on street addicts who abuse heroin. The reasons for limiting this search to HAs are:

- Opiates constitute the primary drugs of abuse in most drug treatment programs, so these findings would have a significant relevance to most of the drug abuse programs in the nation;

- The literature overwhelmingly focuses on characteristics of opiate addicts, perhaps because of their availability in drug treatment programs and prisons.

- Other than marijuana studies, there is a relative paucity of research on personality characteristics of addicts who abuse other drugs besides heroin, except when these abusers are contrasted with a heroin-using group, so these studies are likely to appear in this review as well.

- While marijuana studies are plentiful, they often rely on college students, and a primary marijuana-abusing client is a rarity in most drug treatment programs.

ASSESSMENT INSTRUMENTS

By looking at the assessment instruments used in this research, we can determine the areas of personality functioning that have captivated the interest of researchers. The following is a rank order of the most frequently used personality tests and scales that appeared in this literature: the Minnesota Multiphasic Personality Inventory (MMPI), the Eysenck Personality Questionnaire/Maudsley Personality Inventory, Rotter's Locus of Control Scale, Zuckerman's Sensation Seeking Scale, the Beck Depression Inventory, the Adjective Check Lists, the Tennessee Self Concept Scale, Rorschach, the Addiction Severity Index, the 16 Personality Factor Questionnaire, and Figure Drawings. We can infer from these measures that investigators have focused largely on such areas as general personality traits and symptoms, introversion/extraversion, locus of control, sensation seeking, depression, psychological need structure, self-concept, and something akin to unconscious conflicts.

COMMENT ON METHODOLOGICAL ADEQUACY OF THE LITERATURE

Barnes (1979) has made a useful distinction between the preclinical personality (those traits and behaviors exhibited prior to the onset of addiction) and the clinical personality (how the patient presents following the onset of addiction) of the drug abuser. All the research cited here pertains to the clinical personality of the drug addict. We have no studies whatsoever that have tested people prior to the development of their addiction. However, we are not arguing that these traits did or did not predate addiction. We merely suggest how a typical drug addict tends to appear on psychological tests and what areas show improvement with treatment. We find the concept of the "addictive personality" not useful, clinically or otherwise, whereas a description of the

clinical state of the addict, including his personality, is central to the assessment process itself.

Most of the research is based on samples of males. Only recently has literature appeared dealing with the personality traits of female addicts.

The methodological adequacy of some of the studies varies, especially in determining an adequate control group with which to compare addicts. For a more in-depth understanding of this issue, the reader is referred to articles addressing this problem (Craig 1979b; Nathan and Lansky 1978).

PERSONALITY CHARACTERISTICS OF HEROIN ADDICTS

Locus of Control

Since locus of control is a major content item at this conference, I want to make sure that I cover the studies that have used this as a measure to study HAs.

Locus of control measures the extent to which a person perceives gratification and rewards as emanating from personal actions and responsibility (internal locus of control), or whether they are perceived as emanating from luck, fate, chance, or the assistance of others (external locus of control). An internal locus of control is more often associated with good psychological adjustment, while an external locus of control is linked to maladjustment and psychopathology.

Probably, after hearing this definition, one would predict that HAs have an external locus of control orientation, but there are conflicting findings in the literature.

Seven studies have found HAs to have an internal locus of control. For example, Berger and Koocher (1972) found an internal locus of control, plus a significant drop in externality, following an announcement that a treatment facility would close. Here the addicts were not depending on luck, fate, or help from others to find alternatives. This suggests that locus of control can be subject to environmental fluctuations as well as being a generalized trait. No evidence was reported to show that directionality was maintained over time. These results may simply reflect the addict's need and resourcefulness at locating another source of supply.

Berzins and Ross (1973) found that black addicts were more external than white addicts, female addicts of both races were more external than males of both races, and black female addicts were more external than other comparison groups. However, 85 percent of the total sample of 1,400 had an internal locus of control.

Callichia (1974) found HAs on methadone maintenance to be more internal than abstinent addicts. It would have been interesting

to note whether or not any changes in control orientation occurred after placement on methadone maintenance, but this study design did not permit such a finding.

Studies using a trait approach to locus of control have demonstrated that addicts become more internal after 18 months in a therapeutic community (De Leon et al. 1973) and after 9 weeks on methadone maintenance (Henick and Domino 1974).

Two other studies (Smithyman et al. 1974; Platt and Scurra 1974) also found HAs to have an internal orientation.

Now for the apparent conflict: Five studies have found addicts to have an external locus of control (De Leon et al. 1973; Obitz et al. 1973; Obitz et al. 1974; Manganello 1978; Pearlstein 1980). The Pearlstein study compared locus of control in 38 HAs, 34 alcoholics, and 21 amphetamine users. The amphetamine group were more externally directed than the HAs and the alcoholics.

Two studies found HAs to be undifferentiated in directionality (Langrod et al. 1983; Platt 1975).

Methodology seems to account for these differences. In almost every case where no control group was used and where addict scores were compared to published norms of college students, HAs were found to be externally directed. In studies which used relevant control groups, results generally showed HAs to be internally directed.

There are two issues that I want to address now. First, does it make any difference whether addicts are internal or external in orientation, and, second, how can drug addicts be internal anyway?

As to the first issue, locus of control as an orientation is irrelevant unless it can be shown to be related to something else more important. For example, in the Langrod et al. study (1983), the hypothesis was tested that methadone maintenance patients with an internal locus of control would be more likely to be willing to begin detoxification. Results showed a "nonsignificant trend" in support of that hypothesis. To a statistician, a nonsignificant trend is no trend at all, and the null hypothesis is accepted. Thus, having an internal locus of control was not much different from having an external locus of control, when it came to beginning methadone detoxification. A more promising lead seems to be in the area of "detoxification phobia" (Milby et al. 1980). I am involved with a project now with Dr. Milby at the Veterans Administration Medical Center in Birmingham. We believe that many patients have developed a clinical phobia about methadone detox, and plan to test this idea in a multicenter project. I suspect that this will bear more fruit than considering their locus of control.

Second, Strassberg and Robinson (1974) found that addicts with an internal locus of control had higher levels of self-esteem, better

psychological adjustment, and higher motivation to achieve success, and that locus of control orientation was not correlated with length of drug use.

The idea of a HA having an internal locus of control, as indicated by the literature, seems paradoxical. I suspect that they are "pseudointernals." It is quite possible that the internal locus of control seen in addict self-reports is largely a cognitive and intellectual self-report that does not match day-to-day behavior. It seems to serve a defensive function and to reinforce group norms that assert that they are in charge of their lives. However, I suspect that HAs do not behave as if they were internal.

At the risk of getting "soft," let me cite some clinical material that seems consistent with my view.

Wellisch et al. (1970) have reported on a relationship dyad among HAs where the male member is supported and taken care of by the female member, who typically adopts the role of pseudomother for her male partner; hence the term "easy rider" syndrome. Outwardly, the male appears to be along for the joy ride and looks independent. Inwardly, he is passive-aggressive in the fullest sense, extremely dependent on someone to guide him through life. When the relationship ends, he finds someone else to play this role in his life.

Ganger and Shugart (1966) further report that the aggressive behavior that some addicts exhibit toward their families when high is actually "pseudoassertive" behavior that plays an important role in family dynamics and that results in keeping the addict addicted and dependent.

What is actually seen in these two examples is behavior that is very externally oriented under the appearance of an internal orientation.

Sensation Seeking

Sensation seeking as a trait, suggested as a possible factor in the onset of heroin use, explores the tendency of addicts to engage in thrill, adventure, and altered states of consciousness.

Most studies indicate that drug addicts have higher scores in sensation seeking than normals (Galigio and Stein 1983; Platt 1975). This seems to hold true for drug use in college students (Zuckerman et al. 1972) and for addicts on methadone maintenance. Sensation seeking traits probably predated their involvement with opiates (Kohn et al. 1979). Drug addicts seem to show a preference level of stimulation in sensation-seeking experiences that is not seen among nonusers (Reith et al. 1975). Sensation-seeking scores have been related to hallucinogen use in members of a labor union (Khavari et al. 1977) and to the frequency of hallucinogen use among Hispanic males in residential treatment (Kaestner et al. 1977). They also have been positively related to stimulant and

hallucinogen use and negatively related to the use of depressants (Carol and Zuckerman 1977; Galigio and Stein 1983).

White addicts show higher levels of sensation seeking than black addicts (Kaestner et al. 1977; Sutker et al. 1978). Addicts who were higher in sensation seeking also used more categories of drugs, had an earlier age of onset of first drug use, and cited curiosity as their initial motive for using drugs.

Female addicts did not differ from male addicts in sensation seeking (Sutker et al. 1978), and no differences occurred among groups with high rates of parole success compared to recidivists (Platt and Scurra 1974) on sensation-seeking traits. Successful treatment in a therapeutic community decreased sensation-seeking traits among addicts, but no comparable reduction was observed for addicts in prison (Skolnick and Zuckerman 1979).

I would like to make one last point. Eyre et al. (1982) found that 22 percent of a population of 157 HAs reported childhood histories of hyperactivity. Craig (1984a) reported that, based on almost 500 MMPI profiles, HAs typically have high Scale 9 (hypomania) scores. All this seems to correlate with some central nervous system "something." I would like to see a group of HAs with high sensation-seeking scores and high Scale 9 scores in studies designed to address the following questions: Do they have histories of hyperactivity? Are their EEGs abnormal? What would the results of CAT/PET scans show, when equated with HAs without high sensation seeking and high hypomania scores?

SUMMARY OF PSYCHOLOGICAL TEST ASSESSMENTS

What follows is a summary of my 75-page review. You will have to trust that what I am now reporting is true, since few references. other than my own summary (Craig 1985b), will be presented:

- Opiate addicts, as a group, score in the average range of IQ level; this finding is true among a variety of addict subgroups and is independent of the type of intelligence test used to make the assessment.

- Addicts show no group differences in development of moral values and function largely around Kohlberg's Stage 3 (preconventional) level of moral reasoning. Any deficiencies observed in this area by addicts are due to defective ego controls rather than to deficits in moral reasoning.

- Addicts tend to score in the mild to moderate range of depression on most psychological tests and rating scales. These depression scores subside with treatment.

- Drug addicts are undifferentiated with respect to the traits of introversion/extraversion.

- Most addicts score in the direction of internality on locus of control orientation, as opposed to alcoholics who score as externally oriented. However, this is misleading and merely reflects a cognitive belief which addicts hold as a defense--a belief that is not matched by their behavior. Locus of control is also subject to temporary fluctuations based on environmental threats. Addicts' locus of control moves toward greater internality following appropriate treatment.

- Psychiatric studies show that drug addicts have a paucity of major psychiatric syndromes and neuroses and a plethora of personality disorders and character disorders. Psychological tests confirm this finding. This is not to say that major psychiatric syndromes cannot coexist with drug addiction, but merely that such a condition is the exception.

- All studies found that addicts have a poor self-concept, which improves with certain types of treatment.

- Addicts have a higher need for sensation seeking than normal controls.

- Addicts are field dependent, relying on their environment to give them structure and support.

- Studies testing addicts' need hierarchies have often found them to be high in self-reported dominance, aggression, succorance (dependence), change, heterosexuality, and autonomy, and low in endurance, affiliation, and nurturance. They report themselves to be high in need for achievement, but their daily behavior does not match this report. On most tests, addicts would be described as hostile, demanding, aggressive, rebellious, irresponsible, playful, impulsive, and independent, making the establishment of a treatment alliance quite difficult.

- Opiate abuse results in little or no impairment in cerebral functioning (except for acute effects), as measured by neuropsychological tests given up to 9 weeks following abstinence. When differences have been found, they have been described as mild and detectable only with specialized tests, but not suspected clinically.

- A number of variables can influence test findings, particularly time of testing, ethnicity, class of drugs, reasons for seeking treatment, and the presence of coexisting clinical syndromes.

- If the goal is to detect substance abuse with psychological tests, then the MacAndrew Alcoholism Scale of the MMPI is currently the best psychologically based scale to provide information about substance-abusing tendencies.

PERSONALITY STRUCTURE OF HEROIN ADDICTS

Research using psychological tests and scales has found the personality of drug addicts to have the components of a weak ego, character-disordered traits, field dependence, and stfmulus augmentation. These findings parallel, but are somewhat different from, similar reports on the alcoholic personality (Barnes 1979).

Weak Ego

Addicts, like alcoholics, have a weak ego, but it is manifested somewhat differently from the personality of alcoholics. Like alcoholics, they have a negative self-concept, show hostility, immaturity, and impulsiveness , and have a low tolerance for frustration. They are oriented toward the present rather than showing goal-oriented behavior toward the future. Unlike alcoholics, they have a strong sexual identity, with high need for heterosexuality but low need for endurance and affiliation. This suggests that addict sexuality may be another area in life where other people (females) are used to gratify and satisfy the addict's need for intimacy without reciprocity or need for lasting attachments.

Character-Disordered Traits

Addicts have traits typical of traditional antisocial psychopathy. Relationships are superficial and instrumental only to the extent that others gratify their narcissistic demands. Depression is mild but chronic and low level. Anxiety is manifested through impulsive behavior and somatic defenses. They aggress to achieve their ends, try to dominate relationships, and are poor treatment risks.

Field Dependence

Addicts are more field dependent than normals, suggesting that they have a higher need for dependency than do normals. They rely on their environment to provide them with structure and support.

Stimulus Augmentation

Addicts cannot tolerate boredom, are playful, want change, are exhibitionistic, high in sensation seeking, and are stimulus augmenters rather than stimulus reducers.

IMPLICATIONS FOR FUTURE RESEARCH

Now that the personality structure of heroin addicts is somewhat in hand, the question remains, "So what?" Where do we go from here?

I think we are at a point in our knowledge where it is no longer sufficient merely to give drug addicts a personality test and then report the results (the one exception might be cocaine abusers,

for whom little information other than demographics presently exists). I believe that future directions should relate personality traits and styles to other variables of interest, particularly treatment response and treatment outcome (Craig 1982b).

This is the direction my own work has taken. For example, we have learned that personality traits, as measured by the MMPI and the Millon Clinical Multiaxial Inventory, are not related to treatment dropout in our program (Craig 1984b; Craig 1984c), whereas interactional concepts have proved to be quite reliable indicators of dropout upon cross-validation (Craig et al. 1982). Relating personality traits to other variables of interest is the direction in which we have to go.

Another important area has to do with effectiveness of treatment, particularly personality change as a result of treatment. Most drug addicts are treated in programs and not in private practice (Craig 1985b). In our own program, we have data that demonstrate the effectiveness of methadone maintenance (Craig 1980) but no data on the effectiveness of our inpatient unit. We are currently using the Adjective Check List, measuring needs, to see if need patterns change after 3 weeks of intensive rehabilitation.

Retrospective studies are needed to determine the personality of drug addicts prior to addiction. A few seminal reports of this kind are available in the alcoholic literature and would be extremely enlightening in the drug abuse literature as well. If NIDA wants to have a real effect in this area, it should create a grant for a researcher to go into a community, select random samples of community residents at risk for and with equal access to drugs, and then follow them over time. The researcher should find out which ones become addicts and which ones do not, then go over their psychological test data to see if any traits or scores distinguish the users from the abstainers. This is what is really needed.

We know quite a lot about how drug addicts appear on psychological tests; now we have to determine what this means.

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Locus of Control and Need for Control Among Heroin Users

Don C. Des Jarlais

INTRODUCTION

"Loss of control" over substance use has long been considered to be one of the primary characteristics that distinguish the true "alcoholic" or "addict" from the "heavy user." The standard conceptualization of full loss of control involves both use to the point at which there are severe negative consequences of substance use for the individual and an inability ever to return to "moderate" levels of use. The purpose of this monograph is to examine possible new research techniques for interdisciplinary study of this central problem in substance abuse. As part of this purpose, we will first review some of our previous research on locus of control among heroin users and then report on our current studies of control over drug use among heroin users.

The concept of locus of control was first developed by Rotter (1966) and was defined in terms of the individual's perception of control over his or her reinforcements. A person with an "internal" locus of control believed that control over reinforcements resided primarily within the individual; thus, rewards were mainly the result of efforts and deliberate choices. Persons with an "external" locus of control believed that control over reinforcements was located outside the individual. and that rewards were primarily determined by factors such as fate, chance, or powerful others.

There is a great volume of research on locus of control in the psychological literature, with the great majority of findings linking internality with positive mental health (Lefcourt 1976). Since drugs are readily identifiable and powerful reinforcers, there was an expectation that strong relationships between locus of control and drug use might be found. Unfortunately, there are contradictory findings as to whether drug users are internal (Berzins and Ross 1973; Carroll, unpublished dissertation; Gross and Morosko 1970) or external (Palmer 1971; Obitz et al. 1973), and, if they are internal, whether they are "true" internals (Berzins and Ross 1973; Carroll, unpublished dissertation) or

"pseudo" internals (Lefcourt 1976). Craig (this volume) recently reviewed studies of locus of control among substance abusers and found approximately equal numbers of studies showing drug abusers to be internal, external, and neither internal nor external.

PRIOR STUDY

Several years ago, we conducted a study of locus of control among methadone maintenance patients in an attempt to clarify relationships between locus of control and drug use. We believed that clarification might be achieved by studying a specific behavior--voluntary detoxification from methadone maintenance--that had clear implications for control (Langrod et al. 1983).

Voluntary detoxification was selected as a specific behavior because of its many links to control in patients' lives. Successful voluntary detoxification would objectively increase patients' control over their lives. Patients would no longer have to report to a clinic one or more times per week, receive mandatory counseling, submit urine specimens for analysis, or obtain prior approval for personal or business travel. Voluntary detoxification is also seen by patients as a desired treatment goal that depends upon willpower and effort rather than chance factors.

From the great number of studies that showed relationships between internality and positive mental health, we generated two hypotheses:

- Internality would be positively associated with stated willingness to begin a voluntary detoxification.

- Internality would be positively associated with actually beginning a voluntary detoxification within the 90-day followup period. (A reduction in methadone dosage was required as evidence of actually beginning detoxification.)

These hypotheses were tested in a sample of 115 male methadone maintenance patients, who were given the Rotter Locus of Control Scale, interviewed regarding their perceptions of and willingness to begin a voluntary detoxification, and then followed to see which subjects had actually begun such a detoxification.

The findings from this study did not resolve ambiguities in the relationships between locus of control and drug use. First, the mean score on the Locus of Control Scale was 8.9, which was neither "internal" nor "external" when compared to the means from a large number of other samples. Second, there was only weak support for the first hypothesis , a correlation of 0.15, $p<.11$, between internality and stated willingness to begin detoxification. Finally, there was a reversal of the second hypothesis. Among those subjects who indicated a willingness to begin detoxification, there was a statistically significant negative correlation between actually beginning detoxification ($r=-0.30$ with Locus of Control Scale, $p<.012$) and internality,

REFORMULATION: NEED FOR CONTROL AS A MOTIVE FOR BEHAVIOR

These findings led us to question the value of the concept of locus of control in studying drug use and abuse. Locus of control is conceptualized as a relatively stable personality trait, a belief about how the world works and the person's relationship to the working of the world. Our findings were best interpreted in terms of a varying need for control. Need for control would vary with both the general life situation of the individual and the specific immediate situation. In general (outside of pathologic conditions), control over reinforcers would be valued. Individuals who experience a sense of control over their reinforcers will defend against losing their sense of control, and individuals who experience a lack of control over reinforcers will actively seek means of reestablishing such control.

By definition, drugs are an important set of reinforcers for “drug abusers," and "control" over drug use thus will be an important part of their lives. The methadone patients who felt a lack of control over reinforcers (the "externals") would thus begin detoxification to gain a sense of control. Those methadone patients who experienced a sense of control over reinforcers (the "internals") would avoid actually beginning detoxification, since failure at this important task would be a clear threat to their sense of control. (The likelihood of successful detoxification and abstinence afterward is relatively low, approximately one in six (Des Jarlais et al. 1981)).

Within this reformulation, the Locus of Control Scale can be used as an imperfect measure of need for control. "Externals" would be considered to have an unmet need for control and would be likely to take action that would lead to an increased degree of control over reinforcers. "Internals" would be considered to have their need for control met and would avoid action that would threaten their current sense of control. The scale is thus being used to measure differences in situationally produced motives for behavior, not differences in the personalities of individuals.

This reformulation is consistent with the one area in which there are theoretically plausible and empirically consistent data regarding locus of control and drug abuse. Studies from therapeutic community treatment (De Leon et al. 1973) and methadone maintenance treatment (Henik and Domino 1974) show change from externality to internality during time spent in drug abuse treatment. An unmet need for control over reinforcers would lead individuals to enter treatment, and successful adaptation to treatment would be associated with developing a sense of control over reinforcers in one's life.

PILOT STUDY OF INTRANASAL HEROIN USERS

We have since conducted another study of methadone patients, relevant to relationships between perceived need for control and important drug use behavior.

Acquired immunodeficiency syndrome (AIDS) has become the major health threat to intravenous (IV) drug users in New York City. Over 1,500 IV drug users in the city have contracted AIDS as of September 1985; the total number of cases continues to double approximately every year (New York City Department of Health 1985). HTLV-III/LAV, the virus that causes AIDS, appears to be spread through the sharing of "works" (needles and syringes) among IV drug users (Cohen et al. 1985; Weiss et al. 1985). As part of our ongoing research on AIDS among IV drug users, we conducted a pilot study of persons who had used heroin intranasally (sniffed) to the point where they required methadone maintenance treatment, but who had not become regular drug injectors.

Injecting heroin is a much more physiologically efficient route of administration. (Our subjects estimated that they had to purchase approximately three times the amount of heroin for sniffing to achieve the same effects as by injecting.) Persons who sniff large amounts of heroin are important to study, both in relation to the practical aspects of limiting the spread of HTLV-III/LAV among drug users and in relation to the theoretical issues of control over amount of drug use and route of administration.

We interviewed 16 subjects with histories of intranasal use of heroin who had entered a New York City methadone maintenance program during the previous year. These represented the majority of 20 such persons who had been treated at this particular program over the previous 18 months.

The subjects were relatively young (mean age of 21 years, range of 17 to 24), primarily Hispanic (87.5 percent Hispanic, 12.5 percent non-Hispanic white) and female (62.5 percent). They reported a range of 2 to 9 years of sniffing heroin prior to entry into treatment (mean of 4 years). They had used a variety of other drugs, primarily marijuana and cocaine (not injected), in addition to heroin. Of the 16, 4 had injected heroin but had not continued this route of administration. They reported using an average of $40 per day of heroin (four $10 bags) prior to entry into treatment (range from 1 to 10 bags).

The two questions in the interview that were most relevant to the sense of and need for control were the reasons for not injecting heroin and the reasons for entering treatment. (These questions were open-ended and were asked prior to any questions on AIDS, to reduce any interview demand characteristics. The respondents could give multiple reasons but were not prompted with respect to any particular reason.)

For the question concerning why the subject did not inject drugs, 14 of the 16 respondents mentioned a fear of needles. This fear was often described as originating in childhood experiences with physicians and involved both fear of pain and anxiety/nausea at the thought of bleeding.

The second most frequently given response to the question on not injecting heroin, mentioned by 11 subjects, was the belief that injecting would lead to becoming a "street junkie." A street junkie was described as a person for whom heroin use completely dominated all other activities. For the junkie, all other values, commitments, and relationships were sacrificed to obtaining and using heroin. This sacrificing of all other interests was seen as the final stage in loss of control over heroin use.

Significantly, this stage of loss of control also was seen to involve loss of self-esteem and social respect. In talking about street junkies, subjects made statements such as, "I didn't want to get that low,"and "I couldn't see myself doing that." Respect from others would be lost because being a junkie could not be concealed from others. Both the physical evidence of needle use ("tracks," the scars from frequent injection) and the willingness to "do anything to obtain drugs" (including stealing from friends and relatives, committing serious crimes on a frequent basis) would lead others to learn of one's condition.

Interestingly, none of the subjects specifically mentioned a fear of AIDS as a reason for not injecting drugs, though later in the interview the majority did express great concern about AIDS. Relationships among knowledge of AIDS, personal experience with AIDS victims, and the decision not to inject drugs will be presented in a separate paper.

The majority of reasons given for entering treatment were phrased in terms of control over heroin use. Nine of the respondents stated that they could no longer manage their use of heroin. Physical dependence had developed, efforts to limit use had failed, and they were now devoting large resources to heroin consumption (an average of $40 per day). This situation was often described in terms of "being tired" of the "hassles" involved in obtaining large quantities of heroin.

The second most frequently cited reason for entering treatment was to avoid consequences of heroin use that were foreseen but had not yet occurred. Seven respondents stated that they had entered treatment to avoid impending negative consequences; of these, three wanted to avoid becoming "street junkies," and two wished to avoid becoming bad mothers to their children.

DISCUSSION

The results of the pilot study readily fit with the need-for-control formulation derived from the methadone maintenance detoxification study. Results indicate that individuals will defend against loss of control over their reinforcers, and if loss of control should occur, will actively seek to reestablish control. Avoiding injection was often described as avoiding a fundamental loss of control. Seeking treatment was typically described as an attempt to regain control.

The pilot study results have conflicting implications for the idea that drug abusers are characterized by either an internal or an external locus of control. The pretreatment loss of control over heroin use would be an experience that should induce an external locus of control, while the ability to avoid regular injection of heroin would be an experience consistent with an internal locus of control. Thus, one can generate plausible predictions for either "internality" or "externality" among these intranasal heroin users. Locus of control scores taken at the time of the interviews (after treatment had begun) would not help in resolving these contradictory implications, given the previously cited studies showing movement towards internality with time in treatment.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

From present data, there seems to be little evidence of a consistent relationship between perceived locus of control over reinforcers (as a stable personality characteristic) and substance abuse. This is not to imply that control over drugs as reinforcers is not relevant to substance abuse. Relationships between locus of control and specific behavior, e.g., time in treatment, initiation of voluntary detoxification, have been found. Drug users report loss of control and maintaining control to be important reasons for behavior such as entering treatment and avoiding injection of heroin.

A formulation of need for control over drug use as a central concern for drug users avoids the problems associated with the conceptualization of locus of control as a stable personality characteristic. Perceived control over reinforcers might not be stable over time; rather, need for control might vary according to a variety of factors including intensity of present drug use, psychophysiological adaptations to repeated drug use, availability of drugs, approval or sanctions from significant others, treatment status, and the user's self-concept.

Instruments and techniques for measuring need for control are clearly needed if this concept is to be studied scientifically. Because need for control is conceptualized as varying across both persons and situations, instruments similar to the state/trait measures of anxiety may be required.

After suitable instruments are developed, longitudinal studies of need for control over drug use will be required. If this need does vary over time, and if it is an important determinant in drug use/abuse behavior, then meaningful results are likely only in studies with time as a variable. Studies that do not include time as a variable will probably replicate the theoretical confusion and empirically conflicting data that characterize the present research on locus of control in drug abuse.

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Personality Characteristics and Self-Abusive Behavior

Donald G. Forgays

INTRODUCTION

Five themes are relevant to self-abusive behaviors, notably tobacco, alcohol, and drug abuse and, to some extent, overeating. The themes are:

- Self-cure of many of these behaviors occurs much more frequently than interventional studies indicate.
- Self-abusers of various kinds may have distinctive personality characteristics, and there may be commonality of certain characteristics across abuse types.
- Subjects' differences may be related to ability to change the abusive behavior, either by themselves or through intervention.
- Personality characteristics may be related in somewhat different ways to each of the various stages of substance use, abuse, and cure or fail potential.
- Intervention and prevention programs and further research are clearly indicated by an analysis which emphasizes individual differences.

While this paper discusses each of these points, primarily the first three are addressed.

SELF-CURE

Studies of therapeutic attempts to intervene in self-abusive behaviors report little success. For example, Leventhal and Cleary (1980) reviewed smoking intervention studies in which the success rate was, at best, 20 percent of the smokers. Success was defined as high reduction or stoppage of smoking 1 year after intervention. Extensive literature reviews are also available for weight reduction interventions for the obese (Stunkard and McLaren-Hume 1959; Wing and Jeffrey 1979). Only about 20 percent of the obese

can expect to lose as much as 20 pounds as a result of intervention. The interventional success rate for alcoholism and drug abuse is expected to be at least as poor as that for smoking and obesity. In many studies, there is considerable postintervention improvement in the behavior of concern, but the rate of recidivism is also great, leaving a small proportion of cures. The dismal results usually reported for therapeutic interventions in these behaviors do not support the notion that we know how to manage these behaviors.

All the more startling, then, are the results of several provocative studies indicating a much higher level of cure. For example, Schachter (1982) reports that as many as 60 percent of heavy smokers are able to quit or greatly reduce smoking. He reports a similar statistic for obese persons who are able to reduce their weight to nonobese standards. In most of these persons, interventional help was not needed for the change to occur. We recently attempted to replicate the Schachter study (Rzewnicki and Forgays, submitted for publication) and found that about 60 percent of our subjects who were smokers were able to self-cure. The percentage of our obese subjects who were able to self-manage their weight was less than that reported by Schachter but higher than that reported in most of the interventional studies.

In a fascinating recent study, Jeffrey et al. (1982) compared three formats of a correspondence course with a standard behavioral group program for smoking reduction and for weight management. Subjects were randomly assigned to one of the four study conditions. These authors report that even the basic home correspondence course was as effective as any of the other conditions and produced significant changes in health behavior. While the home course is an intervention, of course, the process is close to self-management.

Other self-abusive behaviors may also be subject to self-management. For example, Robins et al. (1980) studied a large number of Vietnam veterans 3 years after they had left Vietnam. Many had been frequent users of heroin during the war. The authors reported that users managed to quit using heroin much more often than general interventional data would predict and, again, frequently without any special help. They also reported that some of these former users returned to the use of heroin in this country and were able to give it up once more without help. Other important findings in this study were that heroin users tended to be polydrug users, using all drugs during the same period, and that they were highly likely to have had serious social problems before they began to use drugs. Robins and her colleagues concluded that our society has overemphasized the importance of treatment for heroin and has tended to ignore the severe social adjustment difficulties that such drug users have.

In an interesting book on de-addiction, Brill (1972) reports several case histories of heroin addicts who were able to self-cure. While these individuals indicated that self-management was

difficult to achieve, they also made it clear that certain personality characteristics may have helped them to control these important behaviors.

Several reports have provided data attesting to the voluntary reduction and cessation of marijuana usage (Brown et al. 1974; Raffoul and Cummins 1980; Sadava and Forsyth 1977). Most of the subjects of these studies were college students whose drug reductions were associated with social psychological changes in their status, principally life cycle changes and the acquisition of nonstudent roles. According to the National Commission on Marijuana and Drug Abuse, 1972, about half of those over the age of 18 who had used marijuana stopped using it; presumably many of these were self-cures. Data available from Information Canada (1972) agrees with this finding very closely.

It has been difficult to find evidence of the self-management of alcohol abuse. However, Statistics Canada (1981) provides data on a national sample in which between 5 and 12 percent of drinkers ceased drinking; presumably this was done on a voluntary basis. Percentages varied with age and sex of respondent and were higher for male and older subjects. Even though some of the notions that Pattison et al. (1977) discuss are controversial, they list 74 studies reporting data indicating that former alcoholics not only can be "cured' but can even return to controlled drinking without becoming alcoholics again.

Thus, there appears to be substantial evidence that persons are able to self-manage important self-abusive behaviors much more frequently than the interventional literature would predict. One clear possibility for such large differences in success rates between self-management reports and the interventional studies is that subjects in most of the interventional studies are self-selected and do not represent the self-abuse population. This point is made emphatically by Schachter (1982) and by Rzewnicki and Forgays (1985), for smoking and obesity, and by Taylor et al. (1982) for alcoholism. Indeed, the studies of Schachter and Rzewnicki and Forgays made use of at least 90 percent of the total population of their subjects and thus can be seen to represent well those limited populations. More studies with entire populations should be undertaken to assess better the distortion factor involved in self-selected samples.

A second possibility is that subjects in the interview studies of Schachter (1982) and Rzewnicki and Forgays (submitted for publication) may have made several attempts at self-management before attaining success, while intervention seekers are making only a single attempt, at least in the study proper. Multiple attempts, especially of motivated self-managers, may be more successful than a single attempt, especially one that is other-directed.

A third possibility is that the interventional programs that have been employed to date have been ineffective and may even have

suppressed change which might have taken place otherwise. This point will be elaborated shortly.

Thus, if a great number of persons are able to manage many of these addictive behaviors, largely on their own, we have probably erred in our research by focusing on the hardcore, intransigent, and largely self-selected subjects in our interventional studies and ignoring those who have “cured” themselves. To focus on the successful may throw light on important subject characteristics, intervention designs that may be promising, and prevention possibilities. In my laboratory, we have adopted this approach in ongoing studies of smoking and obesity and are just beginning similar pilot studies on alcohol and drug abuse.

PERSONALITY CHARACTERISTICS OF SELF-ABUSERS

It is an intriguing notion that self-abusive behaviors occur in persons who have specific personality characteristics. If this is so, then information on personality characteristics may point the way to better design of intervention and prevention programs. Is there evidence for such relationships? The answer to this question seems to be a resounding "yes" with respect to smoking, a less vigorous "yes' with respect to alcohol and drug abuse, and an “I don't know" with respect to obesity.

Lilienfeld (1959) has reported that cigarette smokers married more often, moved more frequently, and changed jobs more often than nonsmokers. Veldman and Brown (1969) found that smokers were less well adjusted academically, socially, and physically than nonsmokers, but they state that their smokers did not appear to be "neurotic." Using his own Personality Inventory on a large number of middle-aged male subjects, Eysenck (1963) found that his Extraversion (E) scale was related to cigarette smoking, while pipe smokers tended to be high on introversion (I). The Neuroticism (N) scale was not related to smoking level, but those high on the Neuroticism scale inhaled more deeply. The extraversion finding was replicated by Smith (1970). In a most unusual study of the use of maternity services in Britain, all infants born during a particular week of the year were followed up every 2 years (Cherry and Kiernan 1976). The Eysenck Personality Inventory was administered at the age of 16 years and smoking information obtained at 20 and 25 years of age. These authors confirmed the earlier finding of high extraversion scores for smokers, but also found that smokers were reliably higher on the Neuroticism scale. The neuroticism score was also related positively to the degree of inhalation of smoke. All findings were true for both sexes. In recent work following up his earlier studies, Eysenck (1980) again found that smokers were higher than nonsmokers on the Extraversion scale but that only his female subjects were higher on the Neuroticism scale. Smokers were also higher than nonsmokers on his new Psychoticism (P) scale. While there are small differences in the findings of several studies employing the Eysenck scales, the principal findings appear to be robust.

Zuckerman (1979) reported mixed results with respect to the relationship between smoking and scores on his Sensation Seeking Scales, with some studies finding higher sensation-seeking scores but only for male smokers, not females; other studies found the reverse. Zuckerman suggested that these mixed results might reflect different motives for smoking--smoking for arousal might occur in high sensation-seeking persons, while smoking to relieve social tension might occur in low sensation-seeking persons.

Friedman et al. (1975) attempted to relate cigarette smoking to myocardial infarction. They were not able to confirm a direct relationship but concluded that smoking as a coronary risk factor may vary with psychological status of the person.

The general picture of the relationship between smoking and personality characteristics has been summarized recently by Ashton and Stepney (1982). Smokers tended to be high on Eysenck's scales of Extraversion and Neuroticism. They tended to be high risk takers, and have higher impulsivity and internal sensation seeking. They also tended to be high on Eysenck's Psychoticism scale, which may measure a dimension related to sensation seeking. In general, heavy smokers are poorly integrated persons.

Only a small amount of information is available on the personality characteristics of alcohol abusers. Schwarz et al. (1978) found that sensation-seeking score in college-aged subjects was strongly and positively related to alcohol use, while a measure of anxiety was not. In these subjects, alcohol appeared to serve as a "releaser" for normally restrained social behavior. Zuckerman (1979) reported that persons with high sensation-seeking scores were more likely to try any drug, including alcohol. He reported, however, that alcoholics were not high scorers on his scale but, rather, scored at their normal age levels. The differences between these two reports may simply be the difference between alcohol users and alcohol abusers, but they also suggest developmental differences which should be investigated in a longitudinal design.

Are there unique personality characteristics of the drug abuser? Sutker et al. (1978) reported that drug addicts as a group were high on the Adjective Check List scales of Aggression and Succorance. Zuckerman (1979) found that persons with high sensation-seeking scores were more likely to try any drug than persons with low scores. He reported that high sensation seekers in both student and nonstudent groups were more likely to experiment with a variety of drugs, starting with marijuana. Sensation seeking was found also to be related to drug use in college students by Galizio and Rosenthal (1983). A similar finding has been reported by Khavari et al. (1977), who studied several hundred male and female members of labor unions. They found that while results depended upon the specific type of drug used, the use of psychedelics was strongly associated with the need of their subjects to seek out new and often unconventional experiences. Other findings were that marijuana users were different from users of

other drugs in that they seek social approval and display uninhibited modes of self-expression, while the use of other psychedelics was associated with higher manifest anxiety, tendencies to seek out social stimulation, and extraversion, but not with approval seeking or uninhibitedness.

Recent research on prediction of addiction behavior, including alcohol abuse, has made use of the MacAndrew Scale (MacAndrew 1965; MacAndrew 1979; Rathus et al. 1980). This is an empirically derived scale based on the Minnesota Multiphasic Personality Inventory (MMPI). It appears to be a measure of impulsivity, risk taking, high energy and activity, interest in excitement and stimulation, and so on. The MacAndrew Scale reminds one of the Sensation Seeking Scales and of Eysenck's Psychoticism scale. Wisniewski et al. (1985) have found this measure to be the best single predictor, as compared with a variety of sociodemographic variables, of alcohol and drug use for both male and female subjects.

The picture emerging in these studies appears to be that of a personality profile in which important characteristics are shared by self-abusers of tobacco, alcohol, or illegal drugs. The profile is one of high extraversion, probably some neuroticism, high impulsivity, high risk taking, and a strong need to seek out new and unconventional experiences. There are likely to be sex, developmental, and social-class differences within this generic profile.

The familiar chicken-egg issue permeates these relationships. Do persons having this profile gravitate to abusing situations or does abuse lead to the expression of the profile characteristics? The literature has too little data on this issue. However, the Cherry and Kiernan (1976) research is quite clear on the matter with respect to smoking. Personality measures at age 16 and smoking measures at ages 20 and 25 showed that potential smokers had high extraversion and neuroticism scores before they took up smoking. Thus, it appears that we may be able to predict later self-abusive behavior from earlier personality measures.

PERSONALITY CHARACTERISTICS AND CHANCE POTENTIAL AMONG SELF-ABUSERS

If self-abusers share some personality characteristics which exist before the self-abuse, it would be interesting to know whether personality characteristics can also be related to the ability of an abuser to reduce or stop the abuse. While most such evidence exists for smoking, some does relate to alcohol and drug use.

Some of the smokers in the Cherry and Kiernan (1976) study had given up smoking by the time they were 25 years of age. What were they like? In general, they were extraverts who did not smoke at a high daily level. Specifically, male extraverts who were stable on the Neuroticism scale and who smoked at a low level were most likely to give up smoking; 47 percent of this group were able to

do so by age 25. This proportion drops to 2 percent for the neurotic introverts who smoke at a high level.

Friedman et al. (1979) compared ex-smokers, continuing smokers, and nonsmokers in a large number of white and black male and female members of a health maintenance program. As compared with continuing smokers, smokers who quit had fewer cardiovascular symptoms, smoked fewer cigarettes for a shorter time, inhaled less, were better educated, consumed less alcohol, and differed on several other physiological indices. On a measure derived from the MMPI (not described well in the article), quitters and never smokers scored lower than the persistent smokers. The answers of quitters in the 155 items on this scale were not like those who later developed myocardial infarction. The authors conclude that quitters are more analogous to never smokers than to persistent smokers on several of their indices, including their personality measure.

In his recent book, Eysenck (1980) reports his own data on never smokers, persistent smokers, cured smokers, and failed smokers, using his Eysenck Personality Questionnaire (EPQ) measure. He found significant differences among these four groups on the Psychoticism, Extraversion, and Neuroticism scales, but not on the Lie scale. There were no reliable sex by group interactions. If his data are combined across the sexes, the personality measures for the four groups are as follows:

- Those who never smoked have middle values on the Psychoticism scale, middle values on the Extraversion scale, and low values on the Neuroticism scale.

- Those who persist in smoking have high values on the P scale, quite high on E, and quite high on N.

- Those who try but fail to quit smoking have the highest P scores, the highest E scores, and the highest N scores of the four groups.

- Those who quit smoking have the lowest P scores, lowest E scores, and somewhat elevated N scores.

Two relationships stand out in these data. The first is that persistent smokers and failed smokers are similar in their profiles on this measure and score highly on all three scales, with the failed smoker scoring somewhat higher than the continuing smoker who does not try to stop. The second is that the cured smoker is similar in profile to the never smoker, with the never smoker being somewhat higher on the P and E scores and the cured smoker being somewhat higher on N.

A recently completed smoking intervention study provided heavy-smoking subjects with flotation relaxation in various time distributions, with or without messages that were attempts to modify their attitudes about smoking (Forgays, in press). There were two

waiting-list control groups; one received the messages over the telephone and the other did not. All subjects took a battery of personality tests before active intervention, and each was followed for over a year to see whether or not any changes in smoking behavior had taken place. We found, at 1-year followup, that our relaxation groups had reduced their smoking behavior to an extent considerably greater than that most frequently found in the smoking intervention literature. To our surprise, however, we found that our control subjects had reduced their smoking even more, especially the group that had the least contact with us. Since we found that there were quitters in each of the study groups, persons who had reduced smoking appreciably, and subjects whose smoking patterns were unchanged, we decided to compare these three groups on the various personality measures. Remember that each of these new groups represents all six groups of the original study.

The personality measures we employed included the Eysenck Personality Inventory (EPI), the Sensation Seeking Scales (SSS), the Spielberger Trait Anxiety Scale, the Manifest Anxiety Scale, the Rotter Locus of Control measure, the Jenkins Activity Scale, Oerogatis' Symptom Check List-90, and Morris' Ways-to-Live measure.

In comparing the cures with the reducers with the persistent smokers, the following profile emerged:

- On the EPI, the cures were somewhat higher, though not reliably so, on the Extraversion scale, but were reliably higher on the Neuroticism scale than were the reducers and the continuing smokers.

- On Zuckerman's SSS, the cures and the reducers were reliably higher than the persistent smokers.

- On the Spielberger Trait Anxiety Scale, the cures scored higher anxiety than the continuing smokers.

- No reliable differences were found on the Manifest Anxiety Scale, but the cures showed more anxiety than the reducers, who in turn showed more anxiety than the continuing smokers.

- Average scores for the three groups of subjects were about the same on the Locus of Control measure.

- On the Jenkins Activity Scale, reliable differences placed the cure subjects in the direction of Type A (63 percent score), reducers about average (44 percent), and persistent smokers in the direction of Type B (34 percent). Let me emphasize that cures are not Type A and continuing smokers Type B. The scores are not that extreme, but they are significantly different in these directions.

- On the Symptom Check List-90, the cure group is reliably less stable, more somatic, more obsessive-compulsive, and more

anxious than the other two groups, and the reducers tend to have more of all these characteristics than the continuing smokers. Again, I wish to emphasize that these scores are not that extreme; that is, the cures are not emotionally disordered, but they are notably different from the other subjects.

- On the Morris Ways-to-Live measure, the cure group displays a low self-sufficiency pattern but also a high attraction to many different ways to live their lives, compared with the other two groups.

Based on this study, then, the general personality profile of cured smokers is that they tend to be somewhat emotionally unstable, score in the direction of Type A, and are somewhat more anxious than the persistent smokers. They are more obsessive-compulsive, have more somatic complaints, are less secure, are more independent of others in making decisions, and like to do new and different things more than do the continuing smokers. The reduced smokers tend to be in between the cures and the persistent smokers on most of these dimensions.

For alcohol abusers, the data are more sparse. McGovern and Caputo (1983) report that the most significant predictor of treatment outcome for inpatient alcohol detoxification is the locus of control score. Internalizers on this scale tend to be more successful than externalizers in treatment outcomes. This finding would appear to be in accord with the review findings of Craig (1979).

In an interesting study, Hurlburt et al. (1984) compared Alcoholics Anonymous members with nonmembers who were alcoholics, on Eysenck's EPQ scale. They found that members were higher on the Extraversion scale, but lower on the Neuroticism and Psychoticism scales.

Billings and Moos (1983) studied psychosocial processes of recovery among alcoholics and their families. They found that patients who controlled their drinking showed improvements in nondrinking aspects of their functioning, and members of their families showed improved adjustment as well. These recovered families were comparable to matched nonalcoholic families in posttreatment functioning. The relapsed alcoholics and their families suffered from multidimensional impairments. While they did not report on personality measurement as such, it seems clear from their data that the coping behaviors and social resources of these controlled alcoholics and their families, as well ,as the environmental stressors impinging on them, had as much influence on the recovery process as the treatment experiences.

There is little information on sensation-seeking scores of recovered vs. relapsed alcoholics. Zuckerman's (Zuckerman 1979) finding of average SSS scores for alcoholics would not predict such differences, perhaps, but study of the various alcohol groups,

nonuser and abuser, failed and cured, should be undertaken with this instrument.

Data on the personality characteristics of drug users and non-users, ex-users and failed users, are sorely lacking. Designs of the sort described above in the smoking change studies should be undertaken as soon as possible.

While many gaps exist in the data on change of abusive behavior, the studies described at least suggest strongly that personality characteristics are involved in the process.

PERSONALITY CHARACTERISTICS AND THE STAGES OF SELF-ABUSE AND CHANGE

One of the difficulties encountered in the past in attempting to relate personality measures to self-abusive behavior may be the tendency to ignore the possibility that different personality dimensions relate to different stages of abuse. In other words, the kinds of factors that lead to abuse may be somewhat different from those conducive to maintenance behavior, which again may be different from those associated with later change. The picture may be a delicate one, bludgeoned with simplistic research designs and a quest for a magic bullet; i.e., uniform treatment plans for substance abuse problems.

For example, Cherry and Kiernan (1976) found that neurotic extraverts would be more likely to start smoking cigarettes, while stable extraverts would be more likely to stop smoking. Ashton and Stepney (1982) suggested that peer influence was very important in starting to smoke but that other factors, largely personality ones, were related to stopping. Keup (1982) reported that sociological reasons (friends, relatives, and media influence) and psychological reasons (curiosity, enjoyment, novelty, escape) accounted for virtually all the initiation of drug abuse in the subjects he studied. Sadava and Forsyth (1977) found that initiation to cannabis use was largely due to social variables, including social support, sibling models, and the like, while personality variables were largely responsible for the user's stopping the abuse. They found that subjects who were able to stop were less conforming and more independent and that social variables were not important. Social factors regain their importance in relapses to drug use which may occur.

Admittedly, the information above is only suggestive. However, it suggests the possibility of differential dynamics related to initiation of abuse, perhaps to maintenance of the abuse, and to later change. Research designs in the future should take these distinctions into account, especially in investigations of personality characteristics related to abuse pattern.

INTERVENTION, PREVENTION, AND FURTHER RESEARCH

Does the analysis provided suggest intervention, prevention, and further research programs which might be applied to self-abusive behavior? I believe it does.

In planning therapeutic interventions for such behaviors, we should take the personality characteristics of the clients into account. Zuckerman (1979) suggested that we take sensation-seeking score into such account. Cherry and Kiernan (1976) stated that the practical use of their data would include the possibility of allocating clients to different types of smoking clinics. Our own research and that of Eysenck (1980) suggests that matching of client to interventional program will likely be a more successful procedure than attempts to provide a uniform program for all comers; The possible mismatching provided in past interventional programs may be responsible, in part, for the mixed results obtained. It is possible that, under these circumstances, therapeutic intervention may be actually inhibitory for some clients, or perverse, as Schachter (1982) has called it.

For prevention programs, again the key word is matching of campaign to type of subject, following the logic that a uniform program may not be meaningful for subjects with different personalities. Cherry and Kiernan (1976) have proposed that their kinds of results should be incorporated in the design of antismoking propaganda. Zuckerman (1979) has suggested that sensation-seeking score might lead us to provide choices for high sensation seekers other than drugs or crime; such choices might provide unusual experiences in occupations or entertainment avenues. Indeed, it might be less expensive to send kids to Disneyland than to provide high-level therapy programs, especially if they do not work.

To take such a view of prevention is to bend the disease model followed lately. Rather than await the display of self-abusive behaviors and then jump in with therapeutic attempts to "cure the disease," we should, perhaps, consider a prevention paradigm, whether the inoculation is socially or physiologically based.

For research, I propose an epidemiological approach to these issues. For each abusive behavior, we should study those who have the behavior, and those who do not have it; those who have changed the behavior, with and without intervention; and those who have failed to change it. We should certainly pay as much attention to the cases of success as to the failures. And we should emphasize and measure carefully individual differences among subjects, as Eysenck (1981) has recently pointed out. We should attend to the time course of self-abusive behavior and should break down our analyses into the initiation, continuance, and change stages. All of this should be done in carefully controlled studies.

Nothing said here precludes the inclusion of a variety of physiological measures. There must be physiological substrata to these behaviors, whether correlative or causal, and these substrata

should be investigated. Neither has anything been said that precludes the possibility of important genetic contribution to the development of such behaviors, likely through the influence of physiological processes that may underlie specific personality characteristics.

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Sensation Seeking and the Endogenous Deficit Theory of Drug Abuse

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INTRODUCTION

Sensation seeking is a personality trait that is central to an understanding of the biological disposition toward drug abuse. The general definition of the trait is:

> the need for varied, novel, and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experience. (Zuckerman 1979, p. 10)

The most frequent reasons given by users of many drugs, including marijuana, narcotics, and hallucinogens, were "to experience something new" or "curiosity" (Segal et al. 1980). Thus, the primary motive given by the drug users themselves sounds like the trait we have called "sensation seeking." More important, sensation seeking has been shown to be the personality trait that is most consistently and highly related to most types of drug use and is most highly discriminating in comparisons of drug abusers with control populations (Kilpatrick et al. 1976; Segal et al. 1980; Zuckerman 1972; Zuckerman 1979; Zuckerman 1983a). Furthermore, sensation seeking is based on a psychobiological theory that offers a psychopharmacological model for the biological basis of the trait (Zuckerman 1979; Zuckerman 1983a; Zuckerman 1984a; Zuckerman et al. 1983b). Together with traits like extraversion and impulsivity, sensation seeking has been related to the enzyme monoamine oxidase (MAO), which points to the role of central monoamine systems in the trait. MAO, in turn, has been related to drug use and other risk-taking activities. All these topics will be addressed in more detail in this paper.

THE SENSATION SEEKING SCALES (SSS)

The first published form (II) of the SSS contained only a General scale, based on a factor analysis of a broad variety of items written to fit the hypothesized trait (Zuckerman et al. 1964).

The second versfon, form IV (Zuckerman 1971), based on more extensive factor analyses, contained four subscales:

(1) Thrill and Adventure Seeking (TAS): The desire to try risky sports or activities involving elements of speed, movement, and defiance of gravity.

(2) Experience Seeking (ES): The desire to seek experience through the mind and the senses; through music, art, travel, and an unconventional style of life with unconventional friends.

(3) Disinhibition (Dis): The desire for or actual enjoyment of uninhibited and socially extraverted activities, e.g., parties, social drinking, and a variety of sexual partners.

(4) Boredom Susceptibility (BS): A strong aversion to monotony or a lack of change, and a preference for the unpredictable; restlessness in confining, dull conditions.

Forms IV and V contain scales based on these factors. Form IV also contains the General scale carried over from form II. Form V (Zuckerman et al. 1978) contains a balanced scale of 10 items representing each of the factors and a Total score based on all 40 items. Form VI (Zuckerman 1984b) contains only TAS and Dis scales arranged in two sections: one dealing with past experience in sensation-seeking activities, and the other with intentions for future activities.

The many studies establishing the reliability and validity of the SSS have been summarized elsewhere (Zuckerman 1978; Zuckerman 1979; Zuckerman 1983a; Zuckerman 1984a). The SSS have been related to a wide variety of risk-taking activities and a preference for novelty, complexity, and intensity in cognitive styles, art, music, reading, and media presentations. Biological correlates have been found in psychophysiological and biochemical phenomena (Zuckerman et al. 1980), and a large twin study (Fulker et al. 1980) has shown a relatively strong genetic determination for the trait.

Sensation seeking has been correlated with many other personality traits (Zuckerman 1979) including locus of control. Few significant relationships have been found between the SSS and locus of control in college student populations. In patient and prisoner groups the ES, Dis, and BS scales have shown positive relationships with the Locus of Control scale, indicating that high sensation seekers of these types tend to believe in an external locus of control. Of course, in prisoners and hospitalized patients this belief would be quite realistic in terms of their current situations.

SENSATION SEEKING AND DRUG ABUSE

Previous articles have reviewed the area of sensation seeking and drug and alcohol use (Zuckerman 1972; Zuckerman 1983b). Since two of the SS scales contain some reference to drug use (ES and Dis), correlations with these scales alone would be suspect. But in an early study (Zuckerman et al. 1972), drug use correlated with the General and all the subscales in college females, and with all but the Dis scale in males. The Dis scale correlated with the extent of alcohol use in both sexes. Segal et al. (1980). using large samples of 1,095 college students and 350 naval personnel, found the ES and Dis scales to be the most highly predictive of drug use compared to other personality scales, including the Locus of Control scale. The ES scale was consistently the best predictor in all analyses in the college groups; the Dis scale was the best one in two of the three Navy groups. The drug-relevant items had been removed from the SSS before analysis so that the results could not be attributed to content confounding. Findings with the Locus of Control scale were inconsistent from sample to sample, and differences between groups were small.

Kilpatrick et al. (1976) compared nonusers, occasional, and regular users of alcohol and/or drugs in hospitalized veterans. A variety of personality trait measures were used, including the Locus of Control scale. As in the Segal et al. study, the SS scales, particularly ES, Dis, and BS, were by far the best concurrent predictors of regular drug use. The Locus of Control scale did not differentiate among the groups.

Specific Drug Use

According to the earlier optimal level theory (Zuckerman 1969), sensation seekers should be more prone to use drugs of all types; among drug users, the higher sensation seekers should prefer drugs that stimulate high cortical arousal levels rather than drugs that depress arousal. In the Zuckerman et al. (1972) study, high sensation seekers were distinguished from mediums and lows on use of marijuana, hashish, amphetamines, cocaine, and LSD, but not on barbiturates, opium, heroin, demerol, morphine, or tranquilizers. Khavari et al. (1977) found that the SSS correlated with use of marijuana. hashish, and LSD in members of a labor union. However, there were not many users of heroin in these groups. Kaestner et al. (1977) discovered that sensation seeking was related to variety of drugs used by former drug abusers but not to the specific drugs used. Carrol and Zuckerman (1977) found low but significant positive correlations between use of stimulants and hallucinogens and the Dis scale in a former drug abusing group, in contrast to a lack of correlation with use of depressant drugs. Skolnick and Zuckerman (1979) compared hard drug (mostly heroin) and soft drug (polydrug including stimulants) users and found that the soft drug users scored higher on SS scales. Despite these findings showing some relationship between sensation seeking and a preference for stimulant drugs, other findings suggest that young heroin users are high sensation seekers relative to their peers (Platt and

Labate 1976) and that high and low sensation seekers do not react differently to stimulant and depressant drugs (Carrol et al. 1982). However, results on the biological bases of sensation seeking (Zuckerman et al. 1980) have led to a new model for the trait that goes "beyond the optimal level of arousal" of the cortex and suggests that drugs are used because of their effects on neurotransmitters whose activity at moderate levels is rewarding (Zuckerman 1979; Zuckerman 1983b; Zuckerman 1984a).

BIOCHEMICAL CORRELATES OF SENSATION SEEKING

Gonadal Hormones

Sensation seeking, particularly on the TAS and Dis scales, shows consistent age and sex differences: males are higher than females, and scores on these scales decline with age (Zuckerman et al. 1978; Zuckerman and Neeb 1980). These data suggested that high sensation seekers might have higher levels of testosterone than lows, even within sexes. Daitzman et al. (1978) found positive correlations between the Dis scale and plasma androgen and between the Dis scale and plasma estrogen as well, the latter an unexpected finding. The findings were confirmed in a second study (Daitzman and Zuckerman 1980), in which subjects were selected for high or low Dis scores. The high Dis subjects were significantly higher than low Dis subjects on plasma testosterone, 17-ß-estradiol. and estrone. Testosterone also correlated positively with scales of sociability, impulsivity, and heterosexual experience, and negatively with neuroticism scales. Estradiol loaded positively on a factor defined by social deviancy on the positive end and social conformity at the negative end. Although measures of drug use were not included in this study, one would predict that among males drug use, like sensation seeking, would be related to both testosterone and estradiol. The testosterone is related to the normal impulsive extraversion, while the estradiol adds a factor of social deviance that may lead to antisocial activities. Schalling et al. (in press) reported that plasma testosterone correlated with scales of Monotony Avoidance (sensation seeking), aggression, sociability, and preference for physical sports in a group of delinquent boys.

Monoamine Oxidase (MAO)

MAO is an enzyme that regulates the three monoamine systems in the brain. A low level of MAO, measured in blood platelets, has provided an interesting biological marker for various psychiatric disorders, as well as showing significant relationships with personality and antisocial, risk-taking behaviors in humans, activity levels in human neonates. and sociable and dominant behaviors in humans and monkeys (Zuckerman et al. 1980). Low levels of MAO have been found among chronic alcoholics and marijuana users, and low MAO males in normal populations report using more drugs and smoking more cigarettes than high MAO types (Coursey et al. 1979;

von Knorring and Oreland 1985; von Knorring et al. 1984). Platelet MAO is a stable and reliable measure, and one that shows strong genetic determination in twin studies.

Six studies involving nine groups of subjects have reported correlations between MAO and the SSS. In all but one of these groups the correlation was negative, and in six of the nine groups the negative correlation was significant. There is a very large range in the magnitude of the significant correlations, from -.06 to -.66, and the median of the correlations is only -.25. However, the unquestionable existence of the finding, despite the fact that some of the studies were done in Sweden and Spain using translated SS scales and different kinds of subject populations, is interesting. Four studies have been done involving six groups and using the Swedish Monotony Avoidance (MAv) scale. All the correlations were negative, and three of the six were significant despite the fact that the median correlation was only -.22. Four of the samples involved depressed patients, and in three of the four the negative correlation was significant.

It should not be surprising that the typical correlations between biological and personality traits are low. Personality may be affected by MAO in the brain, but we are measuring a marker in the blood. The actual correlation between platelet and brain MAO is not known, although MAO levels in different parts of the brain correlate fairly highly. However, there must certainly be an attenuation of the correlation between brain MAO and the sensation-seeking trait. Even though the platelet MAO measure is fairly reliable, there is some change, as there is for the personality measure. Above all, it would be foolish to expect that a complex personality trait would be determined solely by a single brain enzyme. MAO is one element in at least three complex neurotransmitter systems. While it may have some influence on the activities of these systems at any given time, there are other enzymes, receptors, and interactions between the systems themselves that would also be affecting the activity in each of the systems. The wonder is not that the correlation is low, but that it exists at all. What low MAO may indicate is that one of the factors that stabilize the neurotransmitter systems related to behavioral arousal (dopaminergic and noradrenergic systems) is in deficit; therefore, we might expect large fluctuations in behavior and mood and a failure of negative feedback mechanisms to control these. One example is the bipolar or manic-depressive disorder for which sensation seekers are at risk (Zuckerman 1985). The MAO findings point to the monoamine systems as being involved in sensation seeking and related traits such as impulsivity. Studies have just begun which generally use metabolites of the brain neurotransmitters: norepinephrine, dopamine, and serotonin. These few studies will be discussed next.

Monoamines and Their Metabolites

One of the effects of stimulant drugs such as amphetamine and cocaine is a potentiation of the catecholaminergic systems (dopamine and norepinephrine) in the brain. The euphoria and energy that is initially produced by these drugs may be a function of the increased activity in these systems and their activating effects on the cortex. The opiate drugs undoubtedly act on the opiate receptors, which normally respond to the endogenous opiates (endorphfns) in the brain. Could the attraction of these drugs lie in the normal state of the systems that they act upon? I will return to this question later. First, let us examine the evidence relating sensation seeking and other traits to the monoamines.

A study by Ballenger et al. (1983) examined the relationships of a wide range of biochemical variables to normal and abnormal personality traits, including sensation seeking, in a group of screened normal subjects. Age and body size (height and weight) were controlled through the partial correlation method. Sensation seeking was negatively correlated with plasma dopamine-beta-hydroxylase (DBH) and norepinephrine (NE) in the cerebrospinal fluid (CSF) in males and females and in the total group. The negative correlation with DBH was found in two other studies (Kulcsar et al. 1984; Umberkoman-Wiita et al. 1981). Both the DBH and NE findings would indicate underactivity in the noradrenergic system in high sensation seekers, since DBH is the enzyme involved in the conversion of dopamine to NE in the NE neuron.

Schalling et al. (1984) concentrated on CSF metabolites of serotonin (5-HIAA), dopamine (HVA), and norepinephrine (MHPG) in their study of the relationships between monoamines and personality traits in normals and patients. The serotonin metabolite, 5-HIAA, correlated negatively with Eysenck and Eysenck's (1975) P scale in the normal and two of the three patient groups. Although the Eysencks have used the term "Psychoticism' to describe what this scale measures, some factor analyses that we have completed recently suggest that the P factor reflects unsocialized and impulsive, sensation-seeking tendencies. If one wants to use a diagnostic label for the scale, "Psychopathy" might be a better one than Psychoticism. Persons scoring at the extreme on this scale are liable to engage in unconventional and sometimes antisocial activities and would be expected to be among those experimenting with illegal drugs. The fact that high P scorers in the normal and patient populations tend to be low in serotonin is interesting in view of the clinical and comparative data. Low 5-HIAA levels have been found in the brains of those committing suicide and in the CSF of those attempting suicide, particularly when the attempts are violent in nature (Lidberg et al. 1985). Low levels of the metabolite have also been found in impulsive murderers. The animal literature on serotonin depletion suggests that serotonin serves to inhibit behavior in conflict or frustration situations. A deficit in serotonin is associated with impulsivity and a failure to inhibit behavior even in the face of anticipated punishment. Remembering the definition of sensation

seeking as the "willingness to take risks," one might expect the Monotony Avoidance scale to be related to 5-HIAA. It was negatively related to 5-HIAA in all three patient groups, but the correlation was not significant in the normal group. The dopamine and NE metabolites showed little relation to personality in this study, although the dopamine metabolite, HVA, correlated negatively with P and showed some low negative correlations with Monotony Avoidance, as did MHPG.

A third major study, done at the Autonomous University of Catalonia (Arque et al. 1985), used only indices available from blood, but one of these, plasma MHPG, is regarded as a fair indicator of central noradrenergic activity. This measure correlated negatively with Total, ES, and Dis SS scales in a normal group, but not in a somatoform patient group. Although these findings are consistent with the negative CSF-NE vs. SSS correlation in the Ballenger et al. (1983) study, that study also used plasma MHPG but found no significant correlations between this measure and SS scales.

Endorphins

In a prior section, I commented on the fact that young heroin users were also high sensation seekers, relative to their delinquent peers. There are greater risks entailed in heroin use than in most other types of drugs. The legal penalties are more. severe, and the expense of supporting a strong habit usually necessitates criminal activity. Most users are aware of friends who have "OD'd" (overdosed) and died as a consequence. Perhaps the high sensation seeking in heroin users simply reflects the greater readiness to assume the risks entailed in the search for the sensations of euphoria. As tolerance develops, the high euphoria of the "rush" is harder to achieve, and the user may settle for the modest but more prolonged euphoria of the "nodding." Since the opiates act on endogenous opiate receptors, it is possible that a lack of endogenous opiates, or endorphins, may make exogenous opiates particularly attractive to those with such a biological disposition. This possibility makes the levels of endorphins in sensation seekers a matter of interest in explaining why sensation seekers might abuse drugs whose primary effects are depressant rather than stimulant. Stein (1978) and others have suggested that there are two types of reward mechanisms in the brain: arousal reward associated with activity of the catecholamine systems, and arousal reduction reward related to the endorphin systems.

A study by Johansson et al. (1979) reported significant negative correlations between CSF endorphins and two of the SS scales, Dis and BS, suggesting that those high on these more antisocial kinds of sensation seeking might suffer from a lack of endogenous opf ates . However, the finding was not in drug abusers but in a sample of patients suffering from chronic pain of either a psychogenic or organic origin. The study by Ballenger et al. (1983) in non-drug-abusing normals failed to find any relationships between

sensation seeking and either endogenous opiates or beta-endorphin. Studies of levels of endorphfns in former heroin abusers, who are currently drug free, would be illuminating.

Other Biochemical Findings

Two new findings have recently emerged from the study by Arque et al. (1985). Thyroid-stimulating hormone (TSH) was negatively correlated with Total SSS in both normals and somatoform patients. The implication of this finding might be a high level of thyroid hormone in high sensation seekers or a low level of the hormone in low sensation seekers. These investigators did find a significant positive correlation between T4 and the TAS scale in normals, but not in patients in whom the correlation was low and negative. Reexamination of unreported data in the Ballenger et al. (1983) study revealed significant negative correlations between T4 and both the TAS SS scale and the Eysenck Extraversion scales.

The Spanish investigators (Arque et al. 1985) also found significant negative correlations between acetylcholinesterase (ACH) in both normals and patients. Acetylcholine systems in the brain have been associated with arousal mechanisms, aggression (muricidal) in rats, and depression in bipolar affective disorders. Physostigmine, a potent cholinesterase inhibitor, is reported to ameliorate manic symptoms (Janowsky et al. 1972). ACH terminates activity in the cholinergic system at the postsynaptic membrane. A deficit of ACH in high sensation seekers might have some role in the relationship of the trait to bipolar disorder and manic behavior.

These preliminary findings may be signs that we must look beyond the monoamine systems for a full explanation of the sensation-seeking trait.

ENDOGENOUS DEFICIT THEORY OF DRUG ABUSE AND SENSATION SEEKING

It is interesting that most of the correlations between sensation-seeking and neurotransmitters and neuroregulators are negative in sign. In my Behavioral and Brain Sciences article (Zuckerman 1984a), I suggested that sensation seekers might seek stimulant drugs because they are low in tonic catecholamine system activity and need such drugs to bring this activity up to an optimal level where they feel and function best. The significance of the low MAO levels in sensation seekers and bipolar disorders, as well as in impulsive personalities (Schalling and Asberg 1985), may be a lack of regulation in monoamine systems leading to a positive feedback of sensation-seeking behavior. The low sensation seekers may have a strong biochemical negative feedback which would dampen sensation-seeking activity if it ever got started.

NEW METHODOLOGIES AND THEIR POSSIBILITIES

I have noted how limited the current methodologies are in answering the questions concerning neurotransmitter actions in the brain from levels of peripheral transmitters and metabolites. The new developments in Positron Emission Tomography (PET) offer the possibility of observing the activity of these systems in vivo in the brain. Haier (1985) has already reported some preliminary findings using the PET scan on persons given the Sensation Seeking and other personality scales. Future research using neurochemically selective emission tomography could answer many of the questions that have been raised about the link between sensatfon seeking and drug abuse. Such research is expensive, but the payoff--a basic understanding of what motivates people to derange their neurons with potentially damaging substances--may be well worth the price.

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Control Vs. Lack of Control Over Aversive Stimuli: Nonopioid-Opioid Analgesic Consequences

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INTRODUCTION

It is now well established that the behavior, physiology, and stress pathology resulting from experience with noxious stimulation is markedly dependent upon the organism's control vs. lack of control over the aversive event. The initial finding of differential impact of controllable vs. uncontrollable electric shock was demonstrated by Seligman and Maier (1967). Subjects that were unable to control an environmental stressor such as electric shock showed many deleterious effects of the stress experience. Conversely, if the subjects were able to control or "cope" with the stressor, then none of these stress pathologies were observed, The concept of control can be characterized as the ability, or lack of ability, to alter the onset, termination, duration, intensity, or pattern of an aversive experience. In the experiments reported here, control over shock was accomplished by allowing the subject to turn a wheel in the behavioral chamber in order to terminate shock.

BEHAVIOR AND STRESS CHANGES PRODUCED BY INESCAPABLE SHOCK

The many stress pathologies or deficits observed following exposure to inescapable but not escapable shock have been referred to as "learned helplessness" effects (Seligman and Maier 1967; Maier and Seligman 1976). These deficits include: failure to learn to escape shock in a different situation where escape is indeed possible (Seligman and Maier 1967; Maier and Seligman 1976), subsequent inactivity in the presence of shock (Anisman et al. 1978; Drugan and Maier 1982; Drugan and Maier 1983; Jackson et al. 1978), reduced aggressiveness and dominance in a variety of situations (Maier et al. 1972; Payne et al. 1970; Powell and Creer 1969; Rapaport and Maier 1978), enhanced susceptibility to growth of implanted tumors (Sklar and Anisman 1979; Visintainer et al. 1982), development of gastric ulcers (Weiss 1971), and immunosuppression (Laudenslager et al. 1983).

On a neurochemical level, inescapable but not escapable shock has been shown to produce significant alterations in norepinephrine (Weiss et al. 1981; Anisman and Sklar 1979), dopamine (Anisman et al. 1981), serotonin (Sherman and Petty 1982), acetylcholine (Anisman and Sklar 1979; Anisman et al. 1981), and GABA (Sherman and Petty 1981). Alterations in all of these neurotransmitters have been proposed to be important in the production of inescapable shock-induced deficits.

CONTROLLABILITY OF SHOCK AND NONOPIOID/OPIOID STRESS-INDUCED ANALGESIA

Recently, much interest has focused on the reduction in pain responsiveness following exposure to noxious environmental stimuli such as electric shock, cold water swim, and restraint. This phenomenon has been termed stress-induced analgesia (SIA) and has been reviewed previously (Amir et al. 1980; Bodnar et al. 1980; Chance 1980; Watkins and Mayer 1982). SIA has been demonstrated to be either nonopioid or opioid in nature. For example, under certain circumstances, the analgesic reaction that followed stress was reversed by opiate antagonists (Amir and Amit 1978; Chesher and Chan 1977) and was cross-tolerant with morphine (Chesher and Chan 1977), while in other situations reversal by opiate antagonists and cross-tolerance with morphine did not occur (Bodnar et al. 1978; Hayes et al. 1978). These different reports of opioid vs. nonopioid SIA suggested that both opioid and nonopioid systems were involved in mediating SIA, with some aspect of the stressor determining which form occurred (Grau et al. 1981; Lewis et al. 1980; Maier et al. 1982; Lewis et al. 1981).

Critical factors modulating the appearance of either opioid or nonopioid SIA have included continuity vs. intermittency of stress (Lewis et al. 1980), intensity of the stressor (Terman and Liebeskind 1983), type of stressor (Bodnar et al. 1978), and part of the body shocked (Watkins et al. 1984). Also, the controllability/uncontrollability of the stressor has been shown to be a critical factor in determining the form of SIA observed following a stressor. Both escapable and inescapable shock led to SIA shortly following exposure to stress, but only the SIA resulting from inescapable shock was sensitive to blockade by opiate antagonists (Hyson et al. 1982). Furthermore, a brief exposure to shock, itself insufficient to produce SIA, resulted in an analgesic reaction in subjects given inescapable shock 24 hours earlier (Jackson et al. 1979). It appears that the subjects remained in a "sensitized state" for at least 24 hours following uncontrollable stress. Equal amounts of controllable or escapable shock did not lead to such a reinstatable analgesia (Jackson et al. 1979). Significantly, this reinstated analgesic reaction produced by inescapable but not escapable shock was completely blocked by opiate antagonists (Maier et al. 1980) and was cross-tolerant with morphine (Drugan et al. 1981).

Due to the differential effects of escapable vs. inescapable shock on long-term SIA, an important question is whether any differences

in pain responsiveness occur during the initial exposure to the stressor in the two groups. Drugan et al. (1985c) observed the analgesic time course during either 80 escapable or inescapable shocks of identical intensity and duration (figure 1).

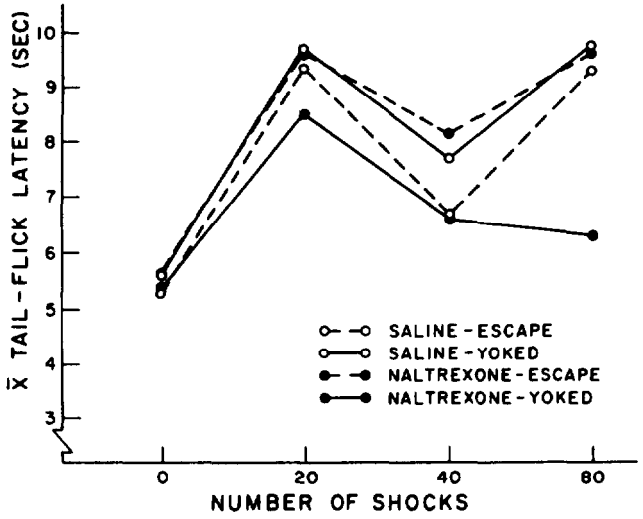

FIGURE 1. *Mean tail-flick latency for subjects receiving either saline or naltrexone (14 mg/kg) 30 minutes prior to 80 escapable or inescapable shocks*

Inescapably shocked subjects showed a "double peak" pattern of analgesia, confirming the prior findings of Grau et al. (1981). Escapably shocked subjects also exhibited this biphasic pattern of antinociception after 20 and 80 shocks. However, pretreatment with the opiate antagonist, naltrexone, completely blocked the inescapably shock-induced analgesia at 80 shocks, while leaving the escape analgesia completely intact. Thus, escapable and inescapable shock exposure resulted in an early nonopioid analgesia following 20 shocks which dissipated rather quickly and was subsequently observed as either a nonopioid or opioid analgesia at 80 shocks for escapably or inescapably shocked subjects respectively.

Until recently, the time course of the analgesia following escapable and inescapable shock had not been studied extensively. Maier et al. (1982) demonstrated that at 30 minutes postshock the escapable shock analgesia returned to control levels, while the inescapable shock analgesia was still present. A more detailed time course of analgesia has since been conducted by Drugan et al. (1985c). Following 80 shocks, the subjects receiving escapable shock showed a very transient analgesia which returned to preshock baseline levels after 10 to 20 minutes, while subjects receiving

inescapable shock remained analgesic for at least 2 hours (figure 2).

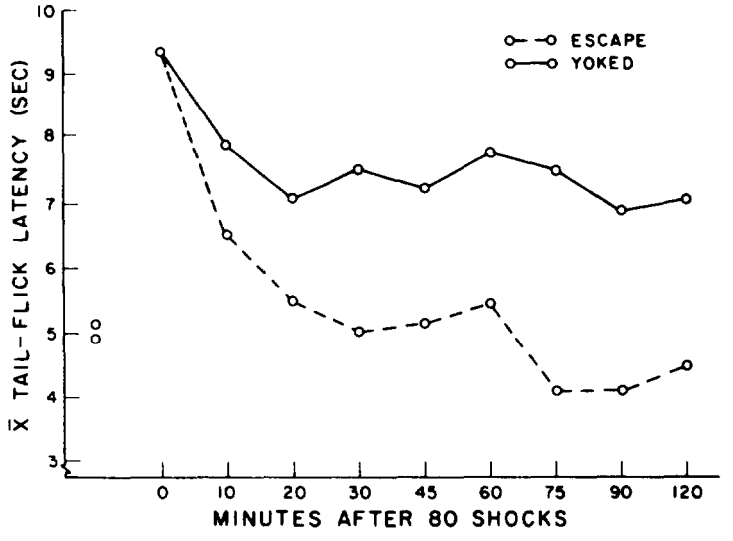

FIGURE 2. *Mean tail-flick latency following 80 escapable or yoked-inescapable shocks*

Thus, the type (opioid vs. nonopioid) and longevity of the analgesic response to shock was markedly different depending on the animal's control over the stressor.

The fact that inescapable shock resulted in an opioid form of SIA and enhanced analgesic responsiveness to systemic morphine (Grau et al. 1981) suggested the possibility that this sort of stress might affect other characteristics of opioid activity, especially dependence. Of particular relevance is the fact that opiate receptor stimulation resulted in dependence. This dependence occurred if the opiates were endogenous or systemically administered (Miglecz et al. 1979). Withdrawal symptoms were evident with time elapsed since administration of synthetic opiates or upon challenge by an opiate antagonist. This phenomenon occurred after acute or chronic opiate exposure (Wei 1981; Wei and Loh 1976). Therefore, inescapable but not escapable shock might be expected to exacerbate withdrawal reactions in response to a challenge of an opiate antagonist. Assessment of opiate withdrawal behavior required an injection of an opiate agonist (i.e., morphine) 30 minutes prior to a challenge by naloxone (Brase et al. 1976). Naloxone by itself did not lead to behaviors indicative of withdrawal. Moreover, earlier exposure to morphine augmented the degree of withdrawal observed, an effect indicating that a single morphine injection followed by naloxone challenge was sensitive to earlier opiate stimulation.

The above procedure for precipitating withdrawal has proven to be ideal for assessing whether prior inescapable shock facilitates withdrawal behavior, possibly because the stress leads to endogenous opioid stimulation. We examined whether prior stress influences precipitated morphine withdrawal and whether the controllability of shock is an important modulating factor (Williams, Drugan, and Maier 1984). Subjects received 2 sessions of 80 escapable or inescapable shocks or restraint (no shock) separated by a 24-hour period. Twenty-four hours following the second day of pretreatment, all subjects received a subcutaneous injection of morphine sulfate (5 mg/kg). After 30 minutes, subjects were injected intraperitoneally with naloxone HCL (5 mg/kg); withdrawal observations began 3 minutes later. The results of this experiment are represented in figure 3.

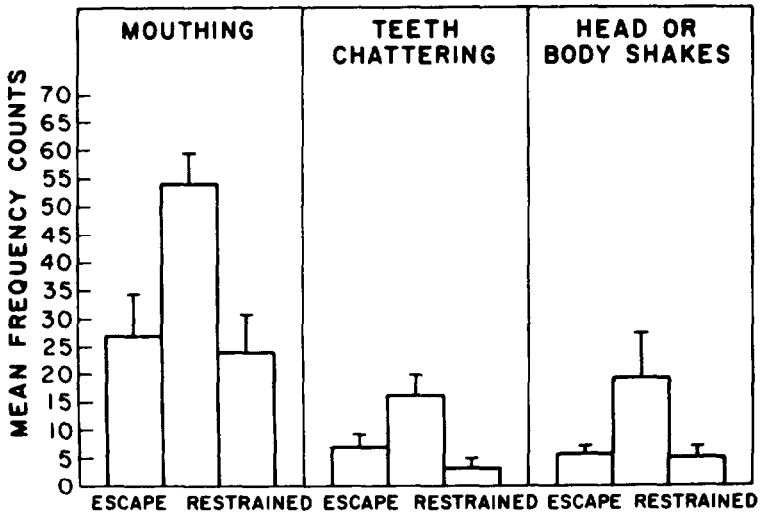

FIGURE 3. *Mean frequency counts of three withdrawal measures for subjects given a SC injection of morphine (5 mg/kg) followed by a naloxone challenge 30 minutes later*

NOTE: Withdrawal testing was conducted 24 hours after two daily sessions of escapable shock, yoked-inescapable shock, or restraint (no shock).

As can be seen, the inescapable shock group displayed a significant potentiatfon of morphine withdrawal. Conversely, subjects receiving the identical amount of escapable shock did not exhibit any increase in withdrawal behavior in comparison to nonshock controls. On this index of opiate withdrawal, the inescapably shocked subjects demonstrated previous opioid stimulation, whereas the escapably shocked subjects did not. Naltrexone administration prior to shock was conducted in order to insure that this enhanced withdrawal response of inescapably shocked subjects was due specifically to previous opioid stimulation. Figure 4 demonstrates

that the enhanced precipitated opiate withdrawal response can be blocked by prior administration of the opiate antagonist, naltrexone.

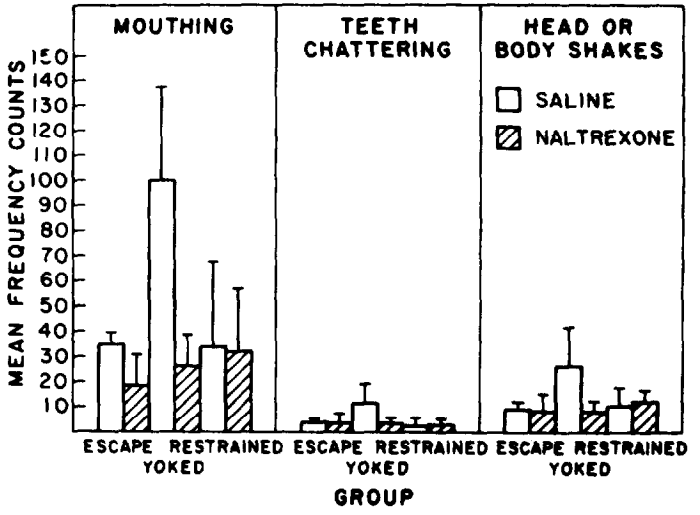

FIGURE 4. *Mean frequency Counts of three withdrawal measures for subjects given an injection of morphine followed by a naloxone challenge 24 hours after two sessions of escapable shock, yoked-inescapable shook, or restraint*

NOTE: Prior to both of the pretreatment sessions. subjects were injected with either saline or naltrexone (14 mg/kg).

The dissociation of nonopioid/opioid activity in controllably vs. uncontrollably shocked subjects is quite puzzling from a mechanistic point of view. Are the two analgesic systems aroused by the different stress experiences separate and unrelated, or does control over shock engage a system which opposes or suppresses the activity of endogenous opioid processes? One way to answer such a question would be to see if prior exposure to escapable or controllable shock would block the appearance of opioid SIA following a session of inescapable shock. These behavioral "imnunization" studies have been conducted, showing that prior experience with controllable shock blocks both short- and long-term opioid analgesia observed following inescapable shock (Moye et al. 1981; Moye et al. 1983). Moreover, a more recent study (Drugan et al., 1985c) has shown that prior experience with a longer session of either escapable or inescapable shocks (80 shocks) has very profound effects on a subject's analgesic responsiveness to a session of 80 inescapable shocks 24 hours later (figure 5).

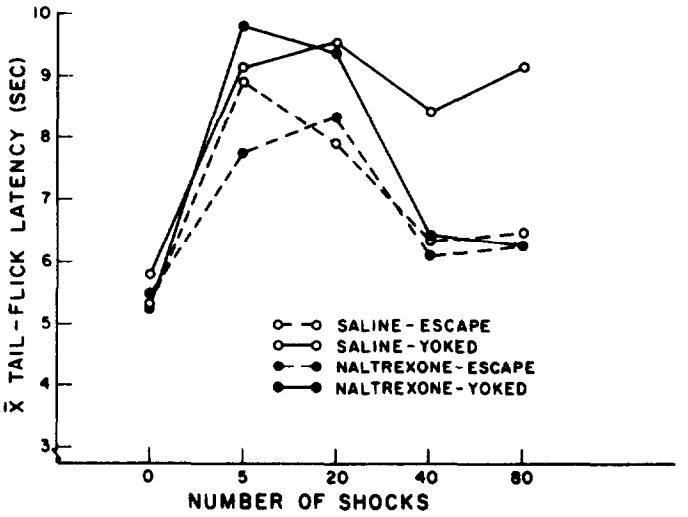

FIGURE 5. *Mean tail-flick latency during 80 inescapable shocks 24 hours following a session of either escapable or inescapable shock*

NOTE: Thirty minutes prior to the inescapable shock on day 2, subjects received an injection of either saline or naltrexone (14 mg/kg).

As can be seen in figure 5, prior experience with controllable or escapable shock resulted in a brief, nonopioid analgesia after 5 and 20 shocks, which rapidly dissipated to control levels; the typically observed opioid analgesia at 80 shocks is completely abolished. However, prior exposure to uncontrollable or inescapable shock hastened the arrival of opioid SIA on the second day of inescapable shock exposure. Instead of being observed at 80 shocks, the opioid SIA was now present at 40 shocks. Thus, prior experience with controllable shock blocked, while prior uncontrollable shock hastened, the expression of opioid SIA. It appears that control over shock engaged an active process that opposed the activation of endogenous opioid processes in response to inescapable shock.

A POSSIBLE MECHANISM FOR THE PROTECTIVE EFFECTS OF CONTROL OVER SHOCK

What mechanism might be responsible for the protective effects of "coping" or control over shock? As previously mentioned, this protective effect of control is observed on SIA as well as many other stress pathologies. Interestingly, control over shock and treatment with benzodiazepines prior to uncontrollable stress both prevent many of the same stress-related effects. For example, benzodiazepines selectively inhibited the increase in plasma corticosterone resulting from inescapable stress (LeFur et al.

1979). Similarly, controllable or escapable shock induced a much more transient rise in plasma corticosterone levels, in comparison to inescapably shocked subjects (Swenson and Vogel 1983). Benzodiazepines reduced gastric ulcers induced in rats by stress (File and Pearce 1981), whereas stress-induced ulceration was observed following inescapable but not escapable shock (Weiss 1971). Benzodiazepines produced a significant attenuation of morphine-induced analgesia when injected intracerebroventricularly (ICV) or into the periacqueductal gray (PAG) simultaneously with a subcutaneous injection of morphine (Mantegazza et al. 1982), while escapable shock given prior to inescapable shock blocked both short- and long-term opioid SIA (Drugan et al. 1985c; Moye et al. 1981; Moye et al. 1983).

The similarities between control over shock and benzodiazepine administration prior to inescapable stress suggested the possibility that anxiety or fear may be a critical factor in the production or prevention of stress-induced opioid analgesia and other stress pathologies. In fact, behavioral studies investigating the relationship between fear and antinociception supported this contention. Specifically, although unconditioned analgesia induced by a stressor is sometimes opioid and sometimes not, conditioned analgesia appears to be opioid in nature (Sherman et al. 1984; Watkins and Mayer 1982). In support of this idea is the finding that conditioned analgesia was reversible by opiate antagonists (Watkins and Mayer 1982). Finally, the analgesia elicited by cues that have been paired with a stressor has been opioid in nature even if the stressor itself led to a nonopioid analgesia (Watkins and Mayer 1982).

If the opioid SIA observed following inescapable shock is in some fashion a result of anxiety or fear, then an antianxiety compound should block or attenuate this effect. Chlordiazepoxide (Librium) is a classic 1,4 benzodiazepine which is known to have potent anxiolytic action in both animals and man. However, it is important to tolerate out the side effects of muscle relaxation and sedation to ensure that the effects of the compound are due to its anxiolytic action. Therefore, prior to experimentation, all subjects were given one injection of 10 mg/kg chlordiazepoxide (CDP) per day for 4 days, to tolerate out the sedative effects. Then, on day 5, half of the subjects received an IP injection of 5 mg/kg CDP, while the remainder of the subjects received distilled water 30 minutes prior to a session of inescapable shock. Twenty-four hours later and 30 minutes prior to reinstating shocks and subsequent analgesia testing, subjects received an IP injection of either CDP or saline (Drugan et al. 1984). Figure 6 demonstrates the impact of a benzodiazepine on the inescapable shock-induced long-term opioid analgesia.

As can be seen in the figure, CDP given prior to inescapable shock completely blocked the long-term opioid analgesia. It is important to note that benzodiazepine administration prior to test on day 2 had no effect. It appears that the initiation of anxiety or fear resulting from the session of inescapable shock set into

motion some sort of process (transmitter depletion?) that is responsible for the expression of the opioid SIA, and possibly for other deficits.

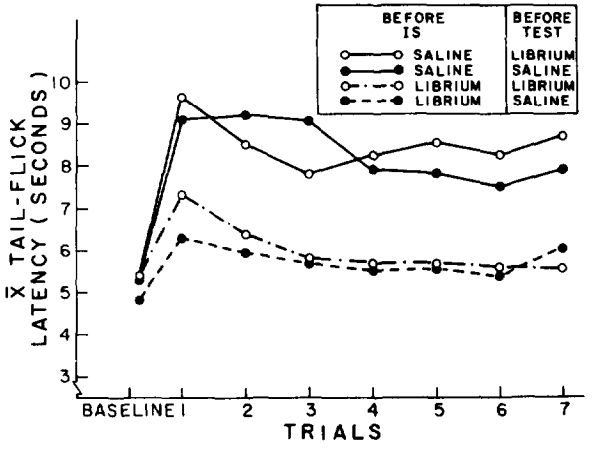

FIGURE 6. *Mean tail-flick latency 24 hours following 80 inescapable shocks*

NOTE: Thirty minutes prior to inescapable shock and tall-flick testing, subjects were given an injection of either distiIled water or chlordiazepoxide (Librium, 5 mg/kg).

Control over shock protects the subject from many of the deleterious effects of inescapable shock in a similar fashion to the benzodiazepines. Does control over shock act in the same way as the pharmacological pretreatment of benzodiazepines prior to stress? The benzodiazepine receptor appears to be functionally coupled to both a gamma-aminobutyric acid (GABA) receptor and an associated chloride ionophore (Paul et al. 1981). It has been demonstrated that benzodiazepines increase GABA binding and can facilitate GABAergic transmission (Biggio et al. 1977; Costa et al. 1978). It is believed that benzodiazepines do not mimic GABA but instead facilitate GABAergic transmission by sensitizing GABA receptors to the natural agonist (Costa et al. 1976). Finally, it has been proposed that it is the GABAergic system that mediates the anxiolytic action of the benzodiazepines (Costa et al. 1976). In support of this notion, GABA-mimetic drugs (e.g., valproic acid) have anxiolytic activity comparable to diazepam in two types of animal tests known to predict the anxiolytic action of drugs (Lal et al. 1980). Hence, if control over shock is working in a similar fashion to the benzodiazepines, then it should result in a facilitation of GABAergic transmission as well. This increase in GABAergic transmission would be reflected in greater GABA effectiveness and/or greater inhibition in the central nervous system (CNS). A technique that gave an index of central GABAergic

processes would be informative in evaluating whether or not control over shock augments GABAergic transmission.

The classic benzodiazepines (i.e., diazepam and chlordiazepoxide) have anticonvulsant properties as well as anxiolytic actions. It is believed that the anticonvulsant action of these drugs is due to their action on the GABAergic system (Schmutz 1983). Drugs such as bicuculline or picrotoxin, which antagonize GABAergic transmission, are known to act as convulsive agents. In fact, GABA-antagonist induced seizures have been used as a behavioral index of the activity level of central GABAergic processes (Soubrie et al. 1980).

Drugan et al. (1985b) used bicucullline-induced seizures in subjects that received escapable shock, inescapable shock, or no shock to assess the impact of controllability of stress on GABAergic tone. Two hours poststress was used as the time point for the precipitation of seizures for several reasons. There is a dissociation between escapably and inescapably shocked subjects on behavioral (Glazer and Weiss 1976), plasma corticosteroid (Swenson and Vogel 1983). and analgesic (Drugan et al., 1985c) indices at this time. The latencies to myoclonus (neck jerk) and clonus (loss of posture) were chosen as dependent variables as these have been used by other researchers in the field (Adler 1969; Greer and Alpern 1977). Figure 7 shows the latency to myoclonus and clonus for all groups given an IP injection of either 4, 6, or 8 mg/kg bicuculline 2 hours postshock.

Interestingly, both control and lack of control over shock dramatically altered the subjects' susceptibility to bicuculline-induced seizure in comparison to nonshocked controls. Escapable shock protected against seizures, while inescapable shock facilitated seizures. In addition, at the effective dose (6 mg/kg), control over shock protected against the lethal effects of these chemically-induced seizures, in comparison to all other groups. More specifically, following the 6 mg/kg challenge of bicuculline, 31 percent of the escapably shocked subjects, 69 percent of the inescapably shocked subjects, 69 percent of the restrained subjects, and 63 percent of the naive subjects died following seizures. Thus, not only did control over shock delay the onset of bicuculline-induced seizures. it also protected against the lethal effects.

CONTROLLABILITY AND GABAERGIC TRANSMISSION: A THEORETICAL MODEL

In sum, it appears that experience with controllable vs. uncontrollable aversive events such as electric shock markedly influence the organism's reaction to the stressor. Exposure to uncontrollable shock leads to a variety of pathologies including opioid stress-induced analgesia. Conversely, exposure to controllable shock results in few if any stress effects and a transient nonopioid stress-induced analgesia. The data presented in this paper suggest that anxiety and fear may play a major role in precipitating many of the stress pathologies and opioid SIA reported.

Since GABA is such a ubiquitous neurotransmitter in the brain, having interactions with many stress- and anxiety-related systems, a theoretical model is proposed to account for the effects of

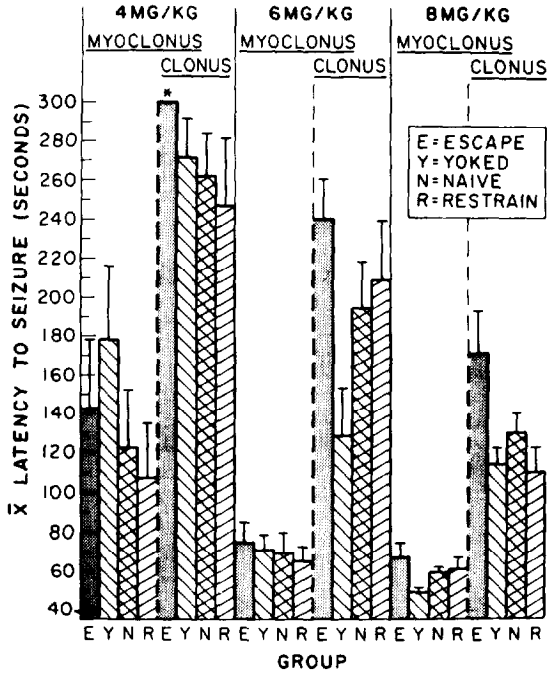

FIGURE 7. *Mean latency to the onset of myoclonic and clonic convulsion following an IP injection of either 4, 6, or 8 mg/kg bicuculline 2 hours following escapable shock, inescapabte shock, restraint, or no treatment (naive)*

NOTE: Vertical bars represent standard errors.

control/lack of control over shock with GABA as the critical link. Figure 8 (Drugan 1984) shows that GABA tonically inhibits many systems thought to be critical in the expression of opioid SIA (hypothalamopituitary adrenal axis) and anxiety (e.g., GABA itself, norepinephrine, and serotonin).

Thus, facilitation or interference with GABAergic transmission is hypothesized to have a profound effect on other critical systems. For example, if control over shock results in GABAergic facilitation, then this should result in an inhibition of the release of corticotropin-releasing factor from the hypothalamus, which would mobilize the hypothalamopituitary adrenal (HPA) axis (Buckingham 1980). Conversely, if lack of control results in an interference

with GABA, then a release of inhibition of the HPA axis would ensue, with release of pituitaryß-endorphin and opioid SIA. In support of this notion, both basal and stress-induced activity of the HPA axis in the rat were found to be reduced when GABA was implanted into the third ventricle and were enhanced by the injection of the GABA-receptor antagonists, picrotoxin and bicuculline (Makara and Starr 1974). This relationship between GABA and the HPA axis is important because the pituitary-adrenal axis has been demonstrated to be involved in the long-term opfoid SIA following inescapable shock. Specifically, either hypophysectomy, adrenalectomy. or dexamethasone will completely block the inescapable shock-induced opioid SIA (MacLennan et al. 1982).

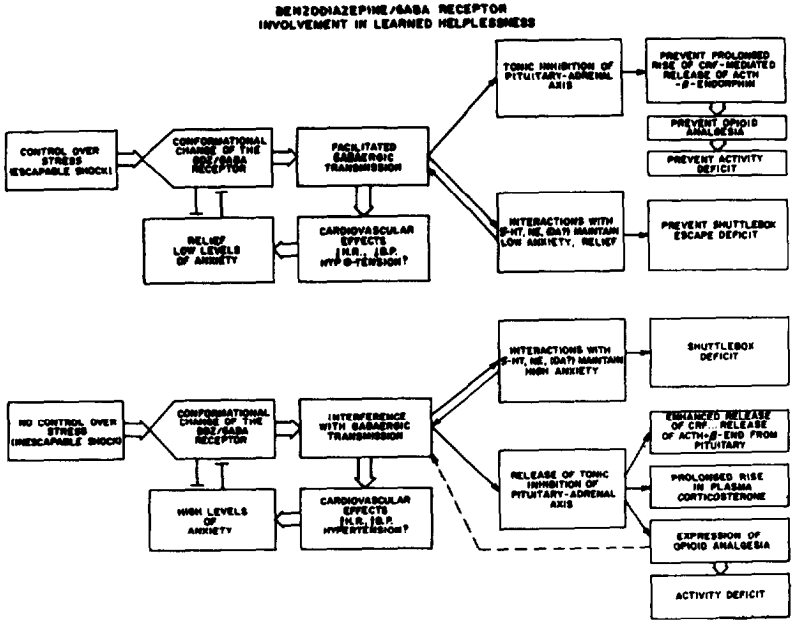

FIGURE 8. *A theoretical model which suggests that the differential impact of escapable vs. inescapable shock is due to their respective effects on the GABAergic system. This differential impact is proposed to alter many important stress-related systems.*

Another relevant interaction of GABA processes is its relationship with other neurotransmitter systems thought to be involved in anxiety-related behaviors. For example, pharmacologically increasing serotonin levels increases anxiety-related behaviors in rats (Iverson 1983). Thus, augmenting serotonergic activity has anxiety-inducing effects. Interestingly, it has been shown that GABAergic neurons terminate on , and exhibit an inhibitory influence on, the raphe nucleus (Gallager 1978), the originating

nucleus for the ascending serotonergic (5-HT) tract, which innervates certain components of the limbfc system thought to be critical in anxiety (i.e., amygdala and hippocampus). Thus, GABAergic facilitation, as observed in subjects able to control shock, might be expected to have anxiolytic effects due to inhibition of the ascending 5-HT system. Conversely, subjects unable to control shock, resulting in interference with GABAergic processes, would be expected to have anxiogenic effects resulting from disfnhibition of this system.

Redmond and Huang (1979) have proposed that the dorsal noradrenergic bundle is important in the production of anxiety. Drugs that are known to reduce the activity of the locus coeruleus (the originating nucleus of the dorsal noradrenergic bundle), such as benzodiazepines, have anxiolytic actions. However, drugs that increase locus coeruleus activity cause anxiety in animals and man, as does electrical stimulation of this area (Redmond et al. 1977). Significantly, GABAergic neurons terminate on, and exert an inhibitory influence on, the locus coeruleus neurons (Iverson 1983). Thus, control over shock, resulting in GABAergic facilitation, might be expected to have anxiolytic action in this system as well, due to inhfbition of locus coeruleus neurons. Finally, inescapably shocked subjects would have an active ascending noradrenergic (NE) system due to disinhfbition of GABA on locus coeruleus neurons, which would result in anxiety.

PURPOSE OF MODEL

This theoretical model was not conceptualized to answer all the questions about controllability and stress effects. Rather, it has been proposed in an effort to provide a certain perspective on how "coping" or control over stress might have protective effects. It is hoped that this model will guide subsequent research on subjects able to control stress, rather than examining merely those unable to control. Our feeling is that the mechanism or process modulating the protective effects of control over stress, once understood and characterized, will result in better fine-tuning of pharmacotherapy in many stress-related disorders in humans.

RELEVANCE TO DRUG ABUSE

At first blush, the data presented in this paper may not seem directly relevant to the study of drug addiction. However, careful reconsideration will reveal that the dimension of controllability over a stressful event, or anxiety/fear, modulates the activity of endogenous opiofds as evidenced by opioid SIA and potentfated morphine withdrawal. In addition, this activation of opiofd systems renders the subject more sensitive to the analgesic effects of systemically administered morphine (Grau et al. 1981). Since the previously mentioned opioid SIA is blocked by pretreatment with a benzodiazepine, anxiety or fear appears to be an important precipitating factor. Thus, learned helplessness has been conceptualized as being an animal model for anxiety-mediated

depression (Drugan et al. 1985a). Since addicts tend to score in the mild-moderate range of depression (Craig, this volume), this model may shed some light on the etiology of addictive behavior in humans.

In a clinical setting, people who have experienced uncontrollability of life events, have chronic anxiety, or possess an external locus of control may be candidates for drug abuse for several reasons. First, as mentioned above, either uncontrollable aversive events or anxiety/fear result in activation of endogenous opioid systems. This "primed" opioid system may alter the individual's first reaction(s) to an opiate (e.g., greater euphoria) in comparison to those of other people. This different action of the opiate may precipitate or hasten the addiction process. In addition, these individuals may be more likely to experiment with drugs as a "coping" mechanism in order to combat their emotional predicament. Thus, this "coping through drug use" and the differential reaction to opiates themselves could be the mechanism responsible for the acquisition and maintenance of drug abuse.

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Behavioral Contingencies Involved in Drug-Induced Neurotransmitter Turnover Changes

Steven I. Dworkin and James E. Smith

INTRODUCTION

Recent advances in techniques used to investigate the neuroanatomical, neurophysiological, and neurochemical mechanisms of action of psychoactive drugs have been substantial. Neuroscientists have not only determined the chemical and physiological effects of these drugs, but also, in some cases, the anatomical locus where these effects are exerted. Investigations of the parameters of opiate action exemplify how these neurobiological techniques have increased understanding of the mechanisms of action of substances that affect behavior. Receptor-binding and autoradiographic distribution studies have shown the complex behavioral effects of opiates to be produced by actions at specific recognition sites in the central nervous system. These techniques have also assisted in the detection and characterization of endogenous substances that interact with these receptors to produce effects that opiates appear to mimic. However, irrespective of how sophisticated neurobiological techniques for investigating the direct actions of drugs become, understanding the basic mechanisms responsible for substance abuse will likely not be possible unless these phenomena are studied in the context of behavioral and environmental variables that result in and from drug self-administration.

CHARACTERISTICS OF SUBSTANCE ABUSE

One necessary component of substance abuse is behavioral--the use or self-administration of the particular substance. Acknowledging this component places appropriate emphasis on the importance of an experimental analysis of the behavioral components of self-administration, while not suggesting that physiological or neurobiological aspects are unimportant. Investigations of the neurobiological consequences of the administration of substances to biological preparations can provide information concerning the necessary conditions for abuse potential. Aside from occasional self-administration of an inappropriate drug or dose regimen (e.g., taking an antibiotic for a cold), there may be some common neurobiological mechanism of action of substances. This mechanism

has been proposed by some to be an action on the mesolimbic-mesocortical dopamine system (Wise and Bozarth 1981) or on the noradrenergic-endorphinergic system (Belluzzi and Stein 1977).

Many substances with abuse liability have several characteristic behavioral effects in common. These agents have response-rate-altering properties that result in modifications of ongoing levels of activity, and stimulus properties that permit humans and non-humans to detect their administration. These substances also have reinforcing properties that result in their ability to maintain high rates and extended sequences of behavior. However, these properties are not invariant and are subject to modification by pharmacological, neurobiological, and behavioral variables (Barrett and Katz 1981; Barrett and Witkin, in press). Psychoactive substances are not qualitatively different from other environmental stimuli that exert control over behavior. Research into the control of behavior by consequent events (operant conditioning) has been beneficial in understanding the behavioral parameters of substance abuse.

The dynamic properties of reinforcers are often overlooked. The same electric shock can serve as a punisher and suppress behavior, a negative reinforcer increasing behavior that results in its termination, and a positive reinforcer maintaining behavior that results in its presentation, even with the same animal (figure 1). Squirrel monkeys initially trained to postpone electric shocks (negative reinforcement) continue to respond when the same intensity shock is made contingent on responding (positive reinforcement). This responding is directly related to shock intensity with higher intensity maintaining higher response rates. Responding extinguishes when shock is eliminated and occurs again when shock is reintroduced. Electric shock can suppress food-maintained responding (punishment) and maintain responding that results in its presentation (positive reinforcement) in different components of a multiple schedule (Morse et al. 1977; Barrett and Katz 1981). The importance of the precise contingencies between responding and shock presentation is indicated by the demonstration that shock can reinforce behavior when delivered under an interval schedule but punish behavior when delivered under a ratio schedule (Branch and Dworkin 1981).

Similar results have been seen with psychoactive substances. Cocaine (figure 2) and nicotine (figure 3) can be both positive and negative reinforcers in the same animal (Spealman 1985). Moreover, nalorphine (a mixed opiate agonist-antagonist) produces severe withdrawal when administered to an opiate-dependent animal, but can also serve as a reinforcer to opiate-dependent monkeys (Goldberg et al. 1971) (figure 4). These and similar findings demonstrate that behavioral history, particularly the different types of contingent relationships between behavior and the delivery of an environmental event , can alter the punishing or reinforcing efficacy of that event.

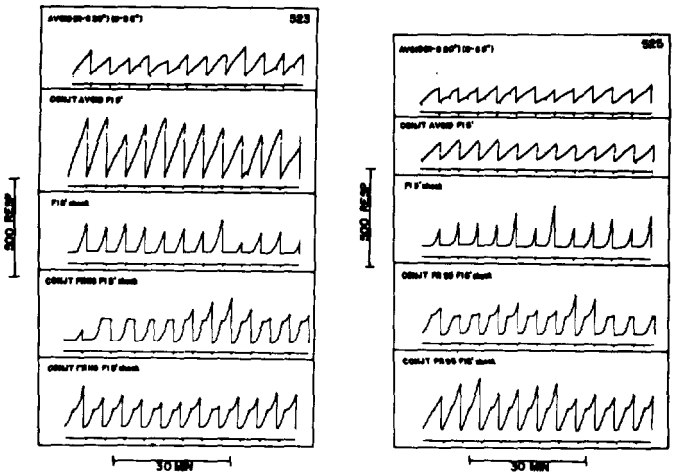

FIGURE 1. *Development of the positive reinforcing effects of response-produced electric shock presesentation to squirrel monkeys*

NOTE: Responding was initially maintained by a Sidman Avoidance schedule where responding postponed shock presentations (upper panels). A conjoint fixed-interval 5-minute schedule of shock presentation was then added to the postponemant schedule. Most responses continued to postpone shocks. However, responses produced shocks on a fixed-interval 5-minute schedule. When the postponement schedule was eliminated, responding was maintained by the fixed-interval schedule of shock delivery (third panel). The addition of a conjoint ratio schedule of response-produced shock eventually eliminated responding by monkey 525. A behavioral history of different contingencies between responding and the delivery of electric shock altered the reinforcing nature of shock, changing It from a negative reinforcer to a positive reinforcer to a punisher. (Branch and Dworkin 1981.)

IMPORTANCE OF CONTINGENCIES

Substances that have profound pharmacological and behavioral effects should not be considered reinforcing until contingent or contiguous relationships between behavior and administration are evaluated. When it has been demonstrated that the behavior that precedes administration is increased in frequency and that the drug has not directly elicited the behavior, then the substance can be considered reinforcing. Reinforcement cannot be assumed in the absence of contingent or contiguous relationships (Skinner 1938).

The effects of noxious stimuli have also demonstrated the importance of behavioral variables. Although the noncontingent presentation of noxious stimuli have been shown to produce many behavioral and physiological changes, other factors have been implicated in stress-related diseases (Weiss et al. 1981). A stress-inducing environment contains at least three components:

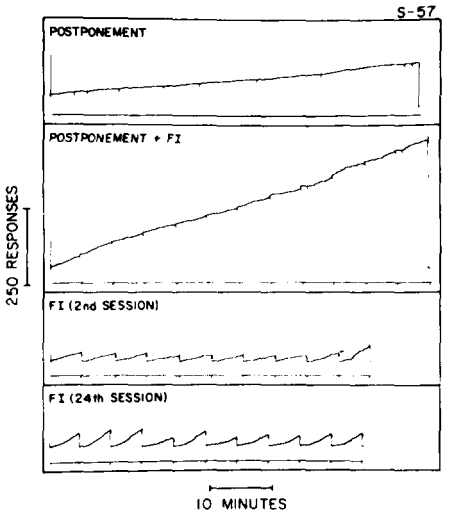

FIGURE 2. *Development of the positive reinforcing effects of* nicotine

NOTE: Responding was engendered and subsequently maintained by a nicotine postponemant procedure. In the absence of responding, nicotine injections were delivered (first panel). A fixed-interval schedule of nicotine injections was superimposed on the postponement schedule (second panel). After the postponement contingency was eliminated, responding was maintained by the fixed-interval schedule alone (bottom two panels). The behavioral history of the different response contingencies changed the effects of nicotine from a negative reinforcer to a positive reinforcer. (Spealman 1985.) Copyright 1985, Alan R. Liss Company.

(1) a noxious stimulus (usually electric shock); (2) stimuli that are paired with the presence or absence of a pending noxious stimulus (predictability); and (3) a coping response that results in the postponement or termination of the noxious stimulus (control). Several studies have shown that the second two components, considered to be "psychological," can modulate the behavioral, physiological, and neurochemical effects of noxious stimulation (Badia and Culbertson 1972; Seligman and Maier 1967). Procedures used on rhesus monkeys to assess simultaneously the effects of noxious stimulation that could or could not postpone electric shocks have demonstrated the importance of response contingencies (Brady et al. 1958). One monkey received a shock every 20 seconds unless a bar-press response was emitted, which delayed the shock for 20 seconds. A second monkey was yoked to the shock schedule of the responding monkey but had no opportunity to postpone presentations. Thus, the number of shocks delivered to both subjects was the same, but only one monkey could delay them for himself and his yoked partner. This avoiding animal (with control) developed extensive gastrointestinal lesions. Opposite effects were observed when rats were used in a systematic replication and extension of this study (Weiss 1968; Weiss 1971). Yoked rats (without control) developed more and larger gastrointestinal lesions compared to subjects that could delay shocks. It was suggested that the major factor responsible for the differences observed

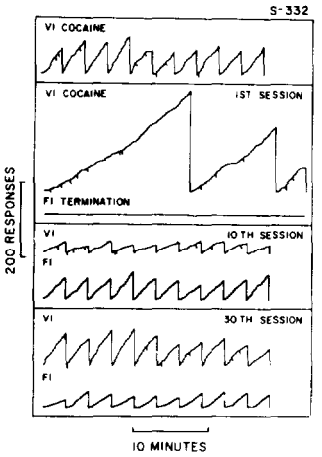

FIGURE 3. *Development of responding simultaneously maintained by a variable-interval schedule of IV cocaine injection and a fixed-interval schedule of termination (time-out from cocaine injections)*

NOTE: First panel shows responding maintained by a variable-interval contingency. Responding on a single lever produced an IV cocaine infusion at variable Intervals averaging 3 minutes. Subsequent panels show responding maintained by two concurrently scheduled contingencies. Responding on one lever continued to produce cocaine injections under the variable-interval schedule. Responses on a second lever were maintained by a fired-interval 5-minute termination schedule. Responses on this lever after a 3-minute fixed Interval of time elapsed terminated the schedule of cocaine injections for a 1-minute time-out period. Thus, responding was simultaneously maintained bv cocaine injections (positive reinforcement) and a time-out from the opportunity to receive additional cocaine infusions (negative reinforcement). (Spealman 1985.) Copyright 1985, Alan R. Liss Company.

between the two studies was the difference in response rates of the shock-postponing animals (Weiss 1971; Weiss 1972). In the first study, monkeys with the highest rates of responding were designated as the avoiding subjects, while a random assignment procedure was used in the rat study. Additional research supported the suggestion that response rates were important in stress-induced physiological changes (Weiss 1968). Animals with the opportunity to postpone electric shock presentation have increased levels of brain neurotransmitters compared to yoked-shock animals. Increases in norepinephrine, dopamine, and serotonin were seen in the hypothalamus, anterior cortex, and brain stem, respectively (Weiss et al. 1981). The ability to control or predict the occurrence of noxious stimuli has considerable behavioral, physiological, and neuropharmacological effects. It is not surprising that similar control over, or predictability of, other environmental stimuli also have profound neurobiological influences.

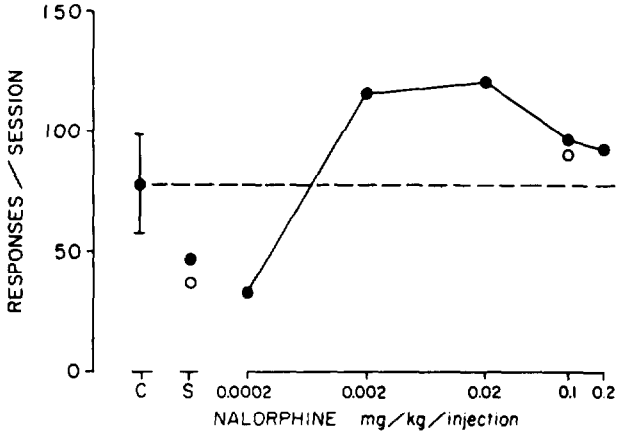

FIGURE 4. *Demonstration of the reinforcing effects of nalorphine delivered to a morphine-dependent monkey*

NOTE: Various doses of nalorphine substituted for contingent morphine injections over a 7 1/2-hour period and maintained higher rates of responding than either morphlne (points above "C" and broken horizontal Iine) or saline (points above "s"). (Goldberg et al. 1971.) Copyright 1971, American Society for Pharmacology and Experimental Therapeutics.

NEUROBIOLOGICAL CONSEQUENCES OF REINFORCER PRESENTATION

The behavioral consequences of reinforcer presentation are thought to result from, and in, changes in neuronal transmission in the central nervous system. Reinforcer presentatfon likely initiates neuronal activity in pathways that mediate and may be "dedicated" to these processes (demonstrated by intracranial electrical self-stimulation). Thus, the neuronal events resulting from reinforcement are the neurobiological substrates of these phenomena. The elucidation of these substrates would include the identification of the neuronal circuits that mediate these processes (figure 5). The identification of each component neuron and the receptors involved in the neuronal circuit would be necessary to such elucidation as would knowledge of the influence of other inputs. Such information is not yet available for even the most simple behavior. However, recent methodological developments such as multiple neurotransmi tter turnover rates, 2-deoxyglucose autoradiography, and neurotransmitter receptor imaging will likely permit significant new advancements.

NEUROBIOLOGICAL SUBSTRATES OF CONTINGENT REINFORCER PRESENTATION

The contingent presentation of an event that increases the probability of the response that preceded its presentation is a reinforcer. The noncontingent presentation of the identical potentially reinforcing stimulus does not appear to have the same

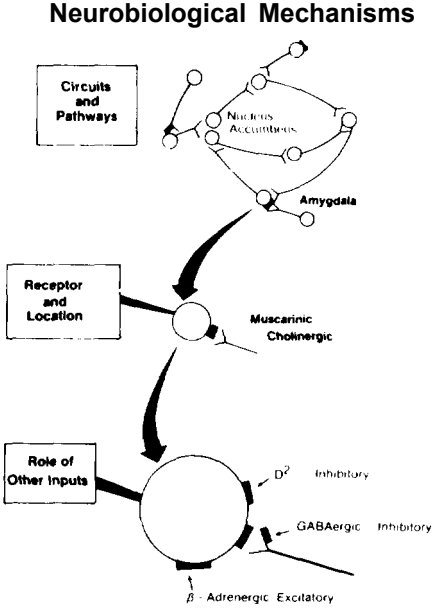

FIGURE 5. *Neurobiological mechanisms*

NOTE: The neurobiological substrates of a behavior would include knowledge of: (a) the neuronal circuits and pathways that mediate the behavior with identification of each component neuron and the neurotransmitters released by each; (b) characterization of end localization of the neurohumoral receptors involved; and (c) the role of other Inputs to each participating neuron.

properties. As previously discussed, response-contingent presentation is necessary for an event to establish reinforcing properties, while response-independent presentation to the same organism cannot be considered a reinforcer and may even be an aversive stimulus. Rats that have produced response-dependent presentation of electrical stimulation to a brain region will respond to terminate the same stimulation-delivered response independently on an identical schedule (Steiner et al. 1969). Drugs with reinforcing properties seem to have similar effects. Monkeys intravenously self-administering cocaine will respond to terminate the opportunity to receive additional periodic cocaine infusions (Spealman 1985). These data suggest that the response-independent presentation of a potentially reinforcing stimulus is not a reinforcer to organisms that have previously exercised control over its presentation. Moreover, the reinforcing nature of a stimulus can be changed by alterations in the contingencies under which it is presently removed.

NEUROBIOLOGICAL SUBSTRATES OF CONTINGENT DRUG PRESENTATION

Neuropharmacologic and behavioral pharmacologic data suggest that the contingent presentation of drugs is clearly different from noncontingent presentation. These differences must result from, and in, differences in neuronal activity between the two conditions. These differences may represent reinforcing neuronal activity and the neuronal processes associated with contingent presentation that are directly related to reinforcement. Investigation of the neurobiological differences between intravenous opiate self-administration and yoked-passive morphine or yoked-vehicle infusion have suggested the involvement of specific neuronal systems in these processes (Smith et al. 1982; Smith et al. 1984a; Smith et al. 1984b).

Neurotransmitter Turnover Rates

Triads of male littermate rats were surgically prepared with chronic jugular catheters and two of the littermates made physically dependent on morphine sulfate with hourly infusions of increasing dosages (3 days each of 1.25, 2.5. 5.0 mg/kg/infusion and 2 days of 10.0 mg/kg/infusion), while the third littermate received hourly vehicle infusions. One of the physically dependent rats was then allowed to self-administer morphine intravenously (10 mg/kg/infusion) with 24-hour access on a fixed-ratio schedule increased from 1 to 10 during the first week. The other physically dependent littermate received identical yoked infusions of morphine, while the third littermate continued to receive yoked infusions of vehicle. When self-administration stabilized (3 to 4 weeks), each littermate was pulse labelled with radioactive precursors to the biogenic amine (0.5 mCi ^{3}Hitryptophan and 1.0 mCi ^{3}H-tyrosine) and the amino acid (0.2 mCi ^{14}C-glucose) neurotransmitters. Groups of litters were sacrificed by immersion in liquid nitrogen after either 60 (n=5) or 90 minutes (n=6), at a time when each self-administering animal was most likely to take another self-infusion (calculated from self-administration intervals for the previous 72 hours). The brains were removed at -20 °C, cut into 1 mm coronal sections, and dissected into 11 brain regions at -20 °C. Each brain region was pulverized in liquid nitrogen and a portion of tissue taken for the extraction and assay of the content and specific radioactivity of the biogenic amine neurotransmitters; another portion was taken for the same determinations of the amino acid neurotransmitters. The half-life was determined for each from a semilogarithmic plot of the specific radioactivities at the two time points, and rate constants and turnover rates were calculated (Smith et al. 1982).

Biogenic Monoamine Turnover Rate Changes

Passive morphine infusion (yoked-morphine vs. yoked-vehicle) resulted in fewer and generally smaller significant changes in dopamine (DA), norepinephrine (NE), and serotonin (5-HT) turnover than did the contingent administration (self-administering animals vs. yoked-morphine infused) (figure 6). Four significant changes

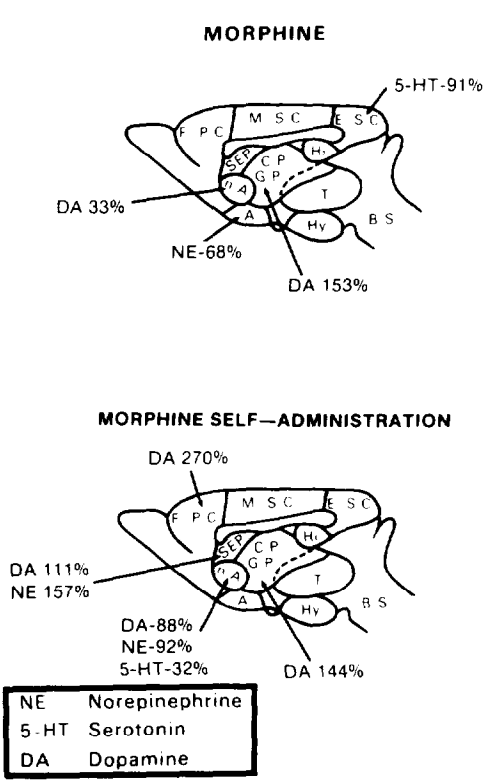

FIGURE 6. *The effects of noncontingent passive intravenous morphine infusion determined by comparing yoked-morphine and yoked-vehicle infused littermates) and contingent intravenous morphine self-administration determined by comparing the self-administering animals with the yoked-morphine infused littermates) on the turnover rates of dopamine, norepinephrine, and serotonin in 11 brain regions*

NOTE: Values are the percent change of the significant differences.

in turnover occurred in the yoked-morphine infused littermates compared to the yoked-vehicle infused animals, while seven significant differences were seen between the self-administering and the yoked-morphine littermates. The decreases in turnover of NE in the amygdala and 5-HT in the entorhinal-subicular cortex likely represent a direct drug effect, since these changes were seen in both drug groups irrespective of the contingency. The increase in DA turnover rates in the caudate nucleus-putamen of the yoked-morphine group was even further increased in the self-administering group, while the increase in the nucleus accumbens was reversed to almost no turnover at all in the self-administering

animals. In one situation, the self-administration contingency exacerbated a change and in the other, it totally attenuated the change and resulted in an even greater effect in the opposite direction. It is interesting to speculate about the underlying basis of these changes. The differences between the contingent control of reinforcer presentation and the noncontingent presentation of a potential reinforcer may not represent simply reinforcing efficacy differences. The potential reinforcer presented noncontingently may activate some pathways that participate in reinforcement when the drug is administered response-dependently (e.g., DA innervations of the caudate nucleus-putamen). Furthermore, noncontingent presentation may have aversive properties resulting in a reversal and change in the opposite direction to that of contingent presentation (e.g., DA turnover in the nucleus accumbens).

Five changes in biogenic monoamine turnover rates appear to be related to the reinforcing properties of contingent self-administration. These include increases in DA turnover in the frontal cortex and septum, the increase in NE turnover in the septum, and decreases in NE and 5-HT turnover in the nucleus accumbens of the self-administering animals.

Amino Acid Turnover Rate Changes

The passive noncontingent administration of morphine resulted in 11 significant changes in aspartate (Asp), glutamate (Glu), and gamma-aminobutyric acid (GABA) turnover, while the contingent self-administration resulted in 22 changes (figure 7). Four turnover rate changes appeared to be direct pharmacological effects of morphine since they were identical in both drug groups, regardless of the contingency. These changes included increases in Asp turnover in the septum, Glu turnover in the nucleus accumbens and septum, and in GABA turnover in the entorhinal-subicular cortex. Five of the other changes in the yoked-morphine group may be related to the differences between contingent self-administration and noncontingent administration, since they were nullified and often significantly changed in the opposite direction in the self-administering animals. These changes included the decreases in turnover rates of Asp and Glu in the caudate nucleus-putamen, Asp in the amygdala, and GABA in the septum, and increases in GABA In the caudate nucleus-putamen and nucleus accumbens. Two significant changes in the yoked-morphine group were even greater in the self-administering littermates. These changes included the increased turnover rates of GABA in the caudate nucleus-putamen and hypothalamus.

Of the 22 changes resulting from the contingent self-administration, 15 appear to be related to the reinforcing properties of intravenous morphine. These include the increases in Asp turnover rates in the frontal cortex, hippocampus, thalamus, motor-somatosensory cortex, and brain stem; increases in Glu turnover in the frontal cortex, hippocampus, amygdala, and motor-somatosensory cortex; and increases in GABA turnover in the frontal cortex,

hippocampus, amygdala, thalamus, motor-somatosensory cortex, and brain stem. Six other changes were reversals of the changes seen in the passive morphine-infused group, which included increases in turnover rates of Asp in the caudate nucleus-putamen and amygdala, in Glu in the caudate nucleus-putamen, in GABA turnover in the septum, and decreases in the nucleus accumbens. The remaining two changes were even greater increases in turnover of GABA in the self-administering littermates in the caudate nucleus-putamen and hypothalamus.

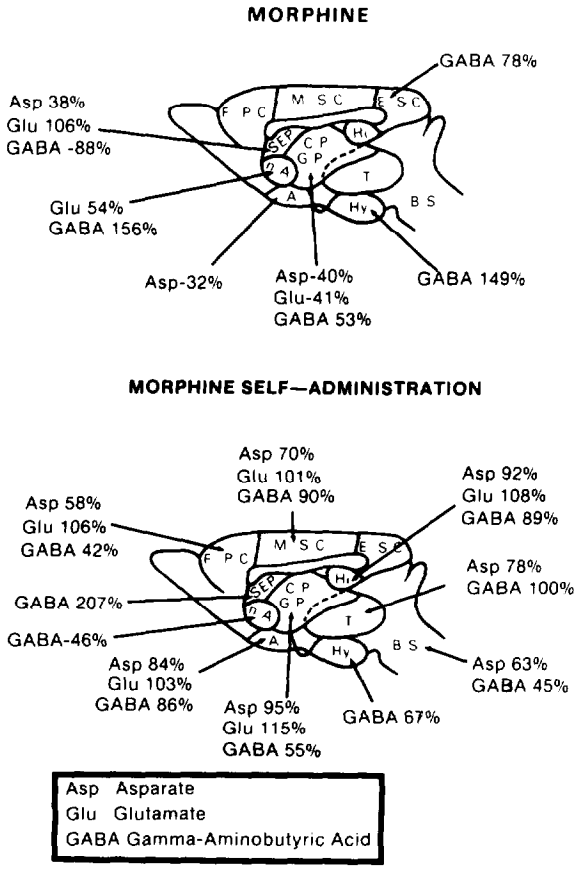

FIGURE 7. *The effects of noncontingent passive intravenous morphine infusion and contingent intravenous morphine self-administration on the turnover rates of aspartate, glutamate, and gamma-aminobutyric acid in 11 brain regions*

NOTE: Values are the percent change of the significant differences.

Acetylcholine (ACh) Turnover Rate Changes

The turnover rates of ACh were determined in 14 brain regions of 14 additional triads of littermates to assess the role of cholinergic neuronal systems in contingent and noncontingent morphine presentation. Three significant changes in turnover rates were seen in the yoked-morphine infused group and four were seen in the self-administering group (figure 8). Two of the three changes in the yoked-morphine infused littermates appeared to be related to the direct effects of morphine, since the changes were seen in both drug groups, regardless of the contingency. These included the increase in turnover in the diagonal band region and the medial septum. The increase in ACh turnover in the frontal cortex in the yoked-morphine group was even greater in the self-administering littermates, while decreases in turnover were seen in the pyriform cortex, nucleus accumbens, and amygdala of this latter group.

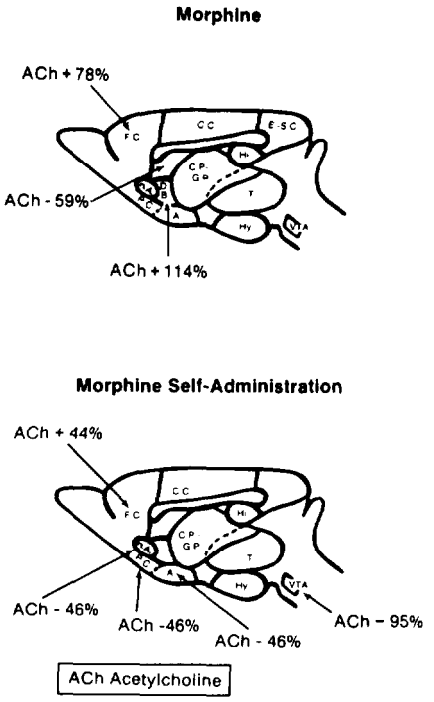

FIGURE 8. *The effects of noncontingent passive intravenous morphine infusion and contingent intravenous morphine self-administration on the turnover rates of acetylcholine in 14 brain regions*

NOTE: Values are the percent change of the significant differences.

The tissue remaining from the litters in which ACh turnover rates were measured was used to determine muscarinic cholinergic- and benzodiazepine-binding characteristics. Scatchard analysis and Hill plots demonstrated significant differences in muscarinic cholinergic-binding between the noncontingent and contingent presentations of morphine (figure 9). Four changes in the yoked-morphine group appeared to be direct drug effects, since these

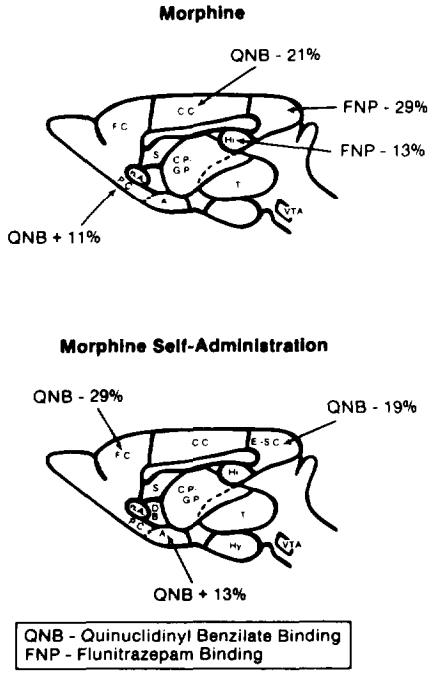

FIGURE 9. *The effects of noncontingent passive intravenoue morphine infusion and contingent intravenous morphine self-administration on the density of binding sites for ^{3}H-quinuclidinyl bensilate and ^{3}H-flunitrazepam determined in eight brain regions*

NOTE: Values are the percent change in B_{Max} for the significant differences.

were also present in the self-administering animals. These include the increase in muscarinic cholinergic-binding in the pyriform cortex and decrease in the cingulate cortex, and the decrease in benzodiazepine-binding in the hippocampus and entorhinal-subicular cortex. Three significant changes in muscarinic cholinergic-binding were observed in the self-administering

animals that appeared to be related to the reinforcing effects of contingent drug delivery. These included the increase in the amygdala and the decrease in the frontal cortex and entorhinal-subicular cortex. The changes in the amygdala and frontal cortex were the inverse of changes in ACh turnover seen in these areas, while the changes in binding in the entorhinal-subicular cortex suggested a net increase in total activity that was not observed as a turnover rate change. The pulse-labelling intervals for ACh turnover were 5 and 10 minutes. The turnover-rate measures may not be representative of the total neuronal activity during the 110-minute interinjection interval. Accordingly, the increases in ACh turnover in the frontal cortex of the yoked-morphine group and in the pyriform cortex and nucleus accumbens of the self-administering animals may not represent net changes in neuronal activity, since no changes in muscarinic cholinergic-binding were observed in these areas. However, the changes in the frontal cortex and the amygdala of the self-administering littermates are consistent with total net changes in activity since inverse changes in binding were observed.

NEURONAL CIRCUITS MEDIATING THE REINFORCING EFFICACY OF CONTINGENT MORPHINE PRESENTATION

Integrating these neurochemical data and data from studies of the effects of pharmacological blockade or neurotoxin lesion on intravenous morphine self-administration with knowledge of neurotransmitter-specific neuronal pathways suggests two neuronal circuits to be involved in the processes maintaining intravenous morphine self-administration, which include its reinforcing efficacy (Smith et al. 1984a). A nucleus accumbens-pre-optic nucleus-amygdala-entorhinal cortex-hippocampus-nucleus accumbens circuit and a frontal cortex-striatum-frontal cortex circuit were identified that included ACh, DA, NE, 5-HT, Asp, Glu, and GABA neurons. Activity in these circuits appears to be modulated by feedforward pathways from brain stem biogenic monoamine systems, while GABA feedback pathways from these circuits appear to modulate activity in these brain stem centers. These circuits may represent general reinforcement systems and not just opiate reinforcement processes, since 2-deoxyglucose autoradiography in the brains of animals intracranially self-stimulating identified many of the same regions as in these intravenous morphine self-administering animals.

OTHER NEUROBIOLOGICAL EVIDENCE FOR DIFFERENCES BETWEEN CONTINGENT AND NONCONTINGENT PRESENTATION OF REINFORCERS

Responding by rats can be maintained by the termination of electrical stimulation of brain regions where such stimulation was previously self-administered (Steiner et al. 1968), suggesting the development of potential aversive properties when control over presentation is removed. The autoradiographic assessment of the distribution of ^{3}H-2-deoxyglucose in the brains of animals electrically self-stimulating intracranially, compared to noncontingent presentation to previous self-stimulators, showed increases

in glucose utilization bilaterally in the medial prefrontal cortex and ventrolateral thalamus, and ipsilaterally to the stimulating electrode in the nucleus accumbens (Porrino et al. 1984). These data suggest that neuronal activity in these regions was increased in the animals receiving contingent presentation of the electrical stimulus. However, no significant differences in the noncontingent stimulated group (not seen in the contingent group) that could be identified as resulting from changes in neuronal activity potentially correlated with the aversive properties of this loss of control over a previously contingent reinforcer were seen.

CONCLUSIONS

The noncontingent intravenous presentation of morphine results in fewer and generally smaller changes in the turnover rates of seven neurotransmitters and two neurohumor binding sites than does the contingent presentation of the drug. Response-contingent drug delivery has greater effects upon these systems than those effects observed to be related to the drug itself. These differences likely result from the reinforcing properties resulting from control over drug presentation. Behavioral consequences appear to determine some of the neurobiological consequences of drug action. Investigations of the biological effects of abused substances should likely include the behavioral context of excessive self-administration, especially if biological treatment approaches are the goal of such research.

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Receptor Regulation as a Function of Experience

Fritz A. Henn, Emmeline Edwards, and David Anderson

INTRODUCTION

Seligman and Beagley (1975) demonstrated that exposure to uncontrollable shock produces a behavioral deficit described as "learned helplessness." This phenomenon transfers across different aversive training and testing contexts; the apparent development of an escape deficit seems to depend on factors such as the nature of the aversive stimulus (Goodkin 1976; Weiss and Glazer 1975), the parameters of the presentation of that stimulus (Anderson et al. 1976; Rosellini and Seligman 1978), and the nature of the escape response (Seligman and Beagley 1975; Wilson and Butcher 1980).

The mechanism by which exposure to uncontrollable shock produces this behavioral deficit remains undefined. However, we have established a psychobiological concept of "learned helplessness," including a distinct behavioral and neurobiological mechanism (Henn et al. 1985). Our laboratory has been studying a modified version of Seligman's "learned helplessness" model in which our experimental animals are exposed to mild uncontrollable shock only. With this approach, we have compared two distinct groups of rats that emerged when subjected to a mild course of uncontrollable shock. The selection was from two different groups of animals: (1) those that showed no deficit in subsequent shock-escape tests, and (2) those that showed a profound learning deficit. This selection has provided a better medium for behavioral and pharmacological manipulations.

ESTABLISHMENT OF A MODEL

Sprague-Dawley rats were used in our experiments. These rats were obtained from Charles River Breeding Laboratories and were delivered to the Division of Animal Resources, where they were kept under standard conditions. Upon arrival, these rats, weighing 150 to 200 gm, were maintained on an ad libitum food and water schedule. Behavioral training and testing sessions were scheduled during the light phase of a 12-hour light/dark cycle.

The critical element of our behavioral, biochemical studies is the consistency and accuracy with which the behavior can be quantified. There have been numerous reports of a learning deficit that occurs after exposure to uncontrollable shock; these reports show only a degree of internal consistency within each investigator's paradigm. Researchers from various laboratories have agreed that there is a behavioral difference between response-deficient rats and rats that have received identical shock but still respond at control levels (Katz 1981). There is a high degree of variability in obtaining the behavioral deficit after inescapable shock training; therefore, in our studies, a revised "learned helplessness" model was used. In our experimental setup, the rats were placed in an experimental chamber with an electrified grid floor. Each chamber measured 12 x 18 x 12 cm. Sides and ceilings were constructed of aluminum and Plexiglas. The floor was constructed of stainless steel rods spaced 1.9 cm apart. During the shock-escape test, a level was mounted 7 cm above the grid floor on one wall. A yellow cue light was placed 5 cm above the lever. Shock was delivered to each chamber by a Coulborn solid-state shock source (model E13-16).

SHOCK TRAINING

Training consisted of placing the rats in the experimental chamber, where they received intermittent inescapable 0.8-mA footshock. Each training session lasted 40 minutes. The onset and offset of the shock being established by a probability generator resulted in an average schedule of 20 minutes of shock with a minimum time of 1.5 seconds between on and off events.

SHOCK-ESCAPE TESTING

Twenty-four hours after training, each rat was individually tested in an escape situation where footshock could be eliminated by a single bar-press. Shock was delivered at the intensity of 0.8 mA in a pulsating schedule of 35 msec on/35 msec off, with the yellow cue light on during the shock period. Shock onset began one trial; pressing the lever, or the end of 60 seconds, shut off the shock. Intertrial intervals of 24 seconds began with the yellow cue light out. Fifteen trials were given in each testing session. Latencies up to 20 seconds before the lever was pressed and the shock terminated were considered to be successful escape from shock. Latencies of 20 to 60 seconds were recorded as failures. Scores were recorded automatically, with nonspecific effects of footshock eliminated by including internal controls in the testing paradigm. Behavioral, pharmacological, and biochemical determinations were carried out for these internal controls. These rats were subjected only to the shock-escape test, enabling us to determine the effects of shock per se. Past experiments in our laboratory demonstrate that these controls routinely do not show significant changes either behaviorally or biochemically from measures on nondeficient or naive rats.

BEHAVIORAL DEFICIT

Behavioral deficits were measured as the number of failures using the following criteria:

- Rats scoring 1 to 5 failures in a 15-trial testing session were not response deficient (ND) and learned the shock-escape test as quickly as controls.

- Rats scoring 11 to 15 failures in a 15-trial testing session were considered response deficient (RD).

In a typical experiment, in which a total of 40 rats were used (10 internal controls; 30 trained and tested in shock paradigm), 30 percent of the trained and tested rats were response deficient (RD), while another 30 percent were nondeficient and responded at a level similar to control rats in the shock-escape test. Rats scoring in the range of 6 to 10 failures were not considered in subsequent analysis. Behavioral and biochemical determinations performed on rats falling into the 6-to-10-failures group revealed a high degree of heterogeneity within the group. In addition, a large percentage of the 6-to-10-failures group exhibited improved shock-escape scores when subjected to additional shock treatment

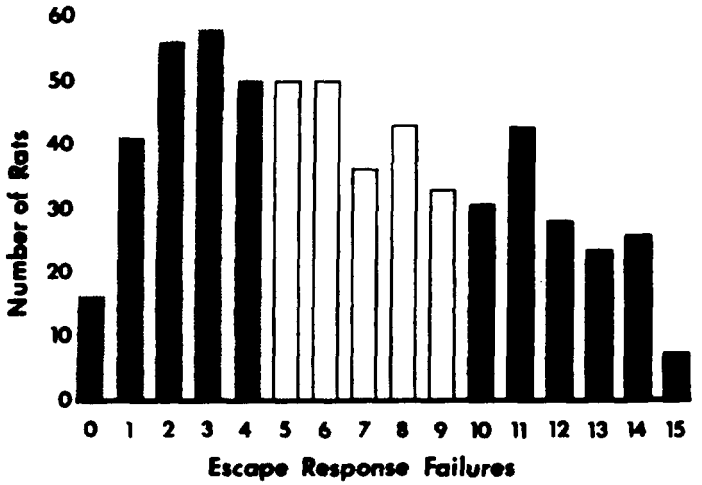

FIGURE 1. *Features of escape responding after exposure to inescapable shock and control responding*

NOTE: The figure shows failures to escape In rats trained 24 hours previously. Dark shading indicates the subpopulation defined as having severe response deficits (RD), while the lighter shadlng denotes animals having no deficit (ND) after undergoing identical treatment. The total number of animals involved was 592, with 27 percent falling in the range of 10 to 15 fall-ures, and 37 percent between 0 and 4 failures.

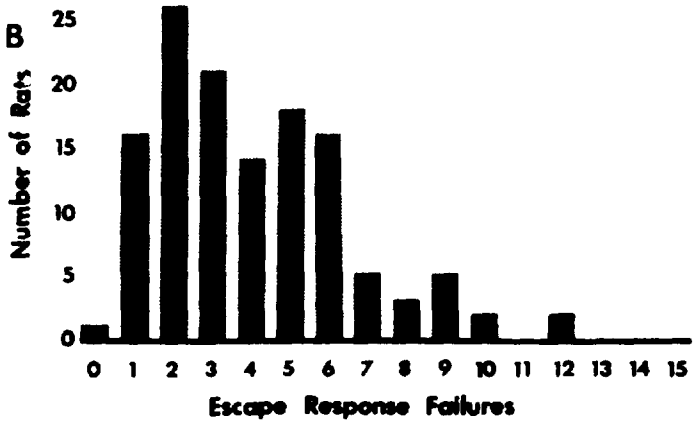

FIGURE 2. *Testing of naive rate: Animals exposed to the escape paradigm with no prior training*

NOTE: Sixty percent of these animals scored 0 to 4.

(repeated training sessions). Biochemical determinations, mainly beta-adrenergic receptor analysis, also revealed a high degree of variability within the group.

The behavioral deficit exhibited after exposure to uncontrollable shock was reversed with time. When deficient rats were again tested in a shock-escape situation, 3 weeks later, their behavior paralleled the behavior of controls.

We noted that the percentage of rats developing the shock-induced behavioral deficit was dependent on the strain of rats used. Routinely, 30 percent of the trained and tested Sprague-Dawley (SD) rats from Charles River Breeding Laboratories (CRBL) developed a behavioral deficit in a shock-escape test, while the Biolabs strain produced only 21 percent of response-deficient (RD) rats. Rats obtained from Taconic Farms and Simonsen Laboratories yielded only 11 percent, respectively, response-deficient rats in the standard training and testing paradigm. This suggested that the behavioral deficit emerging after exposure to mild, uncontrollable shock may involve a genetic component. Our laboratory has undertaken the selective breeding of response-deficient (RD) rats, nondeficient rats, and controls. With data from only three generations of each group, hereditary differences between our selected lines are becoming evident. New litters from response-deficient SD, CRBL rats have produced, under identical conditions of shock training and testing, 44 percent of escape-response-deficient

rats. Conversely, litters from nondeficient SD rats have produced less than 2 percent of animals with a shock-escape deficit. However, the effect of hereditary differences on behavior must be characterized thoroughly by biochemical analysis.

NEUROBIOLOGICAL CHANGES

We have identified some neurobiochemical differences between the two groups emerging after a mild course of uncontrollable shock. These differences may pinpoint the anatomical locus of the behavioral deficit.

NEUROTRANSMITTERS

Various brain regions were analyzed for their concentrations of DA, NE, and 5-HT. These neurotransmitter levels were analyzed by simultaneous assays performed by reverse phase high performance liquid chromatography (HPLC) with electrochemical detection. HPLC determinations of the biogenic amines in various brain regions did not reveal any significant changes in norepinephrine, epinephrfne, dopamine, or their metabolites in response-deficient rats when compared to nondeficient rats. However, in the hippocampus, the serotonin/norepinephrine ratios (5-HT/NE) disclosed some differences between response-deficient rats, nondeficient rats, and controls. In general, small, consistent increases in 5-HT and decreases in NE levels were observed.

RECEPTORS

Beta-adrenergic and serotonin receptors were studied in response-deficient rats, nondeficient rats, and controls. The various brain regions analyzed included the cerebellum, hippocampus, hypothalamus, septum, and anterior neocortex. Major differences in beta-adrenergic receptors were seen in the hippocampus of response-deficient rats. The status of beta-adrenergic receptors was assessed by a filtration assay, using ^{125}I-cyanopindolol (^{125}I-CYP) as the probe. Briefly, hippocampal membrane preparations were incubated for 55 minutes at 37 °C, with increasing concentraions of ^{125}I-CYP (0 to 240 pm) in the presence or absence of 10^{-6}M propanolol used for nonspecific binding determination (Engel 1981).

In response-deficient rats, the beta-adrenergic receptor was up-regulated in the hippocampus, but not in the anterior neocortex nor the septum. Changes in hippocampal beta receptors follow a time course similar to the shock-escape deficit; a strong correlation between beta-adrenergic receptor status and shock-escape deficit scores has been established for the response-deficient rats. Within 3 weeks following the shock-escape test, both failure scores and beta-adrenergic receptor status of response-deficient rats were comparable to controls. Adenylate cyclase responsiveness to norepinephrine was determined in response-deficient, nondeficient, and control rats. Basal and stimulated cyclic AMP

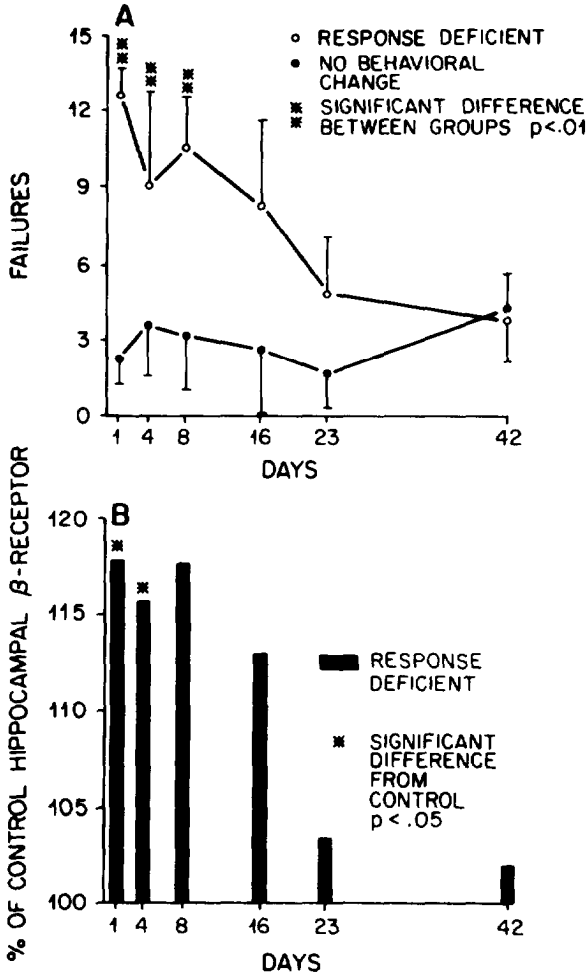

FIGURE 3. *Behavioral and beta-receptor changes with time after exposure to inescapable shock*

NOTE: (A) Rats were trained and tested as described In the text. Cohorts of animals were subsequently retested at 4, 8, 16, 23, and 42 days. Control values throughout the experiment remained at approximately 4+2 failures. (8) Hippocampal beta-receptor measurements were determined using ^{125}I-CYP as the Iigand and assayed In individual animals according to the method of Engle (1981). Binding saturation curves were analyzed using an Eadie-Hofstee transformstion, and B_{Max} was obtained through extrapolation (Zivin and Wand 1982). Data are expressed as percent of control values. Significance was determined using a two-tailed t-test for differences between means.

levels were measured using the protein binding assay of Gilman (1970), in kit form, as provided by Amersham, Inc. Response-deficient rats exhibited a large increase in adenylate cyclase activity in hippocampal slices, indicating that an amplification of the noradrenergic receptor adenylate cyclase system may be linked to the behavioral changes seen in our model of shock-induced deficit. Modifications at the receptor level in response to environmental conditions attest to the plasticity of the central nervous system and to the involvement of neurochemical mechanisms in some behavioral responses. In our modified version of "learned helplessness," there is a biochemical modulation of the brain in response to a purely environmental manipulation. This suggests that certain stimuli, obviously drugs among them, can lead to altered behavioral patterns driven by altered CNS structures.

PHARMACOLOGY

Pharmacological interventions produced a time-dependent reversal of both the shock-induced behavioral deficit and the beta-adrenergic receptor up-regulation characteristic of response-deficient rats. In our drug studies, we followed the schedule of training and testing of our regular paradigm, but shock-escape testing was followed by a 5-day drug treatment. Tested controls were divided into two groups, drug treated and vehicle treated. Simultaneously trained and tested rats were first divided into response-deficient and nondeficient rats, then each of these two groups were further divided into a drug-treated group and a vehicle-treated group.

To date, drug studies performed with our model of shock-induced deficit have focused on compounds known to interact with either noradrenergic or serotonergic systems. Imipramine (10 mg/kg x 5 days), a relatively nonspecific catecholamine uptake inhibitor, reversed the behavioral deficit. The shock-escape score of response-deficient rats improved in 80 percent of the rats re-tested after the imipramine treatment (11.6±1.8 --> 4.2±3.6 failure scores). A number of tricyclic antidepressants, monoamine oxidase inhibitors, and second-generation antidepressants were tested. All clinically effective drugs reversed the learning deficit; nonspecific drugs, such as neuroleptics, sedatives, or stimulants, do not appear to reverse the learning deficit. Among the drugs tested were the relatively specific 5-HT uptake inhibitor fluvoxamine and the novel compound mianserin, thought to act mainly through the 5-HT system. Each of these compounds caused behavior reversal of the deficit.

Interestingly, the reversal of the shock-induced learning deficit was accompanied by a significant down-regulation of the beta-adrenergic receptor in the response-deficient rats. This was expected for the TCAs such as imipramine, which have previously been shown to down-regulate beta receptors. It was surprising that the behavioral changes and down-regulation by betareceptors induced by imipramine appeared to be similar to, but faster than, the down-regulation caused by this compound in naive animals. Imipramine

reversed the behavioral deficit and significantly down-regulated the hippocampal beta receptors (25 percent down-regulation as compared to control). Even more unexpected, mianserin lowered the up-regulation of the beta receptor in response-deficient animals, while causing no change in the hippocampal beta receptor of non-deficient rats. Mianserin had previously been shown not to down-regulate the beta-adrenergic receptors in behaviorally naive rats (Mishra et al. 1980). Mianserin reversed the behavioral deficit and significantly down-regulated the hippocampal beta receptors of response-deficient animals (28 percent down-regulation as compared to control). Hence the up-regulated receptor seen in our animal model may be either more sensitive to presynaptic influences or under the exquisite control of a postsynaptic regulatory process. So, specific drugs may have an exclusive effect on a pathologic transmitter system while exhibiting no control over receptors in a normal or naive animal.

NEUROREGULATORY ROLE OF 5-HT

Studies with mianserin and fluvoxamine suggested that a serotonergic mechanism may also be involved in the mediation of the deficit produced by mild, uncontrollable shock. The decrease of serotonin levels prevented the development of the shock-induced behavioral deficit seen in our model. Sprague-Dawley rats pretreated with PCPA, a known 5-HT synthesis inhibitor, exhibited shock-escape scores similar to nondeficient and control rats (3.0±.17 PCPA treated, vs. 7.6±3.3 saline treated, $t=5.96$, $P<.001$).

Bilateral lesions of serotonergic tracts with 5,7-dihydroxytryptamine (5,7-DHT) also prevented the development of shock-induced behavioral deficit after the training and testing paradigm. Receptor binding assays or S_2 receptors (^{3}H-spiroperidol binding) and S_1 receptors (^{3}H-serotonin binding) in the anterior neocortex and the hippocampus did not reveal any significant differences in either the affinity or the maximum number of sites in response-deficient, nondeficient, or control rats. However, a normal level of 5-HT activity was necessary to maintain beta levels in the hippocampus. Recent experiments in our laboratories revealed a significant down-regulation of hippocampal beta receptors after various treatments known to influence 5-HT levels and 5-HT transmission (B_{Max} in fm/mg protein was 116.5±9.2 in response-deficient rats, vs. 62.8±5.7 in 5-HT depleted rats). These studies suggest that a feedback mechanism between noradrenergic and serotonin systems could act as a mediator of the behavioral and biochemical characteristics of our response-deficient rats. Such an hypothesis would support the work of Sulser (1983), who has suggested that an intact serotonergic input is necessary for the down-regulation of beta receptors by various therapeutic drugs.

Our current data do not disclose a simple relationship linking drug-induced alterations in the 5-HT system, uncontrollable shock, and behavioral deficits. However, we are focusing our research

efforts on the following anatomical circuit for our "learned helplessness" model:

Anterior Neocortex ---> Hippocampus ---> Fornix ---> Septum
GABA NE GABA 5-HT
5-HT

This partial limbic circuit including the hippocampus and the septum is modulated by neurotransmitter and neurohormonal inputs. This complex functional "lobe" receives serotonergic, adrenergic, cholinergic, and peptidergic input in addition to the local circuitry.

DRUG ABUSE RESEARCH

This work points to the interplay of environmental and genetic factors in defining the behavioral response to a defined stimulus. It also shows that the behavioral changes are correlated with the long-term CNS changes, a correlation that points to the adaptive plasticity of the CNS. Since addictive behavior appears to share an interplay between nature and nurture, it may be possible to utilize animals bred for different responses to drug and alcohol exposure in isolating anatomic pathways responsive, by addictive behavior, to these environmental and chemical stimuli. In our model, successful reversal of the deficit is not produced by stimulants such as amphetamine and cocaine as was found by Sherman et al. (1979). The role of stimulants merits further testing; the idea that a particular genetic substrate is required for altered behavior to occur may be a powerful one for research into drug abuse. As a start, we would suggest tests of self-administration under conditions in which there is a wide behavioral response by animals. The fact that stimulants and hallucinogens have actions on amine systems also suggests that the circuit activated in our stress model should be examined under conditions of drug use.

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Clinical and Behavioral Considerations in Emission Tomography Study Design

Reese T. Jones

INTRODUCTION

Quantitative imaging of neuroreceptors in the living brain has only recently passed beyond the "show and tell" demonstration of feasibility and rather fuzzy, low resolution, computer-generated images. Much remains to be done, but there is reason for optimism. As chemists become more skilled in synthesizing high specific activity, high affinity, and positron emitting radioligands. we can expect experiments with Alzheimer's patients (acetylcholine receptors), schizophrenics (dopamine receptors), opiate addicts (the families of opioid receptors), tobacco addicts (nicotine receptors), etc. Many hitherto untestable models of diseases (at least untestable in humans), assumed to involve receptor dysfunction, will be put to the test.

A RETURN TO THE STUDY OF HUMAN PHARMACOLOGY

Positron emission tomography studies of neuroreceptors, particularly quantitative imaging, present a number of challenges to currently popular research strategies. One major challenge is that humans are probably the best subject population. Because of the physics of emission tomography, a large brain is an asset. Given the resolution of existing and likely instruments in the near future, rodent brains are too small. Researchers could use baboons or other large, nonhuman primates; however, the number of large-brain primates available is relatively small compared with humans. Even if available, the recording time to accumulate satisfactory images is so long that the use of unanesthetized or lightly restrained baboons in the usual emission tomography setting is not practical. Studies of anesthetized primates are not the most efficient research strategy if understanding relationships between receptor function and behavior or cognition is the goal. Thus, largely because of the technological constraints, the best research subjects are humans.

The promise of learning about human brain function is the great advantage and justification for support of expensive, innovative

technologies. However, most of what we know for sure about receptor function, binding of drugs to receptors, and neurochemistry comes from rodent tissue cell cultures (often homogenized and separated) using research strategies and approaches that have not had to deal with the problems of clinical studies. This chapter will consider some of the practical problems of dealing with human research subjects in tomography studies.

Despite justified optimism, proper application of emission tomography requires careful thought when posing research questions. It will be a challenge to design experiments that efficiently confirm specific hypotheses rather than simply demonstrate that predictions are correct. A host of neurochemical, chemical, biophysical, and radiologic considerations must be attended to. Other chapters in this volume (Frost, this volume; Snyder, this volume) suggest that with time and adequate resources most of these problems can be managed. Even when procedural and technological problems are solved, some major constraints will remain for the design of experiments by those interested in human behavior or psychology. Limitations on experimental sample size, the special task demands for research subjects in emission tomography studies, feasibility of repeated measures, and uncertainty about which subjects may be adequate controls will test the skills of investigators attempting the early definitive experiments. Although my focus here is on drug dependence research, many considerations are general ones relevant to any emission tomography studies of brain receptor function.

LEVELS OF CHALLENCE DEPEND ON QUESTIONS ASKED

There is a gradation of experiment complexity and demand on the technology, depending on specific questions. To be most useful, the imaging of receptors must provide quantitative indices. At the simplest level, anatomic localization of many types of receptors is obviously feasible; the degree of success will depend mostly on clever chemists producing a ligand with suitably selective and specific high-affinity binding and high-activity labelling. Physicists and engineers must provide high-resolution machines. The studies at Johns Hopkins University, described in other chapters (Frost, this volume; Snyder, this volume), show how a large group of adequately supported scientists can enable us to visualize receptor fields in a living brain. However, it is a long step from the relatively crude anatomic localization of receptor fields to precise quantitative measures of receptor concentration, distribution, and activity necessary to investigate mechanisms of disease states.

One limitation in existing technology is the relatively poor resolving power of currently available imagers, though, at some installations, resolving power close to the theoretical will soon be available. For most neurological diseases that are thought to involve neurotransmitter dysfunction, the variation in neuroreceptor concentrations seems relatively small. The utility of emission tomography to quantify small, and probably variable,

deviations in receptor-field density in small anatomic structures, for example, the locus coeruleus, must await confirmation. The precise counting, or otherwise indexing, of numbers of receptors is a greater task than the semiquantified demonstration of relatively imprecise anatomic localization evinced so far.

The technology must ultimately provide quantitative indices of receptor activity, that is, measures of uptake or turnover of neurotransmitters or other dynamic indices of receptor activity. Measuring levels of neurotransmitters only, be it in the brain or elsewhere, tells relatively little about function and can be misleading. The turnover--the dynamics of neurotransmitters--is what must be determined, which puts a great burden on our still relatively simple kinetic models that relate input and output functions to receptor concentrations. As yet, a complete in vivo validation of relationships between neurotransmitter uptake or turnover measures and receptor concentrations is lacking. Validation in vivo in intact humans may be a formidable task.

MEASURING AMOUNT OF DRUG DELIVERED TO DRAIN

Measuring, even estimating, the actual delivered dose of a labelled ligand to the brain is not a trivial problem. Dose deliverance to a specific region of the body or organ is rarely considered in psychopharmacologic experiments. For example, after IV administration, before the ligand is available to bind to receptors in the brain and emit positrons, it first must traverse the arm, right heart, lung, and left heart before reaching the brain. All the complexities of peripheral binding, disposition, and metabolism must be determined before true quantitative indices of brain measures can be obtained. What is the actual delivered dose of ligand to brain? The dose , unfortunately, is going to be different from the dose injected into a forearm vein. For exampie, the dose, or ratio of injected ligand to brain dose, may vary with different ligands used to selectively label the families of opiate receptors.

There are, of course, research strategies for measuring organ dose. Some strategies are purely matters of proper application of mechanics and plumbing (e.g., carotid artery or lung injections compared with injections by other routes). The knottier scientific problem stems from the vicissitudes of quantifying peripheral drug kinetics, particularly in tissues other than blood. This quantification can barely be done adequately for the clinical pharmacology studies that now go on. The proper application of high technology will force us to deal with the measurement of far smaller quantitative differences in the face of greater unaccounted-for variability in drug kinetics.

SLOW MEASURES OF FAST SYSTEMS

The time necessary to accumulate a quantiffable image (currently, under optimal conditions, about 1 minute; more typically, 15 minutes) places constraints on experimental design and limits

researchable questions. To a great extent, decreasing image collection time is a matter of improving the chemistry and physics of emission tomography. More efficient detection systems and higher-activity ligands will decrease this time, but there still will be a relatively narrow time span to work in when trying to measure dynamic, and probably rapidly changing, neurochemical events relating to a particular mental state or relating receptor function to specific behaviors. Most mental states or behaviors do not hold still for a minute; therefore, the measured receptor activity may only reflect averaged events.

When attempting to measure a steady state (i.e., more trait-like mental conditions), the time required for emission tomogram collection is less of a consideration, and collection can be more leisurely. But when moving further away from trait-determined measures into behaviorally or psychologically dynamic states, then time to accumulate an image becomes a primary consideration for design of experiments. A previously new and exciting high technology development from 25 years ago (brain wave-evoked potentials using an electrical index of brain activity) still has unsolved problems with this limitation in attempting to measure brain function correlates of rapidly changing behavioral, psychological, or subjective states.

HOW RELIABLE ARE THE INDICES?

One tradeoff in using high-activity ligands is the dosimetry factor, particularly, a more rapid cumulative exposure to radiation. When beginning experiments with any new technology, the optimal research strategy should include measures of reliability, whatever the measure. Reliability data will not rapidly accumulate since, with current technology, repeated doses of labelled ligands may, by increments, rapidly exceed recommended radiation exposure, at least in the case of normal, nondiseased volunteer research subjects. Of course, when performing a procedure on someone with an illness and the procedure is to that patient's benefit, higher radiation doses may be rationalized (assuming it is a well-designed experiment). Nevertheless, cumulative radiation dose remains a constraint for the near future,

A related consideration that has relevance to the use of high-affinity ligands and also depends on metabolic considerations is that adding any drug, maybe even at what are assumed to be, pharmacologically speaking, "tracer" doses, may perturb the biological system, particularly as the ligand becomes more potent and more specific. Traditionally, most perturbations of a biological system are thought to have a finite time course. It is assumed a repeated drug challenge will give a similar response some hours, days, or perhaps weeks later. But what if this new technology provides the ultimate in sensitivity to small changes in receptor function? Does that mean that the neuroreceptor correlates of differences in sensitivity to opiates, as shown by behavioral indices months or perhaps even a year after a single dose, may now be evident? This possibility makes repeated-measure experiments a

little more complicated to interpret, assuming that emission tomography provides a very sensitive measure.

MERGING NEURORECEPTOR AND PSYCHOLOGICAL MODELS

Other chapters in this volume (Frost, this volume; Snyder, this volume) discuss neurochemistry, radiologic physics, and a variety of psychological models and constructs. Implicit in this unusual mix of topics is a hope or a promise that there should be some linkage of emission tomography measures of neuroreceptor function and psychological measures of function, states, and traits (e.g., sensation seeking, locus of control, and dependence). Actually demonstrating such quantitative relationships, no matter how high the technology, certainly will be akin to finding the Holy Grail.

Optimism should be tempered slightly by noting that, in much simpler biological models (e.g., rodents or their isolated organs in Ringer's solution), relationships between receptor-binding kinetics, receptor function, and psychological function or behavior have been modest demonstrations at best and, for the most part, have not been thoroughly investigated. The question of why clearly demonstrated and consistent relationships between receptor kinetics and an organism's function are relatively rare, becomes relevant when considering the application of an extremely high-cost, relatively high-risk technology to address questions such as the relationship between receptor kinetics in one organ system (in this case, the brain) and behavior or mood. Is it a consequence of inadequate technology that thus far this has been only tenuously demonstrated when using simpler technologies, or is there a problem with our models?

WHAT RESEARCH SUBJECTS TO STUDY?

The already complicated list of subject populations appropriate for the study of drug-dependence-related phenomena becomes more complicated if one considers the subtypes of drug users described in Dr. Forgays' chapter (Forgays, this volume). A minimal list of populations in which one might expect differences in receptor and/or psychological profiles and functions now includes the following groups:

- Nondrug users ("normal people") who have never used;
- Drug users who are not patients in treatment and who:

  (1) have no history of treatment,
  (2) have a history of failed treatment,
  (3) want to stop, or
  (4) do not want to stop using drugs;

- Former drug users, posttreatment;
- Former drug users who are self-determined quitters, who have never sought treatment.

This additional level of complexity of user vs. nonuser, treatment vs. nontreatment subclassifications results from the considerations discussed in Dr. Forgays' chapter. One must assume that there should be neurochemical/neurotransmitter and psychological state/trait correlate differences for these subgroups. If not, why should one, a priori, assume no differences?

Patient selection considerations in studies of the neurochemistry or neurophysiology of any drug are complex. Given the special constraints of emission tomography, subject selection becomes even more important. For example, if a researcher studies current and regular users of a drug (either the drug of interest or other drugs), then abstinence syndromes become a potential confounding problem. When studying opiate receptors, is it best to withhold tobacco or coffee from the typical tobacco-smoking, coffee-drinking research subject before the experiment (as is often the case) for 4, 8, or 12 hours, or is it best to allow regular drug use? Depending on the researcher's choice, the research subject is studied in the midst of some ill-defined withdrawal state that must have neurochemical correlates, or in the midst of an equally ill-defined drug-induced state, or perhaps somewhere between these extremes. If a research subject is a regular user of almost any psychoactive drug, there will be no readily attained, steady, non-drug state. Given the kinetics of most commonly abused or used psychoactive drugs, the subject is either entering or leaving a drug-induced state. A steady (or nondrugged) state in pharmacokinetic/dynamic terms is illusionary in psychopharmacologic experiments employing people who use psychoactive drugs.

WHO ARE THE CONTROL OR COMPARISON RESEARCH SUBJECTS?

Researchers typically recruit a control sample of some sort of "nondrug" users. Questions arise such as, who are they? do we consider caffeine a drug? if we include caffeine users, do they get their usual caffeine before the experiment, and what are the implications of caffeine use on adenosine receptors and related neurochemical consequences? Because there are no clear guidelines, to a great extent, the research questions must be constrained. Much of what we know of neurochemistry has been generated by studies of inbred, relatively pure genetic strains of rodents or their even simpler isolated ileum strips or vas deferens; such experimental preparations do not exist in human studies. Furthermore, is a completely nondrug-using (no alcohol, coffee, tobacco, etc.) human control subject a proper control for many things? I doubt it. If diet to some extent alters neurochemistry, should we control or manipulate that as well?

One solution to the problems deliberately or accidentally posed by recruiting addicts of one type or another is to create models of dependent individuals in relatively short-term experiments. This solution is feasible and, I would argue, not unethical with proper informed consent. Some preliminary research questions may be tested with the emission tomography technique by giving opiates, stimulant drugs, or depressant drugs to nondrug users (or almost

nondrug users) for a long enough period of time to produce a sufficient state of dependence.

SAMPLE SIZE

Generally, emission tomography studies that will include large numbers of subjects in single experiments are unlikely. Large here refers to large in the statistical data sense. Even though the cost of an emission tomography experiment will gradually decrease as technological efficiency is improved, it will still remain relatively expensive to conduct this procedure for each test subject. Considering the cost of cyclotron time or other means of isotope generation, chemical synthesis and cleanup, personnel, and amortization of rapidly depreciating equipment (obsolescence is a rapid process in high technology), the total cost to a granting agency or an institution for each subject tested in experiments such as those considered in this volume is in the range of $2,000 per test session. A pilot experiment could easily cost $10,000 or more to study six subjects.

WILL GOOD MODELS BE PREMATURELY REJECTED OR BAD ONES LINGER?

If a goal is to relate receptor level neurochemical phenomena and psychological phenomena, particularly concepts such as locus of control, sensation seeking, or personality variables, studies with sample sizes of six, or even two or three times that size, are not likely to be very informative. Good hypotheses and ideas may be prematurely discarded simply because of tests without adequate statistical power. Erroneous assumptions of the existence of relationships resulting from small sample sizes are less of a problem. False assumptions of the presence of a phenomenon tend to be disproven with replication. However, possibly good ideas or good hypotheses relevant to drug dependence, if not confirmed by the first hundred-thousand-dollar tomography study, may not be studied again for some years, if ever. The size of samples most likely to be studied makes impractical the testing of neuropsychological relationships that usually appear as 0.3 correlations where only 10 percent of the shared variance is accounted for.

High technology research studies are not frequently repeated, since only a relatively limited number of research groups will have resources to repeat such an experiment and often will not be inclined to do so. Eventually, when isotope generators become portable and readily available and when inexpensive emission tomography transducer rings approach the price of a personal computer, this situation will change. But even when the hardware becomes more available, the nature of quantitative receptor imaging is such that the system complexity, the demands on the subjects, and the enormous array of attractive new experiments will make replication less common than should be the case with a developing technology. Even poorly posed research questions in this area of inquiry have such enormous intellectual appeal that it is unlikely that an investigative group would take time to replicate

someone else's work rather than proceed with their own "new" exploratory or, as they might rationalize, more definitive demonstrations of answers to their own questions.

THE TEST SETTING AND SPECIAL CONSEQUENCES

Currently, and likely for the near future, emission tomography recording procedures demand relative immobility from research patients. This need will decrease as technology and chemistry improve, but it will remain to some degree. Computer processing of images will improve the situation and correct for some movement, but for ultimate high resolution, relative immobility will remain a requirement. Thus, many behavioral tasks will be awkward to run during data collection. Subjects with impaired ability to cooperate present additional problems.

The mental task assigned to a patient undergoing tomography may be important. We have learned from emission tomography metabolic studies that the working areas of the brain have different characteristics, different metabolic patterns, and different blood flow than relatively quiescent areas. As more sophisticated research questions are posed, one might assume that this will be true of receptor function, probably even more so. There probably is no test condition whereby we can assume that a patient is not performing some mental task or operation. The typical instruction, "Just relax and don't think about anything," merely gives an enormous range of options to a patient. The instruction, "Take the number 938 and successively subtract 7, add 1 to each remainder, then give the final value at the end of the experiment," assigns a more specific, limited, and operationally defined task. The experience during quantitative EEG recordings (an earlier high technology development which some researchers thought would elucidate brain functions) suggests that individual differences and uncontrolled variance can be reduced by assigning a task. Almost any task is better than no task. Simply instructing a person whose head is inside a transducer ring to "lie still and don't do or think about anything" is a task most humans appear not to be able to carry out.

A potential problem may arise when assigning tasks. At some level there should be interactions between psychological constructs such as locus of control, sensation seeking, introversion/extraversion, and neurochemical/receptor function. The demands of the test situation certainly will alter state, both psychological and physiological, during the test procedure. Thus, the interactions of trait differences and state effects will need to be kept in mind when using a sensitive, high resolution procedure purportedly measuring correlates of mental function. When dealing with linear, monotonic functions, the complexity may be unravelled. However, when nonmonotonic, nonlinear, inverted U, and other complex mathematical functions describe relationships among receptor function, psychology, and behavior, clever experiments are necessary if we are to understand these complex relationships.

CONCLUSION

The application of high technology to the study of human brain function does not make the design of proper experiments any easier. As the sensitivity and specificity of brain function measures improve, attention must be paid to experimental design considerations that were previously less important because our measurement techniques were cruder.

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