Laboratory Behavioral Studies of Vulnerability to Drug Abuse

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Introduction

Cora Lee Wetherington and John L. Falk

Despite all the progress that has been made in various areas of drug abuse research, there is an extremely important fundamental issue that remains unsolved. After initial use of an abused drug, why do some individuals proceed to abuse or dependence, while others do not? Why are some people apparently "protected," while others are unprotected or vulnerable? What are the factors that produce this vulnerability; are there factors that protect against it? These are basic, fundamental questions to which answers are desperately needed to make major progress in preventing drug abuse.

On August 2-3, 1994, the National Institute on Drug Abuse (NIDA) held a technical review, "Laboratory Behavioral Studies of Vulnerability to Drug Abuse," in Bethesda, MD, to address this issue from the perspective of laboratory behavioral studies. The technical review served to review the current status of the research in this field, to review the progress that has been made, and to identify future research needs and directions, including the identification of technical and methodological issues The presentations and discussions provided a very rich source of information on expanding the current research approaches taken in basic laboratory studies with humans and animals. Numerous recommendations were made for moving into new research directions, tackling thorny methodological and theoretical issues, expanding current methodologies, and exploring areas of research that get at the heart of the fundamental nature of the development of drug dependence. This research monograph is based on presentations and discussions from that technical review.

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Toward an Account of Individual Differences in Drug Abuse

James H. Woods

What is drug addiction? It is drug taking on the part of the individual that is usually excessive, harmful to the individual or his/her social environment, and which therefore presents a significant public health problem. The chapters in this technical review deal with the variety of issues of why drug addiction affects only some of us. As documented in these chapters, many of us are exposed one or more times to drugs with abuse potential, yet only a few of us go on to demonstrate drug addiction. Why is this the case? Some believe, as I do, this to be a central, vexing question—addressed often, but not yet satisfactorily answered.

We are offered a rich set of points of view on this question in this monograph. Each is a compelling if different approach to this difficult question. Which of the approaches has the broadest scope and offers the richest avenues for advancing understanding? How can we modify our animal models of addiction to take individual variation into account? How can we best evaluate hypotheses derived from complex epidemio-logically based human studies, and can these hypotheses be tested in animal models? Which of the models is likely to provide the most compelling answer to the central question of individual vulnerability? Which is likely to provide the most testable answer?

Before dealing with specific discipline-related issues, comments should be made on two contributions of epidemiological interest. Dr. Mary McCaul's chapter describes the difficult issue of finding the sources of effect of family history of abuse upon offspring, especially in situations where a host of variables contribute outcome measures. Dr. Ralph Tarter and his colleagues describe an elegant lifespan scheme for elaborating these and other influences where they take a specific measure, DSM diagnosis, as their endpoint. A common problem shared by these types of studies is that single variables that they are measuring, such as unconventional friends or tolerance to deviancy, contributes little per se to the likelihood that drug abuse develops. Dr. Harriet de Wit takes a more experimental approach to human differences in drug abuse by studying normal subjects who may differ in their subjective response to benzodiazepines. She has found that anxious individuals and those with a history of moderate alcohol

consumption show an increased positive response to diazepam and a decreased negative response to diazepam, respectively.

From the perspective of the researcher who has dealt with animal models in which drugs act as reinforcers that control drug taking, discussions of epidemiological issues such as family history may seem unnecessary. When the dose is appropriate, when the behavioral requirements are relatively simple, and when the route of administration assures rapid access of the drug to the brain, drugs come rapidly to serve as reinforcers in animals.

Rodents and primates, without significant individual differences, develop regular, consistent patterns of drug taking. If the opportunity is provided, within weeks, primates develop patterns of drug taking that typically require years of drug taking to develop in human abusers. For example, monkeys become physiologically dependent on intravenously available ethanol within a few days of initiating self-administration; humans may require years of oral ethanol consumption before they show withdrawal signs when they stop drinking. Similarly, monkeys show binge patterns of intravenous cocaine self-administration and the concomitant fasting, insomnia, and self-mutilation, which develops much more slowly in human cocaine abusers.

It is intellectually relevant to the broader problem of individual differences to acknowledge that, under these circumstances, the behavioral arrangements produce drug abuse in all cases! This is vastly different from the findings of other researchers who deal with problems of individual differences in people, only a small percentage of whom ever demonstrate the behavior with drugs that are captured in virtually all cases in rodents and primates. In order to model the problem posed by individual differences in drug abuse, the animal researcher needs to weaken the environmental control of the drug reinforcer to allow other types of variables to exercise influence on behavior. Unfortunately, as suggested by Dr. Marilyn Carroll, the emphasis of animal studies of drug abuse is usually on good baselines of drug-taking behavior, and animals that show reluctance to provide these baselines may be discarded without mention.

Behavioral researchers, however, have begun efforts to study individual differences in drug taking in animal subjects. They have started to evaluate some of the host of behavioral variables that may influence initiation, maintenance, and “relapse” (a reinstigation of drug taking following a period of self- or experimenter-imposed

abstinence) of drug taking. One should not suppose necessarily that there are unique variables that will influence these somewhat artificially imposed distinctions on drug-taking behaviors. Drs. Susan Schenk and Emily Davidson as well as Dr. Carroll note that, in some conditions, simple exposure to the drug of abuse may hasten initiation or relapse. Dr. Michael Nader points to important modulatory behavioral histories that are able to suppress drug taking.

Dr. John Falk takes the novel tactic of examining the discriminative control of excessive drug taking and how the control may be transferred among different consequences (drugs). He makes the important point that this control may change behavior significantly without the drug exerting a reinforcing function. No doubt, in different human situations involving drug taking, variables other than the drug itself may control drug-taking behavior, a point made as well by Dr. Tarter and his colleagues.

The researchers who are interested in the contribution of the biological disposition of the subjects are well represented by the contributions of both Dr. Nick Goeders and Dr. Vincenzo Piazza. These investigators are assessing the influence of stress as expressed through the hypothalamic-pituitary axis on vulnerability to drug abuse. In rodents, it appears that this contribution can be direct and strong.

Dr. Goeders has shown that cocaine is a more potent and stronger reinforcer in animals that have been exposed to noncontingent shock. Corticosterone itself acts as a reinforcer and augments the reinforcing effects of cocaine, and if steroidogenesis is blocked metabolically by administration of metyrapone or ketoconazole, the reinforcing effect of stimulants is reduced or abolished. Dr. Piazza and his colleagues have shown that a rat's locomotor response to a novel situation predicts its stimulant-taking behavior, as well as its likelihood to select a stressful environment. Therefore, human propensity to take drugs may also be related to the amount of stress in their environment, and the individual physiological and behavioral reaction to that stress. Taken together, these studies represent an interesting approach to potential individual variation that will no doubt soon receive attention in primate and human studies. Since the study of steroid effects has taught us in other contexts that long-term effects of steroids should be considered from both organizational and activation points of view, it will be interesting to examine both types of steroid effects in future studies.

From a different "biological" standpoint, Drs. Blake Gosnell and Dean Krahn consider the evidence that vulnerability to drug taking might be considered as appetitive disorders. There is a growing literature, especially in alcohol-related studies, for such differences in animals. For example, animals that consume sweets excessively tend to consume more ethanol. Mechanisms for these effects appear to be elusive at present.

From the genetic perspective, Dr. Frank George's contribution emphasizes the impressive accomplishments that selective breeding studies have made in identifying potential individual differences in sensitivity to ethanol's reinforcing effects. Different aspects of ethanol-related behavior have been bred in mice. Some of them (e.g., serotonin receptor density) are related to, and many of them (e.g., sensitivity to ethanol's stimulant or depressive effects) are not related to the establishment of a reinforcing effect of ethanol in these animals. This approach is likely to continue to be helpful for analyses with ethanol and other drugs. Other genetic approaches that were not represented at the Technical Review but that are very interesting and relevant are those involving transgenic mice that are lacking specific receptors (e.g., dopamine, opioids) and, in addition, those that involve the attribution of effect quantitatively to particular gene loci. What remains to be determined is whether these findings in rodents reflect similar and equally relevant dimensions of human physiology and behavior.

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Acquisition and Reacquisition (Relapse) of Drug Abuse: Modulation by Alternative Reinforcers

Marilyn E. Carroll

Most of the behavioral pharmacology research that has examined variables controlling drug self-reinforced behavior has been concerned with well-trained steady-state levels of drug-maintained responding. Little attention has been directed toward transition states such as the initial acquisition of drug-reinforced responding or reacquisition of responding after a period of abstinence (relapse). It is especially important to have animal models for these stages of the addiction process because ethical considerations do not allow these processes to be thoroughly studied in the human laboratory. The purpose of this chapter is to describe animal models for acquisition and reacquisition (relapse) of drug self-administration and to examine the effect of nondrug alternative reinforcers on these processes.

ACQUISITION

Acquisition of drug self-administration is a process that may occur at different rates depending upon the species, the individual animal, type of drug, drug dose, route of administration, and the drug and behavioral history of the animal. Advantages of studying acquisition are that (1) the speed of acquisition may be an indicator of reinforcing efficacy; (2) since behavior has not yet reached its maximum levels, it allows for assessment of factors that increase and decrease drug-reinforced behavior; (3) all animals are used in the analysis, giving an estimate of the total proportion acquiring. In maintenance studies, nonresponders are often screened out, and percent of total tested is often not reported; and (4) identification of factors that reduce or prevent acquisition may be useful in developing prevention strategies in humans. Disadvantages of using these models are that (1) since subjects can acquire only once, group designs are necessary; (2) since there is high variability in rates of acquisition, large group sizes are needed; (3) the procedure is too expensive to be used with nonhuman primates; and (4) there are no standardized criteria across studies that clearly define when acquisition has occurred.

ACQUISITION METHODS

In many acquisition studies, animals are simply allowed exposure to the drug either orally or intravenously, contingent upon an operant response such as a lever press or nose poke for a fixed period of time each day. Acquisition is considered complete when responding asymptotes. When two or more groups are compared for rates of acquisition, the curves are statistically analyzed to determine the number of days before their rates are significantly different. Often the latencies to asymptote are different, but both groups eventually self-administer comparable amounts of drug. A variation of this method, and one which may reduce intersubject variability, is when the experimenter gives each animal one or two priming injections of the drug at the start of each daily session. Another method for reducing variability is to previously train the operant response (e.g., lever pressing) with food reward. While both of these methods reduce variability, they may accelerate acquisition to the point where group differences are not apparent.

Autoshaping is another method that has been used to reduce variability without increasing the speed of acquisition. According to this method, which was originally used to train pigeons to key-peck for food (Brown and Jenkins 1968), a stimulus associated with the response manipulation is presented (e.g., key light, lever extension), followed by delivery of the reinforcer (e.g., food, drug infusion). When the animal makes physical contact (e.g., lever touch) with the manipulandum, the stimulus is extinguished and the reinforcer is immediately delivered. When responding reliably occurs immediately at stimulus onset, acquisition has occurred. In a recent study, this model was applied to drug reinforcement (Carroll and Lac 1993), and an additional criterion for acquisition was used. During a 6-hour session later in the day, the lever remained extended and each lever press resulted in a cocaine infusion. When the mean daily infusions were 100 or more for 5 consecutive days, acquisition was considered complete. The 5-day period was chosen because inspection of individual pilot rats' daily infusion records indicated that most rats went from almost no responding to asymptotic responding (300 infusions) in 5 days; thus, the 5-day time period captured the entire acquisition process. An advantage of the autoshaping model is that during training the rate of acquisition can be accelerated or delayed by manipulating the time interval between stimulus offset and delivery of the reinforcer (Messing et al. 1986). For instance, when there was a 1-second delay between lever retraction and cocaine infusion, 70 percent of the rats met the acquisition criterion in a mean of 9 days

(Carroll and Lac 1993), whereas when there was a 2-second delay, 70 percent of another group acquired in 23 days (Specker et al. 1994).

There is a wide range of variables that affect the rate of acquisition of drug self-administration, and these may be categorized as *organismic* or *environmental*. A subset of environmental variables that has been studied consists of *drug history* variables. Behavioral history factors is another subset of environmental variables; this will be discussed in a chapter by Nader in this volume. The following organismic variables predict enhanced acquisition of drug self-administration. Higher rates of locomotor activity in an open field test were related to more rapid acquisition of responding for intravenous (IV) amphetamine (Piazza et al. 1989). Rats with lower locomotor activity scores eventually self-administered the same amounts of amphetamine, but their acquisition process was longer. In recent studies rats have also been selected for high and low intake of sweets (Gosnell and Krahn 1992) or fats (Krahn and Gosnell 1991), and rate of acquisition and level of ethanol intake is higher in high preferrers than the low preferrers. Recent attempts have been made to replicate these findings with the IV route of self-administration and rats selected for high and low sweet preference. High sweet preference was related to IV morphine (Gosnell et al. 1995) but not cocaine (Gahtan et al., in press) self-administration.

There have been few studies of gender effects on acquisition of drug self- administration. In one study it was reported that female rats more readily consumed a caffeine solution than male rats, but only under conditions of restricted feeding. Genetic differences in acquisition of ethanol, opiate, and stimulant drugs have been studied by selective breeding experiments and in comparisons of inbred rat and mouse strains. These findings are reviewed by George (1987, 1993, this volume). Generally, strains of rats that have higher intakes of sweet liquids also more rapidly self-administer drugs. Age is another organismic variable that may determine the speed of acquisition of drug abuse; however, systematic investigations are not available. Anecdotally, acquisition is accomplished more readily in younger rats.

Environmental factors that alter the acquisition of drug self-administration may include social factors, feeding conditions, and the availability of nondrug alternative reinforcers. Various forms of stress have been tested for their effects on acquisition of drug self-administration. Tailpinch was reported by Piazza and coworkers (1990) to facilitate acquisition of amphetamine self-administration;

however, similar forms of pain- inducing stimuli (e.g., hotplate, footshock) had no effect on the acquisition of cocaine self-administration (Ramsey and van Ree 1990). A brief period (15 minutes) of restraint stress facilitated the initiation of oral opioid (Shaham et al. 1992) and ethanol (Rawleigh et al. 1994) self-administration. Certain forms of social stress also increase the acquisition of drug self-administration. For instance, Ramsey and van Ree (1993) reported that rats that observed other rats receive footshock had an accelerated rate of cocaine acquisition, although footshock itself did not enhance acquisition. A recent report indicated that the stress of exposure to a conspecific intruder for 60 minutes elevated the dose-response curve for IV cocaine self-administration (Miczek et al. 1994).

Feeding conditions are an important variable affecting all phases of the addiction process, from acquisition to withdrawal and relapse. In early drug self-administration studies, food deprivation was used non-systematically to encourage acquisition in rats that were slower to acquire. Often food was withheld before the drug session, and then a small piece of food was taped to the lever to increase the amount of behavior directed toward the lever. Later, the effects of feeding conditions on acquisition of drug self-administration were specifically examined, and it was found that when rats had unlimited access to drugs such as cocaine, etonitazene, and phencyclidine, dramatic increases in the rate of acquisition occurred within 8 hours after the daily food allotment was withheld (Carroll et al. 1981). Studies in rhesus monkeys have also shown that food restriction resulted in more rapid acquisition of oral phencyclidine self-administration (Carroll 1982). Not only were the total intakes per day lower in free-fed animals, but the patterns of responding during daily 3-hour sessions differed considerably. When food-deprived, animals drank steadily from session onset and consumed most of their drug in the first hour. When food-satiated, there was often a delayed onset of drinking, and the pattern was sporadic throughout the 3-hour session (Carroll 1982).

In a recent study, the percent of rats acquiring cocaine self-administration was compared in three groups of rats: one receiving 8 to 12 g of food per day, one that received 20 g, and a third that had unlimited access to food and consumed approximately 25 g of food per day (Carroll and Lac 1993; Lac and Carroll 1994). The autoshaping procedure was used to provide an objective and quantitative means of measuring acquisition. Each group consisted of 13 rats. The rate of acquisition was inversely related to the amount

of food consumed. Seventy percent of the 8 to 12 g, 20 g, and unlimited groups met the acquisition criteria (a mean of 100 infusions in 5 consecutive days) in 6, 9, and 19 days, respectively. In both groups with restricted food access, 100 percent of the rats acquired within the 30 days allowed; however, only 71.4 percent of the rats in the unlimited food access group acquired. The food-satiated rats that did acquire showed a much slower rate of acquisition than the food-restricted groups. These findings suggest that increased access to food prevents and/or delays the acquisition of cocaine self-administration.

Recently this study was extended to examine the contribution of food deprivation history (Specker et al. 1994). One group of rats was given a food-deprivation history by restricting their food intake for 1 to 2 weeks when they were 30, 90, and 140 days old according to a procedure described by Hagan and Moss (1991). Several weeks after body weights had recovered, the rats were challenged with butorphanol (a drug that increases feeding), and food intake was recorded for 4 hours. Compared to age-matched controls, the group with the feeding history consumed more food and ate for a longer period of time after the butorphanol injection. Several weeks or months later, when both groups were tested in the autoshaping cocaine acquisition paradigm, the group with the food deprivation history acquired cocaine self-administration more readily; 86 percent of the group (versus 69 percent of the control group) met the acquisition criteria within 30 days.

The effects of food on acquisition may be due to the caloric value of food and its ability to satisfy a biological need, or it may be due to its palatability and secondary reinforcing effects related to taste and ingestion. To examine this question, palatable substances that have little or no caloric value have been tested for their effects on acquisition of drug self-administration. In the first study (Carroll and Lac 1993) there were 4 groups of 12 to 13 rats each. The groups varied in a 2 x 2 factorial design according to whether or not they had a 3-week history of glucose and saccharin (gl/sac) exposure in the home cage and whether or not they had gl/sac available during the 30-day autoshaping phase. Thus, the groups ranged from no gl/sac exposure to continuous gl/sac exposure, and two groups were exposed to gl/sac either before or during auto-shaping. The group with no current or prior exposure and the group with only prior gl/sac exposure in the home cage acquired most rapidly with 70 percent of the group meeting the criterion in a mean of 9 and 10 days, respectively, and 100 percent of those groups eventually met the criteria. Thus, a history of exposure to an alternative reinforcer did

not affect acquisition. The group that had maximum exposure to gl/sac was the slowest to acquire with only 50 percent of the group meeting the criteria, and those that did acquire met the criteria in a mean of 25 days.

In a subsequent study, a noncaloric substance, saccharin, was used to examine the contributions of amount of food versus palatability on cocaine acquisition. The results of the three feeding conditions (8 to 12 g, 20 g, and unlimited food) were previously described; however, in this study three additional groups were compared. The daily amounts of food were the same except powdered saccharin (0.2 percent wt/vol) was mixed with the ground food to increase palatability. When saccharin was added to the food, cocaine acquisition was delayed in the 20 g and unlimited access groups. Without saccharin the mean days to acquisition for 70 percent of the rats was 6 and with saccharin the mean was 14 in the 20-g group. In the unlimited access group that did not have saccharin, 77 percent of the group acquired by day 19, while only 31 percent of the unlimited saccharin-food group acquired in a mean of 26 days. Thus, amount of food and palatability of food are factors that may function separately or additively to delay and/or prevent acquisition of drug self-administration.

Drug history also has been one of the major variables of interest in studies of acquisition of drug self-administration. The history may occur prenatally or prior to testing acquisition in adult rats. For example, prenatal exposure to morphine from gestational day 7 to parturition resulted in enhanced acquisition of cocaine and heroin self-administration in rats (Ramsey 1991). In other types of studies, rats have been pretreated with various drugs for approximately 10 days before acquisition testing. There are several examples whereby pretreatment or sensitization to a drug results in more rapid acquisition of self-administration of that same drug. This has been demonstrated with amphetamine (Piazza et al. 1989), cocaine (Horger et al. 1990), and methamphetamine (Woolverton et al. 1984). In these studies, drug pretreatment immediately preceded acquisition. However, in a recent extension of these studies the 9-day amphetamine pretreatment period preceded amphetamine acquisition testing by 45 days, and the latency to acquire was shorter (3 days) than in a saline-pretreated control (6 days) (Valadez and Schenk 1994). These findings suggest that pretreatment may have long-lasting effects on the readiness to acquire drug self-administration.

Pretreatment or sensitization effects have also been shown across different drugs. For instance, Ramsey and Van Ree (1990) pretreated

rats with naltrexone (1 mg/kg) for 12 days, and these rats acquired IV cocaine self-administration more rapidly than those treated with saline. Pretreatment-enhanced acquisition effects have been demonstrated with amphetamine pretreatment (PTX) and cocaine self-administration (SA) (Horger et al. 1992), caffeine PTX and cocaine SA (Horger et al. 1991), and nicotine PTX and cocaine SA (Horger et al. 1992). In these studies, 9 pretreatment days occurred 1 day before acquisition began.

SUMMARY - ACQUISITION MODELS

The results of the acquisition literature to date have identified many factors that accelerate acquisition, such as history of opiate or stimulant drug intake, history of food deprivation, current food deprivation, and current access to caffeine. In contrast, there are few reports of factors that inhibit or prevent acquisition. Initial findings indicate that an increased amount of food and/or increased palatability of food slows or prevents acquisition of cocaine self-administration.

RELAPSE

In this chapter, relapse is operationally defined as reinstatement of behavior that was previously reinforced by a drug. In the clinical setting this translates to the reinstatement of regular drug use after a period of abstinence. A variety of factors contribute to relapse behavior, and there are many parallels between humans and animals in terms of variables that produce relapse. For instance, external stimuli such as places, equipment, and visual and auditory characteristics of the environment and internal stimuli such as exposure to small amounts of drug, dieting, or mood states like stress or anxiety reinstate drug-seeking behavior in both animals and humans.

External stimuli and their role in relapse has been carefully studied in human drug abusers, and extinction of external cues has become a successful treatment component (Childress et al. 1986, 1988). There have been only a few animal studies of external stimuli and relapse. In one series of studies, Davis and Smith (1976) trained rats to self-administer morphine in the presence of a buzzer. When saline had replaced morphine and responding extinguished, reintroduction of the buzzer reinstated responding that was similar in magnitude to drug-reinforced behavior. The relapse behavior could be prevented by exposing subjects to the buzzer cue during saline extinction.

Considerably more experimental attention has been directed toward the role of internal stimuli in relapse, and that is the focus of this chapter. In early studies conducted by Stretch and Gerber (1973) monkeys were trained to self-administer IV amphetamine. When saline was substituted for drug, responding extinguished, but responding (now reinforced by saline) was reinstated to levels that were indistinguishable from drug-reinforced behavior by a single experimenter-administered injection of amphetamine.

RELAPSE METHODS

A procedure was developed by de Wit and Stewart (1981, 1983; Stewart 1983) in rats to examine the effect of priming injections of drug on reinstatement of responding previously reinforced by drug. In this procedure rats self-administered drug for approximately 2 hours each day. Saline or vehicle was then substituted for drug, and behavior was allowed to extinguish for a specified period of time (e.g., 1 hour). This procedure has been slightly modified by others (e.g., Comer et al. 1993, in press; Wise et al. 1990). Typically, during the first hour after saline substitution there is a 5-minute pause in responding while technicians are in the room changing the pumps from drug to saline (Comer et al. 1993). There is then a burst of responding that peaks in 10 minutes and decreases to almost no responding by the end of the hour. The total amount of extinction responding during the first hour of saline substitution may be nearly as high as the drug-maintained responding during the previous hour when drug was available. However, responding during the subsequent 4 to 5 hours is low. After the predetermined extinction period has elapsed, a priming injection is given either IV through the cannula system (de Wit and Stewart 1981, 1983) or intra-peritoneally (Worley et al. 1994). Only saline is delivered after each response; no further drug self-administration is available. The test for reinstatement is usually a comparison of responding when a drug versus saline prime is given. In order that other stimuli associated with the injection apparatus (e.g., pump sounds and vibrations, technicians entering the room) do not gain stimulus control over reinstatement, it is necessary to give frequent saline priming injections. According to one protocol, drug primes are separated by 3 or more days of saline primes (Comer et al. 1993); however, others may give several sessions per day (Shaham et al. 1994).

The relapse model has been used to examine a number of variables such as drug dose, temporal aspects, and crossover effects with other

drugs of abuse. It also allows for the study of treatment drugs and the role of nondrug alternative reinforcers on vulnerability to relapse. As in the case of acquisition, many factors facilitate the behavior; few have been found to prevent or reduce it. The effect of the priming injection is dose dependent with higher doses producing a reinstatement of responding that is nearly as great as the drug-reinforced behavior during the first 2 hours of the session. The dose needed to obtain the maximum reinstatement responding is often higher than the training dose used during self-administration. In contrast, initial studies have indicated that the training dose does not seem to be related to the reinstatement effect (Comer et al., in press). Cocaine training doses of 0.2, 0.4, and 1.0 mg/kg produced dose-dependent increases in extinction responding, but they had no effect on the dose-dependent increase in responding produced by the priming injection. Shaham and coworkers (1994) have also altered the maintenance dose of heroin, and even when saline replaced heroin as the maintenance drug, they found a consistent reinstatement effect after a heroin prime, regardless of training dose.

There are many questions that could be asked about the temporal aspects of this model. For instance, how long can the interval be between the last self-administered injection and the priming injection? de Wit and Stewart (1981) compared intervals of 10, 30, 60, 120, and 180 minutes and found reinstatement at all intervals, but as the interval increased, the magnitude of the effect decreased. Recently Shaham and colleagues (1994) reported reinstatement in heroin-trained animals after 3 to 4 days. Another question regarding temporal aspects is how many times can the priming effect be tested before the priming stimulus loses its effectiveness at reinstating responding? Comer and colleagues (1993) found that priming injections could be repeatedly administered as much as 20 times, and priming dose-effect curves could be replicated within subjects. They did find that in some rats the first priming injection produces a greater effect than those that occur later; thus, order of dosing and other experimental manipulations should be counterbalanced across subjects.

The reinstatement studies have involved only a few self-administered drugs (e.g., heroin; cocaine; amphetamine; and thiamylal, a barbiturate), but the effect appears to generalize well across drugs. In contrast, a wide array of drugs have been tested as priming agents. Other drugs of abuse have been used to evaluate potential risks of polydrug abuse, and therapeutic agents have been tested because their ability to produce relapse would contraindicate their use in treatment. A partial list of the priming drugs that have been tested is found in table 1. Generally,

TABLE 1. *Drugs that have been tested in the relapse model.*

	Self-Administered Drug		
	Cocaine	Heroin	Thiamylal
Drugs that produced a priming effect and function as reinforcers	amphetamine[cd] apomorphine[cd] bromocriptine[h] caffeine[i] cocaine[b-e] codeine[e] morphine[c-g]	amphetamine[cde] bromocriptine[h] heroin[cd] morphine[c-g]	secobarbital[e] pentobarbital[e] butabarbital[e] phenobarbital[e]
Drugs that produced no priming effect and function as reinforcers	buprenorphine[b] diazepam[e] ethanol[ch] etonitazene[b] heroin[cd] methohexital[ch] methylamphetamine[e] naltrexone[bg] secobarbital[e]	cocaine[be]	amphetamine[e] cocaine[e]
Drugs that produced no priming effect and do not function as reinforcers	chlorpromazine[e] clonidine[dh] desipramine[a] demethyltryptamine[e] nalorphine[g] naloxone[e] naltrexone[bg] saline[a-h]	apomorphine[cd] clonidine[h] nalorphine[g] nicotine[bg] saline[a-h]	

KEY: a = Comer et al. (unpublished data); b = Comer et al. (1993); c = deWit and Stewart (1981); d = deWit and Stewart (1983); e = Slikker (1984); f = Stewart (1984); g = Stewart and Wise (1992); h = Wise et al. (1990); i = Worley et al. (1994).

reinstatement is produced by drugs that share the same pharmacological class as the self-administered drug; however, there is some asymmetrical crossover between the opiate- and stimulant-type drugs. Another notable feature on table 1 is that all of the drugs that reinstate behavior function as reinforcers. Some of the drugs that do not reinstate opiate- or cocaine-trained behavior also do not function as reinforcers. In addition to drug-induced reinstatement of behavior, in a recent study it was reported that footshock stress produces a substantial reinstatement of cocaine-trained responding even more

than a month after the last self-administered dose (Shaham and Stewart 1994).

Treatment drugs have been assessed in two different ways using the reinstatement model. First, they have been given as priming injections to determine whether drugs that suppress self-administration stimulate relapse. For example, bromocriptine is a dopamine D_2 receptor agonist that suppresses cocaine self-administration in animals (Kleven and Woolverton 1990) and reduces cocaine craving in humans (Dackis and Gold 1985), and it decreases cocaine-induced craving in a laboratory setting (Jaffe et al. 1988). However, Wise and coworkers (1990) found that bromocriptine produced a dramatic reinstatement of responding in heroin- and cocaine-trained rats. There is also an example in the clinical literature whereby the antidepressant drug desipramine, which has reportedly reduced cocaine craving and associated depression in abstinent patients (e.g., Gawin and Kleber 1984; Kosten et al. 1987) actually stimulates relapse to cocaine use (Weiss 1988). Other drugs that are used therapeutically have failed to reinstate cocaine-trained responding. These include buprenorphine (Comer et al. 1993), naltrexone (Comer et al. 1993; Stewart and Wise 1992), and nalorphine (Stewart and Wise 1992).

A second approach to the study of therapeutic drugs in the relapse model is to determine whether treatment drugs prevent or reduce relapse. For example, Comer and coworkers (1993) produced a dose-dependent reinstatement effect when rats trained to self-administer cocaine were given priming injections of cocaine 1 hour after saline was substituted for cocaine. Pretreatment injections of buprenorphine (0.025 to 0.4 mg/kg), a partial mu opiate receptor agonist, and naltrexone (1.6 and 3.2 mg/kg), an opiate antagonist, were given 30 minutes before the priming injection. Etonitazene, a full mu agonist, was also used as a pretreatment drug to determine whether buprenorphine effects were mediated by its agonist or antagonist properties. Buprenorphine and etonitazene produced a dose-dependent decrease in the reinstated responding produced by a high priming dose of cocaine (3.2 mg/kg). Naltrexone had no effect, suggesting that buprenorphine's effect was based on agonist actions of the drug. An interesting result was that a single buprenorphine pretreatment reduced the reinstatement effect when cocaine priming injections were given on 2 consecutive days. That the cocaine self-administration occurring immediately before the second priming injection was not reduced on the second day when reinstatement was

suppressed suggests that relapse behavior may be more sensitive to drug treatments than ongoing self-administration.

ALTERNATIVE NONDRUG REINFORCERS

Another strategy for modifying relapse behavior is to alter the availability of alternative nondrug reinforcers in the environment. For instance, Higgins and coworkers (1991, 1993, 1994*a*, *b*), Dolan and Kiernan (1976), and Englehart and associates (1992) have used nondrug reinforcers in a clinical setting to reduce cocaine and alcohol abuse, respectively. In animal studies there are several examples of reduced drug self-administration when nondrug reinforcers are concurrently available (Carroll, in press, Carroll and Rodefer 1993, Carroll et al. 1989). Nondrug reinforcers that have been used in these studies have included increased amounts of food and highly preferred dietary substances that have little or no caloric value (e.g., gl/sac or saccharin).

As in the case of acquisition behavior and steady-state maintenance of drug self-administration, feeding conditions are an important determinant of the magnitude of the reinstatement effect. In a recent study, feeding conditions were manipulated by providing different rats with 8 to 12 g, 20 g, or unlimited access to food each day and then testing them in the cocaine-relapse paradigm with several priming doses of cocaine: 0 (saline), 0.32, 1.0, and 3.2 mg/kg. In addition, each group was tested when fed immediately before or after (conditions counterbalanced) the relapse test session (Comer et al., in press). Feeding before or after the session was done to compare the effects of acute (20 g fed after) versus chronic (8 to 12 g) fed after food deprivation as well as to determine the contribution of absence of food versus body weight loss as factors that alter the relapse effect. When rats were fed before the session, 8 to 12 g or 20 g were placed in the chamber 1 hour before the session. Under the unlimited food condition, food was freely available up until session onset. The feeding conditions had no effect on the number of cocaine infusions self-administered during the first 2 hours of the session. This was an unexpected result based on previous studies (Carroll 1985, Carroll et al. 1981) that showed increases in cocaine self-administration about 8 hours after food deprivation. In previous studies cocaine was available 24 hours per day, and the lack of effect in the recent experiment may have been due to the relatively short (2-hour) access to cocaine.

The extinction responding that occurred during hour 3 was markedly increased in the group that received 8 to 12 g of food after the session compared to the groups receiving 20 g or unlimited food. The groups receiving 20 g or unlimited food after session were not significantly different from each other. Also, when the feeding groups were fed before the session, extinction responding was low and did not differ across groups. In an earlier study, the effect of food deprivation on extinction responding was examined more thoroughly (Carroll 1985). Rats were trained to self-administer cocaine by providing access to the drug for daily 24-hour sessions for 11 days, and every third day they received 8 to 12 g of food. On intervening days they had unlimited access to food. Saline replaced cocaine, and over the next 12 sessions behavior extinguished; free food was available during this time. Subsequently, food deprivation was reinstated every third day. On these days high rates of responding were also reinstated despite the fact that only saline was released from the pump. Several control groups were included to evaluate the importance of introducing the food deprivation condition during an early part of acquisition. If a group was preexposed to food deprivation for 3 weeks prior to the onset of the experiment or during the 12-day extinction phase, cues associated with food deprivation did not later reinstate responding. Furthermore, if a group of rats was only food satiated during their 11-day exposure to cocaine, food deprivation later produced only small increases in extinction responding.

In the recent feeding study, reinstatement of responding after the priming injection during hour 4 also increased as the amount of food available decreased. At all food levels and for both presession and postsession feedings there was a systematic increase in reinstatement as the dose of the priming injection increased. Thus, restricted feeding dramatically increases the reinstatement of responding in response to a single priming injection.

A comparison of the effects of food deprivation on cocaine self-administration, extinction, and reinstatement suggests that extinction and relapse may be more sensitive to changes in feeding conditions than ongoing drug self-administration.

In an extension of the reinstatement research an alternative nondrug, noncaloric reinforcer was made available during the cocaine relapse procedure to determine whether as in the case of acquisition, reinstatement of responding would be suppressed (Rawleigh, unpublished data, 1994). Saccharin (0.2 percent wt/vol) was added to the daily supply (16 g) of ground food. Another group received only

standard rat chow, and both groups were fed both before and after session while being tested with several priming doses of cocaine: 0 (saline), 0.32, 1.0, and 3.2 mg/kg. Although previous work indicated that saccharin admixed food was preferred to standard food (Lac and Carroll 1994), saccharin had no effect on extinction (hour 3) and/or relapse (hour 4) responding using this paradigm.

SCHEDULE OF REINFORCEMENT

Another variable that has recently been explored using the relapse model is schedule of reinforcement. A goal of an ongoing study is to compare the magnitude of reinstatement responding when drug and saline are available under different fixed-ratio (FR) schedules (e.g., FR 2, 4, and 8) (Rawleigh et al., unpublished data, 1994). The increased fixed ratio had no effect on cocaine infusions during the 2 hours of cocaine self-administration, but extinction and relapse responding decreased as the fixed ratio increased.

A subsequent part of the experiment will examine the effect of increasing fixed ratio only during the cocaine self-administration phase.

SUMMARY - RELAPSE MODELS

In summary, the relapse model is also useful for identifying variables that may serve as risk factors in humans who are trying to remain drug abstinent. Both external stimuli and internal cues can elicit reinstatement of responding. Factors that enhance relapse behavior are priming injections of drugs from the same pharmacological class as the self-administered drug. Only drugs that function as reinforcers act as primes to reinstate responding, but they may be as benign as caffeine. Factors that enhance relapse behavior are higher priming doses, lower response requirements, stress, and food deprivation. Relapse behavior is reduced or eliminated by exposing the animal to the external or internal cues during the initial period of drug abstinence (extinction).

RECOMMENDATIONS FOR FUTURE RESEARCH

The acquisition model is in need of an objective, standardized method of defining when acquisition has occurred. The autoshaping method meets many of the criteria, but the procedure is not a close simulation of the acquisition process in humans. In addition, more work is needed to identify factors that prevent or slow the acquisition process. This would serve as a model of prevention for designing programs to be applied to humans. Similarly, the relapse model must be expanded to closer approximate the human condition. Longer delays between drug self-administration and relapse testing should be imposed. Again, it will be of value to examine factors that suppress or prevent relapse. Also, it is important to evaluate environmental stimuli other than drug injections (e.g., feeding conditions, stress) that could potentially trigger relapse. Finally, with both the acquisition and relapse models it is important to continue to explore the interaction between drug and nondrug rein-forcers. This will lead to a better understanding of how environments lacking in these alternatives to drug use may accelerate the process of drug dependence, and how these nondrug events may be used in a therapeutic setting. It has been stated in the literature that use of drugs such as alcohol and marijuana may provide a gateway for more serious drug use (e.g., cocaine, opiates) (Pagliaro and Pagliaro 1993); however, the animal data reviewed here suggest that more benign agents such as food or caffeine may also provide a gateway for other drug use. There is certainly epidemiological evidence for widespread use of caffeine and excess food, especially in children, teens, and young adults. Further research is needed to know whether or not misuse of these substances eventually facilitates drug abuse.

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The Influence of Behavioral and Pharmacological History on the Reinforcing Effects of Cocaine in Rhesus Monkeys

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INTRODUCTION

Animal models of drug self-administration have been shown to be valid predictors of human drug abuse (Griffiths et al. 1980; Johanson 1978; Johanson and Schuster 1981; Spealman and Goldberg 1978; Woolverton and Nader 1990). In drug self-administration studies, if responding leading to the presentation of the drug occurs at higher rates than vehicle-maintained responding, then the drug is said to function as a positive reinforcer and have abuse liability. The focus of the research described in this chapter will be to examine the interactions of several environmental and pharmacological variables with the reinforcing effects of cocaine in rhesus monkeys, with emphasis on the long-term effects of these experimental histories. One of the goals of this chapter will be to address technical or methodological issues regarding animal models of drug self-administration. To this end, published data as well as preliminary data will be presented. Although the scientific community urges the presentation of group data, most animal experiments in behavioral pharmacology are conducted on an individual-subject basis. Consequently, to highlight further the methodological issues regarding the influence of environmental and pharmacological variables in modifying cocaine self-administration, most of the data presented will be individual-subject data, rather than group data.

All of the research described in this review will be from studies involving the self-administration of cocaine, intravenously, by rhesus monkeys. Each monkey was surgically prepared with a chronic indwelling intravenous (IV) catheter located in a major vein (internal or external jugular, femoral or brachial vein). Monkeys were individually housed in sound-attenuating cubicles, with visual access to the lab and other monkeys. In all of the experiments, cocaine self-administration was maintained under a fixed-interval (FI) 5-min schedule. Under an FI 5-min schedule, the first response after 5-min results in the presentation of cocaine (IV). This schedule was chosen

because response rates under FI schedules can vary without substantially affecting reinforcement frequency. Zeiler (1977) has suggested that FI responding is sensitive to variables that are imposed without being explicitly prescribed by the schedule (which he called "indirect variables"). Urbain and colleagues (1978) have suggested that because of these indirect variables, responding maintained under FI schedules may be more malleable to operant history or to other determinants of drug effects.

BEHAVIORAL HISTORY AND COCAINE SELF-ADMINISTRATION

Introduction

It has been well established that the behavioral effects of drugs can depend on how behavior is controlled by the environment (Barrett and Katz 1981; Dews and Wenger 1977; Kelleher and Morse 1968). More recently, evidence has accumulated that the individual's behavioral history can have a significant and long-lasting influence on the behavioral effects of drugs. The study of the interactions of behavioral history with drug effects, including drug reinforcement, are important for several reasons. From a clinical perspective, if drugs are abused because of their behavioral effects, and these effects can be modified by prior experience, a better understanding of historical variables will be beneficial to understanding the etiology, maintenance, and treatment of drug abuse (Barrett et al. 1989). From a preclinical perspective, as McKearney (1979) stated:

> [E]xhaustive knowledge of how a particular class of consequent events controls behavior may be valuable information, but its generality is greatly limited if seemingly well-established relationships change completely when the subject's prior experience is different (p. 41).

In treatment settings, drug abusers appear sensitive to contingencies of reinforcement and to changes in schedules of drug availability (Budney et al. 1991; Crowley 1984; Higgins et al. 1993; Stitzer et al. 1979*a*, 1979*b*, 1980) and, consequently, identification in animals of conditions under which drug-seeking behavior could be reduced for extended periods might have direct practical applications. There is evidence with human and nonhuman subjects that prior training under certain schedules of reinforcement can produce long-lasting changes in behavior maintained by nondrug reinforcers (Nader and Thompson

1987, 1989; Urbain et al. 1978; Weiner 1964, 1969). These experiments all assessed the influence of prior experience on behavior maintained under FI schedules, because responding under this schedule is a sensitive baseline from which the effects of historical variables can be assessed (Poling et al. 1980).

Weiner (1964, 1969, 1981) showed that reinforcement schedule history could influence the behavior of human subjects responding under FI schedules of reinforcement. In one study (Weiner 1969), responding by one group of subjects was first maintained under a fixed-ratio (FR) schedule, while subjects in a second group responded under an interresponse-times > t-sec (IRT) schedule. For both groups, the reinforcer was point accumulations. Responding by both groups was subsequently maintained under an FI schedule. Weiner (1969) reported that subjects with an FR history responded at higher rates, compared to subjects with an IRT history; this effect was still evident after 40 sessions. A similar effect of reinforcement schedule history was observed when responding was maintained under a variable-interval (VI) schedule (Weiner 1965). Taken together, these results showed that performance of humans could be systematically changed by a history of responding under certain schedules of reinforcement.

Urbain and colleagues (1978) extended the Weiner results by showing that the rate-altering effects of *d*-amphetamine in rats were influenced by behavioral history. These investigators found that rats initially trained under an FR schedule had higher rates of responding under an FI schedule compared to rats initially trained under an IRT > t-sec schedule. Pretreatment with *d*-amphetamine decreased high rates of responding by FR-history rats and increased low rates of responding by IRT-history subjects. The effects of reinforcement schedule history on FI response rates have been replicated in pigeons (Nader and Thompson 1989), providing the third species to show such orderly effects. In addition, the behavioral effects of methadone were different depending on the reinforcement schedule history of the subjects, suggesting generality of the influence of behavioral history across several drug classes. (See Nader et al. 1992 for more detailed evaluation of these results.)

Effects of Different Cocaine-Reinforcement Histories on Cocaine-Maintained FI Responding

Although it is clear that behavioral history can have long-lasting influences on current behavior, as well as modifying the rate-altering effects of drugs, very little research has been conducted using drug

self-administration (Ator and Griffiths 1993; Schenk et al. 1987; Spealman 1979). Two recent studies have found that FR or IRT reinforcement schedule histories could produce significant and persistent changes in rates of cocaine self-administration in rhesus monkeys (Nader and Bowen 1995; Nader and Reboussin 1994). The primary goal of the first experiment (Nader and Reboussin 1994), was to utilize an A-B-A design to determine whether interpolated training under FR or IRT schedules of cocaine self-administration could modify previously established FI rates of cocaine-maintained responding. It should be pointed out that in all of the studies reviewed previously, the subjects were initially trained under an FR or an IRT schedule, prior to exposure to the FI schedule. An important advantage to using an A-B-A design, in which subjects are initially trained under an FI schedule, is that it allows for the assessment of the effects of behavioral history in each animal (i.e., a within-subjects effect), in addition to the between-groups assessment. This point regarding A-B-A designs can be thought of in two ways: (1) from a preclinical perspective, because of the expense of purchasing and training new animals, it is common to use subjects in several experiments without knowledge of the long-lasting influence of previous reinforcement schedule histories; and (2) from a clinical perspective, the individual comes to the clinic with a self-administration history and the question is: Can behavioral interventions be used to modify the rates of drug-seeking behavior for long periods of time?

Methods

In this experiment, eight experimentally naive rhesus monkeys were initially trained to respond on the left lever under an FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation and cocaine dose-response curves were determined (condition "A"). After approximately 100 sessions under the FI schedule, the monkeys were ranked according to response rates, and pairs of monkeys were randomly assigned to one of two groups (condition "B"). Four subjects were trained to respond on the right lever under an FR 50 schedule, while the other four monkeys were trained under an IRT > 30-sec schedule of 0.03 mg/kg/inj cocaine presentation. Timeouts (TOs) of 2 minutes and 5 minutes were scheduled after each cocaine injection under the FR or IRT schedule, respectively. (See Nader and Reboussin 1994 for more details.) This counterbalanced assignment precluded the possibility that monkeys with the highest FI rates would be assigned to the FR group and that monkeys with the lowest FI rates would be assigned to the IRT group. After 65 sessions under these

conditions, responding on the left lever was again maintained under an FI 5-min schedule of 0.03 mg/kg/inj cocaine (condition "A"). In order to assess whether the effects of behavioral history were transient, the dose of cocaine was not changed for at least 60 consecutive sessions, after which the cocaine dose-response curves were redetermined. In this way, it could be determined whether previously established stable rates of drug-maintained responding under the FI schedule would be increased or decreased by different behavioral histories.

Results

The baseline rate of responding (Å1 SEM) under the FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation, prior to different reinforcement schedule histories, was 4.02 (Å0.33) responses/min and the cocaine dose-response curve was characterized as an inverted U-shape function of dose, with peak responding at 0.03 mg/kg/inj. In condition "B," the mean (Å1 SEM) rate of responding maintained by cocaine 0.03 mg/kg/inj was significantly higher in the four monkeys responding under the FR 50 schedule (66.80Å5.6 responses/min) compared to rates maintained under the IRT > 30-sec schedule (2.62Å0.2 responses/min).

The major finding from this study was that FR-history monkeys had significantly higher rates of responding under the FI 5-min schedule compared to IRT-history subjects (Nader and Reboussin 1994). Within-subjects data comparing the effects of FR- and IRT-histories on FI response rates are shown in figure 1 for two animals. For monkey 9123, the mean rate of cocaine-maintained responding under the FR 50 schedule was 45.12 responses/min, while the mean rate of responding by monkey 9120 under the IRT > 30-sec schedule of 0.03 mg/kg/inj cocaine presentation was 0.76 responses/min (figure 1, filled symbols). After 65 sessions under the FR or IRT schedule, responding was again maintained under the FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation. Following an FR history, FI response rates by 9123 were significantly higher than pre-FR history baseline rates, for 60 consecutive sessions (figure 1; open symbols versus shaded area). In contrast, FI response rates by 9120 were significantly lower than pre-IRT history baseline rates, for 60 consecutive sessions.

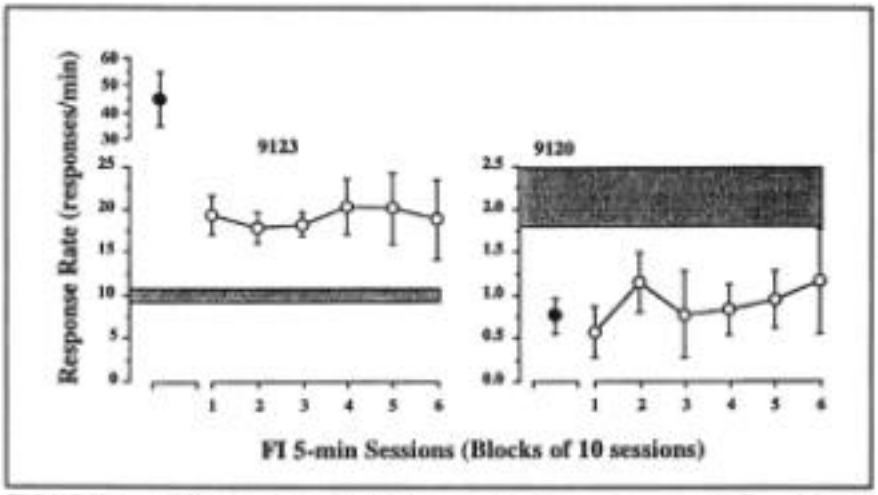

FIGURE 1. *Effects of an FR 50 history (left panel) or an IRT > 30-sec history (right panel) on rates of cocaine-maintained responding under an FI 5-min schedule. For all data, the dose of cocaine was 0.03 mg/kg/inj. Each point represents the mean response rates for 10 sessions; vertical lines represent 1 SD. The filled symbols represent the mean rates under the FR 50 or IRT > 30-sec schedule. The shaded area represents the "prehistory" mean rate under the FI 5-min schedule (±1 SD). Notice that the scales on the ordinate are different for each monkey.*

SOURCE: Data from experiment by Nader and Reboussin (1994).

These results replicate earlier findings in rats, pigeons, and humans and extend those results to drug-maintained responding and a within-subjects analysis. An interesting question that is generated from this study is how the initial FI history influenced rates of cocaine-maintained responding under an FR 50 schedule. In the present study, there was no correlation between baseline FI rates (i.e., pre-FR history) and response rates maintained under the FR 50 schedule. In fact, the highest mean FR 50 rate of responding (125 responses/min) was generated by a monkey with one of the lowest FI baseline rates (approximately 2.0 responses/min).

It should be pointed out that this is the first study in which cocaine self-administration (by any route) was maintained under an unsignaled IRT > t-sec schedule. Cumulative records depicting the changes in response rate and pattern of cocaine self-administration (0.03 mg/kg/inj) that occurred as a function of training sessions under the IRT > 30-sec schedule for monkey 9122 are shown in figure 2.

During the early sessions, responding was characterized by fairly high rates followed by several cocaine injections within a short period of time. As shown in the cumulative record, the majority of cocaine presentations occurred during the last 30 minutes of the session (figure 2, top panel). By session 65, responding by monkey 9122 had come under schedule control and this animal made 93 responses to receive 30 cocaine injections under an IRT > 30-sec schedule (figure 2, bottom panel). In an effort to attenuate the rate-increasing effects of cocaine, a 5-min time out (TO) followed each injection. However, in preliminary examination it appears that TO values as low as 2 minutes do not change rates of cocaine-maintained responding under an IRT > 30-sec schedule. It has not yet been determined what the effects of removing the TO would be on IRT > 30-sec responding, once this schedule is controlling response rates.

Regarding performance under the IRT schedule, the mean rate of responding under the IRT > 30-sec schedule was not significantly lower than the "prehistory" rates maintained under the FI 5-min schedule (4.02Å0.33 versus 2.62Å0.20 responses/min). When these experiments were designed, it was hypothesized that the most important contribution of the IRT history would be the number of reinforced IRTs. To meet this end, 5-min TOs were scheduled after each injection and sessions ended only after the monkeys received 30 injections. Thus, irrespective of whether it took the monkeys 2.5 hours or 8 hours to complete the session, it was certain that at the end of the session each monkey had 30 reinforced IRTs that were greater than 30 seconds. These contin-gencies probably resulted in "higher" rates of responding than would be expected, since response rates did not influence total session cocaine intake. Despite these procedural caveats, the IRT history still resulted in significant reductions in rates of responding under the FI 5-min schedule (Nader and Reboussin 1994).

One of the purposes of this chapter is to describe methodological issues involved in studying the influence of environmental variables on cocaine self-administration. To this end, it would be beneficial to describe the performance of one of the "outlier" IRT-history monkeys. As compared to the pre-IRT baseline, FI response rates by monkey 9127 were significantly higher for 60 consecutive sessions following exposure to an IRT > 30-sec schedule (figure 3, compare shaded area and open symbols), despite the fact that response rates under the IRT contingency (filled symbol) were not different from the prehistory baseline FI rate

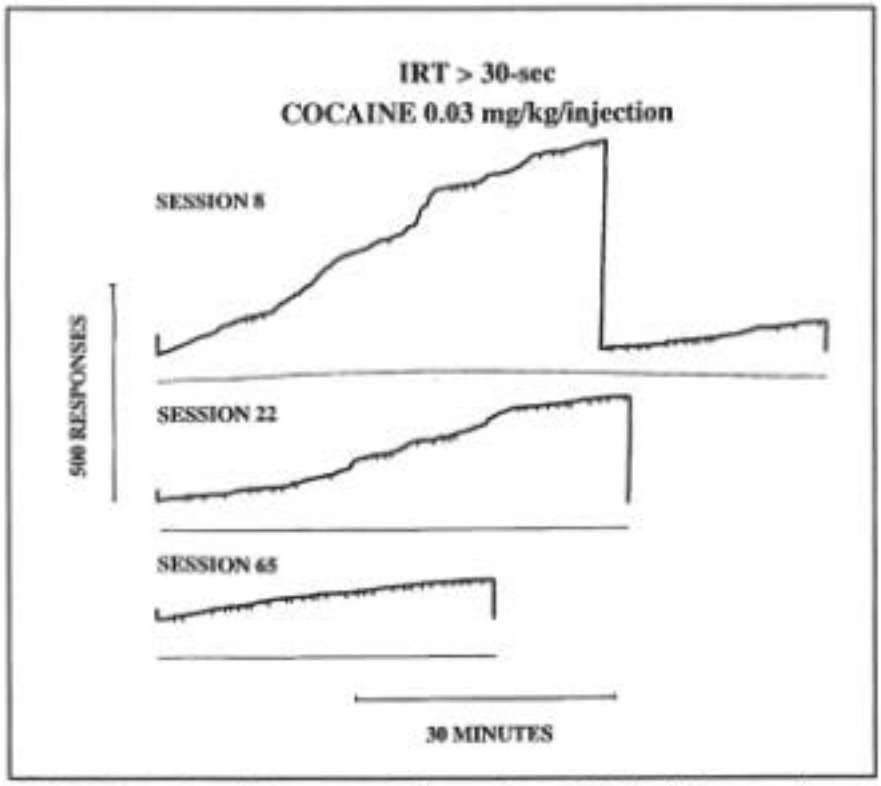

FIGURE 2. *Cumulative records for monkey 9122 depicting cocaine (0.03 mg/kg/inj) self-administration under an IRT > 30-sec schedule during sessions 8 (top panel), 22 (middle panel), and 65 (bottom panel). Deflections of the stepper indicate cocaine injections. During the 5-min TO following each injection, the cumulative recorder was not running.*

(figure 3). Clearly, the IRT-history had a significant effect on response rates under the FI schedule. However, the effects in monkey 9127 were in the opposite direction as was seen in the other three monkeys.

A question that comes up immediately is what aspect of the IRT history resulted in decreases in cocaine self-administration in monkey 9120 but increases in cocaine-maintained response rates in monkey 9127? (See figures 1 and 3.) One possibility is that the pattern of responding under the IRT > 30-sec schedule was different in monkey 9127 and this response pattern subsequently influenced FI response rates. Figure 4 shows the mean IRT distributions for monkeys 9120 and 9127 at three

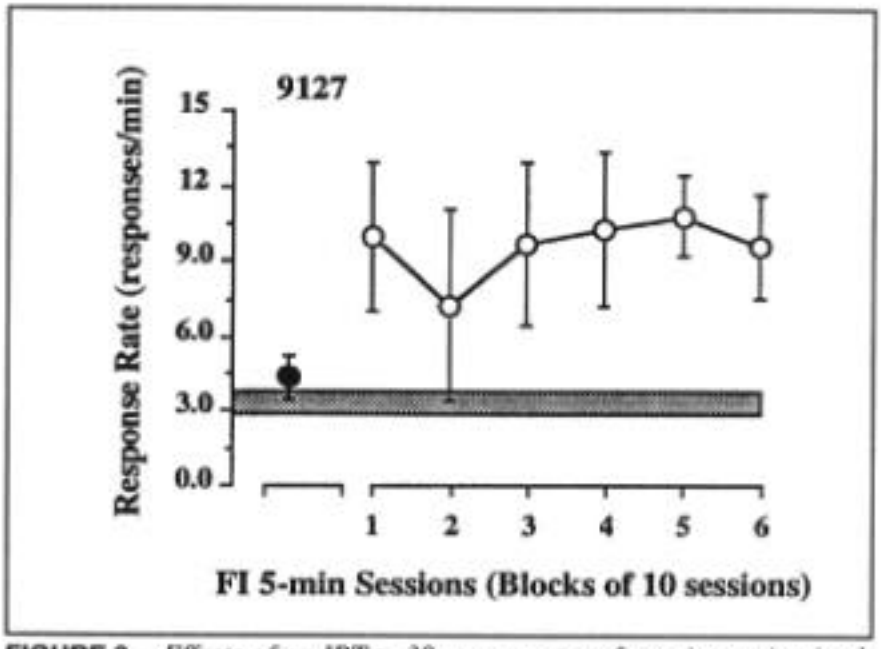

FIGURE 3. *Effects of an IRT > 30-sec on rates of cocaine-maintained responding under an FI 5-min schedule, in monkey 9127. Each point represents the mean response rates for 10 sessions; vertical lines represent 1 SD. The filled symbols represent the mean rates under the IRT > 30-sec schedule. The shaded area represents the "prehistory" mean rate under the FI 5-min schedule (±1 SD).*

SOURCE: Data from experiment by Nader and Reboussin (1994).

different periods during IRT > 30-sec training (sessions 1 through 5, 30 through 35, and 60 through 65). For monkey 9120, changes in the pattern of responding, as represented by the IRT distribution, across the 65 training sessions, indicated that there were substantial decreases in the frequency of short IRTs (< 5 sec) and an increase in the frequency of long IRTs (> 30 sec) with continued exposure to the IRT > 30-sec contingency. In contrast, for monkey 9127 the pattern of responding under the IRT schedule was very different from that observed in the other three monkeys. During the first five sessions under the IRT > 30-sec schedule, the modal IRTs were at 11 to 15 seconds (approximately 18 percent of total responses). By sessions 61 to 65, nearly 55 percent of the responses were spaced between 1 and 5 seconds. Thus, for this monkey, continued training under the IRT > 30-sec schedule resulted in leftward shifts in the IRT distribution (figure 4).

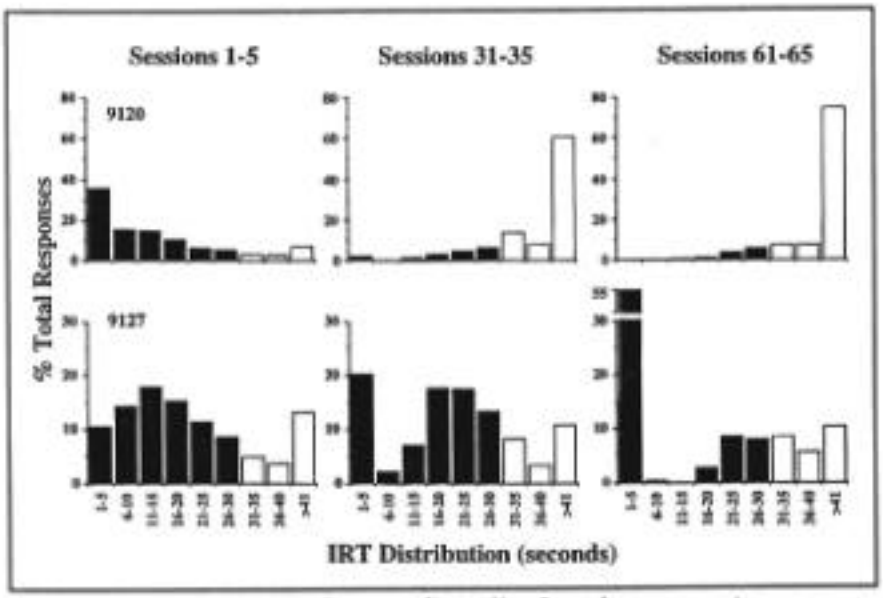

FIGURE 4. *Frequency of responding (% of total responses) as a function of interresponse time (IRT) for monkeys 9121 (top panels) and 9127 (bottom panels), when cocaine (0.03 mg/kg/inj) self-administration was maintained under an IRT > 30-sec schedule. Each histogram represents the mean of five sessions, as determined at three different periods of training. Open bars represent reinforced IRTs.*

SOURCE: Data from experiment by Nader and Reboussin (1994).

Monkey 9127 was retrained under the IRT > t-sec contingency in an effort to decrease FI rates. Initially, the IRT value was 30 seconds for 24 sessions and was increased to 40 seconds for 27 additional sessions. Response rates under the IRT > 40-sec schedule were significantly lower than rates under the FI 5-min schedule (see table 1) and the IRT distribution was shifted to the right relative to the pattern of responding observed under the IRT > 30-sec schedule. By the end of the IRT > 40-sec training, the frequency of short IRTs decreased from 55 percent to 41 percent, while the frequency of IRTs greater than 30 seconds increased to nearly 30 percent. Following exposure to an IRT > 40-sec schedule, response rates under the FI 5-min schedule remained significantly lower than previous FI rates by 41 to 63 percent (table 1). Thus, training under a longer IRT contingency resulted in long-lasting decreases in response rates under an FI 5-min schedule of cocaine presentation.

TABLE 1. *Effects of IRT > 40-sec training on rates of responding (responses/min) for 30 consecutive sessions under an FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation in monkey 9127*.*

Posthistory** FI	IRT > 40	FI Block 1	FI Block 2	FI Block 3
8.16 (1.8)	3.28 (1.0)§	3.58 (0.7)§	7.23 (1.1)	4.66 (0.8)§

KEY: * = Data are expressed as the mean response rate (+1 SD) for 10 sessions; ** = Represents data from the last 10 sessions prior to retraining under IRT > 30- and 40-sec schedules; § = $p < 0.0001$ compared to post-history FI rates.

In summary, results from this experiment indicate that self-administration histories involving FR or IRT schedules can substantially modify rates of cocaine-maintained responding under FI schedules. These differences in FI response rates were still apparent after 60 consecutive sessions. In addition, cocaine dose-response curves were determined prior to FR- or IRT-histories and again after at least 60 sessions under the FI schedule ("post-history"). No pre- versus post-history differences in the cocaine dose-response curve were found in the IRT-history group. In contrast, the FR history resulted in significant rightward shifts in the cocaine dose-response curve, indicating that the effects of a high-rate history generalized across cocaine doses. (See Nader and Reboussin 1994 for more details.)

Effects of Different Food-Reinforcement Histories on Cocaine-Maintained FI Responding

The aspects of an organism's experimental history that accounts for changes in behavior or in the behavioral effects of drugs has not been clearly elucidated. For example, in studies that have found differences in response rates under FI schedules following FR or IRT histories, the behavior was maintained by the same reinforcer under all conditions. An important issue in the present context is whether a history of responding maintained by a nondrug reinforcer, under a particular schedule of reinforcement, can influence the rate of cocaine-maintained responding. In an effort to extend the earlier findings regarding cocaine self-administration and reinforcement schedule

history (Nader and Reboussin 1994), the effects of a behavioral history of low-rate or high-rate responding maintained by food presentation, on the acquisition and maintenance of cocaine-maintained responding under an FI schedule, were examined (Nader and Bowen 1995).

Methods

Eight experimentally naive rhesus monkeys were initially trained to respond on the right lever under either an FR 50 or an IRT > 30-sec schedule of food reinforcement (1 g banana-flavored pellets). After 65 sessions of food-maintained responding, monkeys were surgically prepared with indwelling IV catheters, and 0.03 mg/kg/inj cocaine was contingent on left lever responding under an FI 5-min schedule. As in the earlier study, in an effort to examine whether the influence of behavioral history was transient, the baseline dose of cocaine (0.03 mg/kg/inj) was available under the FI 5-min schedule for at least 60 consecutive sessions, after which a cocaine dose-response curve was determined. The FR 50 schedule generated high rates of food-maintained responding (90.12Å6.2 responses/min), while response rates under the IRT > 30-sec schedule were low (1.87Å0.1 responses/min). These rates were similar to the rates maintained by cocaine presentation in the Nader and Reboussin (1994) study.

Results

The major finding from this study was that across the first 60 sessions, response rates under the FI 5-min schedule were significantly higher for FR-history monkeys compared to IRT-history subjects. In addition, the differences between the groups increased as a function of number of cocaine self-administration sessions, suggesting that the effects of a food-reinforcement history were persistent, not transient (Nader and Bowen 1995). These results demonstrate that behavioral histories involving nondrug reinforcers can significantly influence rates of cocaine-maintained responding under FI schedules.

For the FR-history group, response rates were extremely high on the first session of cocaine self-administration and declined rapidly over the next three to five sessions. Cumulative records from the first five sessions under the FI 5-min schedule of cocaine (0.03 mg/kg/inj) presentation, after an FR history of food-maintained responding, are shown in figure 5. It is important to remember that these monkeys were cocaine naive prior to the first session of cocaine availability and that there was no training under the FI 5-min schedule. On the

first session of cocaine availability, responding by monkey 5565 persisted at high rates for the entire 4-hour session. Across the next three sessions responding declined by this monkey, while reinforcement frequency remained near maximum. By session 5, response rates began to increase, relative to session 4; for most FR-history subjects, these increases in FI 5-min response rates continued for the remaining 55 sessions of 0.03 mg/kg/inj cocaine availability. These records demonstrate the rapid change in response rates and patterns when environmental contingencies are modified.

Because there was no explicit training to self-administer cocaine under the FI 5-min schedule, it is possible to compare the rate of acquisition of cocaine reinforcement in monkeys with different histories of food reinforcement (for more detailed discussions of drug acquisition see Carroll, this volume; Carroll and Lac 1993; Carroll et al. 1989; Schenk, this volume). Response rates by FR-history monkeys went from 90.1 responses/min (average food-maintained rate) to 0.6 responses/min in the first four cocaine sessions, and then began to increase across the remaining 56 sessions of cocaine availability (see figure 5). Despite the fact that food and cocaine availability were scheduled on different levers, it is possible that the rapid decline in rate was due to extinction of food-reinforced responding and the gradual increase represented acquisition of cocaine self-administration.

One of the difficulties in interpreting the data in terms of acquisition of cocaine reinforcement is how to differentiate “acquisition” from extinction of food-reinforced responding. In an effort to evaluate the data with regard to acquisition, three assumptions were made (see Nader and Bowen 1995): (1) responding during the first five sessions under the FI 5-min schedule could not be used to measure cocaine acquisition because performance was confounded by extinction of food-reinforced responding and by the direct effects of cocaine on extinction; (2) for each monkey, performance after 60 sessions was an indication of stability under the FI

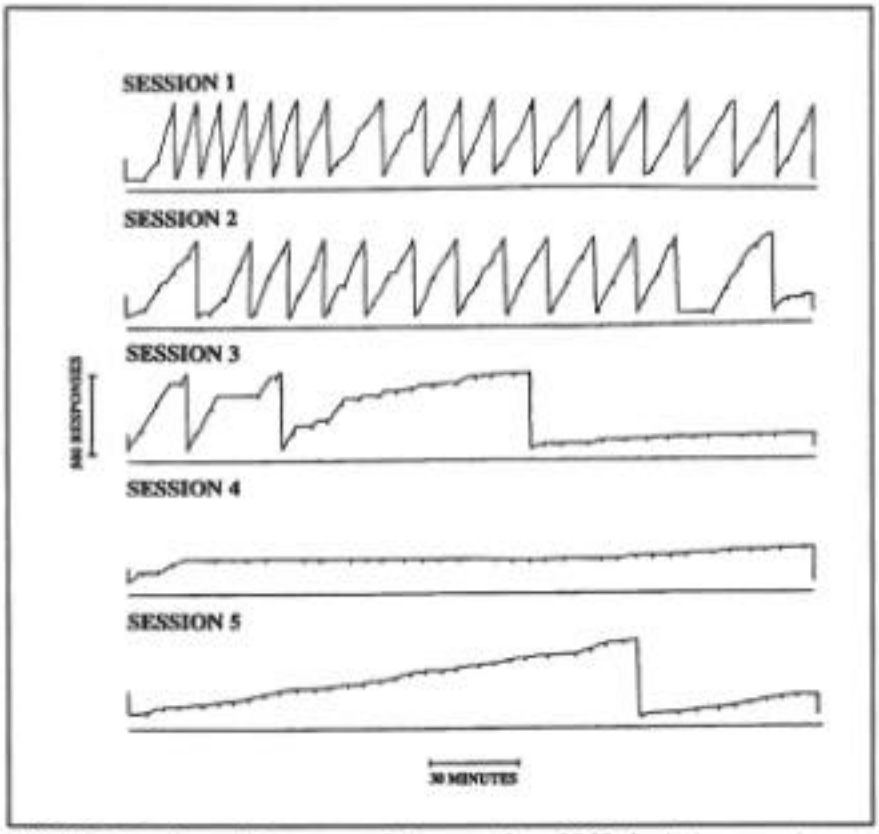

FIGURE 5. *Cumulative records for monkey 5565 depicting cocaine (0.03 mg/kg/inj) self-administration under an FI 5-min schedule during the first five sessions of cocaine availability. Prior to session 1, this monkey was cocaine naive, and responding had been maintained by food presentation under an FR 50 schedule for 65 sessions. There was no training under the FI 5-min schedule. Deflections of the stepper indicate cocaine injections.*

SOURCE: Nader and Bowen (1995).

schedule; and (3) acquisition was complete when performance occurred at > 80 percent of the mean of sessions 56 through 60. Examination of both response rate and cocaine intake data revealed that IRT-history monkeys acquired cocaine self-administration more rapidly than FR-history monkeys. That is, fewer sessions were necessary to achieve performance > 80 percent of stability for IRT-history subjects compared to FR-history monkeys. These results suggest that an FR history disrupted acquisition of cocaine self-administration under an FI schedule, irrespective of how self-administration was defined (i.e., rate or intake). It is important to

note that after several months under the FI schedule, the FR-history group had higher rates of responding compared to response rates observed in IRT-history monkeys. Thus, with continued exposure, a reinforcement schedule history that retards acquisition can result in the maintenance of high rates of cocaine-maintained responding.

As mentioned earlier, this is the first study investigating the effects of reinforcement schedule history on FI response rates that has utilized different reinforcers in the "history" and FI phases of the experiment. Interestingly, when comparisons are made between the two experiments described in this section, experimentally naive monkeys initially trained to self-administer cocaine under an FI 5-min schedule, on average, had higher baseline rates of responding compared to monkeys initially exposed to an FR 50 schedule of food reinforcement; the lowest rates of responding observed in both studies were generated by monkeys with an IRT > 30-sec history of food reinforcement. These results further highlight the profound effects of behavioral history on rates of cocaine-maintained responding. (See Nader and Bowen 1995 for more details.)

PUNISHMENT CONTINGENCIES AND COCAINE SELF-ADMINISTRATION

Introduction

When punishment contingencies are utilized, it is assumed that the behavior will remain low even when the contingencies are removed, i.e., the behavioral history will result in long-lasting decreases in behavior. Operationally defined, punishment is the reduction in the probability of a response following either the presentation ("positive" punishment) or the removal ("negative" punishment) of a stimulus (see Azrin and Holz 1966). Johanson and Fischman (1989) have suggested that resistance to the effects of punishment can be used to measure the strength of a reinforcer. If this hypothesis is correct, procedures that can be shown to enhance the effects of punishment on cocaine self-administration may do so by reducing the reinforcing efficacy of cocaine. One of the first studies designed to examine the effects of positive punishment on cocaine self-administration was conducted by Grove and Schuster (1974). In that study, monkeys self-administered cocaine under a multiple FR 1 schedule in which responding was punished in one of the two components. Response-contingent shock decreased cocaine self-administration in the punished component, in an intensity-dependent manner. However, the investigators reported increased rates of cocaine self-

administration during the unpunished component for some monkeys (Grove and Schuster 1974). An interesting possibility proposed by Grove and Schuster (1974), but a hypothesis that has remained untested, is that the increases in response rates and cocaine intake in the unpunished component were related to the phenomena of behavioral contrast (see Reynolds 1961*a*). From a treatment perspective it would be clearly beneficial to identify procedures in which cocaine self-administration remains reduced even when the contingencies that first led to decreased drug use have changed.

Using a discrete-trials choice procedure in which rhesus monkeys were given a choice between two alternatives of IV cocaine, Johanson (1977) reported that if the doses were the same, response-contingent shock would decrease the frequency of choice for that alternative. However, the effects of shock could be attenuated by increasing the cocaine dose administered concurrently with the punishing stimulus. In another study from that laboratory, Bergman and Johanson (1981) reported that intermediate shock intensities only transiently decreased cocaine self-administration; complete recovery from the suppressant effects of the punisher occurred within four sessions. These results suggest that positive punishment may not be an effective method for maintaining decreases in cocaine self-administration.

The effects of negative punishment on cocaine self-administration, by contrast, have not been examined. While both positive and negative punishers can suppress responding equally, they are considered distinct processes (Branch et al. 1977). For example, McMillan (1967) found that response-contingent TO, an example of negative punishment, typically suppressed responding throughout the session, whereas the effects of response-contingent shock dissipated within a session. In addition, negative punishment is more analogous to the drug treatment programs that remove individuals from environments in which drugs are available. There is some preliminary data suggesting that negative punishment can successfully decrease cocaine use in humans (Crowley 1984). The experiments described below are preliminary studies designed to systematically evaluate the effects of negative punishment on cocaine self-administration. These data highlight important methodological considerations involved when studying the effects of punishment contingencies on drug self-administration.

Methods

Rhesus monkeys were trained to respond under a two-component multiple FI 5-min schedule of cocaine presentation. Each component lasted 30 minutes and cycled twice per session. Through all phases of the experiment, the cocaine dose available was the same in each component. Initially, responding was maintained by 0.03 mg/kg/inj cocaine. When responding was stable, a cocaine dose-response curve was determined (saline, 0.01 to 0.3 mg/kg/inj). Each dose was available for at least five sessions and there was a return to baseline (0.03 mg/kg/inj) for at least five sessions between test doses.

After completion of the cocaine dose-response curve, the schedule in the second component was changed to a conjoint FI 5-min cocaine, VI 30-sec TO schedule. In this component, the first response after 5 minutes still resulted in cocaine presentation but, on average, the first response after 30 seconds resulted in a TO. The TO value was initially 10 seconds. During the TO all stimuli within the chamber were extinguished and responding had no consequence (although it was recorded). The FI clock continued to run during the TO. Thus, cocaine was still available following the first response after 5 minutes, irrespective of how many response-contingent TOs were delivered. This is an important methodological consideration because if the FI clock stopped during the TO, it could be argued that reductions in cocaine-maintained responding were due to changes in the FI schedule, not to the negative punishment contingency. When responding in both components was stable, one of two manipulations was made: either the cocaine dose was changed or a different TO value was studied (0, 10, 30, or 60 seconds).

Results

Under the unpunished multiple FI 5-min, FI 5-min schedule, monkeys typically received the maximum number of cocaine injections per session (20) except when the highest cocaine dose (0.3 mg/kg/inj) was available. There were differences in rates of responding in both components, but no systematic differences between subjects. As described earlier, there were several considerations to be made from these studies. First, because there are currently no data on the effects of negative punishment procedures on drug self-administration in animals, the ability of response-contingent TO to suppress cocaine self-administration was examined. A second purpose of these studies was to examine how unpunished cocaine self-administration would be modified under the multiple schedule of reinforcement in which responding in the other component was punished. As previously mentioned, Grove and Schuster (1974) reported that response-

contingent shock presentation suppressed responding in the punished component, but increased self-administration in the unpunished component. These investigators also reported that rates of self-administration increased above prepunishment baselines when the positive punisher was removed. Thus, a third consideration was to examine whether similar phenomena occurred when the negative punishment contingency was removed. In addition, complete cocaine dose-response curves were determined in order to assess whether the effects of negative punishment could be attenuated by higher doses of cocaine, as was reported with positive punishment (Johanson 1977).

Data from one monkey (5514) will be used to describe the effects of negative punishment on cocaine self-administration (figure 6). When the TO value was 0 seconds (i.e., the schedule was a multiple FI 5-min, FI 5-min), cocaine-maintained responding was characterized as an inverted-U shaped function of dose, in both components (figure 6, open symbols). It is important to note that responding was consistently lower in the "punished" components (i.e., components 2 and 4), even when the TO value was 0 seconds (figure 6). This result may suggest that a history of negative punishment contingencies can produce significant and long-lasting reductions in cocaine self-administration.

The effects of response-contingent 10-sec TOs on unpunished and punished responding are also shown in figure 6 (closed symbols). When responding was maintained by 0.03 mg/kg/inj cocaine and the schedule in the second component was changed to a conjoint FI 5-min cocaine, VI 30-sec TO schedule, response rates decreased to approximately 45 percent of unpunished baseline (figure 6, right panel, compare open and closed symbols). It can be seen that the suppressant effects of response-contingent 10-sec TO could not be overcome by increases in cocaine dose. That is, the negative punishment contingency resulted in a downward shift in the cocaine dose-response curve (figure 6). These results demonstrate that negative punishment contingencies can decrease rates of cocaine-maintained responding.

With regard to unpunished responding (i.e., components 1 and 3), there were no changes in the cocaine dose-response curve as a consequence of

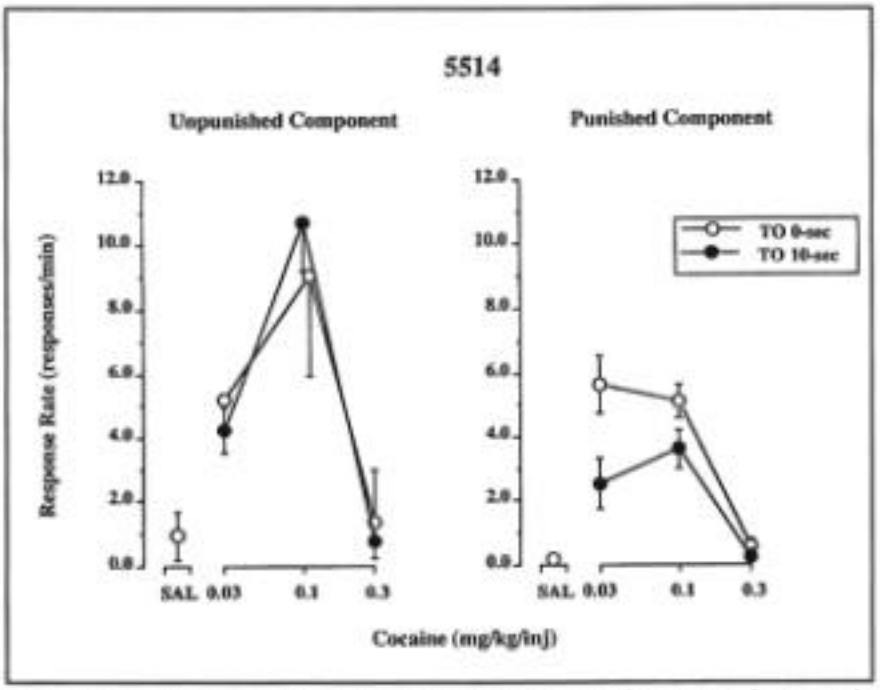

FIGURE 6. *The effects of negative punishment and cocaine dose on the rate of responding in monkey 5514 self-administering cocaine under a multiple FI 5-min, conjoint FI 5-min, VI 30-sec schedule. Data represent the mean of the last 3 sessions of a dose and condition.*

punishing responding in the other components (figure 6, left panel, compare open and closed symbols). Thus, unlike what was observed with positive punishment, no behavioral contrast was evident when responding was suppressed by negative punishment contingencies. Of course there are several differences between this experiment and the Grove and Schuster (1974) study that may account for the qualitative differences in the unpunished component. For example, the schedule of reinforcement was FR 1 in the latter study and FI 5-min in the present study. Such schedule differences, as well as baseline rates of responding, may have accounted for the different results. In addition, it should be pointed out that there was also no evidence that response rates increased above prepunishment baselines when the schedule was changed from conjoint FI 5-min, VI 30-sec to a simple FI 5-min schedule. Although these data are preliminary, the results suggest that negative punishment contingencies significantly decrease rates of cocaine self-administration. Clearly, more research is necessary to systematically compare the effects of positive and negative punishment on drug self-administration.

Another characteristic of positive punishment contingencies, described earlier, is the observation by Bergman and Johanson (1981) of between-session tolerance to the rate-suppressing effects of electric shock presentation. At this point, no evidence of attenuation in the suppressant effects of the negative punishment contingencies on cocaine-maintained responding has been observed. In addition, in preliminary data collected, there is an orderly decrease in response rates as a function of TO length. These results parallel the results from Grove and Schuster (1974) in which they reported an intensity-dependent decrease in rates of cocaine self-administration. In one monkey tested at a TO value of 60 seconds, punished responding was decreased by approximately 70 percent of baseline. Interestingly, there was a reduction in unpunished response rates of approximately 50 percent. No such "response induction" (see Reynolds 1961*b*) was observed with positive punishment contingencies and cocaine self-administration (Grove and Schuster 1974). Again, this may be due to different experimental protocols. For example, it is well known that at high enough shock intensities responding will be completely suppressed and no between-session tolerance will develop (Bergman and Johanson 1981). However, when those shock intensities are studied in the context of discrete-trials choice (Johanson 1977), monkeys will still self-administer the dose available as the unpunished alternative. Thus, response induction was not seen with positive punishment when studied under a discrete-trials choice procedure.

As can be seen, there is still a great deal to be learned about the efficacy of punishment contingencies in decreasing drug self-administration. From a basic science viewpoint, direct comparisons of positive and negative punishment procedures on drug self-administration have not been conducted. From a clinical viewpoint, negative punishment contingencies are already operating in the drug abuser's environment and a better understanding of how these contingencies mediate drug use would be of obvious value.

PHARMACOLOGICAL HISTORY

Introduction

This chapter has attempted to highlight some important methodological issues regarding environmental modulation of the reinforcing effects of cocaine in monkeys, with emphasis on the long-term effects of these behavioral histories. Before closing, the role of pharmacological history in mediating the reinforcing effects of drugs will be briefly discussed. This issue is especially important in primate research because it is common to use the same animals in several experiments. For the most part, this is an advantage of using primates: within-subject comparisons of the effects of several independent variables, across years of study, can be made. However, it is important to keep in mind that experimental (including pharmacological) history can have long-lasting effects on behavior, and important information can be gained from studying history, rather than simply controlling for it.

One of the most frequently used protocols in drug self-administration research is the substitution procedure. In this procedure, animals are first trained to self-administer a drug with known abuse liability and then test compounds are substituted for that drug. If response-contingent presentation of the test drug maintains rates that are higher than rates maintained by drug vehicle, then the test drug is functioning as a reinforcer and has abuse liability. When cocaine is the baseline drug, experiments utilizing a substitution procedure have shown that compounds that bind to dopamine D_1 (Self and Stein 1992; Weed et al. 1993), D_2 (Woolverton et al. 1984; Yokel and Wise 1978), and D_3 receptors (Caine and Koob 1993; Nader and Mach, in press) can function as reinforcers, maintaining rates higher than those maintained by vehicle presentation. It is important to remember that when the presentation of an agonist maintains high rates of responding, the results only suggest the possibility that a receptor subtype is involved in the reinforcing effects of the baseline drug (in this case, cocaine). However, by comparing the reinforcing effects of a test compound in substitution procedures versus acquisition in drug-naive animals, an indication of the importance of pharmacological history, as well as the neuropharmacological changes that occur as a consequence of long-term drug exposure, can be assessed (Nader and Mach, in press).

Methods

Substitution Procedure. Three cocaine-experienced monkeys had been self-administering cocaine for 2 to 3 years prior to the start of this study. Responding was maintained under an FI 5-min schedule of IV cocaine (0.03 mg/kg/inj) presentation, during daily 4-hour sessions. When responding was stable, a cocaine dose-response curve was determined, as described earlier. After completion of the cocaine dose-response curve, various doses of the dopamine D_3/D_2 agonist 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) were substituted for the baseline dose of cocaine. Each dose of 7-OH-DPAT was available for at least three consecutive sessions; there was a return to cocaine (0.03 mg/kg/inj) between 7-OH-DPAT doses.

Acquisition in Cocaine-Naive Monkeys. After the reinforcing dose range of 7-OH-DPAT was established in three cocaine-experienced animals, 7-OH-DPAT self-administration was evaluated in six cocaine-naive monkeys under two different protocols. For three cocaine-naive monkeys, various doses of 7-OH-DPAT were available under a low FI schedule (initially an FI 15-sec schedule), during daily 4-hour sessions. The lever was frequently baited with sucrose pellets to facilitate the association between a response, the illumination of the lever lights, and the delivery of an IV injection of 7-OH-DPAT. After approximately 14 sessions, 0.03 mg/kg/inj cocaine was made available for self-administration. Three additional cocaine-naive monkeys were first trained to respond under an FI 5-min schedule of food presentation and then 7-OH-DPAT (0.003 to 0.03 mg/kg/inj) was substituted for food. After completion of the 7-OH-DPAT dose-response curve, cocaine was studied.

Results

In cocaine-experienced monkeys, when substituted for cocaine, 7-OH-DPAT functioned as a reinforcer in all three monkeys. Response rates varied as a function of dose and were characterized as inverted U-shaped; intake increased in a dose-dependent manner (Nader and Mach, in press). These results are in agreement with previously published results using rats (Caine and Koob 1993) and provide a direct comparison of the reinforcing potency of the two compounds. 7-OH-DPAT was 0.5 to 1.0 log units more potent than cocaine, with peak rates maintained at 0.003 or 0.01 mg/kg/inj 7-OH-DPAT.

In all six cocaine-naive monkeys, 7-OH-DPAT-maintained responding occurred at very low rates; an effect that was opposite to

results observed in the substitution study. For monkeys in which 7-OH-DPAT was available under low FI schedules, little or no responding could be maintained in any of the monkeys. After 10 to 13 sessions of 7-OH-DPAT availability, cocaine was made available to these animals and response rates increased within one to four sessions, indicating that the catheters were patent and that cocaine functioned as a reinforcer in these animals. After these monkeys were allowed to self-administer cocaine, 7-OH-DPAT was again made available and functioned as a reinforcer. Response rates maintained by 7-OH-DPAT were still substantially lower than rates maintained by monkeys with an extensive cocaine history. These results suggest that prior cocaine exposure modified the reinforcing effects of 7-OH-DPAT (Nader and Mach, in press).

Others have reported on the importance of pharmacological history in the reinforcing effects of opiates, dissociative anesthetics, benzodiazepines, and NMDA antagonists (Beardsley et al. 1990; Bergman and Johanson 1985; Schlichting et al. 1970; Young and Woods 1981; Young et al. 1981). When pharmacological history has been shown to be important, one mechanism that is frequently discussed is that the test compound shares discriminative stimulus effects with the baseline drug. According to that hypothesis, 7-OH-DPAT functioned as a reinforcer in cocaine-experienced animals, but not in cocaine-naive animals, because 7-OH-DPAT shares discriminative stimulus effects with cocaine. Consistent with this hypothesis is recent data demonstrating that 7-OH-DPAT can substitute for cocaine in monkeys trained to discriminate cocaine from saline (Lamas et al. in press; Spealman 1994).

Results from the first three cocaine-naive monkeys suggest that a cocaine history was an important determinant of the reinforcing effects of 7-OH-DPAT. However, it is possible that 7-OH-DPAT functioned as a reinforcer because of the monkeys' exposure to the FI schedule (i.e., behavioral history), not because of their pharmacological history involving cocaine. However, this apparently was not the case, since monkeys that were first trained to respond under an FI 5-min schedule of food presentation responded at very low rates when 7-OH-DPAT was made available (Nader and Mach, in press). Thus, training the animal to respond under the FI schedule did not enhance the reinforcing effects of 7-OH-DPAT.

Results from the present study suggest that behavioral mechanisms (i.e., discriminative stimulus effects and FI histories) may not be involved in the low rates of 7-OH-DPAT self-administration in

previously cocaine-naive monkeys. A second possibility is that neuropharmacological changes as a consequence of prior cocaine exposure modified the reinforcing effects of 7-OH-DPAT. For example, it is possible that long-term cocaine exposure resulted in an upregulation of dopamine D_3 and/or D_2 receptors. However, studies utilizing the noninvasive imaging technique positron emission tomography (PET), have shown that D_2 receptor densities are lower in cocaine abusers (Volkow et al. 1990, 1993), suggesting a downregulation of D_2 receptors with chronic cocaine exposure. In preliminary PET studies, a similar reduction in D_2 binding in cocaine-experienced monkeys compared to cocaine-naive controls has been observed (R.H. Mach, M.A. Nader, and R. Ehrenkaufer, unpublished observations). A more probable explanation for the present results is that chronic cocaine exposure resulted in reductions in basal dopamine levels that enhanced 7-OH-DPAT binding to D_3 receptors, although this latter hypothesis will have to be tested further.

The most important point of this study is that the combination of a substitution procedure in animals self-administering cocaine and acquisition in cocaine-naive animals revealed possible behavioral (i.e., discriminative control) and/or neuropharmacological changes that are a consequence of long-term cocaine exposure. These data suggest that it is possible to track the timecourse of these behavioral and neuropharmacological changes by having "probe" sessions in which 7-OH-DPAT is frequently substituted for cocaine. From a treatment perspective, these results suggest that 7-OH-DPAT would have low abuse liability in cocaine-naive individuals. With regard to treating cocaine abusers, the fact that 7-OH-DPAT functions as a reinforcer after chronic cocaine exposure suggests that compliance would be high.

CONCLUSIONS

This chapter has reviewed the influence of several environmental and pharmacological variables on rates of cocaine self-administration. To this end, the experiments had the same primary goal: to study the effects of current environmental contingencies and the long-term consequences of these experimental histories on rates of cocaine self-administration. Behavioral histories could increase (i.e., FR histories) or decrease (i.e., IRT > 30-sec histories) rates of cocaine-maintained responding. Importantly, behavioral histories involving nondrug reinforcers could also significantly influence cocaine self-administration. Negative punishment contingencies were extremely

effective in reducing cocaine-maintained response rates. Also, the fact that response rates were lower in the punished component, even when the punishment contingency was removed, suggests that behavioral histories involving negative punishment can produce long-lasting reductions in cocaine self-administration. Although the focus of this chapter was on environmental variables, the effects of pharmacological history were also discussed. The inclusion of pharmacological history in this chapter was by no means arbitrary. There is a growing database on drug-behavior interactions modifying the behavioral effects of drugs. (See Barrett et al. 1989 for reviews.) Perhaps future research will show that a combination of behavioral and pharmacological treatments will be the most clinically effective strategy. For example, while it has been shown that administration of dopamine D_3 agonists decrease cocaine-maintained response rates (Caine and Koob 1993), it may be that these pretreatments will be significantly more effective when combined with certain behavioral histories, environmental contingencies, or environmental contexts. That is, the identification of potential pharmacotherapies for cocaine abuse will be enhanced by a better understanding of the behavioral variables that modify the reinforcing effects of cocaine.

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Stimulant Preexposure Sensitizes Rats and Humans to the Rewarding Effects of Cocaine

Susan Schenk and Emily S. Davidson

A great deal of research has focused on initiation into drug use and factors that increase the risk of initiation or protect against it. Initiation into the use of some drugs (such as alcohol) is extremely common, whereas initiation into use of other drugs (such as cocaine) is less frequent (Kandel 1975). Regardless of initiation rate, most individuals who try a particular drug do not continue into a pattern of abuse, although different substances appear to differ in their abuse potential. For example, many adults in the United States can be considered "social" drinkers, but a much smaller percentage are considered "problem" drinkers. The abuse potential of cocaine is considered to be much higher among those individuals who continue to use on a regular basis. Newcomb (1992) found that about 15 percent of young adult alcohol users had developed a pattern of dependency, whereas about one-third of those who had used cocaine within the previous 6 months showed a pattern of dependency. Thus, different substances appear to differ in abuse potential, but, in addition, different individuals also vary in their vulnerability to abuse. A wide variety of psychological and social factors contribute to this variability; the purpose of this chapter is to present a series of animal studies, and more limited human data, which suggest one biological model that may explain differing responses to cocaine. Different individuals, as a result of previous exposure to other stimulants, may initially experience cocaine as more (or less) positive; these different responses will influence the likelihood of continuing to take cocaine and the timecourse for the development of a pattern of abuse.

Propensity to self-administer stimulants in animals can be experimentally altered via a number of environmental and pharmacological conditions. For example, rats that were reared in socially isolated conditions developed cocaine self-administration in adulthood with shorter latencies than rats that were reared in groups (Bozarth et al. 1989; Schenk et al. 1987). Repeated application of four 1-minute daily exposures to tailpinch also facilitated the development of amphetamine self-administration by rats (Piazza et al. 1990). Exposure to the self-administered drug can also increase the responsiveness of rats and monkeys to the subsequent effects of

the drug (Downs and Eddy 1932; Horger et al. 1990; Lett 1989; Piazza et al. 1989; Woolverton et al. 1984). Therefore, following exposure to these environmental or pharmacological variables, subjects appear sensitized to subsequent drug exposures. During the past two decades, models have been developed to investigate the conditions under which behavioral sensitization occurs and to try to understand the neurochemical basis for this phenomenon.

BEHAVIORAL SENSITIZATION: A MODEL FOR THE DEVELOPMENT OF COCAINE ABUSE

The earliest reports of sensitization with repeated stimulant exposure (Downs and Eddy 1932) observed that chronic treatment with cocaine resulted in a progressive increase in motor activity with repeated lower dose exposures. More recent experiments (Post and Rose 1976; Robinson and Becker 1986) have attempted to quantify sensitization to cocaine's motor-activating effects more elaborately. The results have indicated that behavioral sensitization primarily functions to increase the maximum behavioral output. In other words, the motor-activating effects of a given stimulant dose appear to increase. The dose-response curves for this behavioral effect may not be shifted to the left but, rather, may be shifted up vertically for effective doses of the drug. In addition, the effects of intermittent exposure also appear to be enduring, lasting for several months following the treatment (Robinson and Becker 1986; Robinson et al. 1988; Zahniser and Peris 1992). Finally, both a context-dependent and a context-independent form of sensitization appear to be operating. These two forms may be separable and may be dependent on long-term changes in different neuronal substrates. The context-independent form of sensitization has been hypothesized to be due to interactions between dopamine (DA) and other neuronal systems in the somatodendritic regions of the ventral tegmental area (Kalivas and Stewart 1991).

The use of motor activity as a behavioral assay has many advantages. For example, it is a relatively simple assay requiring no sophisticated surgical procedures. Also, drug-induced motor activation is easily quantified. Portions of the circuitry for drug-induced motor activation have been well delineated, at least for psychomotor stimulant-induced hyperactivity, and they are known to be dependent on mesocorticolimbic DA systems. The overlap of these systems with those underlying the reinforcing effects of these drugs led to the formulation of a psychomotor stimulant theory of addiction (Wise and Bozarth 1987). If correct, then a study of the factors that

contribute to the development of sensitization to the motor-activating properties of psychomotor stimulants may relate to the development of drug abuse. However, there are numerous reports in the literature of manipulations that differentially affected motor activity and self-administration, with a report from the laboratory of the senior author of the theory (R.A. Wise) discussing these differences with a specific focus on sensitization (Wise and Munn 1993). The possibility is raised at the end of that paper that "some modification of the various psychomotor stimulant theories of reward will be necessary" (page 199). Thus, effects of manipulations on motor activity may not always reflect manipulations in reward-related behavior. As a result, self-administration models have been used to address directly the basis for a predisposition to drug abuse.

The development of cocaine self-administration in laboratory animals is highly variable (Deneau et al. 1969), and the retrospective reports of reactions of humans to their initial cocaine exposure range from highly positive to negative (Davidson et al. 1993). In the authors' laboratory, a great deal of variability in the latency to acquire cocaine self-administration by rats is routinely observed suggesting that the variability is due to differences in the sensitivity of rats to cocaine's reinforcing properties. That is, some rats may become more quickly sensitized to cocaine's reinforcing properties than others.

Using alternate paradigms, a small number of investigations have attempted to demonstrate sensitization to the reinforcing effects of drugs with repeated exposures. For example, Lett (1989) demonstrated an increase in the conditioned place preference produced by repeated cocaine or morphine exposure and Shippenberg and Heidbreder (1995) have shown a shift to the left in the dose-response curve for cocaine-induced conditioned place preference following two exposures to cocaine. Kokkinidis and colleagues (Kokkinidis and Zacharko 1980; Predy and Kokkinidis 1984) have shown sensitization in the ability of repeated injections of amphetamine to potentiate the reinforcing effects of brain stimulation, although it has been suggested that these sensitizing effects on brain reward mechanisms may be site specific (Wise and Munn 1993).

Studies using the self-administration paradigm have consistently demonstrated sensitization to the reinforcing effects of drugs following preexposure. For example, Woolverton and colleagues (1984) found that the reinforcing effects of methamphetamine were enhanced following preexposure. Doses that were initially

subthreshold for self-administration became capable of maintaining responding in two out of three monkeys following a period of intermittent methamphetamine administration. Therefore, the dose-response curve for self-administration shifted to the left following the stimulant exposure. Piazza and colleagues (1989, 1990) have similarly shown that preexposure to four noncontingent administrations of 1.5 mg/kg amphetamine was sufficient to turn rats that had initially failed to self-administer amphetamine into reliable self-administrators. This more direct examination of the development of drug reinforcement involving an examination of the development of intravenous (IV) self-administration provides support for the notion that responsiveness to the reinforcing effects of drugs of abuse can be increased by preexposure. The investigation of factors that contribute to the development of the proposed sensitization will ultimately lead to an understanding of why some subjects appear susceptible to drug abuse whereas others appear to be relatively resistant.

This has been the objective of the research in the authors' laboratory during the past several years. The working hypothesis has been that the magnitude of the initial reinforcing effects of cocaine (latency to acquisition of a response that produces IV infusions) is determined, in part, by the pharmacologic history of the animal. In this chapter, data from both rats and humans are presented that support this hypothesis.

ANIMAL STUDIES

The study of sensitization to cocaine's reinforcing effects has been influenced greatly by learning theorists of the 1950s. The basic principle that the strength of a reinforcer and the latency to acquisition of a response that produces it are inversely related was clearly demonstrated in these earlier studies. When either food or sucrose served as the reinforcer for lever pressing or T-maze running, rats receiving higher concentrations of sucrose (Guttman 1953) or larger quantities of food (Reynolds 1950) acquired the task with shorter latencies. In studying the acquisition of cocaine self-administration, this basic principle has been applied to assess the effects of pharmacological treatments on the reinforcing efficacy of cocaine.

Since studies examining the response to the initial reinforcing effects of cocaine in the self-administration paradigm were sparse,

establishment of criteria to be used to determine the latency to acquisition of cocaine self-administration was the authors' first concern. Subsequently, the authors examined the relationship between the latency to acquisition of cocaine self-administration and the dose of cocaine that served as the reinforcer. Finally, the authors assessed the effects of preexposure to a variety of stimulants on this dependent measure.

Determination of Latency to Acquisition of Cocaine Self-Administration

The authors' self-administration laboratory contained 16 operant chambers, each containing two levers. Depression of one results in the delivery of a cocaine infusion whereas depression of the other has no effect. The experimental protocol involved a single experimenter-delivered "priming" infusion of cocaine at the start of each daily session. Thereafter, the infusions were delivered on a fixed ratio (FR) 1 schedule of reinforcement by depression of the active lever. Therefore, there was no training of lever pressing. Rather, the latency to spontaneous acquisition of the operant task was examined.

To achieve this latency measure, the authors developed a set of criteria for acquisition of self-administration that would determine the day on which a rat develops a preference for the active lever. First, the number of reinforced responses for an individual rat must exceed the criterion set by the number of inactive lever responses of the group. Second, individual active lever responses must exceed individual inactive lever responses.

A criterion number of active lever responses was determined for each rat based on the average number of inactive lever responses for the group, as illustrated in figure 1. The average number of active and inactive lever responses for a representative group of rats given daily 2-hour sessions of access to cocaine (0.25 mg/kg/infusion) is shown. On the first day of testing, responding on both levers is high; with repeated days of testing, responding on both levers is initially reduced, and then active lever responding increases steadily until day 9 of testing.

The shaded region of this panel represents the upper limit of a 99 percent confidence interval placed about the mean number of inactive lever responses. This upper limit was chosen as a cutoff to establish the day on which each rat has acquired self-administration (Horger et al. 1991, 1992).

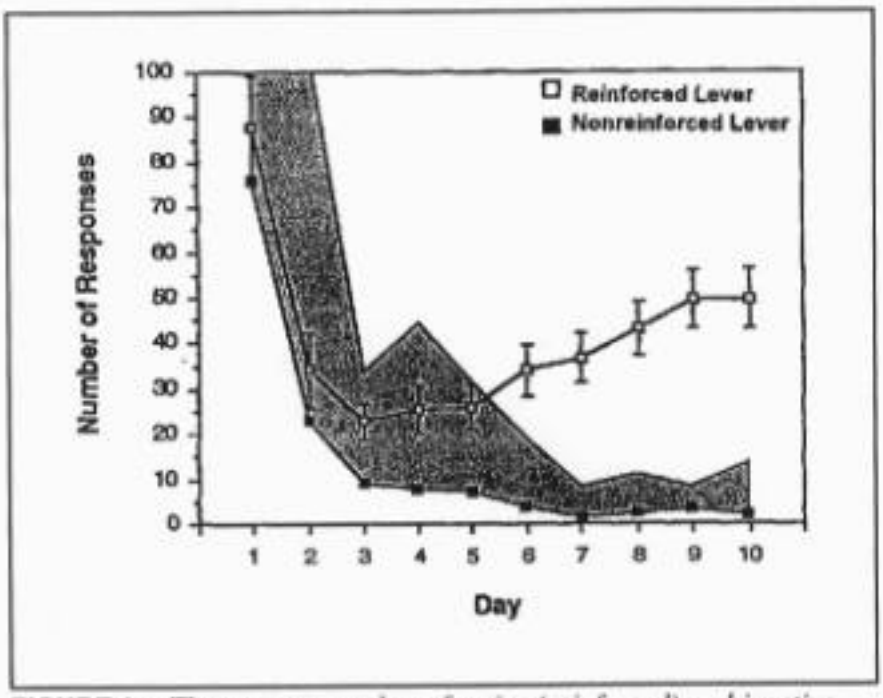

FIGURE 1. *The average number of active (reinforced) and inactive (nonreinforced) lever responses for a representative group of rats (N = 10) self-administering 0.25 mg/kg/infusion cocaine over 10 days. The shaded region shows the upper limit of a 99% confidence interval placed about the mean number of inactive lever responses. This upper limit is a cutoff that establishes one criterion for the number of active lever responses that are required on each day of testing in order for self-administration to be considered reliable.*

This method of data reduction provides a means of comparing acquisition of self-administration that is not based on absolute rates of responding but, rather, is based on the *relative* rates of cocaine taking. This becomes particularly important when acquisition of self-administration of different doses of cocaine is compared (where ultimately rates are dramatically different) or when comparing the effects of manipulations that may alter absolute intake without necessarily altering latency to acquisition. As shown below, this also standardizes the data to answer the question of whether a manipulation affected the acquisition of cocaine self-administration.

Although the method of data reduction reported here is one that has been published by the authors' laboratory (Horger et al. 1992), it is noteworthy that

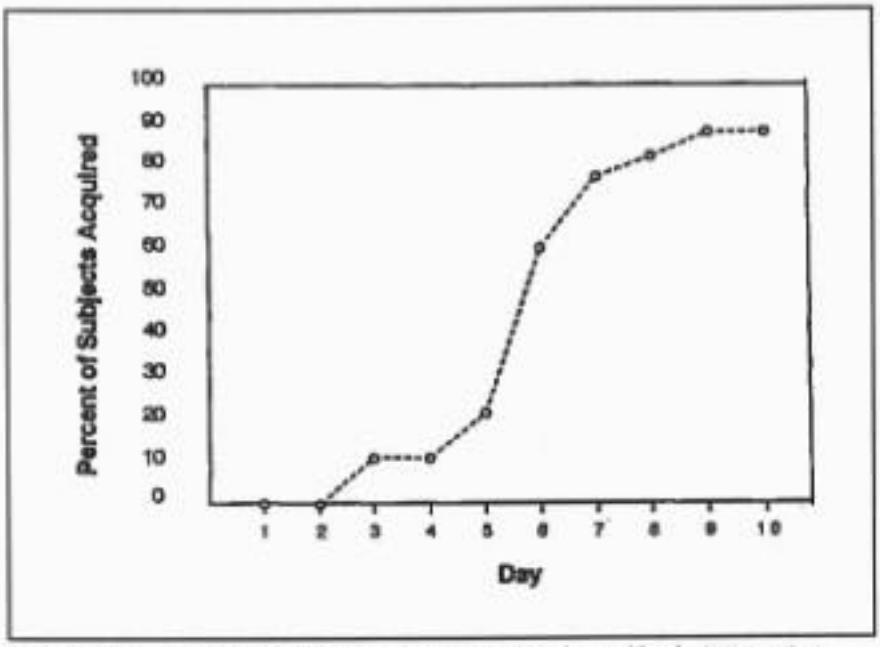

FIGURE 2. *Application of the three criteria for self-administration allows one to reduce the raw data to a curve relating percentage of subjects that had acquired cocaine self-administration to each day of testing. In this group of rats (raw data are presented in figure 1), the percentage of rats that acquire cocaine self-administration (exceeding the inactive lever response criterion (figure 1) and have a greater number of active than inactive lever responses) increases between days 3 and 9 of testing. Some rats appear more sensitive to cocaine's reinforcing properties since they acquire self-administration with fewer days' exposure.*

application of a number of other "reasonable" criteria provide exactly the same curves. For example, if the criteria of 30 active lever responses and a ratio of active:inactive responses of 3:1 are used to determine the day on which each rat acquired cocaine self-administration, the acquisition data (percentage of rats that meet the criteria on each day of testing) are as shown in figure 2.

Dose Dependency of the Latency to Acquisition of Cocaine Self-Administration

If this measure of the acquisition of cocaine self-administration is a measure of sensitivity to cocaine's reinforcing properties (i.e., those rats that are more sensitive will meet the criteria with shorter latencies), then latency to meet the criteria should be inversely

related to reinforcement magnitude (i.e., dose of cocaine). In a study designed to assess this assumption, acquisition of cocaine self-administration was determined for three cocaine doses (0.125, 0.25, and 0.5 mg/kg/infusion). When the criteria for self-administration are applied to these data, the dose dependency is clearly and statistically demonstrated (see figure 3, adapted from Schenk et al. 1993). When higher doses of cocaine serve as the reinforcer, the acquisition curve is shifted to the left with more animals acquiring the operant with a shorter latency than when lower doses serve as the reinforcer. These data lend support to the hypothesis that larger doses of cocaine are more efficacious than smaller doses.

Effects of Pretreatment With Psychostimulants

The authors' initial studies determined equipotent doses of psycho-stimulant drugs to be used in the pretreatment phase of the subsequent self-administration experiments. First, dose-response curves for the motor-activating effects of various stimulants were determined. Horizontal activity was measured in open field boxes (38.1 (38.1 (38.1 cm) with grid floors. For caffeine, methylphenidate, cocaine, and amphetamine, there was an initial increase in activity with increasing doses. As the dose was further increased, horizontal activity decreased slightly. Peak drug effects were found for 20.0 mg/kg caffeine, 20.0 mg/kg methyl-phenidate, 10.0 to 20.0 mg/kg cocaine, and 1.0 mg/kg amphetamine.

The effects of nicotine were also examined. The profile of the acute motor-activating effects of this drug was different than for the other stimulants in that the initial exposure produced motor depression. With repeated exposures, however, tolerance developed to the depressant effects and an excitatory effect was observed (Horger et al. 1992). A dose of 0.6 mg/kg (base weight) was used since repeated exposure produced increases in motor activity that were comparable to the acute effects of the other stimulants. Doses of the other stimulants that produced peak increases in motor activity were used in subsequent self-administration experiments.

In an initial study (Horger et al. 1990) both the motor-activating effects of cocaine (10.0 mg/kg, intraperitoneally (IP)) and the acquisition of IV cocaine self-administration (0.225 or 0.45 mg/kg/infusion) were determined for rats having received 12 daily exposures to cocaine (10.0 mg/kg, IP) or the saline vehicle. Exposure to cocaine under these conditions led to a sensitized response to a challenge injection when the behavioral output of interest was

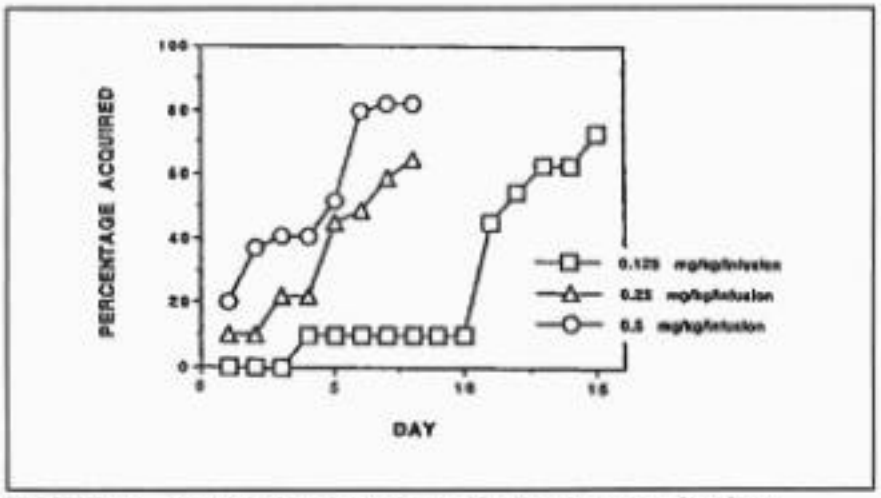

FIGURE 3. *Acquisition of cocaine self-administration for three separate groups of rats that acquired self-administration of three different doses of cocaine (N = 14-22). There is a shift to the left on the curve relating the percentage of subjects that had acquired cocaine self-administration on each day of testing with increasing doses of cocaine. Chi-square analyses confirmed that the differences between the curves for adjacent doses were significant. Thus, the latency to acquisition of cocaine self-administration is inversely related to dose.*

horizontal motor activity. Exposure to cocaine reduced the latency for acquisition of self-administration of both cocaine doses and increased the percentage of rats that reliably self-administered the drug within the 9-day test period.

Followup studies examined the effects of preexposure to nicotine and amphetamine on these same measures. Animals were pretreated with nine daily exposures to either amphetamine (1.0 mg/kg, IP) or nicotine (0.6 mg/kg base weight, subcutaneously (SC)). Repeated exposure to amphetamine resulted in progressive increases in motor activity and cross-sensitization to cocaine-induced motor activation (Schenk et al. 1991*b*). Initial exposure to nicotine produced primarily motor suppression. However, with repeated exposure, an excitatory effect of nicotine emerged. When the effects of cocaine on motor activity were subsequently assessed, the nicotine-exposed animals were tolerant and failed to show an excitatory response to any dose of cocaine tested (2.5 to 20.0 mg/kg, IP). When the acquisition of cocaine self-administration (0.25 mg/kg/infusion) was measured in rats exposed to either nicotine or amphetamine under

identical preexposure parameters, latency to acquisition of self-administration was reduced by exposure to both drugs. Thus, cross-sensitization to the reinforcing effects but not to the motor-activating effects was apparent. Further, the magnitude of the shift to the left in the acquisition curve for self-administration was comparable for both nicotine- and amphetamine-exposed rats.

The effects of repeated caffeine administration on motor activity were also measured. The effects of this drug were fairly consistent with repeated exposures (Schenk et al. 1989); neither sensitization nor tolerance was observed. However, when cocaine was administered following preexposure to caffeine, the motor-activating effects were enhanced when compared to vehicle-exposed animals. Thus, although repeated caffeine failed to modify the effects of an acute caffeine injection, it effectively sensitized rats to the motor-activating effects of cocaine. When caffeine (20.0 mg/kg, IP) was administered once daily for 9 days the latency to acquisition of cocaine self-administration (0.25 mg/kg/infusion) was also significantly reduced (Horger et al. 1991). Therefore, caffeine preexposure also sensitized rats to the reinforcing effects of cocaine.

In all of these initial studies, the preexposure treatments were administered in the test cage. Although there was no indication in the activity tests that there were conditioned effects associated with the exposure regimen, it was entirely possible that context-dependent sensitization contributed to the effects observed in the self-administration paradigm. In order to minimize the contribution of these potential conditioning factors, the pretreatments were subsequently administered in the homecage. Under these conditions, the effects of nine daily amphetamine exposures (2.0 mg/kg, IP) on acquisition of self-administration of a number of cocaine doses were tested (0.125 to 0.5 mg/kg/infusion, Schenk et al. 1993).

Application of the criteria revealed the dose dependency of these data (figure 4). As the dose of cocaine was increased, the latency to acquisition of cocaine self-administration was reduced. Most importantly, the curves for each dose of cocaine, when compared to the same data from control rats that were preexposed with saline, are shifted to the left. That is, during the early days of testing more of the amphetamine-exposed rats acquire self-administration of each dose of cocaine. Thus, amphetamine exposure increased the initial reinforcing effects of cocaine in a manner comparable to increasing the dose of the drug. These data also suggest a context-independent form of sensitization.

Persistence of the Sensitization Effects

All the data shown earlier were derived when self-administration testing began 1 day following the last of the pretreatments. Thus the data represent the immediate sensitizing effects of stimulant exposure. To investigate the persistence of these sensitizing effects, acquisition of cocaine self-administration was assessed 45 days following the last amphetamine pretreatment (2.0 mg/kg once daily for 9 days). A single dose (0.25 mg/kg/infusion) of cocaine for self-administration was tested. Amphetamine-preexposed rats still demonstrated a reduced latency to acquisition of cocaine self-administration, suggesting that sensitization to cocaine's reinforcing effects is enduring (Valadez and Schenk 1994).

As a preliminary test of whether preexposure to other stimulants produces similar enduring sensitization to cocaine's reinforcing effects, the effects of caffeine and amphetamine exposure on acquisition of cocaine self-administration (0.125 mg/kg/infusion) were compared when testing began 3 weeks following the last of the pretreatment injections. As in the earlier studies, caffeine (20.0 mg/kg, IP) or amphetamine (1.0 mg/kg, IP) were administered in single daily injections for 9 days. The effects of preexposure with caffeine were persistent; effects were apparent 3 weeks following the last of nine daily injections and were

comparable in magnitude to the effects of preexposure with nine daily injections of 1.0 mg/kg amphetamine (figure 5). Therefore, these effects are enduring.

Sensitization: A Kindling Phenomenon?

Since behavioral sensitization is enduring, the underlying mechanisms are likely to involve long-term changes in brain structure and function. Studies of electrical kindling of the brain, a widely accepted model of neural plasticity, have implicated the glutamate system and in particular enhanced sensitivity of the N-methyl-D-aspartate (NMDA) receptor (McNamara et al. 1988).

Data also suggest that the NMDA receptor may be critically involved in the development of behavioral sensitization produced by repeated exposure to dopaminergic agonists (Trujillo and Akil 1995). Sensitization to the motor-activating effect of cocaine was blocked by coadministration of the non-competitive NMDA receptor antagonist

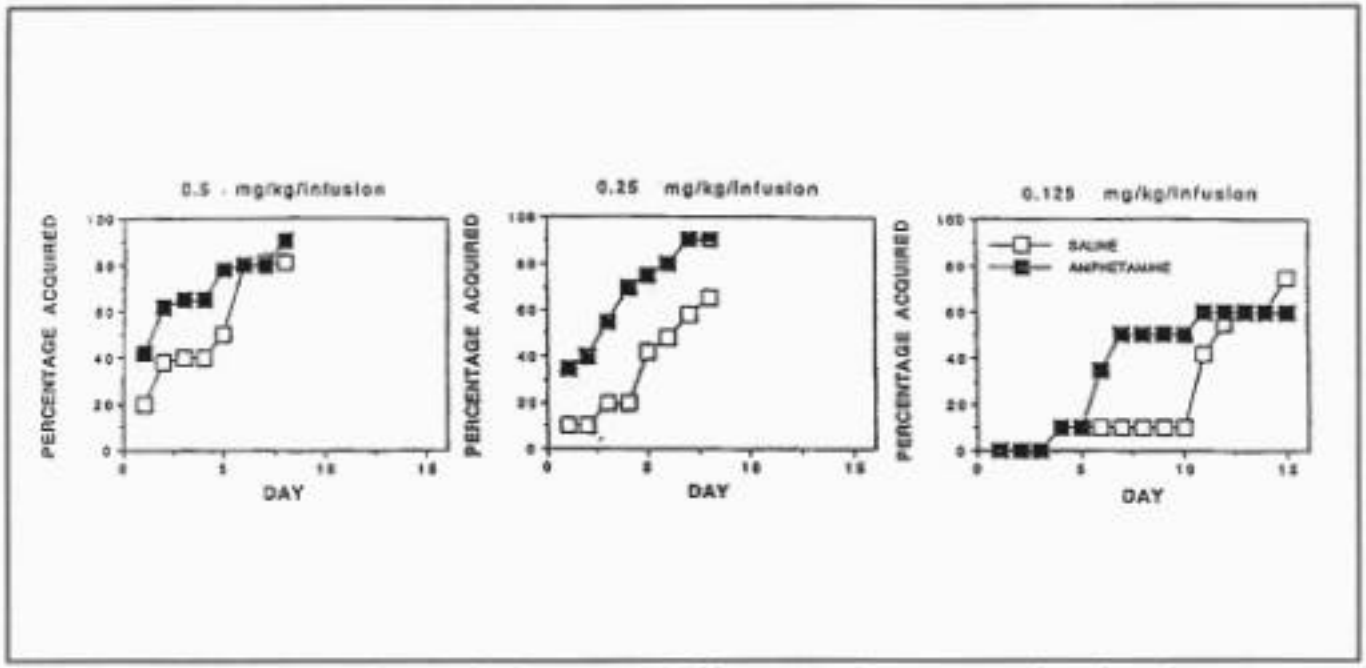

FIGURE 4. *The percentage of control subjects (N = 14-22; nonstimulant preexposed) and amphetamine-exposed subjects (N = 10-25) that acquire cocaine self-administration on each day of testing is inversely related to dose of cocaine. Further analyses indicated that differences in latency as a function of amphetamine exposure were apparent for each dose of cocaine tested.*

SOURCE: Adapted from Schenk et al. (1993).

MK-801 (dizocilpine) (Karler and Calder 1992; Karler et al. 1989). Coadministration of MK-801 also blocked the ability of amphetamine to sensitize rats to the behavioral effects of subsequent injections (Wolf and Khansa 1991). This effect appears to be manifested in the ventral tegmental area (VTA) or amygdala since local injections of MK-801 into these sites (but not into the nucleus accumbens) blocked the ability for a single injection of high-dose cocaine (30 mg/kg) to sensitize rats to the effects of a second lower dose (15 mg/kg) injection (Kalivas and Alesdatter 1993). Since a critical role for glutamatergic NMDA receptors in neuronal plasticity has been demonstrated, blockade of the NMDA receptor should block the development of sensitization as it does the development of electrical kindling if sensitization produced by pre-exposure to stimulants represents a form of pharmacological kindling (McNamara et al. 1988; Morimoto et al. 1991).

In a preliminary test of this possibility, rats were pretreated with nine daily injections of either amphetamine (2.0 mg/kg, IP) or saline (Schenk et al. 1993). Half of each group were also given an injection of either MK-801 (0.25 mg/kg) or the water vehicle. Thus, this was a 2 (2 design to assess the effects of NMDA receptor blockade on the development of sensitization produced by amphetamine preexposure. One day following the last of the pretreatments, acquisition of cocaine self-administration (0.25 mg/kg/infusion) began. Amphetamine-pretreated rats had reduced latencies for the acquisition of cocaine self-administration. When the amphetamine-pretreated rats were also administered MK-801 (0.25 mg/kg, 30 minutes before each amphetamine injection), acquisition of self- administration proceeded as for saline-pretreated rats. That is, MK-801 had blocked the development of sensitization to cocaine's rewarding properties produced by exposure to amphetamine. The 9-day preexposure regimen whereby rats received MK-801 by itself did not alter the latency to acquire cocaine self-administration. Because of the role of glutamate and NMDA receptors in the development of electrical kindling, electrical kindling may be a means of sensitizing the mesolimbic inputs to the nucleus accumbens and VTA. Using multiple stimulation sites, it may be possible to establish which of these glutamatergic projections are involved in the plasticity that is observed with sensitization to cocaine's effects.

There are data implicating the medial prefrontal cortical reward substrate in the phenomenon of sensitization. First, the acquisition of medial prefrontal cortical self-stimulation is a protracted process (Corbett et al. 1982), suggesting that repeated stimulation of this site

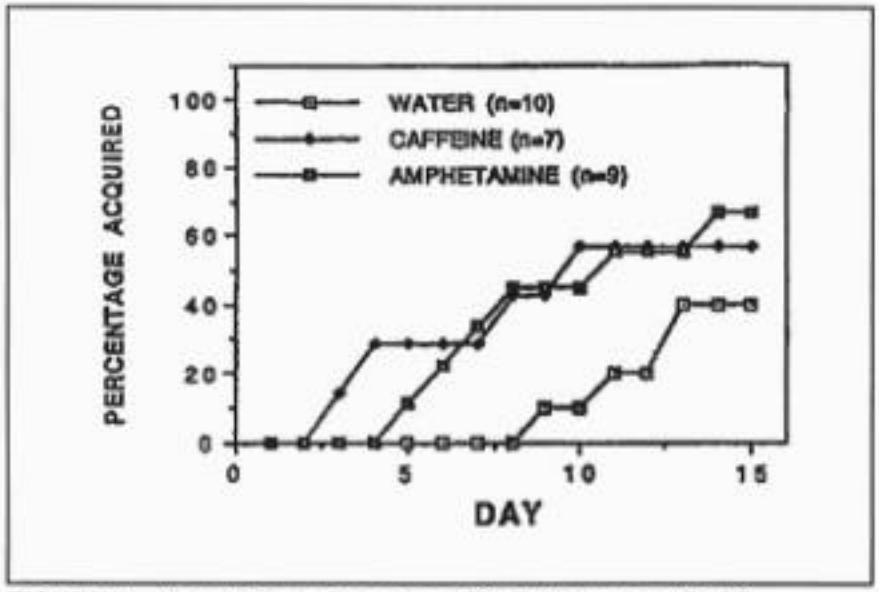

FIGURE 5. *Acquisition of cocaine self-administration (0.125 mg/kg/infusion) for rats that had received nine daily injections of amphetamine, caffeine, or the water vehicle. Self-administration testing began 3 weeks following the last of the injections. When the acquisition criteria are applied to these data, both caffeine and amphetamine shifted the curve to the left. Thus, the effects of preexposure on acquisition of cocaine self-administration are enduring and persist for at least 3 weeks.*

produces sensitization to the reinforcing effects of the stimulation. The latency for this process, however, can be significantly reduced by prior noncontingent delivery of electrical stimulation to the site (Corbett et al. 1982) as well as by prior exposure to amphetamine (West and Michael 1986). Based on this interaction between rewarding stimulation of the medial prefrontal cortex and amphetamine, the authors hypothesized that sensitization may be due to facilitated transmission in a medial prefrontal cortical substrate with repeated activation.

In a study designed to investigate this possibility (Schenk and Snow 1994), single trains of electrical stimulation were delivered either to the medial prefrontal cortex or to the hippocampus. Sham animals were implanted and handled daily but received no electrical stimulation. Daily stimulation sessions continued until stage 5 seizures developed, about 30 to 35 days (Racine 1972). After a 14-day period to allow the immediate effects of the stimulation to

subside, the ability of cocaine (0.0, 5.0, or 10.0 mg/kg) to increase horizontal motor activity was determined. Sham-operated and electrically kindled animals demonstrated a dose-dependent increase in motor activity following cocaine administration. The dose of 5.0 mg/kg was subthreshold, and a significant elevation in motor activity was found following administration of 10.0 mg/kg cocaine. Electrical kindling of the medial prefrontal cortex sensitized rats to the motor-activating effects of cocaine (Schenk and Snow 1994). These rats were more responsive to the 10.0 mg/kg dose of cocaine than either the sham-operated or hippocampal-kindled rats. These effects were not due to a generalized and diffuse activation of the brain since hippocampal kindling did not produce comparable effects. The hippocampal-kindled rats were not different from sham-operated rats in terms of their response to cocaine. Rather, the data suggest that specific activation of prefrontal cortical efferents interacted with cocaine-sensitive sites to enhance the subsequent behavioral response to cocaine. It will be critical to determine whether these effects are also observed when the reinforcing effects of cocaine are measured in the self-administration paradigm. Also of interest will be to examine the effects of kindling of other brain sites, including the amygdala, on the development of behavioral sensitization.

The ability of electrical kindling of the medial prefrontal cortex to enhance cocaine's behavioral effect suggests that repeated activation of prefrontal cortical output cells via their participation in the convulsive activity of the kindled seizures may have sensitized central cocaine-sensitive systems and, as a result, sensitized rats to the behavioral effects of cocaine. Neuro-chemical correlates of the sensitization phenomenon have been obtained in an attempt to address this possibility with a specific outlook to evaluating the role of mesolimbic and mesocortical DA systems.

Neurochemical Correlates of Sensitization to Cocaine's Reinforcing Effects

Given the large database implicating DA in the rewarding properties of cocaine (Roberts and Koob 1982; Roberts et al. 1977, 1980; Robledo et al. 1992; Schenk et al. 1991*a*), it is possible that drug preexposure and kindling of the medial prefrontal cortex facilitated the behavioral response to cocaine by increasing the dopaminergic response to cocaine in these central systems. This hypothesis has been examined using in vivo microdialysis (Horger et al. 1991, 1994). In control rats, cocaine (15.0 mg/kg, IP) caused DA overflow in the ventral striatum (nucleus accumbens) to increase to 200 to 300

percent of baseline. When rats were pretreated with caffeine (Horger et al. 1991) or amphetamine (Horger et al. 1994) under conditions that led to behavioral sensitization, the ability of cocaine to increase DA overflow in the nucleus accumbens was enhanced as compared to saline-pretreated rats. Similar effects of amphetamine pretreatment were found when DA was measured in the medial prefrontal cortex (Horger et al. 1994).

The effect of amphetamine preexposure on the response to cocaine in the prefrontal cortex was different from the response in the ventral striatum. First, the magnitude of the sensitized neurochemical response to cocaine was smaller in the prefrontal cortex. Second, the timecourse of the response to cocaine was different; the response of the cortical substrate was delayed in the amphetamine-preexposed rats relative to both the response in saline-treated controls and to the response of the ventral striatal substrate of amphetamine-treated rats. These differences may be related to differences in autoregulation between these two systems. Another possibility is that the prefrontal cortical system is more responsive to stress than is the ventral striatal system (Sorg and Kalivas 1993). Therefore, the injection regimen itself may produce a larger effect on DA overflow in these amphetamine-pretreated rats due to cross-sensitization. As a result, the effect of amphetamine over and above the effect of stress may be blunted. Unfortunately, this possibility was not addressed in the microdialysis work since, at the time, the interaction between stress and stimulants in producing sensitization to subsequent stimulant administration or stress-induced behaviors was not as well demonstrated. This possibility should be pursued in additional studies.

Another interesting aspect of these neurochemical data is the finding that nicotine exposure failed to increase the response of the mesolimbic or mesocortical DA system to cocaine. This finding is consistent with some of the behavioral data indicating that nicotine exposure failed to sensitize rats to the motor-activating properties of cocaine, but is inconsistent with the self-administration data that indicated sensitization following nicotine preexposure (Horger et al. 1992). Since nicotine preexposure failed to increase the response of either of these systems to cocaine, a different mechanism must account for the behavioral sensitization observed following pretreatment. Thus, although the amphetamine data are consistent with the hypothesis that sensitization in one or both of these DA systems may be a sufficient condition for sensitization to cocaine's reinforcing properties, another system must be responsible for the

enhanced behavioral response to cocaine following preexposure to nicotine.

HUMAN STUDIES

Efforts to evaluate the sensitization hypothesis in humans have taken two forms: The first involves an attempt to document variability of initial response to cocaine, and the second involves evaluating cocaine use and abuse in a group of subjects who had received exposure to a different stimulant.

Initial Response to Cocaine

There is a relative paucity of studies that document variability in response to cocaine's initial effects in humans. Thus, the first step in validating the animal model required determining whether the response to cocaine exhibited variability among a sample of relatively inexperienced users and whether frequency of cocaine use and pattern of use were related to self-reported magnitude of the positive response to cocaine. It was hypothesized (Davidson et al. 1993) that the subjects who responded in a positive way to cocaine would be more likely to use cocaine again and to use it a second time with a shorter latency than subjects who did not experience as positive an initial effect of the drug. To measure the initial response to cocaine, the authors adapted the expectancy questionnaire developed by Schafer and Brown (1991).

Items from scales that had the highest alpha levels, indicating high internal consistency, were used. The questions related to global positive effects of cocaine were of particular interest since these were most likely to be related to abuse potential of the drug. Eight of the questions probed positive aspects of the cocaine experience and seven probed negative aspects.

The data from this sample of college students indicated that there was substantial variability in the magnitude of the initial positive response to cocaine. The mean Global Positive response measured as an average of the individual positive responses was 2.41 (Å standard deviation of 0.722). The relationship between Positive and Negative reaction was not significant ($r(80) = 0.11$), suggesting that the variability was not determined primarily by variability in the dosage of cocaine that had been used. If this were the case, these measures would have been highly correlated.

Two indices of cocaine use were chosen. One was latency to second use since an individual who was at high risk for subsequent abuse might be expected to have a shorter latency between first and second use. The other measure was frequency of cocaine use. It is logical that the greater the abuse potential, the greater the frequency of use of a compound.

It was expected that the initial response would be a good predictor of subsequent use. That is, those with the highest Global Positive responses would be most likely to have shorter latencies to second use and higher frequencies of cocaine use. Support for this hypothesis was obtained. The subjects who had the highest Global Positive scores reported the shortest latency to second cocaine use ($r = -0.43$, $p < 0.001$) and the highest frequency of cocaine use ($r = 0.44$, $p < 0.001$). The Global Negative Effect was not a good predictor of either of these measures of subsequent abuse. However, one Negative Effect question concerning "craving for cocaine" turned out to be the sole predictor of both measures of cocaine use. The correlations between this question ("I was never satisfied when I was on cocaine ... I always wanted more"), and the latency to second cocaine use ($r = -0.32$) or frequency of cocaine use ($r = 0.43$) were higher than for almost all correlations for individual Positive Effects items.

These preliminary data established that the magnitude of the initial positive response to cocaine predicted subsequent frequency of use of cocaine and pattern of use: Higher positive responses on first exposure to cocaine predicted higher lifetime frequencies of use and shorter latencies between first and second cocaine use. A critical question is whether the variability in response to cocaine in humans could be predicted on the basis of pharmacologic history.

History of Stimulant Preexposure

If the animal sensitization model is correct, then a form of sensitization may occur in humans who are exposed to stimulants, and it may engender these individuals predisposed to cocaine's reinforcing properties. This is a difficult hypothesis to evaluate in humans because they may not be very accurate in reporting levels of exposure. Therefore, documented histories of stimulant exposure are preferable. One such group of humans with a medically documented history of stimulant exposure is children who are diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Based on the animal model of cross-stimulant sensitization, one would predict that

methylphenidate exposure may be a risk factor for subsequent use of cocaine in adolescence or adulthood.

There are some retrospective human data to support this hypothesis. A high percentage of treatment-seeking cocaine abusers have been reported to have prior ADHD diagnosis (Cocores et al. 1987; Rounsaville et al. 1991). Similarly, elevated drug use in adults with prior ADHD diagnosis has been reported (Weiss et al. 1979, 1985; Gittleman et al. 1985), although these differences have been mainly attributed to elevated use of alcohol and marijuana.

The interaction among methylphenidate exposure, ADHD, and cocaine use was recently examined by Dr. Nadine Lambert at the University of California, Berkeley (Davidson et al., in preparation) in a sample of individuals in their mid to late 20s who had used cocaine on at least one occasion. These subjects are a subset of a cohort that participated in a study of treatment of ADHD 15 to 20 years ago. At intake, these subjects were classified as either situationally hyperactive (rated by teachers or parents) or pervasively hyperactive (rated by both teachers and parents) as defined on the school and home forms of the Children's Attention and Adjustment Scale.

In this recent followup, three subgroups of these subjects were tested. One was comprised of situationally or pervasively ADHD subjects who also had a medical diagnosis of hyperactivity and had received treatment with methylphenidate for periods ranging from 1 to 10 years. A second group of subjects were ADHD behavior controls who also were situationally or pervasively ADHD, but had not received treatment with methylphenidate or other central nervous system (CNS) stimulants. Severity of symptoms was roughly equivalent for the two groups of ADHD subjects as indicated by equal proportions of situational and pervasive classification of the subjects. The major difference in the two groups was the presence or absence of stimulant medication. A third group was comprised of age-mate controls. These subjects were originally selected from classrooms in which the hyperactive subjects were enrolled and were matched by birth date. ADHD subjects who received stimulant medication provide a unique test because their exposure history does not require retrospective self-reports but rather is determined from medical histories and is therefore a more reliable index of level of exposure.

Frequency of lifetime cocaine use was established on a rating scale of 1 (once or twice), 2 (3 to 9 times), 3 (10 to 19 times), 4 (20 to 39

times), and 5 (more than 40 times). Subjects were administered a computerized version of the DSM-III-R to further assess the presence of cocaine abuse. Generally, this category included frequency of use as well as legal and social problems associated with cocaine use. Questions concerning nicotine, amphetamine, marijuana, and hard liquor use were also included in the followup.

The medicated ADHD subjects showed the highest percentage of cocaine abuse, as indicated by DSM-III-R diagnosis, double that of either the nonmedicated subjects or the age-mate controls. This was not simply a function of greater exposure to the drug since equal percentages of subjects from all groups had tried cocaine at least once.

A hierarchical regression analysis was performed to determine the contribution of various factors to the frequency rating of lifetime cocaine use for the subjects who had used cocaine. The variables (1) gender, (2) presence or absence of ADHD symptoms, (3) presence or absence of conduct problems, (4) presence or absence of stimulant medication, and (5) tobacco exposure (whether or not 100 cigarettes had been smoked lifetime) were entered. As a comparison, the contribution of these variables to marijuana and hard liquor use was also determined.
Eleven percent of the variance in cocaine use, 18 percent of the variance in marijuana use, and 8 percent of the variance in alcohol use was attributed to these variables. Presence of ADHD symptoms or conduct disorder in childhood did not contribute significantly to any drug use. Exposure to stimulant medication contributed significantly to the explained variance in cocaine use ($r^2(145) = 0.034$, $p = < 0.027$), whereas significant amounts of variance in marijuana use ($r^2(195) = 0.001$, NS) or alcohol use ($r^2(224) = 0.0005$, NS) were not explained by early medication history. Tobacco use contributed to the explained variance for use of all these drugs (cocaine: $r^2(145) = 0.07$, $p = < 0.002$; marijuana: $r^2(195) = 0.085$, $p < 0.001$; alcohol: $r^2(224) = 0.055$, $p < 0.001$). Gender, while contributing significantly to variance in the use of marijuana ($r^2(195) = 0.021$, $p < 0.001$) and alcohol ($r^2(224) = 0.065$, $p = < 0.029$) use, did not significantly contribute to the variance in cocaine use ($r^2(145) = 0.003$, NS).

The use of a community-based sample is particularly important because, in this sample, ADHD status and medication status are not confounded as they are in most clinic-based samples. The availability of a behavior-matched nonmedicated group allowed the evaluation of ADHD and medication as separate contributors to the frequency of cocaine use and abuse. That methylphenidate was still capable of

explaining a small but significant proportion of the variance in cocaine use even after approximately 15 years is of great importance. Although this too was predicted by the animal model, which has shown that behavioral and neurochemical sensitization is enduring (Valadez and Schenk 1994), the number of variables that could interact with the medication effect in humans is relatively high. That the effect was still significant attests to the potency of methylphenidate as a sensitizing agent.

Another particularly interesting aspect of the human data was the finding that smoking also explained a significant amount of the variance in the use of cocaine and other drugs. Since nicotine exposure was sufficient for inducing sensitization to cocaine's reinforcing effects in rats, these findings in humans may be another reflection of the sensitization process. It will be important, of course, to determine whether the initiation of nicotine use preceded the use of cocaine.

FUTURE DIRECTIONS

The data presented here represent preliminary studies of the effects of manipulations on the initial reinforcing effects of cocaine. The objective of this research has been to provide animal models that would allow identification of factors that may predispose subjects to cocaine abuse. The results of these studies have been encouraging, particularly when coupled with the results of the human study. Essentially, stimulant preexposure appears to sensitize rats to the initial reinforcing properties of cocaine, and possibly other stimulants, and can explain a significant amount of the variance in cocaine use in humans.

A number of interesting questions have arisen from the results of the studies presented here that warrant further investigation. For example, pretreatment with *stimulants* has consistently been shown to reduce the latency for acquisition of self-administration. A question of great interest is whether these effects are restricted to stimulants or represent a more general phenomenon of drug exposure. An answer to this question will require parametric studies aimed at comparing the effects of a number of doses of a number of pretreatment drugs (both stimulants and nonstimulants) on the acquisition of cocaine self-administration.

Another question of interest is whether the positive sensitizing agents (stimulants and whatever other drugs prove to provide similar effects on latency to acquisition of self-administration) produce effects that are specific to cocaine reinforcement or also generalize to nondrug reinforcers. The answer to this question will require parallel investigations into the effects of preexposure on self-administration of alternate reinforcers.

These preliminary data pave the road for additional parametric work to "nail down" the phenomenon. For example, experiments that examine the effects of combinations of doses of effective drugs will determine whether a common neurochemical mechanism underlies sensitization produced by drug preexposure. Additional experiments will be required in order to establish what that mechanism is. This may be particularly telling in light of the differences in the ability of amphetamine and nicotine preexposure to alter the response of central dopaminergic systems to cocaine.

Finally, examination of longitudinal databases, such as the one at Dr. Lambert's laboratory at the University of California, Berkeley, may allow for further validation of the animal models and may allow additional variance in cocaine use to be explained by other variables.

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Stress, the Hypothalamic- Pituitary-Adrenal Axis, and Vulnerability to Drug Abuse

Nick E. Goeders

In nonlaboratory settings, social users of cocaine are sometimes able to control their drug intake so their patterns of use do not escalate to levels that would increase their risk of dependency and toxicity (Siegel 1984). This suggests that there may be factors in addition to the primary reinforcing properties of cocaine that determine why some individuals can remain casual recreational users while others progress to compulsive drug use. Individual reactivity to anxiety or stress, either mitigated or induced by cocaine, may represent one such factor that could influence the awareness or perception of the reinforcing efficacy of the drug. Clinical evidence supports the concept that anxiety may be involved in the etiology of cocaine use and/or withdrawal. For example, initial cocaine use produces profound subjective feelings of well-being and a decrease in anxiety in humans (Gawin and Ellinwood 1988, 1989). Interestingly, some of the major symptoms observed during withdrawal from chronic cocaine intoxication can also include severe anxiety as well as restlessness, agitation, and depression (Gawin and Ellinwood 1989). In fact, a subpopulation of chronic cocaine users may actually be self-medicating to regulate painful feelings and psychiatric symptoms via their drug use (Gawin 1986; Khantzian 1985; Kleber and Gawin 1984), especially since increased rates of affective disorders and anxiety are observed in these individuals (Brady and Lydiard 1992; Kilbey et al. 1992; Rounsaville et al. 1991). Cocaine has even been reported to precipitate episodes of panic attack in some individuals (Anthony et al. 1989; Aronson and Craig 1986; Washton and Gold 1984). Since panic disorder only became apparent following chronic cocaine use in many of these cases, the drug may have functioned as a precipitating as well as a causative factor in a neurobiologically vulnerable individual (Aronson and Craig 1986). Since environmental events can also influence the onset and/or duration of anxiety and depression (Brown et al. 1973; Leff et al. 1970; Lloyd 1980), changes in the amount, severity, or perception of environmental stress may actually predispose sensitive individuals to engage in compulsive drug use.

COCAINE AND BENZODIAZEPINES

Benzodiazepines are among the most widely prescribed drugs for the pharmacological management of anxiety. These drugs are also useful in the emergency room for the treatment of some of the medical compli-cations associated with cocaine intoxication, since convulsions are often apparent following an acute overdose. These seizures can be treated with intravenous (IV) diazepam (Gay 1981; Tarr and Macklin 1987), but not dilantin (Tarr and Macklin 1987). Furthermore, as mentioned earlier, some of the major symptoms associated with cocaine withdrawal often include severe anxiety, restlessness, and agitation (Crowley 1987; Gawin and Ellinwood 1989; Tarr and Macklin 1987). However, even though anxiety appears to be involved in the etiology of cocaine use and withdrawal in humans, and diazepam is clinically useful in the treatment of acute cocaine intoxication, benzodiazepines are not usually recom-mended as the treatment of choice for cocaine withdrawal because of the concern that the use of these drugs might result in a secondary dependence (Wesson and Smith 1985). Nevertheless, data from the author's laboratory have suggested a potential involvement of benzodiazepines in some of the behavioral and neurobiological effects of cocaine.

Chronic cocaine administration (20 or 40 mg/kg, intraperitoneally (IP) for 15 days resulted in differential effects on benzodiazepine receptors in various regions of the rat brain (Goeders 1991; Goeders et al. 1990*b*). In general, cocaine decreased benzodiazepine receptor binding in terminal fields for the mesocorticolimbic dopaminergic system, while increasing labeling in terminal fields for the nigrostriatal system. Statistically significant decreases in benzodiazepine receptor binding in the medial prefrontal cortex and increases in the ventral tegmental area (VTA) were still observed up to 2 weeks following the final injection, suggesting that benzodiazepine receptors in these brain regions may be especially sensitive to the effects of cocaine. However, the results from these experiments do not provide useful information regarding the involve-ment of these receptor systems in cocaine reinforcement since the noncontingent administration of a drug is not, by definition, reinforcing. A reinforcer is an event that increases the probability of the behavior that resulted in its presentation. The following experiments were therefore designed to investigate the effects of self-administered cocaine on benzodiazepine receptor binding (Goeders et al. 1991). Binding was compared between animals that self-administered cocaine and animals that received simultaneous, yoked infusions of cocaine or saline to

determine the potential involvement of these receptor systems in cocaine reinforcement.

Adult male rats originally derived from the Fischer 344 strain and weighing 275 to 325 g at the start of the experiments were used. These rats were divided into seven groups, consisting of three littermates each. The first littermate from each triad was trained to self-administer cocaine (1.0 mg/kg/infusion in 200 L delivered over 5.2 seconds) on a fixed-ratio 2 (FR2) schedule of reinforcement during daily 6-hour sessions. The second rat from each litter received a simultaneous, identical infusion of cocaine, and the third rat received saline each time that the first rat pressed the response lever twice. Sessions were conducted 7 days per week, and the rats were exposed to cocaine or saline for 30 days. The effects of self-administered cocaine on benzodiazepine receptor binding were visualized using [3H]flumazenil under standard autoradiographic conditions (Goeders 1991). The direct pharmacological effects of response-independent cocaine administration were estimated by comparing receptor binding changes in the brains of the yoked-cocaine animals with those from the yoked-saline littermates, while differences between the self-administration and yoked-saline littermates potentially represent a combination of the effects of the general pharmacological as well as the reinforcing actions of cocaine. Benzodiazepine receptor binding was increased in the frontal cortex and decreased in the substantia nigra and VTA in both the self-administration and the yoked-cocaine groups compared to their yoked-saline littermates. Comparisons between the yoked-cocaine and yoked-saline animals also revealed significant reductions in benzodiazepine receptor binding in the hippocampus that were not observed in the self-administration treatment group. However, there were also significant changes in receptor binding between the self-administration and yoked-cocaine treatment groups that may indicate receptor changes specifically related to cocaine reinforcement. Benzodiazepine receptor binding was significantly increased in the medial prefrontal cortex and nucleus accumbens and decreased in the caudate nucleus and globus pallidus of the self-administration rats compared to yoked-cocaine animals. Benzodiazepine receptor binding was also decreased significantly more in the VTA of the self-administration rats compared to yoked-cocaine controls. These data demonstrate that benzodiazepine receptor binding was significantly altered in “reinforcement relevant” brain regions associated with ascending dopaminergic systems (i.e., medial prefrontal cortex, nucleus accumbens), suggesting that these effects may indeed be related to cocaine reinforcement.

In IV self-administration studies, pretreatment with the benzodiazepine receptor agonist chlordiazepoxide significantly decreased drug intake in all rats tested (Goeders et al. 1989). The effects of chlordiazepoxide on self-administration were attenuated when the unit dose of cocaine was increased from 0.5 to 1.0 mg/kg/infusion, suggesting that chlordiaze-poxide may have decreased rather than augmented the reinforcing effects of cocaine. However, since the decreases in drug intake may have resulted from nonspecific effects on the ability of the rats to respond following pretreatment with higher doses of chlordiazepoxide, the next study was initiated. Alprazolam was investigated since this benzo-diazepine receptor agonist has been proven to be clinically effective in the treatment of anxiety and panic attacks (Chouinard et al. 1982) and has been proposed to be useful in the treatment of some types of depression (Dawson et al. 1984; Feighner et al. 1983; Rickels et al. 1985).

Alprazolam was tested in adult male Wistar rats under a multiple schedule of IV cocaine presentation and food reinforcement (Goeders et al. 1993). The rats were implanted with chronic indwelling jugular catheters under pentobarbital anesthesia (50 mg/kg, IP) with methyl-atropine nitrate pretreatment (10 mg/kg, IP) using previously reported procedures (Goeders and Guerin 1994; Koob and Goeders 1989; Roberts and Goeders 1989). Following surgery, the animals were injected with sterile penicillin G procaine suspension (75,000 units intramuscularly (IM)). The swivel and leash assembly was always connected during the experimental sessions, even during training for only the food reinforce-ment component of the schedule. At the end of each session, the leash was disconnected and a dummy cannula inserted into the guide before the rats were returned to their homecages. After at least 4 days' recovery from surgery, the animals were trained to respond under a multiple schedule of IV cocaine presentation and food reinforcement.

Cocaine was available during 1 hour of the session under an FR4 schedule of reinforcement. During the other hour of the schedule, food presentation was available under a discrete-trial, FR10 schedule of reinforcement. A timeout period, during which all stimulus lights were extinguished and responses on the food lever were counted, but had no scheduled consequences, followed each food presentation. This timeout period was individually adjusted so as to be comparable to the average interinfusion interval generated during the cocaine component of the schedule for each rat so that similar temporal patterns of reinforcer presentation were obtained under both components of the multiple schedule. When stable baselines of

responding were obtained under both components of the multiple schedule, the animals were pretreated with alprazolam (0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg, IP) or vehicle (1 mL/kg, IP) 30 minutes prior to the start of the behavioral session. Alprazolam was dissolved in a propylene glycol/ethanol (80:20) vehicle. Following initial exposure to alprazolam, responding maintained by both cocaine and food was significantly reduced. However, tolerance quickly developed to the sedative effects of alprazolam on food-maintained responding, while no reduction in the effects of the drug on cocaine self-administration was observed. The results of these experiments demonstrate that alprazolam decreases cocaine self-administration without affecting food-maintained responding, suggesting that these effects may result from specific actions of benzodiazepines on cocaine reinforcement rather than nonspecific effects on the ability of the rats to respond.

The neurobiological effects of cocaine also include actions on other neurotransmitter and neuropeptide systems thought to be involved with stress and anxiety in humans. Chronic cocaine administration increases the synthesis and turnover of gamma-aminobutyric acid (GABA) and decreases [3H]GABA binding in the rat striatum (Gale 1984). Acute, noncontingent cocaine administration increases plasma levels of adrenocorticotropin (ACTH), beta-endorphin, and corticosterone (Forman and Estilow 1988; Moldow and Fischman 1987), possibly through a corticotropin-releasing factor (CRF)-induced mechanism (Rivier and Vale 1987; Sarnyai et al. 1992). Cocaine also stimulates the release of CRF from rat hypothalamic organ culture systems (Calogero et al. 1989) and decreases CRF binding primarily in brain regions associated with the mesocorticolimbic dopaminergic system (Goeders et al. 1990*a*). Since CRF has been reported to be involved in a variety of neuropsychiatric disorders including depression and anxiety (Gold et al. 1984; Nemeroff 1988), the anxiety and depression associated with chronic cocaine use in humans may also be related to the effects of the drug on the release of this endogenous "stress peptide." The effects of benzodiazepines on cocaine self-administration may also be related to the effects of these drugs on corticosterone and other "stress" hormones and peptides. For example, benzodiazepines may decrease plasma corticosterone or may attenuate cocaine-induced increases in plasma concentrations of the hormone to specifically decrease cocaine reinforcement.

COCAINE AND STRESS HORMONES

The acquisition of psychomotor stimulant self-administration in rats is increased by a variety of stressors including social isolation (Schenk et al. 1987), repeated exposure to tailpinch (Piazza et al. 1990*a*) in the adult offspring of female rats exposed to restraint stress during pregnancy (Deminière et al. 1992), and in rats exposed to other rats subjected to electric footshock (Ramsey and Van Ree 1993). It has been reported that rats which exhibit a relatively high response to a novel environment are more likely to self-administer amphetamine than rats which show a lower reaction to novelty (Piazza et al. 1989; 1990*b*), suggesting that behavioral and physiological responses to stress may indicate individual abuse liability. High responding rats exhibit a greater locomotor response to a challenge injection of amphetamine and a prolonged elevation of plasma corticosterone in response to novelty than do low responders (Piazza et al. 1991*a*). High responding rats also display a greater cocaine-induced locomotor response and an increased dopamine (DA) response in the nucleus accumbens than do low responders (Hooks et al. 1991). Environmental conditions (Maccari et al. 1991) or even exogenous infusions of corticosterone (Piazza et al. 1991*a*) can increase the likelihood that a rat will acquire self-administration with low doses of amphetamine, suggesting that changes in activity within the hypo-thalamic-pituitary-adrenal (HPA) axis may be involved in the abuse liability of stimulant drugs.

The effects of exposure to response-contingent (controllable stress) and noncontingent (uncontrollable stress) electric footshock on the acquisition of IV cocaine self-administration in rats have also been investigated (Goeders and Guerin 1994). Adult male Wistar rats were housed singly in an American Association for Accreditation of Laboratory Animal Care (AAALAC) accredited animal care facility on a reversed 12-hour light/dark cycle (lights on at 18:00 hours) with free access to water. Food availability was restricted to maintain the rats at approximately 85 to 90 percent of their free-feeding body weights. The rats were initially screened for their responses to a novel environment as well as the locomotor-stimulating effects of an acute cocaine injection, since other investigators have suggested that the behavioral and neuroendocrine responses of rats to a novel environment can be used to predict vulnerability to self-administer amphetamine (Piazza et al. 1989, 1990*b*). These rats were subsequently divided into six groups of three each based on their similar responses to the novel environment and cocaine to reduce any potential individual variability within the various triads of rats. Each animal was then implanted with a chronic indwelling jugular catheter under pentobarbital anesthesia (50 mg/kg, IP) with methylatropine nitrate pretreatment (10 mg/kg, IP) as described earlier. Following surgery, the animals were injected with sterile penicillin G procaine suspension (75,000 units, IM) and were allowed a minimum of 4 days to recover from surgery.

The groups of three rats were initially trained to respond under a discrete-trial, FR10 schedule of food reinforcement as described previously (Goeders and Guerin 1994). Once stable baselines of responding were obtained, electric footshock was introduced to two of the three rats. The first rat received a random-ratio 15 schedule of shock presentation as described previously (Goeders and Guerin 1994). The second rat in each triad responded on the same schedule of food reinforcement except that shock presentation was yoked to food lever responding by the first rat. The third rat also responded under the same schedule of food reinforcement but was never shocked. Plasma corticosterone was determined (Gwosdow-Cohen et al. 1982) once stable baselines of responding with electric footshock were obtained for all three rats in a triad, but one session prior to the initial exposure to cocaine self-administration. Each rat was anesthetized with methohexital sodium (5 mg, IV) via the IV catheter while still in the behavioral chamber, and 500 L of tail blood was collected into heparinized tubes. The blood was centrifuged, and the plasma was separated and stored frozen at -20% C until needed. Plasma corticosterone was determined following extraction with methylene chloride by radioimmunoassay using the antibody of G. Niswender of Colorado State University. The cocaine component of the multiple schedule was introduced at the start of the next behavioral session. Each triad of rats was initially tested with a very low dose of cocaine (i.e., 0.031 mg/kg/infusion). After approximately 3 to 5 days of exposure to this dose, the unit dose of cocaine was gradually increased, with the concentration doubled every 3 to 5 days so that each triad of rats was tested with 0.031, 0.0625, 0.125, 0.25, and 0.5 mg/kg/infusion cocaine, followed by a saline substitution (cocaine extinction).

There were significant differences in plasma corticosterone among the three treatment groups. Rats exposed to noncontingent shock (0.6 milliampere (mA)) exhibited significantly elevated plasma corticosterone (162.0Å21.2 ng/mL) when compared to the no-shock (68.4Å6.6 ng/mL) control animals ($t = 3.920$, $p < 0.05$). Although plasma corticosterone values for rats exposed to response-contingent footshock (109.0Å18.9 ng/mL) fell between those for rats in the noncontingent and no-shock-treatment groups, the differences were not statistically significant. A two-factor analysis of variance on the average number of infusions self-administered per session indicated a significant interaction between the various cocaine doses and the different treatment conditions [$F(2,12) = 6.04$, $p < 0.0001$]. In every triad of rats, the animals without control over electric footshock presentation (noncontingent shock) were more sensitive to cocaine. Figure 1 is a quantal dose-response curve that depicts the percentage of rats that self-administered cocaine (i.e., 25 or

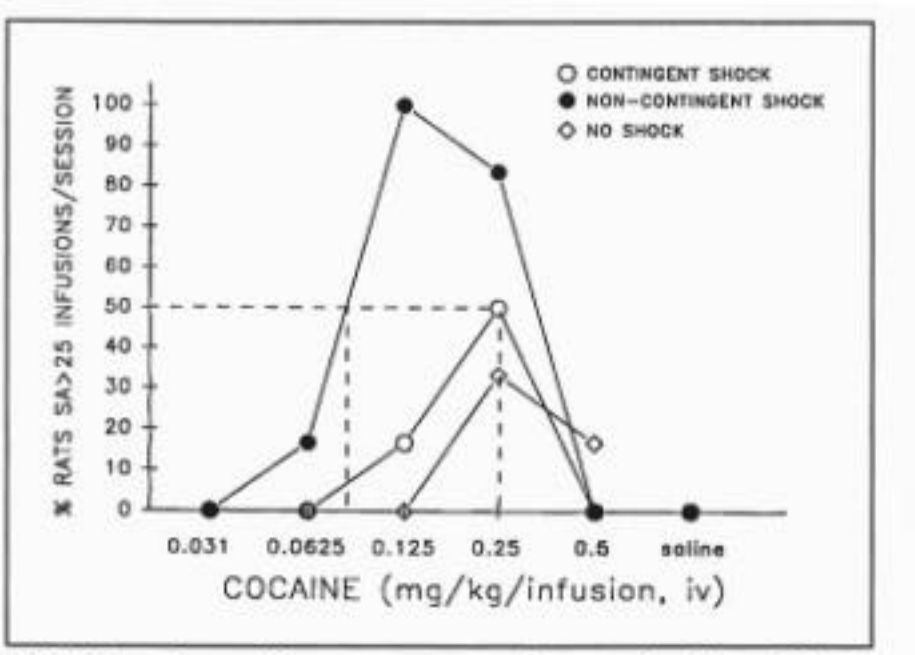

FIGURE 1. *Quantal dose-response curve depicting the effects of the treatment conditions on cocaine self-administration. ED_{50}'s are indicated by the dashed lines.*

more infusions/session) in the three different treatment conditions as a function of cocaine dose. Exposure to noncontingent electric footshock shifted the dose-response curve upward and to the left, indicating that these rats were more sensitive to the reinforcing effects of cocaine at every dose except the highest dose tested (i.e., 0.5 mg/kg/infusion). It is important to note that even though the first and second rats from each triad received the same number of electric footshocks at the same time during each session, only the second rats (without control over stress) consistently appeared more sensitive to cocaine. In general, rats from the other two groups did not self-administer cocaine until the higher concentrations were tested (i.e., 0.25 or 0.5 mg/kg/infusion). These higher concentrations are within the same range of doses used to train experimentally naive rats to self-administer cocaine, indicating a relative lack of effect of the response-contingent or no-shock-treatment conditions on the acquisition of self-administration in these rats. In addition, when the rats from these other treatment groups did self-administer the drug, rates of self-administration were generally lower than observed by rats exposed to noncontingent shock.

Interesting relationships were revealed between plasma corticosterone and cocaine self-administration. There were significant positive

correlations for all three treatment groups ($p < 0.05$) between the number of infusions delivered with the 0.125 mg/kg/infusion dose of cocaine and plasma corticosterone measured before the first exposure to the cocaine self-administration component of the multiple schedule (Goeders and Guerin 1994). These correlations appeared to roughly correspond with the acquisition, or lack thereof, of self-administration with this dose. This relationship between stress-induced elevations in plasma cortico-sterone and cocaine self-administration has now been investigated in an additional 33 triads (i.e., 99 rats). A very small percentage of these rats acquired self-administration with the lowest dose of cocaine tested (i.e., 0.031 mg/kg/infusion, N = 7), while the majority of rats acquired self-administration with the 0.125 mg/kg/infusion dose as previously reported (Goeders and Guerin 1994). There were no differences in plasma corticosterone between the rats that acquired cocaine self-administration with the 0.031 mg/kg/infusion dose compared to those rats from the same triads that did not. However, there were significant differences between these rats in the locomotor response to novelty measured before exposure to electric footshock. These data suggest that individual factors (i.e., response to novelty, see Piazza et al. 1989), which may or may not be associated with the response-contingent versus noncontingent electric footshock paradigm described earlier, were likely involved in this extremely low dose cocaine self-administration for this small percentage (i.e., 7 percent) of the rats tested. On the other hand, plasma corticosterone resulting from the different treatment conditions was significantly different between rats that acquired cocaine self-administration with the 0.125 mg/kg/infusion dose compared to rats from the same triads that did not, although there were no differences in their locomotor responses to novelty. In fact, there was a significant positive correlation between the amount of cocaine self-administered per hour and plasma corticosterone measured prior to exposure to the drug ($r = 0.92$, $p < 0.005$). Although plasma corticosterone ranged from 17 to 220 ng/mL for rats that self-administered no more than 1 mg cocaine/session, plasma corticosterone was always greater than 150 ng/mL for every rat that eventually self-administered 4 or more milligrams of cocaine per hour (i.e., > 32 infusions/session) at the 0.125 mg/kg/infusion dose. These data suggest that plasma corticosterone must be greater than 150 ng/mL for stable self-administration to occur. For example, plasma corticosterone was occasionally higher than usual (i.e., > 150 ng/mL) in rats from the first treatment group, and these rats were more likely to self-administer low doses of cocaine. Conversely, on rare occasions plasma corticosterone was not increased as high as expected (i.e., <

150 ng/mL) in the rats exposed to noncontingent footshock, and these rats were not as likely to self-administer low doses of cocaine as similarly treated rats with greater stress-induced increases in the hormone. Mean plasma corticosterone for rats from the first treatment group was 102.5Å9.8 ng/mL for rats that did not self-administer low doses of cocaine compared to 181.3 Å 10.2 ng/mL for rats that did. On the other hand, mean plasma corticosterone was 215.2Å10.6 ng/mL for rats from the second treatment group that self-administered low doses of cocaine compared to 132Å6.3 ng/mL for those rats that did not. These data suggest that plasma corticosterone measured before exposure to cocaine must be above a critical threshold (e.g., 150 ng/mL) for subsequent low-dose cocaine self-administration to occur.

For some of the triads, plasma corticosterone was also measured following exposure to the cocaine component of the multiple schedule. Plasma corticosterone was significantly elevated in rats from all three treatment groups during cocaine self-administration (259.1Å14.5 ng/mL, response-contingent shock; 237.9Å18.8 ng/mL, noncontingent shock; 271.8Å24.5 ng/mL, no shock) provided that doses of cocaine that would maintain responding were tested. However, when the dose of cocaine was increased to that which would maintain self-administration by all three rats in a triad (e.g., 0.25 or 0.5 mg/kg/infusion), there were no longer any significant correlations between plasma corticosterone measured prior to exposure to cocaine and self-administration, indicating that at these higher concentrations cocaine increased plasma cortico-sterone above a critical threshold, even for rats that had low precocaine corticosterone. In other words, the cocaine injections alone were sufficient to increase plasma corticosterone above the critical threshold necessary for cocaine reinforcement (e.g., 150 ng/mL) regardless of whether the rats had previously been exposed to noncontingent or response-contingent footshock or had never been shocked. When the cocaine dose would not maintain self-administration, plasma cortico-sterone was markedly lower in rats from all three groups. In other experiments when the animals were first trained to self-administer cocaine (0.25 mg/kg/infusion) before the introduction of the food reinforcement/shock component of the multiple schedule, there were no effects of controllable or uncontrollable electric footshock on cocaine maintained responding, further indicating that the cocaine injections alone had already increased plasma corticosterone above a critical threshold for “reinforcement.” In other words, the cocaine-induced increases in plasma corticosterone likely masked any further

increases in the hormone induced by electric footshock since the cocaine injections were by definition already reinforcing.
Since the results from the experiments described earlier suggested that increases in plasma corticosterone resulting from response-contingent and noncontingent electric footshock presentation were related to cocaine self-administration in rats, this experiment was designed to further examine the role of the HPA axis in cocaine reinforcement. Nine bilaterally adrenalectomized (ADX) and six sham-operated control (SHAM) adult male rats (Wistar) were used. A separate group of 11 ADX rats received corticosterone replacement in the drinking water throughout the experiment (CORT). The rats were housed singly in an AAALAC-accredited animal care facility on a reversed 12-hour light/dark cycle (lights on at 18:00 hours) with free access to water (SHAM), 0.9 percent saline (ADX), or 0.9 percent saline with corticosterone (100 g/ mL, CORT). Food availability was restricted to maintain the rats at approximately 85 to 90 percent of their free-feeding body weights. Each animal was implanted with a chronic indwelling jugular catheter under pentobarbital anesthesia (50 mg/kg, IP) with methylatropine nitrate pretreatment (10 mg/kg, IP) as described previously. After at least 4 days' recovery from surgery, the rats were trained to respond under an FR1 schedule of food reinforcement with the catheter and leash assembly attached. When responding stabilized, plasma corticosterone was determined immediately prior to the end of the session. The animals were then allowed access to IV cocaine by depressing a lever on the opposite side of the experimental chamber. Cocaine was available Tuesday through Friday during daily 1-hour sessions. Food (100 presentations) was available each Monday to ensure that the animals could still complete the response requirement. Each rat was initially tested with a very low dose of cocaine (i.e., 0.031 mg/kg/infusion). The cocaine dose was then doubled each week so that each rat was tested with 0.031, 0.0625, 0.125, 0.25, 0.5, and 1.0 mg/kg/infusion cocaine, followed by a saline substitution (cocaine extinction).

Plasma corticosterone was significantly reduced in the ADX rats (8.0Å7.8 ng/mL) compared to the SHAM-operated controls (72.4Å13.5 ng/mL) or the ADX rats with corticosterone replacement (40.5Å11.6 ng/mL). There were no differences among the three groups of rats with respect to responding under the food reinforcement schedule. A typical inverted U-shaped dose-response curve for cocaine self-administration was generated by the control rats. However, the ADX rats did not self-administer cocaine at any dose tested. The dose-response curve for the ADX rats with corticosterone replacement (CORT) fell between the curves for rats

from the other two treatment conditions. These data support the results and conclusions obtained in the experiments described earlier and suggest that plasma corticosterone may be necessary for cocaine reinforcement.

The results of the preceding experiments suggest that plasma corticosterone is important for the acquisition of cocaine self-administration in rats. The following experiments were therefore designed to investigate the effects of a reversible pharmacological adrenalectomy on the maintenance of this behavior using metyrapone. Metyrapone blocks the 11 beta-hydroxylation reaction in the production of corticosterone, thereby resulting in decreases in plasma concentrations of the hormone. Adult male Wistar rats were implanted with chronic indwelling jugular catheters as described previously. After at least 4 days' recovery from surgery, the animals were trained to respond under an FR4 schedule of cocaine reinforcement (0.25 mg/kg/infusion) during daily 1-hour sessions. When stable baselines of self-administration were obtained, the animals were pretreated with metyrapone (5, 25, 50, 100, and 150 mg/kg, IP) or vehicle 1 to 4 hours prior to the start of the behavioral session. Metyrapone pretreatment resulted in significant dose-related decreases in both plasma corticosterone (202.1Å9.1 ng/mL, vehicle versus 103Å7.3 ng/mL, metyrapone) and cocaine self-administration, suggesting that cortico-sterone is important for the maintenance as well as the acquisition of cocaine self-administration. Taken together, the data presented here suggest that drug-induced increases in plasma concentrations of stress hormones (e.g., corticosterone) may be involved in the initiation as well as the maintenance of cocaine self-administration. This relationship between stress hormones and reinforcement is not a new concept. The administration of ACTH or its analogs increases alcohol consumption in rats (Krishnan and Maickel 1991; Krishnan et al. 1991; Nash and Maickel 1988), and corticosterone pretreatment facilitates the acquisition of IV amphetamine self-administration in "nonpredisposed" rats (Piazza et al. 1991*a*). IV infusions of ACTH have even been reported to maintain self-administration in some rats (Jouhaneau-Bowers and Le Magnen 1979), while corticosterone has also recently been reported to maintain oral (Deroche et al. 1993) as well as IV (Piazza et al. 1993) self-administration in rats. Glucocorticoid administration has also been reported to result in euphoria and dependence in humans (Dixon and Christy 1980).

Interestingly, the mesocorticolimbic dopaminergic system appears to be involved in some of the neurobiological effects of both cocaine and

stress. The effects of cocaine include an inhibition of DA uptake, most likely mediated through the binding of the drug to a receptor associated with these uptake sites (Kennedy and Hanbauer 1983; Ritz et al. 1987). IV self-administration studies have implicated the mesocorticolimbic, but not the nigrostriatal, dopaminergic system in cocaine reinforcement in rats since DA depletion within brain regions associated with this system attenuate drug intake (Roberts and Koob 1982; Roberts et al. 1980), and since DA levels in the nucleus accumbens measured using in vivo microdialysis increase during self-administration (Pettit and Justice 1989). The drug is also self-administered directly into the medial prefrontal cortex, but not into the nucleus accumbens or VTA (Goeders and Smith 1983), suggesting that this brain region may also be involved in the initiation of cocaine reinforcement. Discrete response-contingent infusions of cocaine decrease DA turnover at the site of self-injection in the medial prefrontal cortex, while increasing the utilization of the neurotransmitter in the nucleus accumbens (Goeders and Smith 1993). In agreement with these data, rats predisposed to self-administer amphetamine (high responders) also have a lower 3,4-dihydroxyphenyl-acetic acid (DOPAC) to DA ratio (i.e., turnover) in the prefrontal cortex and a higher ratio in the nucleus accumbens and ventral striatum than low responders (Piazza et al. 1991*b*). Stressors have also been reported to affect the mesocortical dopaminergic system. Dopaminergic neuronal activity measured in vitro in the prefrontal cortex is selectively activated following electric footshock in rodents (Deutch et al. 1985; Thierry et al. 1976). In vivo microdialysis studies have demonstrated that footshock stress (Abercrombie et al. 1989), as well as more mildly stressful stimuli such as handling and tailpinch (Cenci et al. 1992), increase DA overflow in the medial prefrontal cortex to a much greater degree than in either the nucleus accumbens or striatum. Restraint stress also increases the release of DA in brain regions associated with the mesocorticolimbic system (Imperato et al. 1989). Adrenalectomy attenuates this response, but exogenous injections of corticosterone can reinstate the DA response in ADX rats (Imperato et al. 1989).

Stress hormones also appear to influence DA neurotransmission. Glucocorticoid receptor binding sites have been identified on DA neurons in the VTA (Harfstrand et al. 1986). Chronic corticosterone administration increases dopaminergic activity (Wolkowitz et al. 1986) and alters normal responses to DA receptor agonists (Faunt and Crocker 1988), although the determination of a facilitating or inhibitory role for adrenocortical hormones depends on the specific behavioral test and conditions. Depletion of glucocorticoids by

adrenalectomy decreases both D_1 and D_2 DA receptor binding in the rat brain, and this effect is reversed following glucocorticoid replacement (Biron et al. 1992), suggesting that these hormones are involved in the modulation of central dopaminergic activity. Since stress and cocaine appear to affect similar neurochemical and neuroendocrine processes in rodents, then stress may sensitize the animals to the behavioral effects of cocaine (Kalivas and Duffy 1989), possibly resulting in changes in the reinforcing properties of the drug. Therefore, brain regions associated with the mesocortico-limbic dopaminergic system may be involved in the stress-induced facilitation of cocaine self-administration.

SUMMARY AND FUTURE DIRECTIONS

In summary, the data presented in this chapter have revealed an interesting relationship between stress-induced activation of the HPA axis and cocaine reinforcement. Benzodiazepines are among the most widely prescribed drugs for the pharmacological management of stress and anxiety. Agonists such as chlordiazepoxide and alprazolam specifically reduced cocaine self-administration in rats, possibly by decreasing the reinforcing efficacy of the drug. Self-administered cocaine increased benzodiazepine receptor binding primarily in discrete brain regions associated with the mesocorticolimbic dopaminergic system (i.e., nucleus accumbens and medial prefrontal cortex). Since these same brain regions have also been implicated in cocaine self-administration, the changes in benzodiazepine receptor binding might be directly relevant to cocaine reinforcement. Noncontingent electric footshock stress facilitated the acquisition of IV cocaine self-administration in rats. Footshock, as well as other stressors, also increase dopaminergic activity within the mesocorticolimbic DA system, suggesting that stress may sensitize rats to cocaine reinforcement. In addition, individual drug intake for these rats was correlated with plasma corticosterone measured before exposure to cocaine, indicating that the hormone must increase above a critical threshold for cocaine infusions to maintain self-administration. Adrenalectomy eliminated the acquisition of cocaine self-administration, and this behavior was reinstated with corticosterone replacement. Metyrapone, a corticosterone synthesis inhibitor, also reduced ongoing cocaine self-administration, suggesting that cortico-sterone may be involved in the maintenance as well as the acquisition of IV cocaine self-administration in rats. Future directions for this research might include investigations of the effects of specific corticosteroid receptor agonists and antagonists on IV cocaine self-administration in rats. These experiments would determine if the effects of stress on cocaine self-administration are actually mediated though the binding of stress hormones to corticosteroid receptors. The effects of

agonists and antagonists for both types of corticosteroid receptors (i.e., mineralo-corticoid and glucocorticoid) should be investigated. Cocaine self-administration may be attenuated by blocking the interaction of stress hormones with corticosteroid binding sites using specific receptor antagonists. On the other hand, corticosteroid receptor agonists might shift the dose-response curve for cocaine self-administration to the left.

The data reported here are potentially of great importance not only to the scientific community but to the general population as well. Some people appear to be able to use cocaine "recreationally" without escalating their patterns of use to levels that pose severe health threats, while other individuals are not able to control their drug intake (Siegel 1984). A better understanding of the behavioral and neurobiological variables potentially involved in why some individuals are able to control their cocaine use while others are not is important for the more efficient and effective treatment of cocaine abuse in humans. The data from these experiments suggest that controllability over environmental stress with resultant effects on the HPA axis may be one such variable. If certain individuals are more sensitive to stress, especially if they find themselves in an environment where they do not feel that they have adequate control over this stress, then these individuals may be more likely to use cocaine and other drugs of abuse. This could occur whether the person is an executive in a high-level stress position or a teenager living in a low-income, inner-city environment with no hope of ever advancing. This hypothesis is in agreement with controlled clinical investigations of the relationship between posttraumatic stress disorder (PTSD) and alcohol and drug abuse disorders. Vietnam theater veterans with PTSD experienced more severe drug and alcohol abuse problems than theater veterans without this disorder and were at greater risk for both forms of substance abuse (McFall et al. 1991; McFall et al. 1992). Other investigators have also reported an increased risk of alcoholism in men exhibiting a hyperreactive response to stress (Finn et al. 1992; Sher and Levenson 1982). Therefore, the continued investigation of the behavioral and neuroendocrinological variables involved in why rats without control over experimental stress are more vulnerable to self-administer cocaine may provide a useful model for understanding the behavioral and biological mechanisms involved in the genesis of cocaine use and dependence. In addition, this model might also be used to test pharmacological and behavioral treatments that may be potentially useful for human users of this and other abused substances.

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Behavioral and Biological Factors Associated With Individual Vulnerability to Psychostimulant Abuse

Pier Vincenzo Piazza, Véronique Deroche, Françoise Rougé- Pont, and Michel Le Moal

INDIVIDUAL VULNERABILITY TO ADDICTION

It is common knowledge that enormous individual differences in drug intake exist in humans (de Wit et al. 1986). A large number of people have tried drugs at least once, but for most of them drug use consists in single or few nonrenewed experiences. Among people that persist in taking drugs, drug use can remain an occasional behavior that is limited, for example, to weekends or parties. Finally, only some subjects among drug users develop drug abuse, i.e., a compulsive drug use that becomes the principal goal-directed behavior of the subject (O'Brien et al. 1986). The origin of the peculiar vulnerability to develop drug abuse observed in some individuals is one of the principal questions to be answered about addiction.

Individual differences in the vulnerability to develop a drug habit may be explained using two very different points of view. The first is a drug-centered vision of addiction. It consists in saying that: "Drug abuse is the consequence of the modifications induced in the brain by repeated drug intake. Repeated exposure to the drug, through the development of tolerance, sensitization and conditioning, induces drug dependence, which is the real cause of abuse. In this case vulnerable individuals are the ones who, because of the environment that surrounds them (peer and/or social pressure are the most cited causes), have greater chances to be, and actually are, the most exposed to the drug." The second vision may be considered as an individual-centered theory of addiction. It consists in saying that: "Drug abuse is the consequence of a peculiar, pathological reaction to the drug. In this case vulnerable individuals are the ones who, because of a specific functional state of the biological substrates that interact with the drug, can experience such a peculiar drug effect."

An individual-centered theory of addiction can be developed around two different ideas. First, it could be said that individual vulnerability

to drugs is a drug-specific phenomenon. In this case, drug-vulnerable subjects would differ from drug-resistant ones for drug-induced behaviors, but would not show any other behavioral perturbation. The second point of view would lead to consider vulnerability to drugs as a symptom of a larger behavioral disorder. One idea that may be developed on this line would be, for example, to consider drug abuse as one of the possible behavioral expression of an addictive personality. This would imply that subjects who are vulnerable to drugs may also be vulnerable to develop other addictive behaviors, such as bulimia, sensation-seeking, or pathological gambling. Indeed a certain comorbidity between drug abuse and other addictive behaviors, such as sensation-seeking, has been found in humans (Zuckerman 1984).

Understanding the part played by the drug and the one played by the individual in determining drug abuse is a fundamental step in defining the goals of addiction therapies. If a drug-centered vision can fully explain drug abuse, then addiction should be considered as a neurotoxic disease. In this case the treatment of this condition should be achieved by two combined strategies. The first is to suppress drug availability. The second is to try to reverse the biological effects of repeated drug intake. On the contrary, if drug abuse originates from the interaction of the drug with a peculiar individual substrate, the approach to drug abuse should not differ from that of other behavioral pathologies. In other words also for addiction, it would be necessary to develop a real therapy that counteracts the biological peculiarity that makes some subjects respond in a pathological way to the drug. This disease concept of drug abuse is strengthened even more if it could be proven that compulsive drug intake is a symptom of a larger addiction disorder. In this case, suppression of drug availability would really appear as a poor measure.

AN EXPERIMENTAL APPROACH TO INDIVIDUAL VULNERABILITY TO ADDICTION

The study of the origins of individual vulnerability to drugs needs the fulfillment of two essential experimental conditions. First, all the subjects should have equal access to the drug under identical environmental circumstances. Second, the behavioral and biological features of the subject should be characterized before the exposure to the drug. Only the satisfying of these two conditions will allow evaluation of the weight of exposure to the drug and of preexisting individual differences in determining vulnerability to drug abuse. These experimental requirements are almost impossible to realize in

human studies, but they can be easily achieved by experimental research on animals. Indeed, in stable laboratory conditions, animals self-administer, either intravenously or orally (Pickens and Harris 1968; Schuster and Thompson 1969; Weeks 1962), almost all the drugs abused by humans (Yokel 1987).

Individual Differences in Drug Self-Administration

Individual differences in the propensity to develop drug intake are easily evidenced in the laboratory rat (Deminière et al. 1989). For example, when low doses of psychostimulant drugs are used, and the behavior is studied in the acquisition phase, only some laboratory rats acquire intravenous (IV) self-administration (Piazza et al. 1989, 1990*b*, 1991*b*, 1993*b*). Propensity to develop psychostimulant self-administration not only exists, but can also be predicted by the behavioral reactivity of an individual to stressful situations, such as the exposure to a novel environment (Piazza et al. 1989, 1990*b*, 1991*b*). Indeed, a positive correlation exists between locomotor response to novelty and the amount of amphetamine taken during the first days of testing for IV self-administration.

Individual differences in the propensity to develop drug self-administration can be represented by dividing animals into subgroups on the basis of their locomotor response to novelty (figure 1, top panel) (Piazza et al. 1989, 1990*b*, 1991*b*). The first subgroup, the high responders (HRs), contains all the animals with an activity score above the median of the entire group. The second subgroup, the low responders (LRs), contains all the rats with an activity score below the median of the whole group. When HR and LR animals are tested for IV self-administration of amphetamine (between 10 and 30 g/ inj), HRs will acquire self-administration whereas LRs will not (figure 2, right panel) (Piazza et al. 1989, 1990*b*, 1991*b*). Similar results have been obtained when HRs and LRs are tested for self-administration of cocaine (100 g/ inj) (Piazza et al., unpublished results). Differences in psycho-stimulant self-administration between HRs and LRs do not simply reflect differences in threshold sensitivity to the reinforcing effects of this class of drugs. In fact, during the first days of testing for self-administration, both groups self-administer amphetamine or cocaine at similar rates. However, this behavior rapidly extinguishes in LRs whereas it is stabilized and maintained in HRs (Piazza et al. 1990*b*, 1991*b*, 1993*b*). This result suggests that LRs are not insensitive to the reinforcing effects of the drugs at the dose used, but that psychostimulants have a stronger

reinforcing effect in HRs than in LRs. This hypothesis is supported

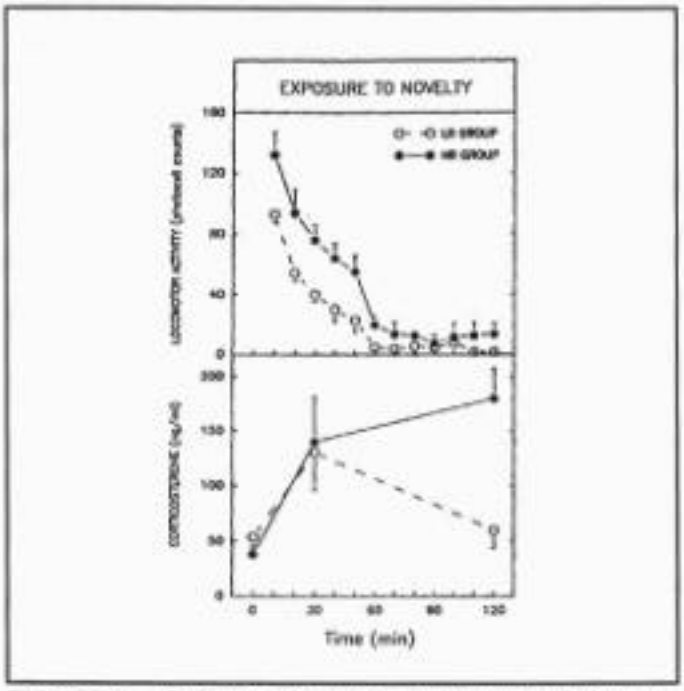

FIGURE 1. *Behavioral (upper) and hormonal (lower) responses to novelty of rats in the HR and LR groups. The two groups differed in total locomotor activity in the novel environment. Plasma corticosterone in the two groups varied differently over time.*

by recent results obtained in the authors' laboratory (Deroche et al., unpublished results) testing cocaine self-administration in HRs and LRs over a large range of doses (1, 0.5, 0.25, 0.125, 0.062, 0.031, and 0.016 mg/kg/inj). When the training dose was 1 mg/kg/inj, both LRs and HRs developed drug self-administration and showed the classical bell-shaped dose-response curve. However, for all the doses tested, the rate of responding was higher in HRs than in LRs. Similar results were found when the dose was maintained constant (1 mg/kg/inj), and the rate of responding was analyzed as a function of the ratio, i.e., the rate was higher in HRs than in LRs over a large number of ratios.

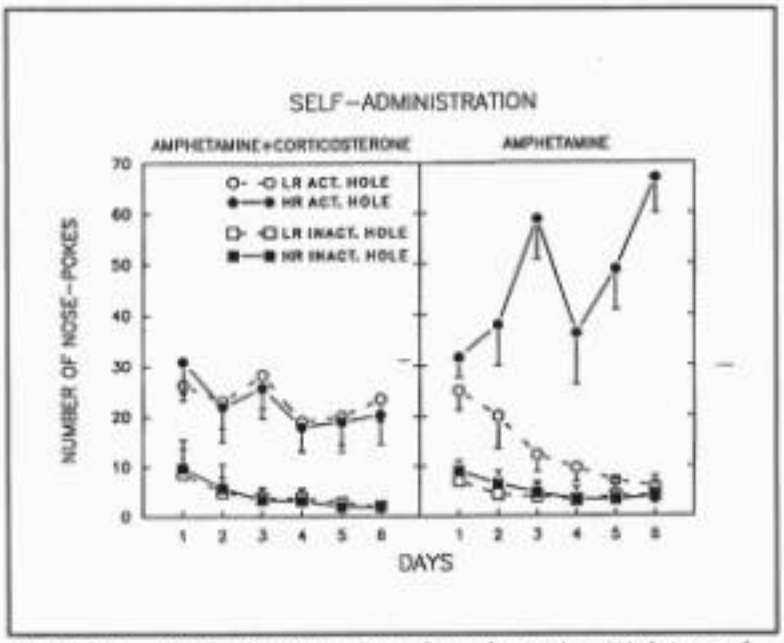

FIGURE 2. *Self-administration of amphetamine (right) or of amphetamine+corticosterone (left) in HR and LR animals. LR animals acquired self-administration of amphetamine when also administered corticosterone but progressively stopped to self-administer amphetamine alone. HR rats self-administered amphetamine in both cases. Self-administration is indicated by a higher number of nosepokes in the hole eliciting drug injections (act. hole) as compared to those in the control hole (inact. hole).*

Individual Differences in Drug-Mediated Behaviors

HR and LR rats also differ for other psychostimulant-induced behaviors. HRs show a higher sensitivity to the psychomotor effects of ampheta-mine and cocaine, displaying a higher locomotor response to systemic and intra-accumbens injection of these drugs (Exner and Clark 1993; Hooks et al. 1991, 1992*a*, 1992*b*, 1992*c;* Piazza et al. 1989, 1991*b*). HRs also seem more sensitive to develop conditioning of the motor effects of amphetamine. For low doses of amphetamine (0.5 mg/kg)

conditioning of amphetamine-induced locomotion was developed by HRs but not by LRs (Jodogne et al. 1994).

HRs and LRs also differ for amphetamine-induced sensitization, though contrasting results have been found on this issue. Some authors have shown that sensitization is exclusively developed by HRs (Hooks et al. 1992*c*), whereas in other laboratories (Exner and Clark 1993; Piazza et al. 1989) sensitization appears prevalently in LRs. In these experiments, after sensitization LRs no longer differed from HRs for amphetamine-induced locomotion and self-administration (Exner and Clark 1993; Piazza et al. 1989). Differences in sensitization of HR and LR animals in different experimental conditions may be explained by uncontrolled differences in the establishment of a stimulus-control of sensitization (Stewart and Badiani 1993). Thus, it has been shown that the expression of sensitization in HRs is under the control of the environmental cues that have been associated with the effect of the drug, whereas sensitization is not under such a control in LRs (Jodogne et al. 1994). In other words, in conditions that facilitate a stimulus-control of sensitization, HRs should show a higher sensitization than LRs, whereas when the influence of conditioning is minimized, sensitization may exclusively appear in LRs.

Individual Differences in Novelty- and Food-Directed Behaviors

HR and LR rats not only differ for drug self-administration, but also for their seeking for novel and stressful situations (Dellu et al. 1993). As said before, HRs show a higher locomotor response to a forced exposure to novelty than LRs. HR animals also show a high preference for novelty when given the choice between a familiar and a novel environment. Furthermore, when the two groups of animals are placed in a novel environment containing two compartments, a closed, dark one and a white, open, illuminated one, HRs explore the illuminated compartment sooner and more extensively than LRs (figure 3). In rodents, the light compartment is considered to be the more stressful situation. These behavioral features of HRs resemble the sensation-seeking traits observed in humans and defined as ". . . the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences" (Zuckerman 1984).

HR and LR rats also differ for their reactivity to other reinforcing stimuli such as food. In particular, HRs show a higher speed of eating than LRs (Piazza et al., unpublished results). Speed of eating was evaluated as the

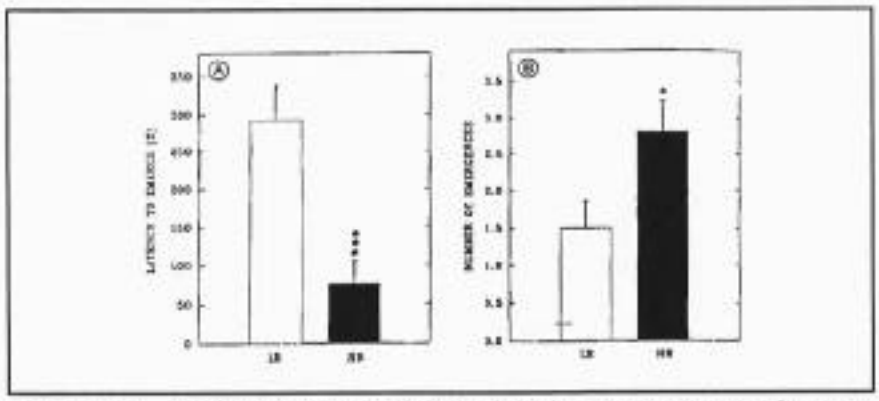

FIGURE 3. *Exploration in the light and dark emergence test. Latency to emerge (A) and number of emergences (B) from the dark compartment to the brightly illuminated one in HR and LR rats. The bars represent means±SEM of the first 5 min of a 10-min session.*** = $p < 0.001$, * = $p < 0.01$.*

time spent by mildly food-restricted rats (90 percent of their body weight) to consume a calibrated pellet (1 g) having a banana flavor (Whishaw et al. 1992). This measure showed large individual differences that were very constant for each individual both within and between sessions. The mean time required to eat one pellet in HRs was around 39.3Å1.6 whereas in LRs the amount of time was 50.4Å2.1 ($p < 0.01$). Higher speed of eating in HRs may be considered as an index of a higher sensitivity to the reinforcing effects of food in HR animals and may also be an index of compulsive behavior.

Higher sensitivity in HRs to food reinforcement is supported by another set of experiments that evaluated the behavioral response of HR and LR rats to the withdrawal of a reinforcing stimulus. Withdrawal of a reinforcer generates a peculiar class of behaviors defined as adjunctive (Falk 1961). These behaviors have the characteristic of not being *regulatory*, in other words, they are dissociate by the original physio-logical goal. Adjunctive behaviors are also characterized by large individual differences in the propensity to develop these behaviors. For example, certain food-restricted rats submitted to an intermittent schedule of food delivery (one 25 mg food pellet every minute) develop, during the interpellet interval, a nonregulatory drinking, and intake, in only 30 minutes, an amount of water that can be the double of the quantity normally drunk in 24 hours (Falk 1961). This behavior-defined, schedule-induced polydipsia (SIP) has been interpreted as an index of the frustration of the subject to the withdrawal of the reinforcement (Falk 1961). HRs have been found to acquire SIP (figure 4) more readily than LRs in the

authors' laboratory (Piazza et al. 1993*b*) and in other laboratories (Hooks et al. 1994).

Differences between HRs and LRs in preparatory behaviors also suggest that food can strengthen behavior more efficiently in HR than in LR rats. Preparatory behaviors are defined as those behaviors that normally precede and lead to consummatory responses (Jones and Robbins 1992). For example, food-restricted rats that are food deprived and are fed each day in a distinct environment develop a conditioned anticipatory locomotor activity. This activity develops after several pairings (around 10) of food presentation with the given environment. Both HRs and LRs developed conditioned locomotor activity, but this behavior appeared more readily and at a higher rate in HRs than in LRs (Hooks et al. 1994).

In conclusion, animal research has shown that vulnerability to develop drug intake may depend on preexisting individual differences. Propensity to develop drug self-administration can vary among individuals having equal access to the drug in identical laboratory conditions and can be predicted by an unconditioned spontaneous behavior, such as a high locomotor reactivity to novelty. Furthermore, vulnerability to develop drug abuse is associated with higher seeking for novel and stressful stimuli, behaviors that resemble those that characterize the sensation-seeking trait in humans. Animals showing a higher sensitivity to the reinforcing effects of psychostimulant also show a higher sensitivity to the reinforcing properties of other reinforcers such as food. These results support an individual-centered theory of addiction and suggest that drug abuse is just one of the possible behavioral expressions of an addictive personality.

FACTORS DETERMINING INDIVIDUAL VULNERABILITY TO ADDICTION

Research on the origins of individual vulnerability to addiction have focused on the specific role played by mesencephalic dopaminergic neurons, stress and glucocorticoids, as well as on the interactions between these three factors. In particular, it has been hypothesized

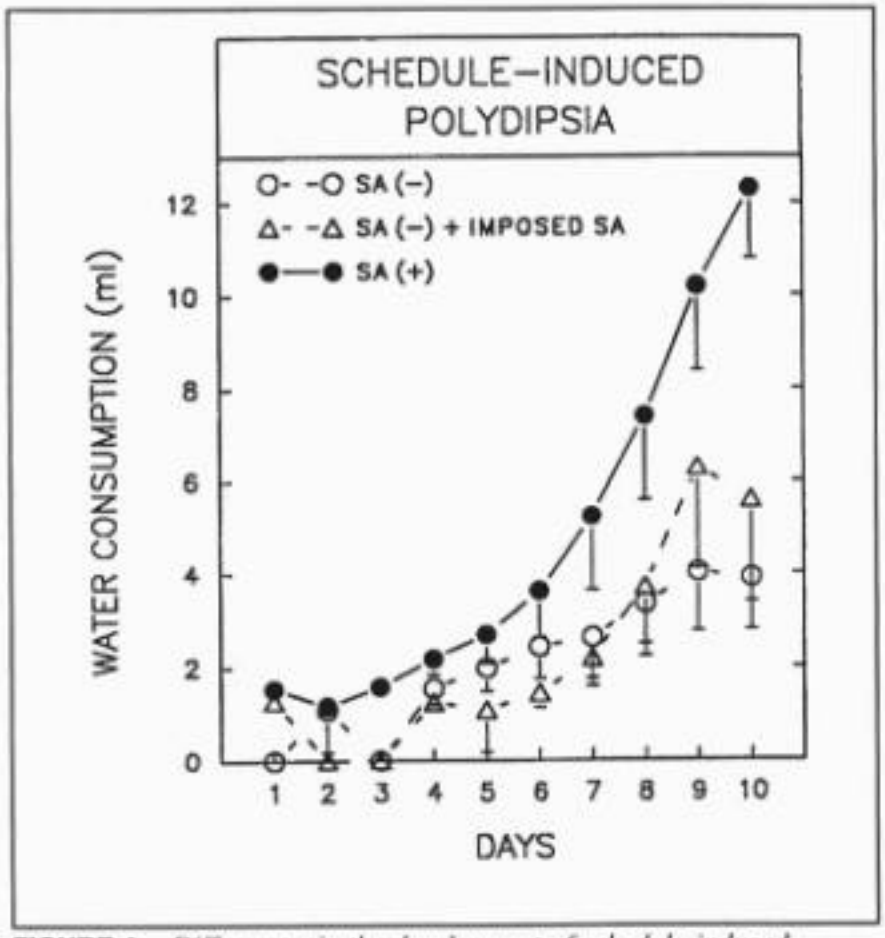

FIGURE 4. *Differences in the development of schedule-induced polydipsia (SIP) between animals predisposed and resistant to develop amphetamine self-administration. SA(+) rats correspond to HRs and SA(-) animals correspond to LRs. Animals have been tested for amphetamine self-administration (10 μg/inj) first and for SIP afterward. Animals that did not develop amphetamine self-administration and that showed a low locomotor response to novelty [SA(-)] did not develop SIP. On the contrary, animals that showed a higher locomotor response to novelty and developed self-administration [SA(+)] also developed SIP. Differences in SIP did not depend on differences in drug exposure since SA(-) rats that received, by means of imposed administrations, the same amount of amphetamine as SA(+) rats did not develop SIP.*

(Piazza et al. 1991*a*) that stress, glucocorticoids, and dopaminergic neurons may be organized in a pathophysiological chain that determines vulnerability to develop addiction. In order to develop this hypothesis, this section will review the relationship that exists between each of these factors and the propensity to develop IV self-administration of psycho-stimulants. Then, in the next section, their possible interactions in a pathophysiological chain will be taken into account.

Dopaminergic Neurons and Vulnerability to Psychostimulants

Mesolimbic dopaminergic neurons, and in particular an increase in the activity of their projection to the nucleus accumbens, may be a crucial factor in determining a higher vulnerability to the reinforcing effects of psychostimulants. Indeed, the reinforcing properties of this class of drugs seem to be mediated by the increased extracellular concentration of dopamine in the nucleus accumbens that they induce (Koob and Bloom 1988; Le Moal and Simon 1991). First, specific neurochemical lesions of the dopaminergic projection to the nucleus accumbens decrease or extinguish, depending on the dose of drug, IV self- administration of psychostimulants (Roberts and Koob 1982; Roberts et al. 1977, 1980). Second, animals will self-administer psychostimulants directly into the nucleus accumbens (Hoebel et al. 1983). Third, specific agonists or antagonists of dopaminergic receptors may respectively increase or decrease the reinforcing properties of psychostimulants (Davis and Smith 1977; Risner and Jones 1976; Roberts and Vickers 1984, 1987). In this respect 7-OH-DPAT, a dopaminergic agonist showing the highest affinity for D_3 dopaminergic receptors, is more potent than agonists with a higher affinity for D_1 or D_2 dopaminergic receptors (Caine and Koob 1993). D_3 receptors are prevalently localized in the nucleus accumbens, whereas D_1 and D_2 receptors have a widespread distribution throughout the brain (Sokoloff et al. 1990).

Individual differences studies support the idea that a higher vulnerability to develop drug self-administration is associated with a higher dopaminergic activity in the nucleus accumbens. Postmortem investigations have shown that animals vulnerable to develop IV self-administration of psychostimulants (HRs) have a higher DOPAC/DA ratio in the nucleus accumbens compared to more resistant subjects (LRs). The DOPAC/DA ratio, which is considered an indirect index of the release of dopamine, is higher in HRs than in LRs both in basal conditions and after exposure to novelty (Piazza et al. 1991*c*). Microdialysis studies have confirmed and extended these results.

Quantitative microdialysis has shown that, in basal conditions, extracellular concentrations of dopamine in HR rats are three times higher than those observed in LRs (Hooks et al. 1992). Furthermore, the percentage increase in extracellular concentrations of dopamine in response to stress (figure 5) (Rougé-Pont et al. 1993) or to the intraperitoneal administration of cocaine (Hooks et al. 1991) is also higher in HRs than in LRs.

A higher dopaminergic activity in the nucleus accumbens is not simply associated with a higher propensity to develop amphetamine self-administration; a causal relationship seems also to exist between these two variables. Very different experimental manipulations, such as
6-OHDA lesion of the amygdala (Deminière et al. 1988) or electrolytic lesion of the raphe (Simon et al. 1980), which have the common property to increase dopaminergic activity in the nucleus accumbens (Hervé et al. 1981; Simon et al. 1988), also increase propensity to acquire amphetamine self-administration.

In conclusion, results obtained with multiple approaches converge in suggesting that a higher dopaminergic activity in the nucleus accumbens may be a condition increasing the vulnerability of an individual to develop psychostimulant self-administration.

Stress and Vulnerability to Psychostimulants

Stressful situations largely interact with the activity of mesencephalic dopaminergic neurons. Two main interactions between stress and dopamine can be singled out. First, following the pioneer work of Thierry and coworkers (1976), it is now widely accepted that acute exposure to most of the situations that are considered experimental models of stress increases the activity of mesencephalic dopaminergic neurons. Second, repeated exposure to stress induces a long-term sensitization of the response of mesencephalic dopaminergic neurons to subsequent activation, and in particular a sensitization of their response to drugs of abuse (Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993).

An increase in vulnerability to psychostimulants can be induced by several conditions considered as models of stress. The first report that points out the strong control that stressors exercise on psychostimulant self-administration is probably the one of Carroll and coworkers,

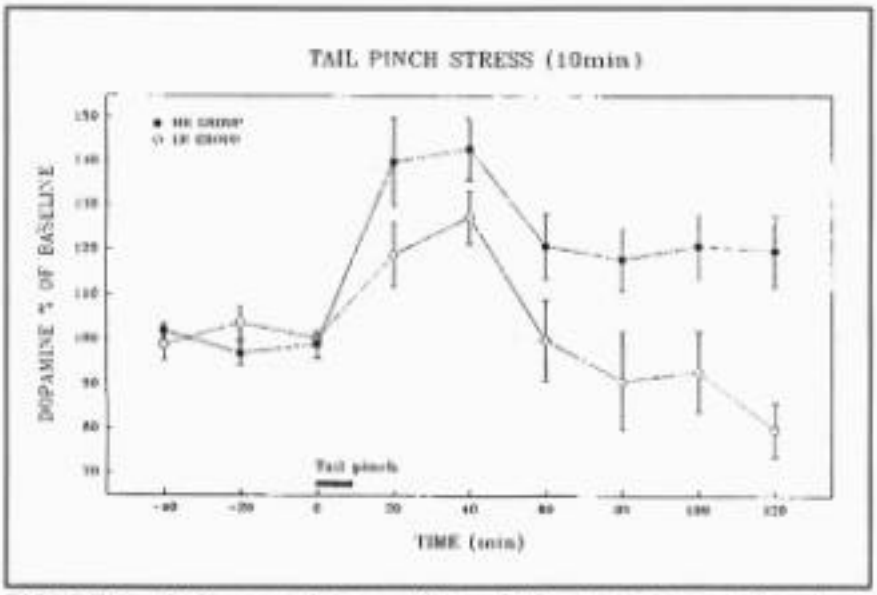

FIGURE 5. *Differences between HR and LR rats in stress-induced increase in extracellular concentrations of dopamine in the nucleus accumbens. Tail-pinch (10 min) was used as stressor. HR rats showed a higher and longer increase in extracellular concentrations of dopamine in response to stress than LRs.*

showing that food restriction increases the efficacy of psychostimulants to act as reinforcers in a self-administration test (Carroll et al. 1979). Subsequent research has shown that a large variety of stressful conditions, occurring during adult life, can increase propensity to self-administer drugs in rodents. For example, a faster acquisition of psychostimulant self-administration has been found in rats submitted to situations that seem relevant from an ethological point of view, such as: (1) social isolation (Deroche et al. 1994; Schenk et al. 1987); (2) social aggression (Haney et al., unpublished results; Miczek et al. 1994); and (3) fixed social hierarchy in high competition colonies (Maccari et al. 1991). Furthermore, more artificial and physical stressors, such as tail-pinch (Piazza et al. 1990*a*) or electric footshock (Goeders and Guerin 1994) also increase propensity to develop psychostimulant self-administration.

Very early experiences, such as prenatal stress, can also increase vulnerability to psychostimulants (Deminière et al. 1992). An increase in the propensity to develop amphetamine self-administration (figure 6, right panel) has been observed in adult rats (4 months old) whose mothers had been submitted to a restraint procedure (half an hour twice a day) during the third and fourth week

of gestation. Prenatal stress not only increases amphetamine self-administration but also the unconditioned behaviors that characterize spontaneously vulnerable subjects. Similarly to the comparison between HRs and LRs, prenatally stressed rats show a higher locomotor response to novelty and amphetamine (figure 6, left panel) as compared to controls (Deminière et al. 1992).

In conclusion, results obtained with multiple approaches converge in suggesting that stressful experiences, very early in life or during adulthood, may be a condition that increases the vulnerability of an individual to develop drug self-administration.

Glucocorticoids and Vulnerability to Psychostimulants

Several observations suggest that glucocorticoids may be one of the factors that mediate vulnerability to addiction. First, glucocorticoid secretion by the adrenal gland is one of the principal biological responses to stress (Selye 1950), and an increase in corticosterone secretion is observed in all those situations that increase the activity of dopaminergic neurons (Bohus et al. 1982; Dantzer and Mormède 1983; Knych and Eisenberg 1979; Sachser 1986). Second, mesencephalic dopaminergic neurons contain corticosteroid receptors (Härfstrand et al. 1986), and glucocorticoids can modify the metabolic activity of aminergic neurons (Rothschild et al. 1985). Third, suppression of corticosterone secretion suppresses dopamine-dependent behaviors, such as schedule-induced polydipsia (Levine and Levine 1989) or wheel running (Lin et al. 1988). Corticosterone, the main glucocorticoid in the rat, seems to be strictly related to individual vulnerability to psychostimulants. As will be analyzed in the next paragraphs: (I) individual differences in cortico-sterone levels are correlated with propensity to develop drug intake (Piazza et al. 1991*b*); (ii) this hormone increases sensitivity to the psychomotor and reinforcing effects of psychostimulants (Marinelli et al. 1994; Piazza et al. 1991*b*); and (iii) corticosterone has proper interactions with reward processes since it can act as a positive reinforcer (Deroche et al. 1993*b*; Piazza et al. 1993*a*).

Individual differences in stress-induced corticosterone secretion are correlated with drug intake during amphetamine self-administration.

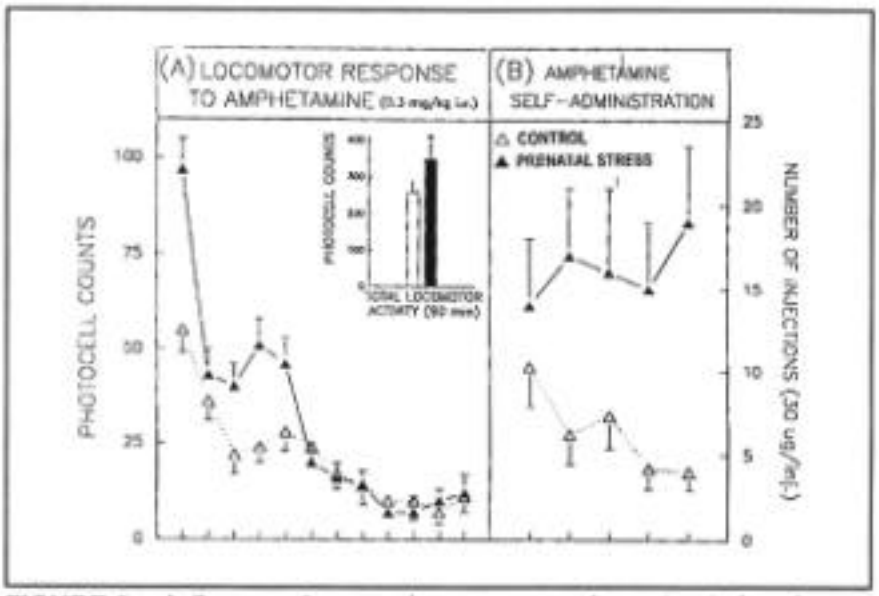

FIGURE 6. *Influence of prenatal stress on amphetamine-induced locomotion (0.3 mg/kg IV) (A) and self-administration (30 µg/inj) (B). Prenatal stress significantly increased both the locomotor response to an IV injection of amphetamine and the intake of this drug over the 5 days of testing for self-administration.*

A positive correlation exists between corticosterone levels after 2 hours of exposure to stress and the intake of amphetamine over the first days of testing in self-administration (Piazza et al. 1991*b*), though no correlation has been found between drug intake and basal diurnal level of cortico-sterone or corticosterone levels 30 minutes after stress. The relationship between corticosterone levels and vulnerability to drugs is exemplified by the comparison of HR and LR rats (figure 1, bottom panel). In response to the exposure to a novel environment, HRs show a longer stress-induced corticosterone secretion than LRs. Differences in corticosterone secretion between HR and LR animals do not depend on their difference in novelty-induced locomotion, instead the opposite seems to be true. First, HR and LR rats still differ in stress-induced corticosterone secretion when the stress used (restraint) prevented the expression of locomotion. Second, suppression of individual differences in stress-induced corticosterone secretion, by fixing corticosterone levels in the range of basal diurnal levels, induces a decrease in the locomotor response to novelty of HRs that no longer differ from LRs (Piazza et al., unpublished results).

Psychomotor effects of cocaine depends on basal corticosterone secretion. Suppression of endogenous glucocorticoids by adrenalectomy reduces of around 50 percent the locomotor response to cocaine, and a cortico-sterone replacement treatment, which reinstates diurnal basal levels of the hormone, totally suppresses the effects of adrenalectomy (Marinelli et al. 1994). Suppression of glucocorticoid secretion similarly reduces the locomotor response to an intra-accumbens injection of cocaine (figure 7) (Marinelli et al. 1994). This result indicates that modulation of sensitivity to cocaine by glucocorticoids involves changes of the mesencephalic dopaminergic transmission in reactivity to the drug. Thus, the locomotor response to the intra-accumbens injection of psychostimulants depends on dopamine (Delfs et al. 1990; Kelly and Iversen 1976).

Reinforcing effects of psychostimulants are also increased by cortico-sterone. Administration of corticosterone induces the acquisition and maintenance of amphetamine self-administration in LR rats, which do not acquire this behavior otherwise (figure 2, left panel) (Piazza et al. 1991*b*). Furthermore, in HR rats, 8 days of treatment with the inhibitor of corticosterone synthesis metyrapone, reduces of about 50 percent the intake of cocaine during a test for relapse (figure 8) (Piazza et al. 1994). More precisely, for this study animals were left to acquire and stabilize cocaine self-administration (100 g/ inj) for 10 days. They were then submitted to a drug-free period of 4 days followed by 8 days of metyrapone treatment (100 mg/kg twice a day). After this period (12 days of cocaine withdrawal of which the last 8 under metyrapone) the testing for relapse started. Animals again had access to cocaine for 5 days and the metyrapone treatment was continued. Metyrapone treatment seemed devoid of major nonspecific motor effects, because it did not modify exploratory and food-directed behaviors (Piazza et al. 1994).

Reinforcing effects of corticosterone have been evidenced using IV self-administration (Piazza et al. 1993*a*). Naive rats tested for corticosterone self-administration will self-administer the hormone (figure 9) showing a dose response curve that resembles that of other reinforcing drugs. Thus, a decrease in the number of injections per session is obtained by increasing the dose per infusion. This is considered to be the animal's attempt to obtain an optimal level of reinforcement. The doses of

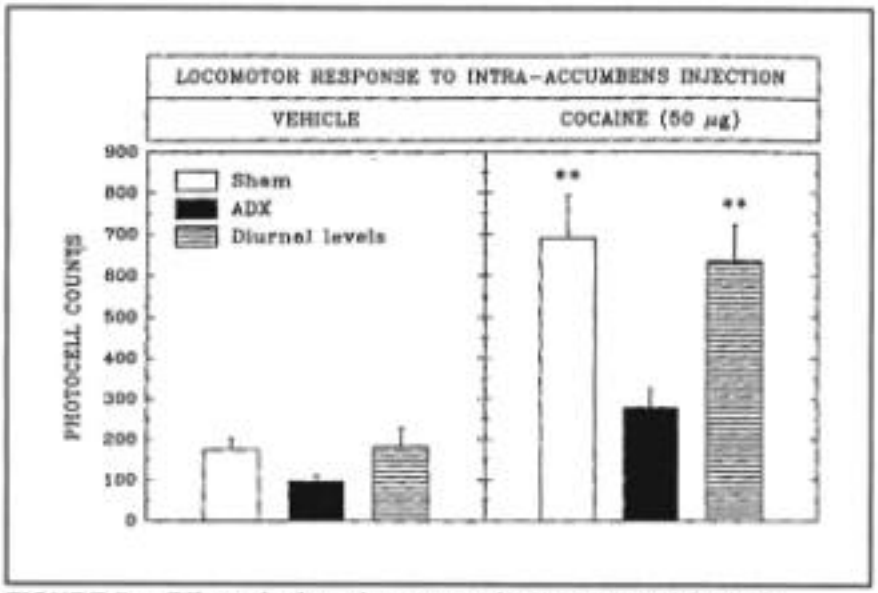

FIGURE 7. *Effect of adrenalectomy and restoration of diurnal corticosterone levels on the locomotor response to intra-accumbens vehicle and cocaine. Groups did not differ in the locomotor response to vehicle. Suppression of corticosterone levels by adrenalectomy (ADX group) reduced the locomotor response to cocaine and the reinstatement of basal diurnal levels of corticosterone reversed this effect. Thus, ADX animals exhibited lower activity scores than both sham (** $p < 0.01$) and diurnal levels (** $p < 0.01$) groups, and the latter two groups did not differ.*

corticosterone that the animals try to maintain constant correspond to plasma levels of corticosterone that are comparable to those induced by stress (around 40 g/100 mL). Positive reinforcing effects could thus be part of the physiological role of corticosterone secretion during stress. Individual differences for self-administration of corticosterone are also observed. HRs rats are four time more sensitive to the reinforcing effects of corticosterone than are the LRs (Piazza et al. 1993*a*).

In conclusion, results obtained with multiple approaches converge in suggesting that an increase in corticosterone secretion may be a condition increasing the vulnerability of an individual to psychostimulant drugs. Furthermore, this hormone not only interacts with the reinforcing properties of other stimuli but also has proper positive reinforcing

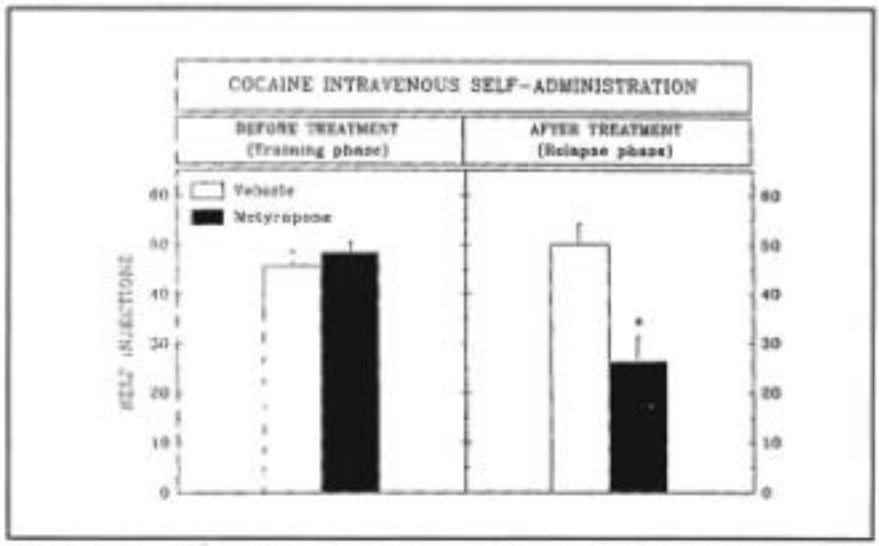

FIGURE 8. *Effect of metyrapone on cocaine self-administration. Bars represent the mean±SEM of the number of injections over the last 5 days of testing in the training phase and the first 5 days of testing in the relapse phase. The two phases were separated by 5 days of acute withdrawal and 8 days of metyrapone treatment (100 mg/kg SC twice a day). Animals in the control (N = 6) and metyrapone (N = 5) group did not differ for cocaine intake before treatment (training phase). In contrast, after treatment (relapse phase) cocaine intake was significantly reduced in animals receiving metyrapone. During the relapse phase the metyrapone treatment was continued.*

effects. These results throw light on the possible role of stress-induced corticosterone secretion in adaptation. Glucocorticoids are thought to prevent an overreaction of physiological mechanisms designed to protect the organism from the effects of stressors. This protective role of glucocorticoids in adaptation to stress is generally attributed to the peripheral action of the hormones and the central effects are rather overlooked. The positive reinforcing effects of glucocorticoids could extend the protection to the central nervous system, helping the individual to defend himself from the highly aversive effects of stress, thereby enabling him to better cope with the stress. However, a particularly high sensitivity to the reinforcing effects of corticosterone, such as that shown by HRs, may have adaptive side effects. Higher

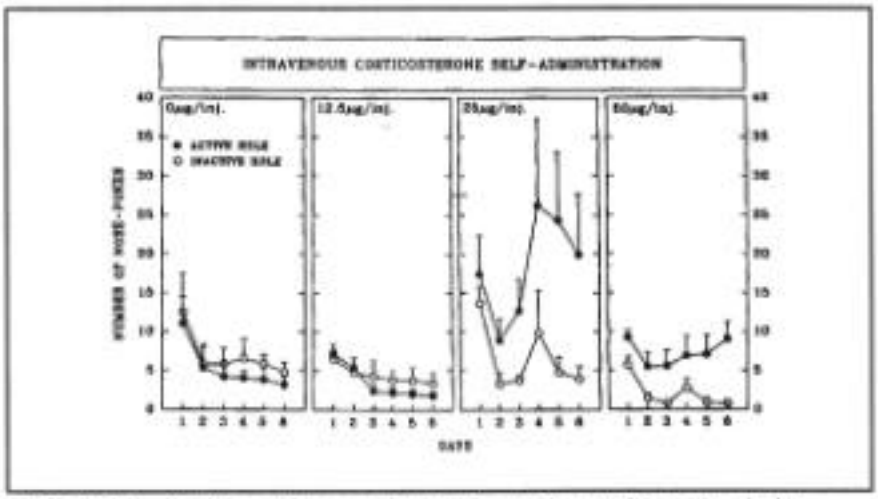

FIGURE 9. *Number of nosepokes in the active and inactive holes during 6 days of testing for corticosterone IV self-administration. Corticosterone-induced self-administration at doses of 25 and 50 µg/inj is indicated by the higher number of nosepokes in the hole eliciting corticosterone injections (active) compared to the control hole (inactive).*

sensitivity to corticosterone may underlie the propensity to seek novel and intense experiences, as well as the higher predisposition to drug abuse shown by individuals with sensation-seeking personality traits.

INTERACTIONS BETWEEN STRESS, CORTICOSTERONE, AND DOPAMINE IN DETERMINING INDIVIDUAL VULNERABILITY TO PSYCHOSTIMULANTS

The data outlined in the previous paragraphs show that stress, cortico-sterone, and dopaminergic activity by themselves can influence the propensity of an individual to develop psychostimulant self-administration. It will be now analyzed if these three factors can be organized in a pathophysiological chain determining vulnerability to addiction. For this purpose, the authors will take into account, step by step, the possible dependence of the effects of one factor upon the activation of the others. More precisely, the first paragraph will analyze if stress-induced sensitization of drug effects depends on stress-induced corticosterone secretion; the second paragraph will analyze if an increase in corticosterone levels can increase the activity of mesencephalic dopaminergic neurons; and the third and

last paragraph will take into account the role played by stress-induced corticosterone secretion on the dopaminergic effects of stress.

Stress, Corticosterone, and Vulnerability to Psychostimulants

Stress-induced sensitization of the behavioral effects of psychostimulants depends on corticosterone. Three lines of observations support this statement. First, blockade of stress-induced corticosterone secretion totally suppresses the increase in the locomotor response to amphetamine induced by different stressful experiences, such as repeated restraint (Deroche et al. 1992*a*) or food restriction (Deroche et al. 1993*a*). Second, repeated injections of corticosterone, at doses that raise the levels of the hormone in the range of those produced by stress, induce sensitization of the locomotor response to amphetamine (Deroche et al. 1992*b*). Third, animals made vulnerable to drugs by previous stressful experiences present an enhanced corticosterone secretion. For example, rats submitted to prenatal stress (Maccari et al. 1995), repeated tail-pinch (Piazza et al. 1991*b*), social aggression (Haney et al., unpublished results; Miczek et al. 1994), or fixed social hierarchy (Maccari et al. 1991), show both a higher propensity to develop amphetamine self-administration and a longer stress-induced corticosterone secretion.

In conclusion, these observations suggest that stress-induced corticosterone secretion may be one of the hormonal mechanisms by which stressful experiences enhance vulnerability to drugs.

Corticosterone and Dopamine

The existence of a pathophysiological chain made by stress, corticosterone, and dopamine implies that glucocorticoids can control the activity of mesencephalic dopaminergic neurons. A set of results recently obtained in the authors' laboratory suggest that glucocorticoids have state-dependent effects on the activity of dopaminergic neurons (Piazza et al., in press). The administration of corticosterone, at doses that induce an increase in the levels of the hormone similar to those induced by stress, increases extracellular levels of dopamine in the nucleus accumbens, but only when the hormone is administered in the dark phase (around 20 percent increase), which corresponds to the period of activity in rodents. Administration of corticosterone during the light period is without effects. Furthermore, in the dark period, the effects of corticosterone on dopamine are higher when the hormone is administered contingently to eating (around 80 percent increase) than when it is

administered in basal conditions. State-dependent effects of glucocorticoids on dopamine are in agreement with previous literature data. First, the effect of corticosterone on membrane potentials is dependent on background neuronal activity (Joels and De Kloet 1992). Second, behavioral effects of glucocorticoids can be different in different periods of the circadian cycle (Kumar and Leibowitz 1988; Temple and Leibowitz 1989), being higher during the dark phase as compared to the light one.

Individual differences also exist in the dopaminergic effects of cortico-sterone. Similarly to what is observed for the reinforcing effects of corticosterone (Piazza et al. 1993*a*), HR animals are more sensitive than LRs to the dopaminergic effects of this hormone. Thus, in response to the administration of the same dose of corticosterone, HRs show an increase in extracellular concentrations of dopamine in the nucleus accumbens that is double the one of LRs. The higher sensitivity to the dopaminergic effects of corticosterone may be the neurobiological substrate of the higher sensitivity to the reinforcing effects of corticosterone observed in HRs.

In conclusion, corticosterone can stimulate the activity of mesencephalic dopaminergic neurons, and these effects are higher in animals that are vulnerable to develop psychostimulant and corticosterone self-administration. This interaction between corticosterone and dopamine is compatible with the hypothesis that these two factors may interact in determining vulnerability to addiction.

Stress, Corticosterone, and Dopamine

In the previous paragraph it has been shown that stress-induced increase in vulnerability to drugs could be mediated by an increase in the activity of dopaminergic neurons and depend on stress-induced corticosterone secretion. This hormone, in turn, can stimulate the activity of the mesencephalic dopaminergic transmission. In order to complete the picture of the interactions between stress, corticosterone, and dopamine, the dependence of the dopaminergic effects of stress on corticosterone should be analyzed.

The dopaminergic response to stress is decreased in subjects in which stress-induced corticosterone secretion is suppressed (Rougé-Pont et al., unpublished results). The increase in extracellular concentrations of dopamine in the nucleus accumbens induced by 10 minutes of tail-pinch is lower in subjects in which corticosterone levels have been

fixed in the range of basal ones by an adrenalectomy associated with a corticosterone pellet implantation (ADX+pellet). Such corticosterone pellets release a stable amount of corticosterone in the range of basal physiological levels (Meyer et al. 1979). In contrast, stress-induced increase in accumbens dopamine is similar to the one of controls if ADX+pellet rats receive, concomitantly with the stress, an intraperitoneal injection of cortico-sterone (3 mg/kg). The injection of corticosterone at this dose raises the levels of the hormone in the range of those observed during stress (Rougé-Pont et al., unpublished results).

Stress-induced corticosterone secretion has different effects on the dopaminergic response to stress of HR and LR rats (Piazza et al., in press). Thus, blockade of stress-induced corticosterone secretion does not modify the dopaminergic response to stress in animals resistant to develop psychostimulant self-administration (LRs). In contrast, the enhanced dopaminergic response to stress that characterizes vulnerable subjects (HRs) is suppressed by blockade of stress-induced cortico-sterone secretion. In other words, after an adrenalectomy associated with an implantation of a corticosterone pellet, HR rats show an identical dopaminergic response to stress as that of LRs that, in turn, are not modified by this manipulation of corticosterone secretion.

In conclusion, stress-induced corticosterone secretion may be one of the biological mechanisms by which life experiences increase the activity of dopaminergic neurons. This last observation supports the hypothesis that stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to addiction.

CONCLUSIONS

The results that have been outlined in the previous paragraphs offer two principal considerations: First, the development of psychostimulant abuse does not seem to be the simple consequence of the proper effects of these substances, but rather the result of their interaction with specific individual substrates. Differences in the propensity to develop psychostimulant intake can be evidenced in animals that have equal access to the drug in stable laboratory conditions. Such individual differences do not arise from uncontrolled experimental errors, since they can be predicted by unconditioned spontaneous behaviors. Furthermore, in animals, vulnerability to take

drugs is associated with a higher propensity to seek other reinforcing stimuli such as novelty or food. The latter results suggest that drug abuse may be the symptom of a more general behavioral disorder, which underlies different addictive behaviors. Second, stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to addiction. More precisely, an increased corticosterone secretion, spontaneously present in certain individuals or induced by stress in others could, by increasing the activity of mesencephalic dopaminergic neurons, determine a predisposed state that enhances the probability that the encounter with rewarding or novel stimuli can result in their abuse. The possibility to modulate the behavioral and dopaminergic responses to psychostimulants by pharmacological manipulations of corticosterone secretion, suggests that manipulations of this endocrine system may constitute the ground for new therapeutic strategies of drug abuse.

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Addictive Behavior With and Without Pharmacologic Action: Critical Role of Stimulus Control

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INTRODUCTION

Addictive behavior with respect to drugs often is viewed as the consequence of a biologic action that has its principal origin in the exposure of a subject to the central nervous action of a drug. One objective of this chapter is to refer briefly to evidence that drug abuse is a special case of excessive behavior that typically develops out of, and is sustained by, an antecedent context that can generate a variety of disturbed and excessive sorts of behavior. Drug abuse is often only one feature of this broader picture of behavioral difficulties displayed by an afflicted individual. Conversely then, by this view drug addiction has its major origins and maintaining conditions in environmental antecedents, rather than being the result of specific drug receptor interactive consequences.

A second, more specific aim is to describe a few experiments that begin to clarify how discriminative stimuli (S^Ds) accompanying the occurrence of excessive behavior with respect to one commodity can lead to the persistent selection of an alternative commodity (e.g., a drug) when such S^Ds are presented in proximity to this second commodity, even in the presence of both commodities.

In previous research, several species of animals have been exposed to intermittent schedules of food pellet delivery, resulting in the induction of concurrent, excessive behaviors (Falk 1971, 1981). Although various, noningestive behavioral excesses have been explored (e.g., aggression, escape, hyperactivity), an ingestive alternative, schedule-induced drug intake, has proven useful in evoking chronic, excessive drug-solution drinking, as well as facilitating otherwise weak intravenous (IV) self-injection behavior (Falk 1993; Falk and Tang 1988). In the present experiments, schedule-induced polydipsia was used to provoke chronic and excessive fluid intake upon which drug overindulgence could develop. In a common arrangement used in the author s laboratory, food pellets are delivered to a deprived rat once per minute during daily, 3-hour sessions, which results in a concurrent overdrinking: a polydipsia of about 100 mL. This is in contrast to the regulatory drinking over 3-hours occasioned by the same number of pellets when they are presented all at once at the beginning of the period: about 10 mL. Schedule-induced

polydipsia is, then, a behavioral, not a physiologic, phenomenon (Falk 1969).

In the IV drug self-administration arrangements used in many animal experiments, the baseline IV saline (vehicle) self-injection rate usually is quite low compared to rates occasioned by substituting drugs with reinforcing potential (Johanson and Balster 1978; Schuster and Thompson 1969). In contrast, the schedule-induced oral intake of water (vehicle) is already excessive. Any additional reinforcing effect afforded by the introduction of a drug into the drinking fluid must be detected against this background of behavior that has *already become excessive* owing to the inducing environmental conditions. An assumption underlying the use of this preparation as an arrangement that illuminates the source and persistence of drug abuse is that, owing to an individual s history and current environment, excessive behavior is likely to be occurring prior to the initiation of an abusive interaction with one or more drugs (Kandel et al. 1985; Tarter, this volume). The conspicuous excessiveness of baseline behavior prior to the introduction of a drug presents an analytic challenge. It is necessary to distinguish between the reinforcing efficacy afforded by the inducing environment and the reinforcing efficacy that might derive from the action of an introduced drug. Although the necessity of making this distinction usually does not occur with the use of the IV drug self-injection procedure, nevertheless, when either an intermittent food or a drug self-injection schedule was available to rhesus monkeys, concurrent, adjunctive IV saline self-injection was persistently maintained (Grant and Johanson 1989; Nader and Woolverton 1992). With oral drug self-administration by rats, various methods have been used to determine whether the availability of a drug solution adds a unique controlling feature to behavior that is already present in excess (Falk 1993).

One obvious arrangement was to allow animals to choose between two concurrently presented fluids under a chronic schedule-induction condition: a vehicle and a drug solution, with the relative left-right positions of the fluid reservoirs alternated or randomized across days. Rats overwhelmingly chose the 5 percent ethanol solution in preference either to water or to dilute glucose solutions (Samson and Falk 1974; Tang and Falk 1977). However, under similar conditions, when animals had cocaine solution and water concurrently available, drinking occurred mainly from the fluid presented at a specific location, a so-called side preference (Falk et al. 1990). Although cocaine concentration was systematically varied, there was no evidence of the development of a preference for the drug. Even though cocaine polydipsia occurred every other day, when cocaine was presented on the preferred side, and elevated serum cocaine concentrations of about 200 ng/mL

resulted, preference failed to develop. Only after cocaine had been available in a compound saccharin-glucose (sac-gl) vehicle, and the vehicle was subsequently slowly changed back to water, was there some evidence for the development of a preference for cocaine.

At this point the issue of whether there may be more involved in the genesis of drug addiction than simply bringing a subject into continued, self-administration contact with an agent possessing a potential for abuse. Although drug solutions have easily discriminable, gustatory effects, additional S^Ds might be required to develop drug preference owing to the generally slower pharmacokinetics of orally self-administered drugs. The success of the ethanol preference experiments may be atypical, since the preference for low concentrations of ethanol to water under a variety of conditions has a gustatory, rather than a pharmacological, explanation. Meisch and his associates (Meisch et al. 1990) were able to transform the preference of rhesus monkeys for an ethanol solution into a preference for cocaine solutions by gradually reducing the ethanol concentration of the solution while increasing the concentration of cocaine, with the position of the drug-solution alternative indicated by a distinctive S^D light. In addition, fluids were made available only contingent upon fixed-ratio (FR) behavior. The following experiment used rats and the schedule-induced polydipsia technique, but incorporated three of the features used by Meisch and colleagues (1990): ethanol preference history, cocaine solution position indicated by an S^D light, and fluid available contingent upon operant responding.

STIMULUS CONTROL AND THE ACQUISITION OF DRUG PREFERENCE

When rats were allowed a history of preferring an ethanol solution to concurrently available water under a schedule-induced polydipsia condition, drug preference was maintained when the solution was gradually changed from ethanol to cocaine (Falk and Lau 1993). In this situation, the animals were given daily 3-hour sessions: concurrent fixed-interval (FI) 1 minute (food), FR6 (water), and FR6 (drug solution). The daily position at which the drug solution was available varied, and its location was indicated by the adjacent presence of a small S^D light. An overwhelming preference for cocaine solution was maintained as was the excessive intake level. Subsequently, caffeine solution was gradually substituted for cocaine solution, and then nicotine solution for caffeine solution. In each case there was a virtually complete preference for the drug solution to water (figure 1). A return to an ethanol preference condition was followed by the gradual substitution of lidocaine solution for ethanol. Lidocaine solution

also was preferred to water (figure 1). Although ethanol, cocaine, caffeine, and nicotine are all known to function as reinforcers, lidocaine has not so functioned, nor is it known to be abused. Except for the initial preference for ethanol solution to water, the likely explanation of the other preferences for drug to water is that they were attributable to the associative history of the S^D with the ethanol solution. After this association, animals continued to choose and ingest the fluid indicated by the S^D, even when that fluid was lidocaine solution. Even more dramatically, in a later stage of the experiment, when the S^D simply indicated an alternative source of water rather than a drug solution, these animals had an almost complete preference for the S^D-indicated source of water compared to the alternative source of water (not shown in figure 1).

PERSISTENCE OF STIMULUS CONTROL OF PREFERENCE WITH AND WITHOUT PHARMACOLOGICAL CONSEQUENCES

The efficacy and durability the S^D had in initiating and continuing to determine the polydipsic choice of several drugs suggested that environmental S^Ds are critical for the development and maintenance of drug abuse. The next experiment was designed to ascertain several features of the S^D control of excessive intakes: (1) the durability of the S^D control of intake when drug content was discontinued, (2) the ability of gustatory properties of a drug solution to serve an S^D function, and (3)-determination of whether a gradual transformation of one S^D controlling condition into another one is a necessary feature in effecting a transfer of how the environment evokes the seeking and taking of drugs, or whether an abrupt S^D change also would permit transfer of control.

Rats from four groups (N = 8 each group) were exposed to a fixed-time (FT) 1-minute food-delivery schedule (FT 1 min) for 3-hour sessions, with one or two sources of fluid freely available (Falk and Lau 1995). For 3 to 4 weeks, a single fluid, 2.5 percent ethanol, was available during the session and was presented at a position to the left or the right of the center position on one panel of a chamber. Drug solution position always was indicated by illuminating an S^D light next to the drinking spout. The FT 1-minute schedule induced a concurrent polydipsia during each session. Two fluids were made available during sessions for the next 2 weeks, 2.5 percent ethanol and water, with the same drug positioning and S^D procedure remaining in effect. Following the establishment of chronic ethanol polydipsia and preference, the composition of the drug solution was altered. Over a 1-month period, its ethanol content was gradually reduced to zero while cocaine concentration was increased to 0.16 mg/mL. This final

cocaine concentration, unadulterated with ethanol, was presented for 16 sessions. The first group of eight rats is shown in figure 2 (top). The leftmost bar shows that 2.5 percent ethanol was preferred to water almost exclusively. The second bar shows the results for the 16-session period for which 0.16 mg/mL cocaine solution and water were concurrently available for ingestion. Cocaine solution was preferred to water almost exclusively. The preference for ethanol to water, and for cocaine solution to water, are features of the remaining groups (figures 2 and 3), which show the results for the other groups. Cocaine milligram per kilogram intakes were similar across the groups and agree with values from the author s previous research presenting this concentration (Falk and Tang 1989; Falk et al. 1990).

After this preference for cocaine solution to water had been maintained for 16 sessions, the groups were then given different treatments, although

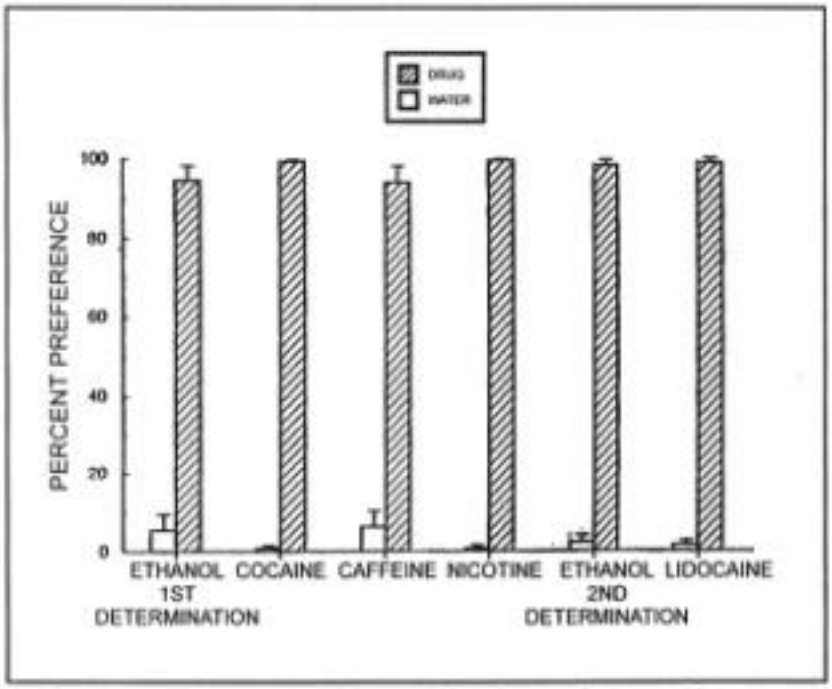

FIGURE 1. *Percentage preference for drug solution and water (concurrent FR6 schedules of 30-s access) under a schedule-induced polydipsia condition (FI 1-min food-delivery schedule). N = 7 animals. Ethanol = 2 percent (v/v); cocaine = 0.16 mg/mL; caffeine = 0.1 mg/mL; nicotine = 0.01 mg/mL; lidocaine = 0.11 mg/mL.*

all continued to receive FT 1-minute schedule-induced polydipsia sessions daily. For the S^D-fade group shown in figure 2 (top), the same fluid choices were continued, but the intensity of the S^D light associated with cocaine was gradually reduced over a 4-week period from full intensity (visual fader setting = 10) to off (fader setting = 0), and then remained off for an additional 4 weeks. Most of the animals continued to show a strong preference for cocaine solution during S^D fading, and the preference remained high for the 4-week exposure period after the completion of S^D fading. (One animal developed a fluid position preference at and beyond fader setting 8.0.) The oral self-administered dose of cocaine is shown by the filled circles and the scale on the right-hand ordinate.

For the cocaine-fade group (figure 2, bottom), the S^D light remained at full intensity, but the cocaine concentration was gradually reduced over a 4-week period from 0.16 to 0 mg/mL, and remained at zero for an additional 4 weeks. The cocaine-fade group continued to prefer the cocaine solution (which was proximate to the daily position of the S^D light) during solution concentration fading, and preference for the S^D-proximate fluid remained at its high-level for the 4-week exposure period after the cocaine concentration had been reduced to zero.

Neither group showed extinction of its preference, nor did the polydipsic intakes of either group decrease. The S^D-fade results demonstrated that a stable, chronic preference for cocaine solution can be maintained in the
absence of the visual S^D if the S^D is gradually faded. The cocaine-fade results indicate that a stable, chronic choice of a water source, which has become associated with the S^D light for cocaine, can be maintained when the cocaine content associated with the S^D is faded gradually.

In figure 3 (top), the center block of five bars indicates the preference for cocaine solution in successive 6-session blocks after the visual S^D was abruptly removed rather than gradually faded. Upon S^D removal, cocaine preference immediately fell precipitously, and out of the group of eight, the number of animals retaining an 80 percent or greater preference for the cocaine solution across the five successive 6-day blocks was: 2, 3, 3, 3, and 3. As a final 10-day control condition, both fluids offered were water, and all animals showed a position preference for the water that was offered in the right-hand position (rightmost bar).

Upon cocaine removal (figure 3, bottom, see the center five 6-session blocks), preference for the S^D-proximate water source fell gradually, and the number of animals retaining an 80 percent or greater preference for the S^D-proximate fluid source across the 5 blocks was: 6, 4, 5, 3, and 2-out of 8. As a final 10-day control condition, the S^D was removed, and all animals showed a position preference for the water that was offered in the right-hand position (rightmost bar).

To summarize, although this experiment demonstrated that, under an S^D condition indicating drug location, a preference for cocaine solution to water could be substituted for a previous preference for ethanol to water, the gradual fading of either the S^D intensity to zero, or the cocaine concentration to zero, left intact a strong preference for the unchanged stimulus condition, either the cocaine solution without the S^D, or the water associated with the S^D. The strong and stable preference, as well as the persistent, excessive level of intake in both cases, indicates that the maintenance of addictive behavior may be attributable as much to the S^D determination of self-administration behavior as it is to past or present pharmacological consequences. In both cases, the stimulus that remained unchanged after the other one was gradually faded (either the S^D light or the cocaine concentration), came to serve strong S^D functions with respect to ingestive preference. Whether the S^D-fade group, which continued to prefer cocaine solution, also continued this preference owing to a reinforcing effect of cocaine cannot be derived from this experiment, although previous evidence from this laboratory is consistent with such an interpretation (Seidman et al. 1992). The rate and amount of 0.16 mg/mL cocaine solution taken in the present

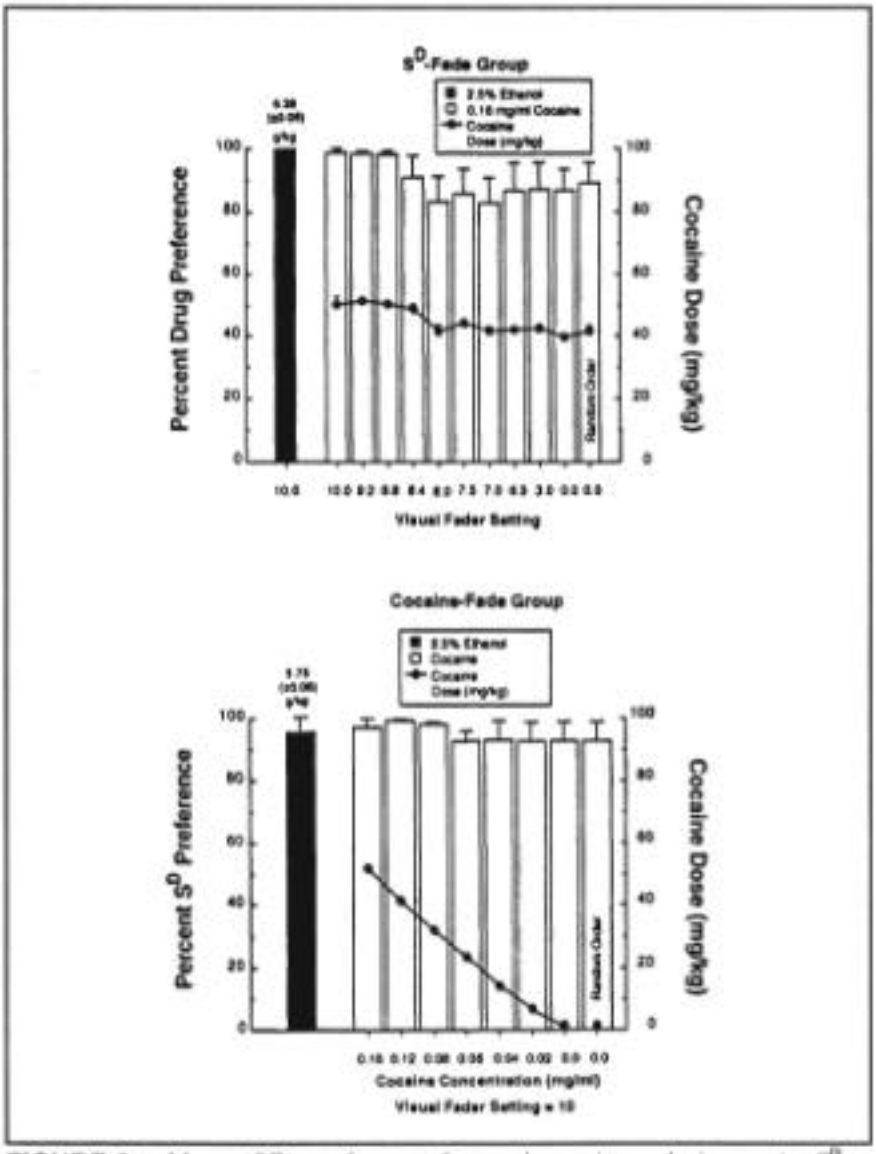

FIGURE 2. *Mean (SE) preference for oral cocaine solution as its S^D was gradually decreased in intensity over 4 weeks from 10 to 0 (top), and preference for S^D-indicated solution as its cocaine concentration was gradually decreased over 4 weeks from 0.16 to 0 mg/mL (bottom). Last two bars (right, top, and bottom) represent an additional 4 weeks for which the terminal condition was maintained. Daily session length = 3 h. N = 8 each group. Concurrent alternative fluid offered was always water. (Visual fader settings are values on linear 10-turn potentiometer.)*

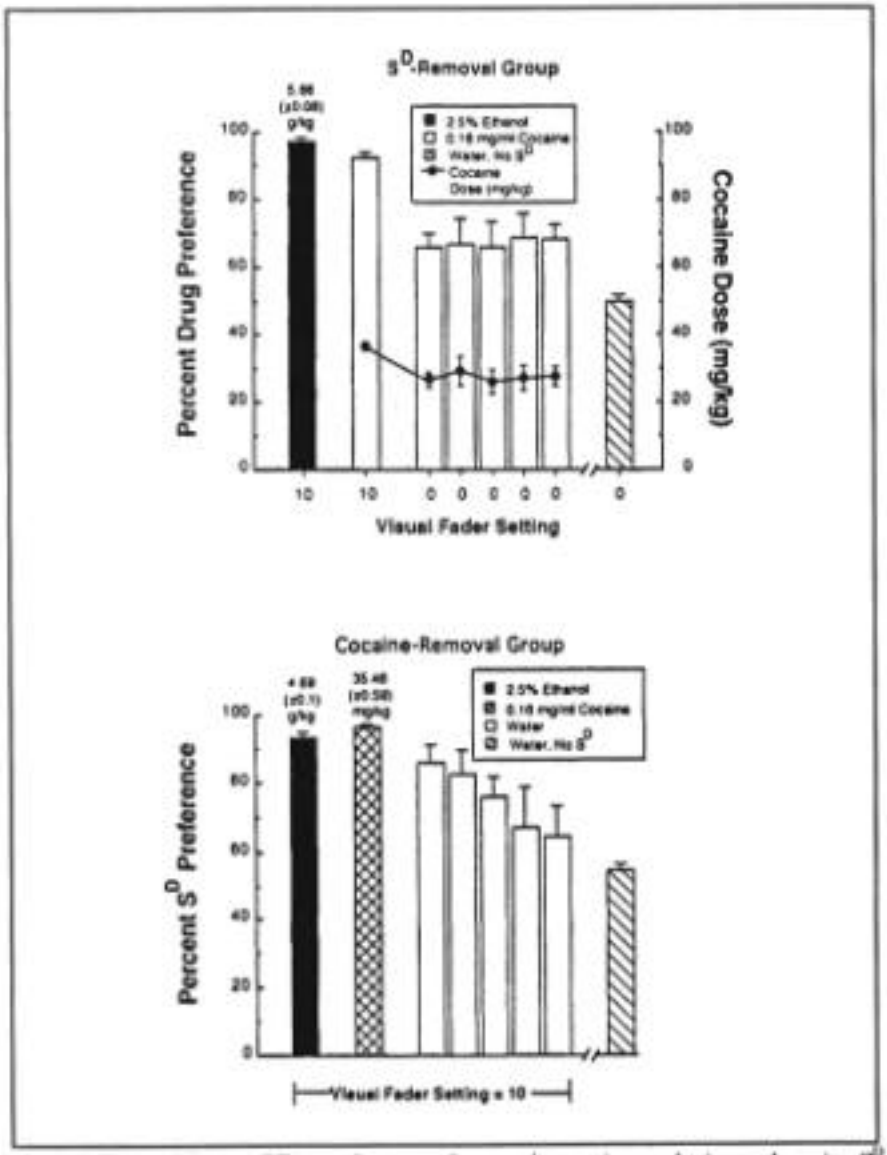

FIGURE 3. *Mean (SE) preference for oral cocaine solution when its S^D was abruptly decreased in intensity from 10 to 0, with middle 5-bar block composed of five consecutive 6-session means (top), and preference for S^D-indicated solution as its cocaine concentration was abruptly decreased from 0.16 mg/mL to water, with middle 5-bar block composed of 5 consecutive 6-session means (bottom). In both top and bottom, the rightmost bar shows final control condition offering water concurrently at both positions without the S^D. Daily session length = 3 h. N = 8 each group.*

experiments produced rat serum cocaine levels comparable to levels observed in humans chewing coca leaves, and was a level sufficient to reinforce behavior in rats as measured by the place-preference method (Seidman et al. 1992).

Within the groups for which the manipulated stimulus was changed abruptly, rather than gradually, individuals were much less likely to come under the enduring S^D control of the unchanged stimulus. The cocaine-removal condition actually left preference behavior more intact than did the S^D-removal condition, which produced a precipitous decrease in the preference for cocaine solution. The combined conditions for the abrupt-removal groups may be analogous to conditions faced by human drug abusers, for whom an abrupt discontinuation of the drug, along with a change in environmental S^Ds, leads to a dramatic and enduring decrease in drug addiction. This phenomenon was documented in the classic epidemiologic study by Lee Robins which found a rapid, unassisted recovery from heroin addiction by the great majority of addicted Vietnam veterans upon their return to the United States of America (Robins 1993).

PRODUCTION OF DRUG PREFERENCE BY AN S^D WITH A NONDRUG HISTORY

Up to this point, the efficacy of the S^D light for determining subsequent drug preferences had been instituted by first associating the S^D with the daily location of a preferred ethanol solution. The question arose as to whether the subsequent drug preferences were instances of animals acquiring polydrug abuse, or if the efficacy of the S^D to determine drug preference could be instituted by associating the S^D with the ingestion of nondrug fluids known to possess reinforcing efficacy in similar experi-mental contexts. The schedule-induced overdrinking of water itself had, some time ago, been demonstrated to be a reinforcing activity (Falk 1966). Rats receiving food pellets under a variable-interval 1-minute schedule of reinforcement developed polydipsia when the water, rather than being made freely available, was provided in small portions contingent upon completions of fixed ratios of lever pressing. Thus, under this schedule-induction condition, the opportunity to engage in water polydipsia was a reinforcing activity sufficient to sustain fixed-ratio behavior. The following experiment was performed to determine whether fluid polydipsia itself, if paired with the S^D light, would be a sufficient condition for instituting a preference for cocaine solution if the S^D was subsequently paired with the location of the cocaine solution.

Two groups of 80 percent body weight rats were given food pellets on an FT 1-minute schedule during 3-hour daily sessions. A

cocaine group (N-= 11) had one fluid, 0.16 mg/mL cocaine solution, available during each session. The daily left-right position of this solution was determined by a quasi-random sequence, and its position was indicated by an adjacent S^D light. A water group (N = 9) was treated similarly except that the available fluid was water. After 27 sessions, animals in both groups were then given a choice between two fluids for 21 sessions, with fluid position varied according to the same quasi-random sequence. The cocaine group was allowed to choose between drinking the 0.16 mg/mL cocaine solution, the position of which was still indicated by the S^D, and water. The water group was allowed to choose between drinking water, which was still indicated by the S^D, and another source of water.

The initial aim of the experiment was to determine if the opportunity to engage in schedule-induced polydipsia under S^D control was an activity with adequate strength as a reinforcer so that the S^D would acquire directive properties sufficient to determine a subsequent polydipsic fluid preference when two fluid sources became available. The results pertinent to this question are shown in figure 4 in the first pair of bars. For both groups, about one-half of the animals came under the control of the S^D light so that 80 percent or more of their polydipsic fluid intake was taken from the source indicated by the S^D. Thus, five animals from the cocaine group drank S^D-indicated cocaine solution in preference to water, and six animals from the water group drank from the S^D-indicated water in preference to the other water source. (These chambers had a moderate asymmetry so that one fluid source was a shorter distance from the pellet receptacle location than was the other one. This feature probably accounted for the position bias (side preference) observed for the other half of the animals. In a replication using an additional water group and symmetrically constructed chambers, all of the animals preferred the water source that was indicated by the S^D to the nonindicated water in the choice phase.)

An unpublished control study had shown that the above provision of a history of a few weeks of polydipsia from a single S^D-indicated water source was crucial for instituting preference for the S^D-indicated source as revealed by the subsequent fluid-choice condition. Naive animals were exposed to a schedule-induced polydipsia condition and a concurrent choice between an S^D-indicated source of water and water not so indicated. Daily fluid position was varied quasi-randomly, but without the initial history pairing polydipsia with the S^D under the single-fluid condition no preference for the S^D-indicated water occurred. Stated plainly, animals had no innate propensity to choose an S^D-indicated water source in preference to one without an S^D. It can be concluded, then, that daily pairing of the S^D with either a cocaine-solution

polydipsia or a water polydipsia is sufficient to endow the S^D with the capacity to determine that the S^D-indicated fluid will be ingested preferentially in a subsequent polydipsic fluid choice situation.

The next phase of this experiment ascertained whether the efficacy of this S^D to control fluid choice was capable of initiating a drug preference. In the present context, this was a question of whether the current power of the S^D, which controlled the choice of water source for six animals in the water group, could come to initiate a cocaine preference for these animals. Figure 4 (second set of bars) shows that when these water-history animals were presented with a choice between an S^D-indicated cocaine solution and water for 10 days, five of the six preferred 0.16 mg/mL cocaine solution to water. The animals in the cocaine group were exposed to an increased concentration of cocaine (0.24 mg/mL) and maintained their preference for cocaine solution to water (second set of bars).

To summarize, at this juncture in the experiment, without the necessity of providing a history of ethanol drinking, about one-half of all the animals had come under S^D control so that they preferred cocaine solution to water. It was then of interest to determine whether exposing all the animals to an association between the S^D and cocaine solution made with a vehicle of greater acceptability than water would increase the subsequent control possessed by the S^D. Given such a history, and then returned to the previous choice between cocaine (in water vehicle) versus water, more of the animals might prefer cocaine solution to water. From this point on, experimental treatments were the same for both groups. Animals were presented with a choice between a 0.24 mg/mL cocaine solution and water, but for 10 days the vehicle for cocaine was a compound solution consisting of 0.08 percent saccharin and 1.5 percent glucose. The effect on preference is shown in figure 4 (third set of bars). Except for one animal, all preferred the cocaine solution, which was indicated by the S^D light as well. Then, over a 32-day period, the compound vehicle solution (sac-gl) gradually was reduced in concen-tration to 0.004 percent saccharin and 0.075 percent glucose, where it

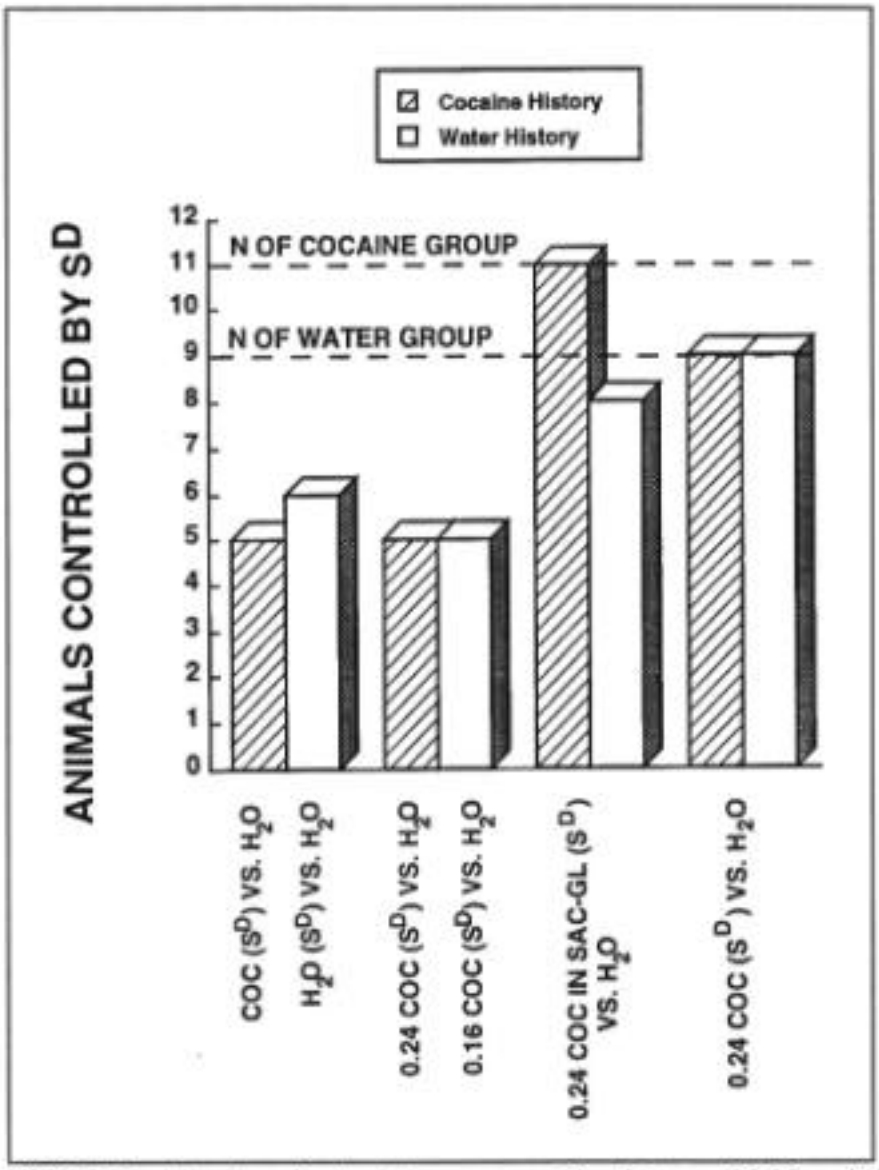

FIGURE 4. *Number of animals in a group with a history of 0.16 mg/mL cocaine solution (with light S^D) polydipsia (N = 11) and in a group with a history of water (with light S^D) polydipsia (N = 9) whose subsequent fluid polydipsia preferential choices were controlled by the S^D.*

remained for 4 days. In the next step, the vehicle became water once again and the 0.24 mg/mL cocaine $+S^D$ versus water choice was presented for 12 days. The rightmost set of bars in figure 4 shows that all except two animals continued to prefer the cocaine solution. Thus, interposing a history of pairing the cocaine plus S^D with a sac-gl vehicle led to an enhanced number of animals choosing cocaine solution polydipsia (compare the second and fourth sets of bars).

In order to determine whether the presence of the S^D was contributing to the strong preference for 0.24 mg/mL cocaine solution to water, the S^D was turned off for 6 days. (The first set of bars in figure 5 is the same as the last set in figure 4, and is presented again to facilitate comparisons.) The removal of the S^D produced a moderate reduction in the number of animals choosing cocaine polydipsia (second set of bars). A further moderate reduction occurred when the S^D was next made to indicate the water source, rather than the cocaine source, for 10 days (S^D reversal, third set of bars). When the S^D was restored for 8 days, so that it now indicated the cocaine solution, there was an increase in the number of animals preferring cocaine, but the total number of cocaine-preferring animals did not attain the previous level (see figure 5, first and last sets of bars). Owing to its recent history of removal and reversal, the S^D might have lost some of its efficacy for determining choice. Indeed, the second and fourth set of bars are almost identical.

The next series of manipulations was designed to combine the 0.24 mg/mL cocaine solution with a dilute sac-gl vehicle in order to enhance the reinforcing value of cocaine solution, while also removing, restoring, and reversing the S^D in blocks of days so as to weaken the efficacy of the S^D in controlling fluid preference. The vehicle for the cocaine solution was 0.032 percent saccharin and 0.6 percent glucose solution for 8 days, which was reduced to 0.024 percent saccharin 0.45 percent glucose (6-days), and then to 0.016 percent sac-0.3 percent gl for a series of S^D manipulations. Figure 6 (first set of bars) shows that with the combi-nation of cocaine, the final dilute sac-gl vehicle, and S^D, all except one of the animals preferred the cocaine solution. Then, for blocks of 4 days each, the S^D was removed, restored, reversed and restored. None of those S^D manipulations affected the preference for the cocaine solution.

The sac-gl vehicle concentration was gradually (8 days) reduced to zero and again all except one animal showed a preference for cocaine solution (figure 7, first set of bars). Upon S^D reversal (10 days), only two of the cocaine-preferring animals lost their preferences (second set of bars). Thus, after the history of combining cocaine with the sac-gl vehicle along with the series of S^D manipulations shown in figure 6, S^D reversal

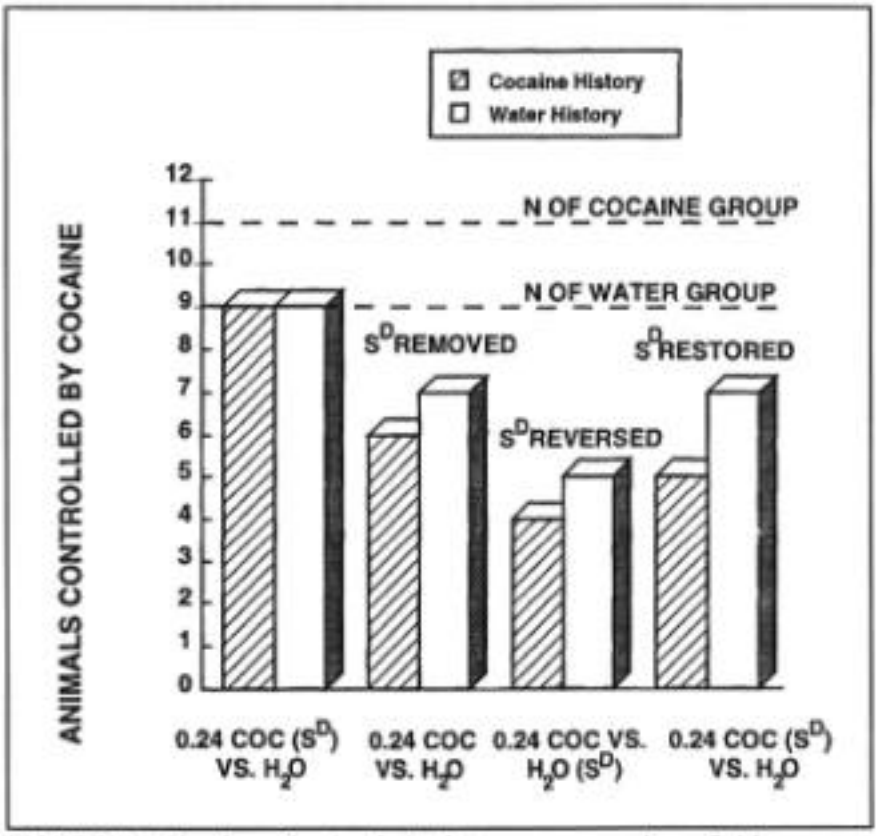

FIGURE 5. *Number of animals in the two groups whose fluid polydipsia preferential choices were controlled by cocaine (0.24 mg/mL) as S^D was manipulated.*

now had very little effect on cocaine preference. The S^D had lost most of its power to control fluid preference. Upon the removal of cocaine (12-days), only one animal s fluid preference was determined by the S^D (third set of bars). Finally, the restoration of a 0.24 mg/mL cocaine fluid source to the situation, together with S^D removal (10 days), resulted in a recovery of cocaine preference, but not for quite as many animals as previously (see figure 5, second set of bars and figure 7, last set of bars).

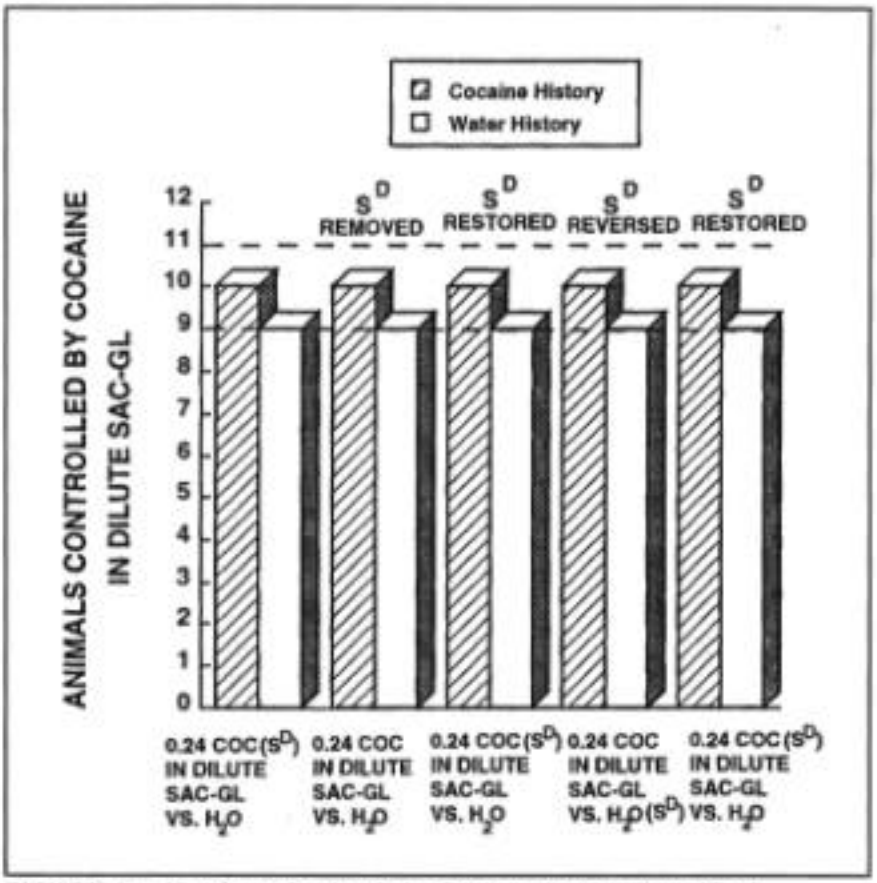

FIGURE 6. *Number of animals in the two groups whose fluid polydipsia preferential choices were controlled by cocaine (0.24 mg/mL) in dilute sac-gl solution as S^D was manipulated.*

PROVISIONAL PRINCIPLES DERIVED FROM THESE AND RELATED STUDIES

A number of provisional principles may be derived from these and previous studies, which begin to clarify the role of environmental and individual history variables in the institution and maintenance of drug abuse.

1. By the simple expedient of making an important commodity such as food available intermittently, excessive adjunctive behavior can be

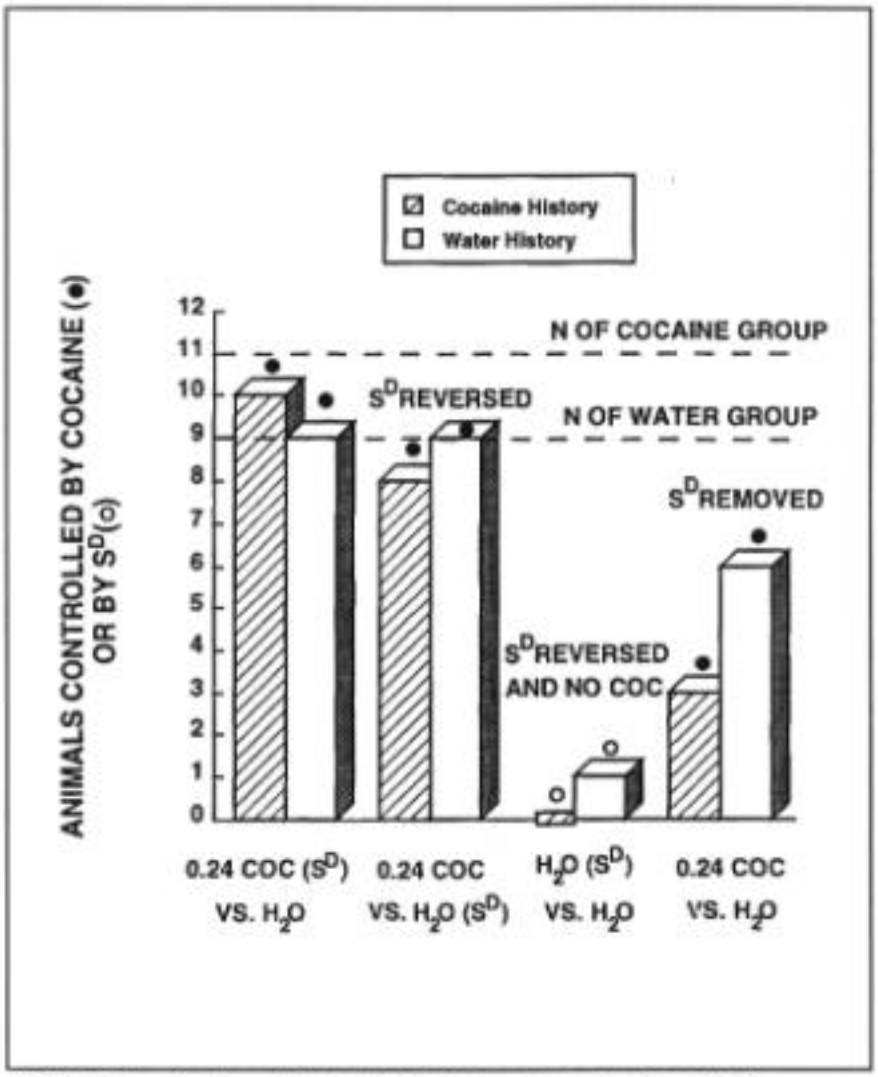

FIGURE 7. *Number of animals in the two groups whose fluid polydipsia preferential choices were controlled by cocaine (0.24 mg/mL, filled circle above bars) or by S^D (open circle over bars) as S^D was manipulated.*

generated, which includes oral vehicle and drug taking, as well as the potentiation of low rates of IV saline and drug self-injection.

2. If adjunctive behavior comes under S^D control, this control can function to transfer excessive behavior preferentially to an S^D-indicated commodity in the presence of behavioral alternatives. The commodity with respect to which the adjunctive behavior is transferred can be a drug possessing potential reinforcing properties of its own, or a substance that is not pharmacologically active. The first two principles combine to suggest that drug abuse and its preferential engagement of behavior can be viewed and manipulated profitably as a special case of excessive behavior

generation. The schedule of availability of important commodities can result in the generation of adjunctive behavior, the discriminative control of which is a function of an individual s behavioral history (Falk 1994).

3. Transfer of S^D control to another S^D (e.g., from an S^D light to a drug gustatory stimulus), or to another commodity (e.g., from S^D-indicated ethanol to cocaine or lidocaine, or from S^D-indicated cocaine to water) occurs with much higher probability when the transfer is done gradually, rather than abruptly.

4. The efficacy of an S^D in controlling preferential choice of a commodity (e.g., cocaine) can be enhanced by having interposed a history of pairing the drug plus the S^D with a drug vehicle of higher oral acceptability. In general, a drug may acquire an increased and enduring reinforcing efficacy for having once been imbedded in a context with enhanced reinforcing features.

5. By effecting a series of S^D removals, reversals, and restorations, the efficacy of the light S^D for controlling preference can be weakened so that preferential control may be transferred to the gustatory S^D properties of a drug.

6. At present, although strong and enduring oral preferential choices for both pharmacologically active and inactive fluids can be instituted by schedule induction and S^D control, the specific, additional contri-bution that an intrinsic reinforcing property of a drug might contribute to this preference has not yet been isolated.

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Taste and Diet Preferences as Predictors of Drug Self-Administration

Blake A. Gosnell and Dean D. Krahn

Several observations suggest that there may be specific, important relationships between taste/diet preferences and drug self-administration. These include reports of: (a) differences in drug self-administration in rats with differing baseline taste or diet preferences, (b) correlations between the intake of saccharin and the intake of alcohol, and (c) changes in drug self-administration when sweet-tasting solutions are provided as alternative reinforcers. In humans, there is a high comorbidity between eating disorders and drug and alcohol abuse. Further, this relationship extends to subclinical levels of each behavior. With a better under-standing of these relationships, it may be possible to use measures of diet and taste preferences, along with dietary manipulations, to predict and reduce vulnerability to drug abuse, as well as to monitor and improve current treatments for drug abuse. Animal and human studies relevant to the relationship between diet and taste preferences and drug abuse will be reviewed below, followed by a brief discussion of the possible mechanism underlying the relationship.

ANIMAL STUDIES

Through selective breeding, lines of rats have been developed that display relatively high or low levels of drug self-administration or drug preference (Li et al. 1979; Schechter 1992; Sinclair et al. 1989). Some inbred strains have also been found to differ from one another in drug self-administration (George and Goldberg 1988; Suzuki et al. 1988, 1992). In many cases, the differences in drug intake are paralleled by differences in the self-administration of other substances. For example, Nichols and Hsiao (1967) selectively bred rats for high or low suscepti-bility to morphine addiction. The groups subsequently displayed corresponding high and low susceptibility to alcohol addiction. Rats of the ALKO Alcohol-Accepting (AA) strain consumed more etonitazene (ETZ) than those of the ALKO Alcohol Non-Accepting (ANA) strain (Hyyatiä and Sinclair 1993) and were also found to self-select a diet higher in fat than that selected by ANA rats (Forsander 1988).

Marks-Kaufman and Lipeles (1982) found that those rats that eventually drank a morphine solution consumed more dietary fat than those that would not drink the morphine solution.

Based on the findings that AA rats eat more fat than ANA rats (Forsander 1988), Krahn and Gosnell (1991) performed a study to determine whether rats with differing diet preferences would differ in their voluntary consumption of alcohol. After measuring macronutrient self-selection in a large group of rats, two subgroups were selected: one group had self-selected a diet containing a large amount of carbohydrate and little fat, and the other consumed large amounts of fat and little carbohydrate; protein intake was similar in the two groups (N = 8 per group). All rats were then placed on a standard lab chow diet, and subsequent alcohol intake was determined. The rats were given daily sessions in which alcohol (4 to 12 percent, v/v) or water was available. Initially, sessions were conducted with rats on a food restriction schedule; in later sessions, food was available ad libitum. During restriction, alcohol was available for only the first hour of the 4-hour daily feeding session. On the final 6 days of the experiment (no feeding restriction), water and 8 percent ethanol (EtOH) were alternated as the fluid presented during daily 1-hour sessions. Non-deprived, fat-preferring rats tended to consume more alcohol than carbohydrate-preferring rats at nearly every opportunity over approximately 4 weeks of repeated exposures to alcohol (4 to 12 percent). When the intake of 8 percent alcohol was compared to the intake of water, fat-preferring rats consumed significantly more alcohol than water (figure 1). Furthermore, they consumed more alcohol than carbohydrate- preferring rats. This study provided evidence for a relationship between fat preference and alcohol intake. It is important to note that when rats were tested for alcohol intake, both groups were maintained on the same diet (i.e., lab chow). Therefore, the observed differences in alcohol intake cannot be attributed to differences in the composition of the maintenance diet, but are more likely to be related to baseline differences in preference.

In contrast to the experiment described earlier, Prasad and colleagues (1993) found no relationship between macronutrient preference and alcohol preference in Sprague-Dawley rats, as measured in tests in which alcohol (6 percent v/v) and water were available continuously for 5 days. They did find, however, that rats of the alcohol-preferring (P) line displayed a significantly greater preference for protein and a decreased preference for carbohydrate than rats of the alcohol-nonpreferring (NP) line. This contrasts with the observation that AA rats consume more fat

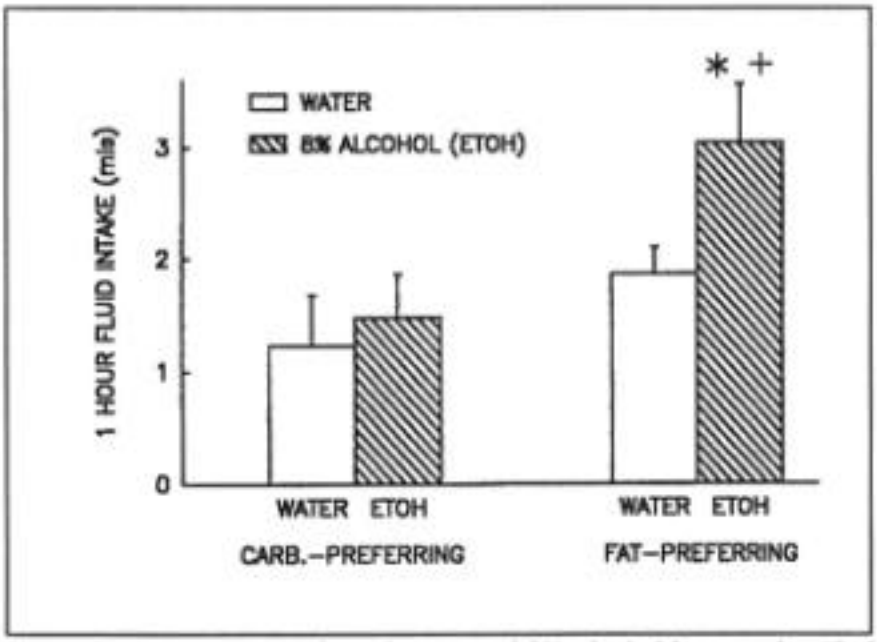

FIGURE 1. *Average intakes of water and 8% alcohol by rats classified as carbohydrate-preferring or fat-preferring. The means are the average of three 1-hr sessions with each fluid for each rat. Fat-preferring rats consumed significantly more alcohol than water (*$p < 0.01$) and significantly more alcohol than carbohydrate-preferring rats (+ $p < 0.05$).*

SOURCE: Krahn and Gosnell 1991, Copyright 1991, Pergamon Press.

than ANA rats (Forsander 1988). Differences between these results and those of Forsander (1988) and Krahn and Gosnell (1991) may be related to methodological differences, particularly the composition of the test diets, the methods for measuring alcohol intake and preference, and the strains of P and NP rats tested.

Sweet taste is another attribute that appears to have some relationship to drug self-administration beyond the fact that sweeteners are frequently added to EtOH solutions to make them more palatable. In alcohol preference studies, the provision of saccharin, sucrose, or fat solutions as options to EtOH caused a decrease in EtOH consumption (Lester and Greenberg 1952). Similarly, the availability of a saccharin-glucose (sac-gl) solution decreased the acquisition and maintenance of cocaine self-administration in rats (Carroll and Lac 1993; Carroll et al. 1989), while the deprivation of a sac-gl solution increased the self-administration of ETZ (Carroll and Boe 1982) and cocaine (Carroll et

al. 1989). In rhesus monkeys, the provision of a saccharin solution as an alternative reinforcer to smoked cocaine base led to a small but nonsignificant decrease in cocaine intake; the decrease was most noticeable at high fixed-ratio (FR) values (Comer et al. 1994). As the FR value was increased, the number of cocaine deliveries decreased, and the intake of saccharin increased.

In rats selected or bred for high and low alcohol self-administration, corresponding high and low intakes of sucrose and saccharin have been noted (Kampov-Polevoy et al. 1990; Sinclair et al. 1992; Stewart et al. 1994). Gosnell and Krahn (1992) tested whether this relationship was reciprocal by measuring EtOH intake in rats selected for differing amounts of saccharin intake. Groups of rats with low, intermediate, or high intake of saccharin were formed on the basis of voluntary saccharin intake in daily 1-hour sessions (N = 8 per group). These rats were then given daily sessions in which alcohol (2 to 8 percent , v/v) or water was available. Initially, sessions were conducted with rats on a food restriction schedule; in later sessions, food was available ad libitum. When food restricted, the groups did not differ in alcohol or water intake. When the food restriction schedule was discontinued, alcohol intake in the intermediate and high saccharin groups was generally higher than that of the low saccharin group (figure 2). On the final series of alcohol sessions, the high saccharin group consumed significantly more 2 and 6 percent alcohol than the low saccharin group and tended to consume more of the other concentrations as well. A paper by Overstreet and colleagues (1993) confirms this positive relationship between saccharin and alcohol preference across several rat strains.

A more indepth study of the saccharin-alcohol relationship was conducted by Bell and associates (1994). From a large group of rats (N = 40), groups representing high, intermediate, and low saccharin preferences were selected (N = 6 per group). These rats were reduced to 80 percent of their free-feeding weights, and EtOH was established as a reinforcer by use of a food-induced drinking procedure in which rats learned to press a lever to obtain water or EtOH solutions. Response rates were measured across acquisition sessions, an FR1-8 series, and a concentration series. There was considerable variability within groups, such that the group means were not significantly different. However, a striking pattern emerged. In nearly all conditions, the mean number of responses for EtOH was higher for the high saccharin group than for the low.

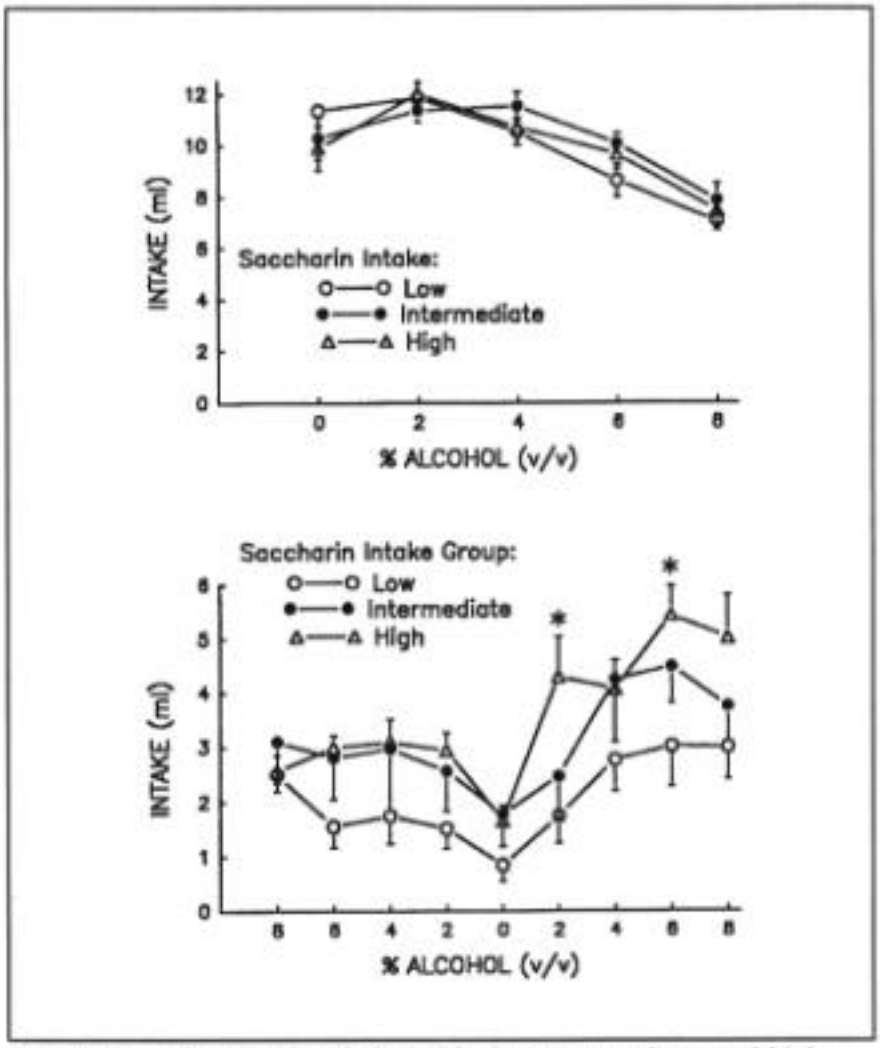

FIGURE 2. *(Top) Intake of alcohol by low, intermediate, and high saccharin-consuming rats (means±SEM, N = 8/group). Each point represents the average of the final 3 sessions at the indicated concentration. Rats were on a food-restricted schedule, and the test session coincided with the first hour of food availability each day. (Bottom) Intake of alcohol by the same groups when food was available ad libitum, except during the test session. Each point represents the average of 2 to 4 sessions. Asterisks indicate significant differences from the low saccharin group ($p < 0.05$, one-tailed Bonferroni t test).*

SOURCE: Gosnell and Krahn 1992, Copyright 1992, Pergamon Press.

Results for the concentration series (at FR1) are shown in figure 3. Under a null hypothesis of no relationship between saccharin and EtOH intake, such a consistent pattern over an extended series of conditions would not be expected. These results, then, offer some support for a relationship between the factors mediating EtOH self-administration and those involving ingestion of palatable foods and fluids.

A positive relationship between the oral intakes of two substances may be related to individual differences in the general propensity to consume any distinctively flavored solutions that are presented. The results of Stewart and colleagues (1994), however, argue against this possibility, at least for the P and alcohol NP rat lines. They found that rats of the P strain consumed more sucrose solution than NP rats, but that the strains did not differ in the intakes of sour (citric acid) or bitter (sucrose octa-acetate) solutions. With sodium chloride solutions, NP rats displayed a higher preference than P rats. They interpret these results as evidence that these rat strains do not simply differ in their acceptance of all flavored fluids.

Gosnell and associates (1995) recently conducted a study that examined the relationship between saccharin preference and intravenous (IV) morphine self-administration. The IV route eliminates the oral route for one of the substances and should minimize the influence of drug taste on self-administration. Rats with a high (N = 8) or low (N = 8) preference for saccharin were selected from a larger group (N = 31). The oral consumption of morphine (0.5 mg/mL) was then measured in these rats with a procedure identical to that used for measuring saccharin preference. In both groups, oral morphine intake was low, and the groups did not differ. Catheters were then implanted in all rats. After recovery from surgery, rats were placed in operant chambers for daily 1-hour sessions. During the sessions, each press of the right lever caused an infusion of 0.04 mg/kg of morphine sulfate. A 30-second timeout period followed the start of each infusion; during this time, lever-presses were counted but did not activate the infusion pumps. No training in the operant chambers was provided. After 10 daily sessions at 0.04 mg/kg/infusion, the dose was increased to 0.08 mg/kg/infusion for 22 sessions, then to 0.16 mg/kg/infusion for 10 sessions. There were 14 rats that completed the study through day 20 of the sessions with the infusion dose at 0.08 mg/kg; 10 rats completed the entire study.

The groups did not differ in the number of infusions obtained at 0.04 mg/kg/infusion. Over the course of the 0.08 mg/kg sessions,

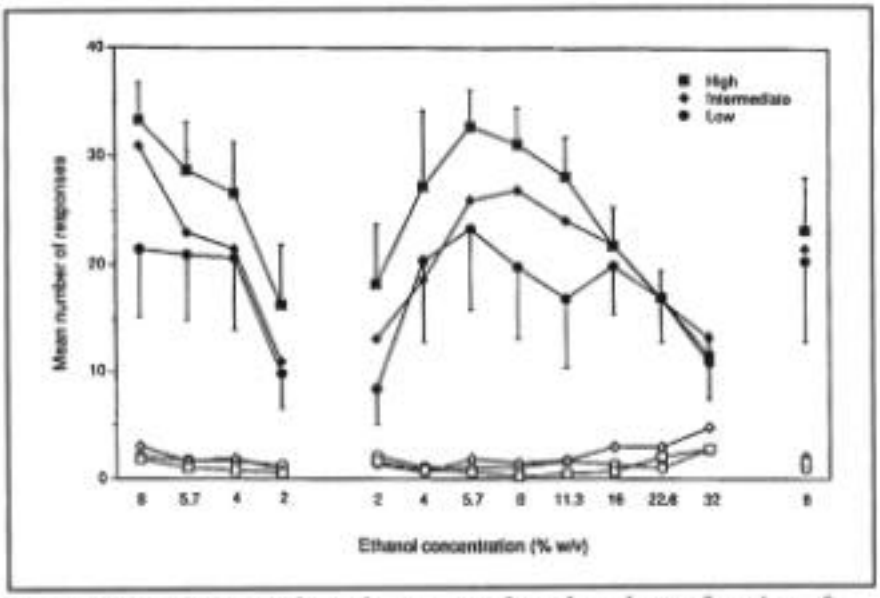

FIGURE 3. *Mean number of responses for ethanol as a function of concentration (% w/v). Each point represents the group mean (N = 6) over the six sessions at each condition; groups represent high, intermediate, and low saccharin preference. Closed symbols represent responses for ethanol, and open symbols represent responses for concurrently available water. SEMs are shown for high and low saccharin groups but, for visualization purposes, not shown for the intermediate group.*

SOURCE: Bell et al. 1994.

saccharin-preferring rats began to self-administer significantly more morphine than rats with a low saccharin preference. For example, averaged over sessions 16 through 20 at this dose, the high-saccharin rats obtained 10.5Å2.3 infusions per session, whereas the low-saccharin rats obtained 4.1Å0.8 infusions ($p < 0.05$). When the dose was increased to 0.16 mg/kg/infusion, rats in the low-saccharin preference group began to self-administer more morphine than they did at the lower dose. In the high-saccharin preference group, there was a decrease in the number of infusions obtained per session. The groups did not significantly differ at this dose. This study suggested that the threshold dose for morphine self-administration may be higher in rats with a low saccharin preference when compared to those with a high saccharin preference. The decreases in self-administration by the high-saccharin group when the dose was

increased to 0.16 mg/kg may represent a compensatory response to the greater amount of drug obtained per infusion. This study supports the hypothesis that saccharin preferences are related to drug self-administration and suggests that the relationship is not due simply to similarity of tastes.

There is also evidence that ingestion of palatable fluids may alter the effects of a drug. For example, chronic or acute intake of a sweet solution (a 10 percent sucrose-0.1 percent saccharin solution) enhanced the rewarding effect of morphine, as measured by the conditioned place preference procedure (Lett 1989). With the "hotplate" procedure for measuring pain sensitivity, Lieblich and associates (1983) have reported that chronic access to a palatable sac-gl solution reduced the analgesic effect of morphine in a line of rats selectively bred for high rates of hypothalamic self-stimulation. This effect, however, may not be specific to sweet tastes or this particular line of rats, as a reduction in morphine analgesia was also observed in Sprague-Dawley rats after 48-hour exposure to solutions of quinine, sac-gl, or sodium chloride (Holder 1988). With the tailflick assay, morphine analgesia increased after long-term access to sweet solutions (> 20 days) (Kanarek et al. 1991; Roane and Martin 1990) and decreased after a shorter period of access to a sweetened solution (3 to 24 hours) (Fidler et al. 1993; Klein and Green 1988). Because the effects of a drug may be related to the likelihood of self-administration of the drug, these results, too, suggest a relationship between palatable tastes and self-administration.

The studies described earlier suggest that drug self-administration may be predictable from diet or taste preferences. A potentially important area for future research is the determination of whether procedures that alter taste or diet preferences have a concomitant effect on drug intake. It is well known, for example, that saccharin preference can be altered through preexposure and/or conditioning; macronutrient preference can also be experimentally manipulated (Gerardo-Gettens et al. 1991; Matsuo et al. 1984; Reed et al. 1992). Measurements of the acquisition or maintenance of drug self-administration after such manipulations will provide some indication of whether vulnerability to drug abuse in humans may be reduced through efforts to improve dietary habits and preferences.

HUMAN STUDIES

There is increasing evidence from human studies that supports the hypothesis that eating behavior and alcohol and other drug use are related. As many as 55 percent of bulimic patients are reported to have alcohol and other drug use problems (Beary et al. 1986; Hudson et al., 1988; Mitchell et al. 1985, 1990; Weiss and Ebert 1983). Conversely, 15 to 40 percent of females with alcohol or other drug abuse problems have been reported to have eating disorder syndromes, usually involving binge eating (Beary et al. 1986; Hudson et al. 1992; Jonas et al. 1987). It is important to note that during binge episodes, bulimics typically ingest large amounts of sweet and/or high-fat foods (Abraham and Beumont 1982; Mitchell et al. 1981; Weltzin et al. 1991). In standardized taste tests with mixtures of sugar and dairy products, however, bulimics were found to have an optimal sweetness preference that was higher than controls and an optimal fat preference lower than controls (Drewnowski et al. 1987).

Krahn and colleagues studied the relationship between dieting and bulimic behaviors and alcohol use and abuse in women entering their freshman year of college (Krahn et al. 1992). Subjects responded to questionnaires regarding a variety of health issues including dieting and bulimic behaviors and alcohol and other drug abuse. On the basis of their responses, subjects were categorized into one of six dieting severity groups ranging from nondieter to bulimic. There was a significant, positive relationship between the frequency and intensity of alcohol consumption and the severity of dieting and bulimic behaviors (figure 4). In a subsequent study with questionnaires and semistructured interviews, it was found that the more severely dieting and binge eating women were more likely to have experienced negative consequences from their drinking and to have met criteria for substance abuse or dependence (Krahn, unpublished observations). The reported likelihood of responding to stress by binge eating, drinking alcohol, using other drugs, going shopping, and exercising were all positively, significantly related to dieting severity, which suggests that these immediately gratifying coping mechanisms may be linked, at least in certain subgroups of young women.

Another study (Bohn and Krahn, unpublished observations) assessed the relationship between self-deprivation of alcohol by alcoholics in their first 6 months of sobriety and their self-reported change in likelihood of binge-eating. Of the 242 men in the study, 37 percent reported at least

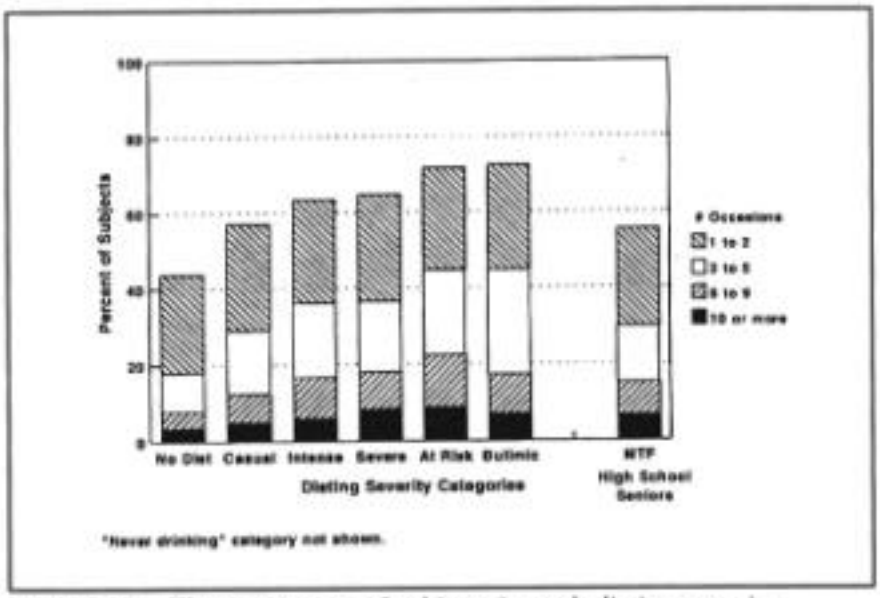

FIGURE 4. *The percentage of subjects in each dieting-severity category who reported each frequency of alcohol use over the last month. The relationship between dieting-severity categories and frequency of alcohol use is significant (γ = 0.21, t = 8.24, $p < 0.001$). Data on the same question from the 1989 Monitoring the Future (MTF) study, obtained from a national sample of high school senior girls with probable or definite plans to graduate from a 4-year college, are included for comparison (Johnston et al. 1990).*

SOURCE: Krahn et al. 1992, Copyright 1992, Ablex Publishing Corporation.

some binging, and 17 percent reported at least weekly binging. Of the 109 alcoholic women, 62 percent reported a history of binge-eating, and 32 percent reported weekly binges. Of those who reported any previous history of binge-eating, more than 50 percent reported an increase in the likelihood of binging associated with a cessation of alcohol use, while about 20 percent reported a decrease in the propensity to binge. Further, 50 percent of all subjects reported that eating caused a decrease in desire for alcohol while only 7 percent reported that eating increased their desire for alcohol. Understanding the interaction of these two appetites may improve treatment for the large number of women alcoholics with comorbid eating disorders and the large number of bulimics with comorbid alcoholism.

In addition to studies of the comorbidity of substance abuse and "pursuit of thinness" disorders, intriguing relationships between drug use and food intake have been reported. For example, sweet cravings and high intakes of sweet foods have been reported for opiate addicts (Morabia et al. 1989; Weiss 1982; Willenbring et al. 1989). In a sample of recovering alcoholics, Yung and colleagues (1983) found that those who achieved the longest periods of postdetoxification sobriety reported increased intake of sugar in beverages. In a study of bulimic female smokers, cessation of smoking caused a selective increase in fat intake (Bulik et al. 1991). Interestingly, in the treatment community, alcoholics are being told to follow one of two conflicting paths: Some are told to avoid sweets, as the use of these foods is viewed as an alternative addiction that primes the alcoholic for relapse (Ketcham and Mueller 1983); others are told to use sweets to decrease the urges for alcohol (Alcoholics Anonymous 1975). Neither of these recommendations, however, has received rigorous scrutiny in treatment trials. Finally, the ability to taste the bitter compound propylthiouracil (PROP) has been linked to both alcoholism and the hedonic response to sweet tastes. Children of alcoholics are more likely to be nontasters of PROP than children of nonalcoholics (Pelchat and Danowski 1992). In a study that classified subjects as likers or dislikers of sweet taste, Looy and Weingarten (1992) found that PROP non-tasters were generally sweet likers. Conversely, sweet dislikers were generally PROP tasters. These studies indicate that the interactions between preference for sweet/fat substances and the preference for and intake of drugs may have a genetic basis.

PARALLELS BETWEEN FACTORS AFFECTING DRUG SELF-ADMINISTRATION AND TASTE/DIET PREFERENCES

In many cases, stress or drug preexposure increases subsequent behavioral responses to a drug and/or self-administration of the drug (Horger et al. 1990; Piazza et al. 1989; Robinson 1993). For example, food deprivation, which may be viewed as a form of stress, is well known to increase the self-administration of a number of drugs (see Carroll and Meisch 1984 for a review). Tailpinch stress increases vulnerability to the acquisition of amphetamine self-administration (Piazza et al. 1990). Immobilization stress was found to increase the oral self-administration of morphine and fentanyl (Shaham et al. 1992), and footshock stress increased the IV self- administration of heroin in rats on a progressive ratio reinforcement schedule (Shaham

and Stewart 1994). Some aspects of taste and diet preferences also appear to be stress-sensitive and/or subject to "sensitization." Although chronic stress generally causes a decreased intake or preference for sweetened solutions (Katz 1982; Pucilowski et al. 1993; Willner et al. 1987), one mild stressor, tailpinch, is known to cause a short-term increase in feeding (see Morley et al. 1983 for a review). When given a choice of four fluids (milk, sweetened milk, sucrose solution, and water), Bertiere and colleagues (1984) observed that mild tailpinch stress caused a preferential increase in sucrose intake. Prenatal exposure to nicotine (in male rats) and cocaine (in humans) has been shown to increase sweet taste preference (Lichtensteiger and Schlumpf 1985; Maone et al. 1992). It should be noted that the effects of prenatal nicotine were observed in adult rats, thus indicating a long-term change (Lichtensteiger and Schlumpf 1985). Food deprivation increases preferences for saccharin (Hursh and Beck 1971; Valenstein 1967), and the intake of dietary fat is preferentially increased after food deprivation or food restriction (Gerardo-Gettens et al. 1991; Matsuo et al. 1984; Reed et al. 1988). Finally, bulimia (a disorder that has many characteristics of addictive behavior) has been found to be related to the amount and severity of previous dieting (Abraham and Beumont 1982; Fairburn and Cooper 1984). As noted earlier, women with anorexia or bulimia have increased preferences for sweet tastes and have increased rates of alcoholism and other substance abuse. Thus, taste and diet preferences appear to be related to subsequent drug self-administration, and may be sensitive to some of the same factors that have been shown to affect drug self-administration.

A POSSIBLE MECHANISM

Correlations in the intakes of two orally self-administered substances may be attributable in part to common taste properties of the substances. For example, EtOH appears to have a taste similar to solutions with a combination of sweet and bitter tastes (Kiefer and Lawrence 1988). It might be expected, then, that the preference for one substance would correlate with the preference for a similar-tasting substance. However, Sinclair and others (1992) have argued that the relationship they observed between saccharin and EtOH intake in P versus NP rats was related to the postingestive effects of EtOH. Hyyatiä and Sinclair (1993) observed that alcohol-preferring AA rats consumed more cocaine and ETZ than did the alcohol nonpreferring ANA line. They suggested that the differences in cocaine intake may be due to differences in sensitivity to bitter tastes, but that strain

differences in ETZ self-administration could not be completely explained on the basis of taste sensitivity. In the study described earlier on the relationship of saccharin preference to IV morphine self-administration (Gosnell et al. 1995), the use of the IV route minimized the influence of morphine taste. These findings suggest that the relationships between diet/taste preferences and drug self-administration are not simply due to taste similarities.

A more likely explanation for the observed positive relationships between the intakes of diverse substances is that they have in common the ability to activate the same neural pathways. The pathway that has received the most attention in regard to reward circuits is the mesolimbic dopaminergic system. Most drugs of abuse activate this system (see Di Chiara et al. 1992 and Wise 1987 for reviews) and differences in drug self-administration have been linked to differences in mesolimbic dopamine (DA) levels, either in the basal or stimulated state (Glick et al. 1992; Hooks et al. 1992). There is much evidence that the mesolimbic DA system is also involved in intracranial electrical self-stimulation (see Phillips and Fibiger 1989 for a review), and it is interesting to note that rats that have been selectively bred for high or low rates of lateral hypothalamic self-stimulation also display relative high and low saccharin consumption (Ganchrow et al. 1981).

Measures of DA release in the nucleus accumbens also support a role for dopamine in the mediation of taste palatability. Mark and colleagues (1991) found that the intraoral application of saccharin increased DA levels in the nucleus accumbens, as measured by microdialysis. A more recent study did not find significantly increased DA release after saccharin ingestion, but did report an anticipatory increase just prior to saccharin intake (Weiss et al. 1993). Dopaminergic antagonists were found to reduce the intake of sucrose solutions (at low concentrations) and to reduce sham-feeding of corn oil and sucrose solutions (Muscat and Willner 1989; Weatherford et al. 1990). The dopaminergic antagonist SCH 23390 also reduced lever-pressing for food, water, and saccharin solutions (see Nakajima 1989). In taste reactivity tests, the antagonist pimozide was found to reduce the hedonic response to intraoral infusions of sucrose (Leeb et al. 1991). The common ability to activate the mesolimbic dopaminergic system, therefore, may underlie the observed relationships between the diet and taste preferences and drug self-administration.

Caine and Koob (1994) have reported that depletion of mesolimbic DA reduced cocaine self-administration but did not affect operant responding for food. While this finding appears to cast doubt upon the hypothesis that food reward and drug self-administration are mediated by a common system, it is important to note that the animals were tested when food restricted. A number of studies suggest there may some critical differences between food ingestion in the deprived state and that which occurs in the nondeprived state. For example, naloxone was found to be more effective in reducing the intake of palatable chow or a sweet solution in nondeprived rats than in reducing intake in food-deprived rats (Levine et al. 1995; Segall and Margules 1989). Morphine had opposite effects on food intake in food-satiated and food-deprived rats (Sanger and McCarthy 1980). Based on studies of conditioned place preference in rats, Bechara and van der Kooy (1992) have argued that deprivation- and nondeprivation-induced motivation may be mediated by different neural systems. This possibility should be kept in mind when assessing the relationships between feeding and drug self-administration, particularly since food deprivation and food restriction are sometimes used to facilitate the intake of both food and drugs.

Compulsive, repetitive consumption of substances of abuse and/or palatable foods in the pursuit of an improved affective state is a core behavior in the syndromes of drug abuse and drug dependence as well as eating disorders such as bulimia or compulsive overeating. If, as suggested by the studies reviewed earlier, a common neural system is involved in mediating taste preferences as well as the reinforcing effects of drugs, then it is not surprising that certain characteristics of substance use and palatable food consumption are similar and correlated. A better understanding of the relationship between drug use and taste and diet preferences may provide new insights into the etiology of eating disorders and substance abuse. It is possible that a test could be developed based on responses to “natural” reinforcers such as palatable foods that would predict vulnerability to alcohol and other drug abuse and drug dependence in humans. Further, monitoring and/or manipulating dietary intake and diet preferences may be useful adjuncts to other treatment programs and may offer a means of predicting the likelihood of a favorable treatment response in certain groups of substance abusers. Finally, it is possible that pharmacological interventions effective in the treatment of eating disorders may prove to be of some value in the treatment of substance use disorders as well. These potential applications, however, will first require additional investigation at the basic and preclinical levels on

both the acquisition and maintenance of drug self-administration and taste preferences.

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Individual Differences in Acute Effects of Drugs in Humans: Their Relevance to Risk for Abuse

Harriet de Wit

It is known that individuals differ in their likelihood of becoming drug abusers. Many people never take any drugs at all, even on a single occasion. Of those who take drugs at least once, only a small number go on to use the drugs on a regular basis, and even fewer go on to use them in excessive quantities or abusive patterns. The differences in numbers of individuals who have ever tried drugs and those who become regular users is roughly illustrated by data from a national household survey (National Institute on Drug Abuse 1992): 37 percent of U.S. adults reported having used an illicit drug at least once in their lives, while only 6.3 percent report having used an illicit drug in the past month. "Illicit drug" here includes marijuana, nonmedical use of psychotherapeutics, inhalants, cocaine, hallucinogens, or heroin. Similarly, in 1993, 43 percent of U.S. high school students reported having tried an illicit drug at least once in their lives, while only 18 percent used any drugs in the past month (National Institute on Drug Abuse 1994). Many individuals limit their use to an initial sampling of the drug. Other individuals become occasional users, but use the drugs in moderation without developing any problems of abuse or dependence. However, a small but significant proportion of young individuals appears to progress rather rapidly (i.e., in their late teens and early twenties) to excessive use, and continue to use drugs despite harmful consequences. Why some individuals and not others are susceptible to drug or alcohol abuse is unclear. Some researchers have investigated risk factors through epidemiological or longitudinal studies designed to detect predictors and correlates of heavy drug use (see Tarter, this volume). Other researchers have used laboratory-based procedures to investigate individual differences in acute responses to drugs. This chapter will focus on a series of studies that used the latter approach to examine individual differences in response to acute doses of benzodiazepines.

Individuals may differ on a wide range of physiological, psychological, and demographic variables, any of which may potentially contribute to the susceptibility to use or abuse drugs. They may differ in biological makeup, either because of inherited factors (such as sex or genetic predisposition to alcoholism) or because of fluctuations in

their current state (e.g., nutritional or hormonal). Individuals may also differ on a range of psychological variables, including their current psychiatric state or their underlying personality traits. Many theories of the etiology of drug abuse postulate that certain psychological states or traits predispose certain individuals to use drugs. Finally, individuals differ in their prior experiences (e.g., history of prior drug use), which, through learning or physiological processes, may affect their pharmacological responses to drugs and thus their susceptibility to use drugs repeatedly. Some of these postulated variables can be investigated under controlled laboratory conditions.

It is widely assumed that the acute subjective, or mood-altering, effects of a drug play an important role in whether it will be abused. This relationship has been well established in comparisons across drugs and across drug classes: there is a good correspondence between drugs that produce euphoria and feelings of well-being and those that are abused (Fischman and Foltin 1991). The relationship is so well established that subjective responses to drugs are often used to screen new agents for abuse liability (Jasinski 1991). The relationship between subjective response to drugs and their abuse liability may also apply to individual differences in vulnerability to abuse drugs. It is known that individuals vary in their subjective and behavioral responses to acute administration of drugs, and these differences may be related to differences in the likelihood of repeated use, or risk for excessive drug use. For example, individuals who experience feelings of euphoria and well-being from a particular drug are more likely to repeat their use of that drug than individuals who do not experience these effects, or who experience unpleasant effects (Haertzen et al. 1983). The relationship between the subjective, or mood-altering, effects of a drug and the likelihood of taking the drug can be investigated in laboratory studies using placebo-controlled, double-blind choice procedures. Individual differences in subjects' responses in these procedures can thus be used to try to identify individuals who might be at risk for excessive drug use.

The author's laboratory has conducted a series of drug preference studies measuring subjective and behavioral effects of drugs in human volunteers. Subjective drug effects are measured using standardized, self-report questionnaires, and behavioral preference is measured by the number of times subjects choose to take an active drug over a placebo. In these studies, drugs from several classes have been investigated, including stimulants, tranquilizers, alcohol, and marijuana (Chait 1993, Chait et al. 1989; de Wit et al. 1987, 1989). Marked

individual differences have been observed in both the quality and magnitude of subjective responses to drugs in humans, and these differences bear systematic and intuitively logical relations to differences in behavioral preference, or the likelihood of consuming the drug in a behavioral test. In some studies it has been found, as might be expected, that subjects who experience the greatest euphoria and who report the highest liking of a drug's effects are the most likely to take the drug during choice sessions. However, depending on the drug and the subject population tested, the relationships between the quality of subjective drug effects experienced and drug preferences may vary. Closer examination of these relationships may reveal potential predictors of risk for substance abuse.

The subjects in the author's studies have been healthy young volunteers (aged 21 to 35), who have no history of substance abuse. This is in contrast to many other studies of drug abuse in humans, which have used subjects with histories of substance abuse. Although individuals with histories of substance abuse are most appropriate for studying certain aspects of drug abuse (e.g., maintenance, withdrawal, relapse), volunteers without extensive drug use histories may be more appropriate for studying vulnerability, or factors that predispose to the *development* of drug use. The subjects in the author's studies were recruited from around a major urban university. Potential subjects were carefully screened to exclude anyone with any history of drug- or alcohol-related problems, and to exclude anyone with psychiatric or medical disorders for which administration of the drug under study would be contraindicated.

The choice procedure used in these studies consisted of a sampling phase (four sessions), followed by a choice phase (three sessions). During the sampling sessions, subjects experienced the effects of a drug and placebo, each associated with a color code. Subjects were instructed to associate any drug effects with the code for later identification. On choice sessions, the subjects were permitted to choose between the two sampled substances, and they ingested whichever substance they preferred. The number of times they chose the drug over placebo was the indicator of preference. Sessions were typically conducted one or two times per week, usually in the evenings in a laboratory-based "recreational" environment, in which subjects were tested in social groups of three or four. The drugs were administered under double-blind conditions, and subjects were told they might receive a stimulant, tranquilizer, placebo, and sometimes alcohol. Other, secondary dependent measures include psychomotor performance, memory and attention, and physiological effects such as

heart rate and temperature. The studies reported here investigated the effects of diazepam, a drug that is commonly prescribed, and is abused, by a small number of individuals (Woods et al. 1992).

The author's laboratory has employed two strategies to study individual differences in responses to diazepam: (a) studies testing a priori hypotheses, in which subjects were recruited based on a criterion or characteristic believed to be potentially associated with abuse or dependence; and (b) posthoc analyses, conducted using data from heterogeneous samples of subjects exploring correlates of drug preference.

A PRIORI STUDIES

The a priori approach has been used in three studies to examine potential risk factors. These are described in detail below. In one study, diazepam preference was compared in anxious versus nonanxious control subjects. This study was based on the self-medication hypothesis of drug use, which postulates that a drug will be more highly preferred by individuals in whom the drug relieves an aversive state (e.g., relief from anxiety). In another study, diazepam preference was compared in moderate versus light alcohol drinkers. Clinical observations indicate that heavier consumption of alcohol increases the likelihood of abuse of benzodiazepines. Therefore, it was hypothesized that diazepam preference would be directly related to alcohol consumption. In a third study, diazepam preference was compared in males with and without a family history of alcoholism. Risk for alcoholism is thought to be in part inherited, and this study investigated whether the presence of family alcoholism would influence responses to another drug, diazepam.

Study 1: Diazepam Preference in Anxious Versus Control Subjects (Chutuape and de Wit 1995)

Participants in this study were 21 volunteers who met DSM-III-R criteria (American Psychiatric Association 1987) for an anxiety disorder and 23 nonanxious control subjects. The subjects in these groups did not differ on demographic characteristics (e.g., sex, age, education) or on their prior experience with drugs. They participated in a seven-session choice procedure, in which diazepam (20 mg) was compared to placebo. In this study, diazepam was administered during sampling sessions in five divided doses of 4 mg each, taken at 30-minute intervals. During the choice sessions, subjects first selected the drug they preferred (i.e., diazepam or placebo) and then also selected the dose they preferred (i.e., from 4 mg to a maximum of 28 mg). Diazepam choice differed between the two groups: whereas the normal control group

chose diazepam on average at about chance level (45 percent), the anxious group chose the diazepam more often than placebo (65 percent drug choice; figure 1). Moreover, subjects in the anxious group on average took higher doses of the diazepam when they chose the drug (average dose 22 mg for the anxious group compared to 18 mg for the control group). These findings suggest that, under these testing conditions, individuals with higher levels of anxiety are more likely to take diazepam. Whether this is indicative of risk of abusing the drug, or whether it is evidence of appropriate self-medication of their anxiety state is not clear. One way to address this question might be to examine the anxious subjects' subjective responses to the drug. Interestingly, the anxious subjects on average did not report measurable decreases in self-reported anxiety after diazepam, but they did report increases on a measure of drug-induced euphoria (i.e., the Morphine-Benzedrine Group scale of the Addiction Research Center Inventory; Martin et al. 1971; figure 2). This pattern of results suggests that anxious individuals might indeed be at higher-than-average risk for repeated nonmedical use of diazepam.

Study 2: Light Versus Moderate Alcohol Drinkers (de Wit and Doty 1994)

In this study, diazepam preference was compared in 13 light drinkers and 14 moderate drinkers. Light drinkers were defined as individuals who drank, on average, one to five alcoholic drinks per week, and moderate drinkers were those who consumed from 7 to 20 drinks per week. Again, these subjects had no history of drug- or alcohol-related problems. It was hypothesized, and found, that heavier drinkers would show a greater preference for diazepam. The moderate drinkers chose the diazepam-containing capsule on 73 percent of available occasions, whereas the light drinkers chose the drug on only 40 percent of occasions. However, despite the relatively high level of diazepam choice among the moderate drinkers, this group did not report significant increases in subjective measures of euphoria. Although they reported feeling the drug's effects and liking these effects, the profile of subjective effects were not indicative of a drug with high potential to be abused. The light drinkers,

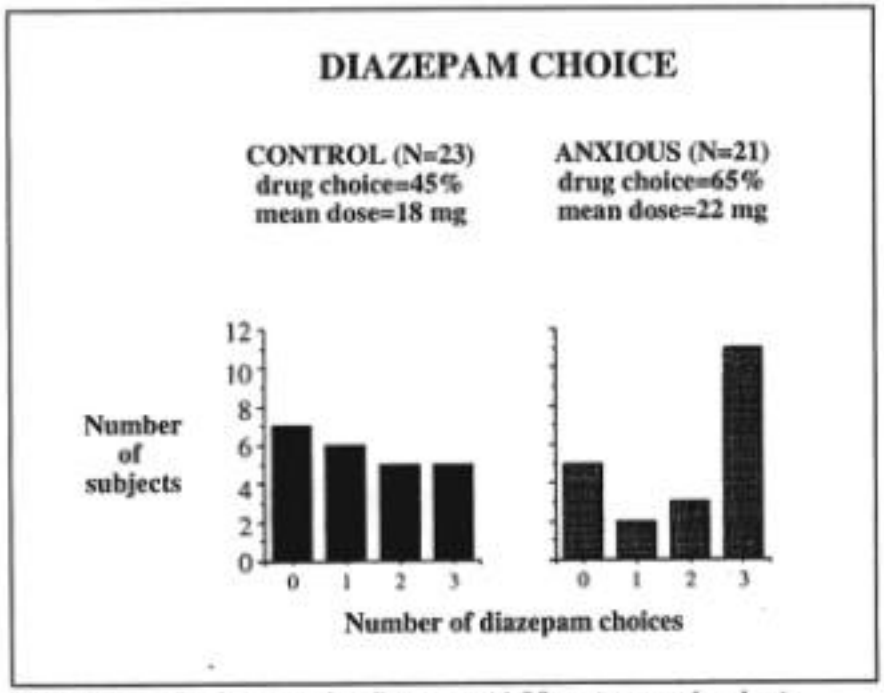

FIGURE 1. *Preferences for diazepam (4-28 mg) over placebo in control subjects (CTL; N = 23) and in volunteers with an anxiety disorder (ANX; N = 21). Bars indicate the number of subjects in each group who chose the diazepam- over the placebo-containing capsules on 0 through 3 of the choice opportunities. Also shown are the mean number of times diazepam was chosen overall, and the mean dose of diazepam taken on sessions when diazepam was chosen.*

on the other hand, reported experiencing apparently aversive subjective effects that were consistent with their relatively low choice: compared to the moderate drinkers, they reported greater confusion, dysphoria, and fatigue. Thus, this study demonstrated that drug use history (i.e., habitual alcohol consumption) did influence preference for diazepam and subjective responses to diazepam. However, the differences in subjective responses indicated that the higher drug choice in the moderate drinkers was due more to a relatively lower sensitivity to the aversive effects than to the drug's euphorigenic effects. Thus, these results suggest that habitual alcohol consumption may slightly, but not strongly, increase the risk for abuse of benzodiazepines.

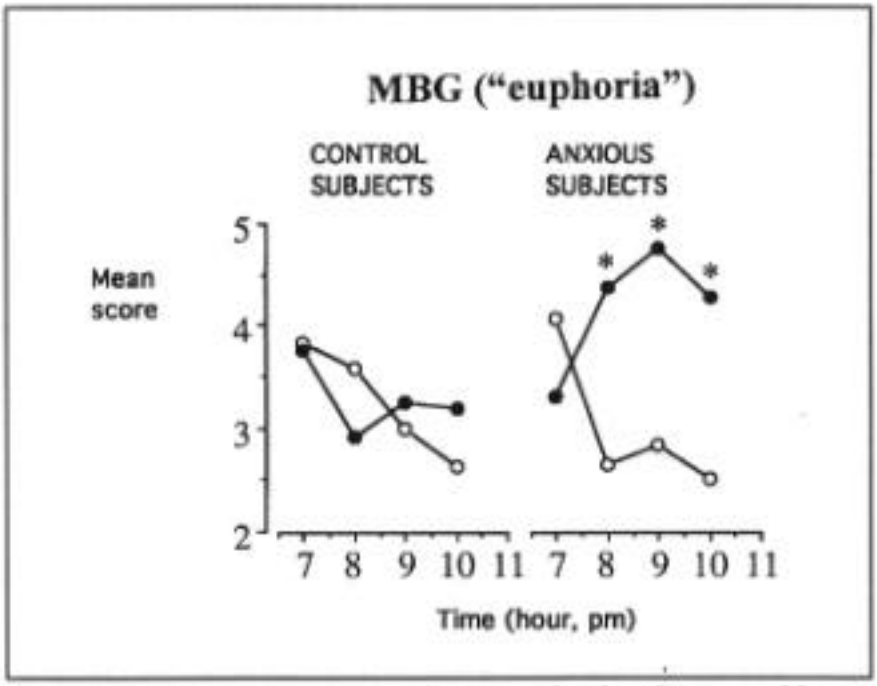

FIGURE 2. *Mean scores on "euphoria" scale after diazepam (20 mg; filled symbols) and placebo (open symbols) in normal controls (CTL; N = 23) and volunteers with an anxiety disorder (ANX; N = 21), before capsule ingestion (7 p.m.) and at regular intervals after capsule ingestion. Asterisks indicate significant differences between diazepam and placebo.*

Study 3: Family History of Alcoholism (de Wit 1991)

In this study, acute responses to diazepam were compared in males with at least one first-degree alcoholic relative (family history positive or FHP) versus males with no alcoholic relatives (family history negative or FHN). The subjects were moderate social drinkers in their early twenties who had no personal history of drug- or alcohol-related problems. The groups did not differ on demographic variables such as age, education, or current or past drug use. This study used the same divided dosing procedure as that described earlier in study 1, in which subjects could regulate their dose during the choice sessions. It was found that FHP subjects chose the diazepam about as often as FHN subjects (FHP 48 percent diazepam choice versus FHN 38 percent diazepam choice), and the FNP group chose only a slightly higher dose of the drug during the choice sessions (24 mg versus 19 mg). There were no significant differences between the two groups in

subjective responses to the drug. Thus, these results suggest that family history of alcoholism is not a strong risk factor for repeated benzodiazepine use.

POSTHOC COMPARISONS

The posthoc approach of comparing subjects who choose a drug most and least often has been used to explore the correlation between drug preference and both intraexperimental variables (i.e., differential responses to drug administration) and extraexperimental variables (e.g., demographic and personality characteristics).

Study 1: Posthoc Comparison of Diazepam Choosers Versus Nonchoosers (Chutuape and de Wit 1994)

Using data from a total of 88 subjects who participated in various diazepam preference studies, this study compared the subjects who chose diazepam on all three choice sessions ("choosers"; N = 32) to those who never chose the diazepam ("nonchoosers"; N = 21). The choosers and nonchoosers were compared on a range of variables, including extra-experimental variables such as demographic characteristics, current and past drug use and psychiatric rating scales, as well as intraexperimental variables mostly related to their responses to the drug. Table 1 shows the data for several representative extraexperimental variables. The choosers and nonchoosers did not differ in gender, age, education, occupation, or marital status. The groups did differ on several measures of self-reported recreational drug use: a significantly higher proportion of diazepam choosers currently used marijuana, and a higher proportion had ever used stimulants. The diazepam choosers also reported heavier current and lifetime use of every other class of recreational drug, although these differences did not reach statistical significance. Thus, greater diazepam preference was correlated with greater recreational drug use. The two groups were also compared on their subjective responses to diazepam: the diazepam choosers showed a very slight decrease in self-reported anxiety after receiving the drug, and an increase in ratings of friendliness, whereas neither of these effects was reported by the nonchoosers. On other measures of diazepam's effects the groups did not differ (e.g., decreased arousal, increased confusion). Thus, these findings suggest that among normal healthy individuals without histories of drug or alcohol abuse, those who report heavier recreational drug use

TABLE 1. *Demographic characteristics and recreational drug use of diazepam nonchoosers and choosers. Nonchoosers selected diazepam over placebo on zero of three choice sessions, and choosers selected diazepam on all three of the choice sessions.*

	Diazepam Non choosers (N = 21)	Diazepam Choosers (N = 32)
Gender (% female)	19	28
Age (mean years)	24.2	24.1
Education		
High school or partial college (%)	33	28
College or advanced degree (%)	67	72
Occupation		
Full-time student (%)	62	47
Marital status		
Single, never married (%)	76	84
Current recreational drug use		
Alcohol use (mean drinks/week)	6.6	9
Caffeine use (mean drinks/week)	10.8	12.4
Current marijuana user (% yes)	9	44*
Lifetime recreational drug use		
Marijuana use: % used > 10 times	57	75
Stimulants: % ever used	38	75*
Hallucinogens: % ever used	29	68
Tranquilizers: % ever used	12	28

KEY: * = Significant ($p < 0.05$) group differences (chi-square test).

are more likely to choose diazepam in a double-blind choice test. There was, however, little evidence that the drug is strongly euphorigenic, even among those subjects who chose the diazepam most consistently.

Study 2: Relationships of Drug Preference to Personality (de Wit and Bodker 1994)

For this analysis, data were also pooled from a series of diazepam choice studies (total N = 96). Subjects who chose diazepam on two or three of the three choice opportunities (N = 54) were compared to those who chose the drug on zero or one occasion (N = 42). The two groups were compared on several measures of personality, including the Tridimen-sional Personality Questionnaire (Cloninger 1987), the Eysenck Personality Inventory (Eysenck and Eysenck 1968), and the Sensation-Seeking Scale (Zuckerman 1979), and a measure of attitudes toward drug use, the Drug Attitudes Scale (Goodstadt et al. 1978). None of these measures were strongly or consistently related to diazepam preference.

In summary, the studies described here illustrate how studying the responses of normal volunteers to acute drug administration may reveal some of the factors that influence interindividual variability in risk for drug abuse. The studies are based on the assumption that individuals who experience positive (i.e., euphorigenic) subjective responses to drugs, and who exhibit preference for a drug over placebo, are more likely to repeat their use of a drug once they have experienced its effects. The actual impact of these individual differences are likely to be limited by the myriad other social and cultural factors that influence drug use outside the laboratory. For example, factors such as limited drug availability, legality and social sanctions against drug use are also likely to be powerful determinants of actual drug use and abuse. Nevertheless, the knowledge that individuals differ in their subjective and behavioral responses to drugs of abuse may be useful in the development of prevention and treatment strategies to reduce the incidence of problematic patterns of drug use.

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Substance Abuse Vulnerability in Offspring of Alcohol and Drug Abusers

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There is clear evidence that a family history of alcoholism is a significant risk factor for the development of alcohol and other drug use disorders. Research also suggests that a family history of drug dependence increases the vulnerability of offspring for future development of drug abuse/dependence, although few such studies have been conducted.

This chapter will provide an overview of a number of areas of research on family history of substance abuse as a predictor of substance abuse vulnerability. First, epidemiological research on family history of alcohol and other drug use disorders will be briefly summarized. Next, laboratory research on potential physiological and behavioral markers for family history risk will be reviewed. There also will be a summary of several recent studies examining the predictive utility of putative markers for identifying those offspring at increased risk for substance abuse development. Finally, methodological limitations and future directions of the laboratory research will be discussed.

EPIDEMIOLOGICAL STUDIES OF FAMILY HISTORY OF ALCOHOL AND DRUG USE DISORDERS

Generally, three different human behavioral genetic methodologies have been used to examine the potential influence of family history of substance abuse: family studies, adoption studies, and twin studies (see review by Pickens and Svikis 1991). There has been convincing concordance across these different methodologies in findings of increased risk for alcohol and drug use disorders in male and, more recently, female family members of affected individuals.

Family History of Alcoholism as a Risk Factor for Alcohol Abuse/Dependence

Well-controlled family studies of alcoholism generally have shown a three- to ninefold increased risk of alcoholism among parents and

siblings of alcoholic subjects as compared with relatives of nonalcoholic subjects (Cotton 1979; Merikangas 1990). Approximately 25 percent of fathers and 5 percent of mothers of alcoholic probands meet diagnostic criteria for alcoholism. Typically, alcoholism risk in male relatives is consistently higher than in female relatives; however, this difference in risk appears to be related to different environmental or biological influences for men and women, and not to gender differences in genetic transmission of alcoholism (Merikangas 1990).

In the first rigorous adoption study on alcoholism, Goodwin and colleagues (1973) found a fourfold increased risk of alcoholism in adopted male offspring of alcoholic fathers as compared with adopted offspring of nonalcoholic fathers; no differential risk for female offspring was observed as a function of family history (Goodwin et al. 1977). A subsequent study by Cadoret and colleagues (1985) confirmed the elevated risk for sons of alcoholics, but also reported significantly increased rates of alcoholism among female offspring of alcoholics as compared with female offspring of nonalcoholics. Overall, average relative risk of alcoholism in male adoptees with as compared to without a family history of alcoholism is 2.4 and in female adoptees 2.8 (Merikangas 1990).

Twin studies have consistently found significantly higher concordance for alcoholism in monozygotic (MZ) twins who are genetically identical, as compared with dizygotic (DZ) twins, who on average share half of their genes (Hrubec and Omenn 1981; Kaij 1960; Kendler et al. 1992; Pickens et al. 1991). When the relative contribution of genetic and environmental factors to alcoholism risk was examined, genetic factors were found to exert a moderate to strong influence on development of the more severe disorder of alcohol dependence for both men (heritability estimate = 0.59) and women (heritability estimate = 0.42), but only modest influence on risk for the less severe disorder of alcohol abuse in men and no influence for alcohol abuse in women (Pickens et al. 1991).

Family History of Alcoholism as a Risk Factor for Drug Abuse/Dependence

To better understand the nature and extent of risk conferred by a family history of alcoholism, it is important to determine whether family history positive (FHP) offspring evidence increased risk for developing psychoactive drug use disorders in general or for alcohol disorders specifically. Several areas of research have suggested an

increased vulnerability to psychoactive substance abuse/dependence in persons with a positive family history of alcoholism.

In a study of self-reported alcohol and drug use by male college students, differences in substance use patterns and associated problems were found as a function of the extent of alcoholism in students' families (McCaul et al. 1990*a*). The greatest levels of alcohol and drug use were found for college students with a high density of alcoholism in their families (first- and second-degree affected relatives), an intermediate level for students with low alcoholism density families (first-degree affected relative(s) only), and the least in students with no affected relatives. Generally, students from high-density families reported: greater use of alcohol, marijuana, sedatives, and cocaine; a younger age at first alcohol intoxication and first use of marijuana; and more experience with less commonly used drug classes such as opiates and hallucinogens. Finally, a greater percentage of these students reported personal alcohol- or drug-related problems as well as family mental health care.

Using adoption study methods, Cadoret and colleagues examined the effects of alcoholism in the biologic parent on the subsequent development of drug use and abuse in the adoptee (Cadoret et al. 1986, 1995). Results indicated that alcohol abuse/dependence in a biological parent directly predicted drug abuse/dependence in the offspring. Additionally, antisocial personality in a biologic parent or psychiatric disturbance in an adoptive parent contributed to increased risk for drug abuse/dependence in the offspring (Cadoret et al. 1995).

In the only twin study to date of clinical drug use disorders, Pickens and colleagues (Pickens et al. 1991) found significantly higher concordance rates for drug abuse and/or dependence in MZ versus DZ male twins, but not female twins, when twins were identified on the basis of treated alcoholism in one member of the twin pair.

Family History of Drug Abuse as a Risk Factor for Drug Abuse/Dependence

Compared with alcohol abuse/dependence, there has been relatively little research on genetic contributions to risk for development of other psychoactive substance use disorders. Earlier clinical studies of genetic factors in drug use generally have focused on patterns of licit drug use by individuals in the general population. Twin studies have reported higher MZ than DZ concordance rates for: cigarette smoking (Kaprio et al. 1981), coffee and tea drinking (Pederson

1981), and tranquilizer use (Pederson 1981). There are a number of factors relevant to the dearth of research on genetic risk for illicit substance use disorders. Historically, there has been a greater emphasis on the role of environmental variables in the vulnerability to drug abuse; the lower population prevalence of drug abuse/dependence as compared with alcohol abuse/dependence makes research exceedingly more complex and difficult; and the illegal nature of much drug use decreases individual's willingness to volunteer for research protocols and increases the difficulty of locating and working with the population.

Using family study methods, Merikangas and colleagues (1992) examined rates of drug use and other psychiatric disorders in the first-degree relatives of opiate-dependent, treated probands. Overall, 69 percent of the siblings of opiate-dependent probands reported use of at least one illicit drug, and 63 percent of the siblings met diagnostic criteria for substance abuse. Most of the siblings with drug abuse reported using a variety of substances. For all drugs, over 90 percent of siblings who tried any illicit drug went on to develop substance abuse. Clearly, the siblings of opiate-dependent probands are an exceedingly high-risk group for substance use disorders.

These investigators also examined the relationships between parental psychiatric disorders and sibling disorders in the relatives of opiate abusers. Maternal alcohol abuse was significantly related to sibling drug abuse, and maternal anxiety or depression was associated with elevated rates of alcoholism, drug abuse, and anxiety or depression in the siblings. In contrast, paternal disorders were specifically predictive of elevated risk for the same disorder in the siblings; that is, paternal alcoholism was significantly associated with sibling alcohol abuse, drug abuse with drug abuse, and antisocial personality with anxiety/depression (Merikangas et al. 1992). These findings suggest greater specificity for transmission of risk of psychiatric disorders between affected fathers and their offspring than between affected mothers and their offspring; however, the small numbers of drug-abusing mothers makes these conclusions tentative.

SEARCH FOR MARKERS THAT MAY BE RELATED TO INCREASED RISK FOR SUBSTANCE USE DISORDERS IN FHPs

These converging lines of evidence for a familial influence on the development of substance abuse/dependence have led to the study of offspring of alcoholics who have not yet themselves developed the disorder. The goal of this research is identification of physiological,

subjective, and/or behavioral markers that are associated with and therefore predict increased risk for development of alcohol dependence in FHP individuals. FHP males and females have been studied while sober and intoxicated from alcohol or other drugs. Potential risk factors may include underlying psychological or biological basal abnormalities that are generally expressed and do not occur solely in the presence of alcohol. On the other hand, hypothesized risk factors may be highly specific to alcohol and may only come into play when alcohol has been ingested. Indeed, many researchers have hypothesized family history differences related to the reward or reinforcement value of alcohol and other psychoactive drugs.

The high-risk research paradigm that has been used to investigate potential markers has been conceptually quite simple. A sample of adolescent or young adult offspring of alcoholics (FHP) is recruited and assessed for the presence/absence or magnitude of the putative marker. Offspring with no familial alcoholism (FHN) are matched to the FHP subjects on a number of potentially important variables, including age, gender, years of education, height/weight ratio, typical and maximum drinking, and recent and lifetime drug use. Typical exclusion criteria include: the Michigan Alcoholism Screening Test (MAST) score suggestive of alcohol problems; DSM-III-R Axis I diagnosis in the subject; significant medical history; and evidence of maternal alcoholism, particularly during pregnancy. Assessments can be conducted with or without an alcohol challenge, depending on the whether the marker is hypothesized to operate under baseline conditions or differentially in the presence of alcohol.

Baseline Differences Between FHP and FHN Youth

A variety of psychological and biological variables have been studied in sober FHP subjects, including body sway, perceptual motor functioning, personality measures, school performance, verbal abilities, abstraction/ conceptual reasoning, and neurological and biochemical measures. The most consistent and robust finding has been reduced amplitude in the P300 component of event-related potentials (ERPs) elicited by visual stimuli in young FHP subjects as compared with FHN subjects (Begleiter et al. 1984; Hill et al. 1988; Steinhauer et al. 1987; Whipple et al. 1988). For example, Hill and Steinhauer (1993) reported significantly reduced P300 amplitudes during a visual discrimination task in multigenerational, high-density FHP prepubertal boys compared with their age-matched FHN controls; interestingly, no significant differences were observed as a

function of familial alcoholism in young female subjects. It is thought that ERPs reflect memory updating operations during information processing. Importantly, there is evidence that P300 amplitude and latency are genetically influenced. The importance of familial alcoholism as a determinant of P300 deficits has received further support from two recent studies with adult alcoholics (Cohen et al. 1995; Pfefferbaum et al. 1991). Across five brain areas (frontal, central, parietal, occipital, and temporal), Cohen and colleagues (1995) found no differences in P300 amplitude between low-density alcoholics and controls; in contrast, high-density alcoholics showed significant P300 reductions in every brain region compared with controls. Differences in resting EEG activity have not been reliably obtained as a function of family alcoholism history (Cohen et al. 1991; Kaplan et al. 1988; Pollock et al. 1983).

FHP youth also have been shown to have increased body sway (static ataxia) in the absence of alcohol as compared with FHN youth (Hegedus et al. 1984; Hill et al. 1987; Lipscomb et al. 1979). For example, Hill and colleagues (1987) examined sway in 8- to-14-year-old males and females. On average, FHP youth had 3.3 male and 0.3 female first- and second-degree relatives who were alcoholic. Over repeated trials with eyes open and closed, FHP youth evidenced greater body sway both front to back and side to side than FHN youth. Interestingly, many of these same measures now are being examined in young offspring of drug abusers. However, the hypotheses under investigation in this research relate primarily to the effects of in utero drug exposure on these youth and not potential genetic risk markers.

The Effects of Alcohol Challenges on Offspring of Alcoholics

A wide range of variables also have been studied using an alcohol challenge procedure in which responses of adult male offspring of alcoholics and matched FHN males are examined following equal doses of alcohol. Early reports were generally consistent in findings of decreased sensitivity to ethanol on a number of measures in FHP as compared with matched FHN subjects at equivalent blood alcohol levels. For example, FHP subjects have demonstrated less subjective intoxication (O'Malley and Maisto 1985; Pollock et al. 1986; Schuckit 1980*b*, 1984), decreased body sway (Schuckit 1985), and less impairment on the pursuit rotor task (Schuckit 1980*a*). With an increasing number of laboratories engaged in this area of research, there has been increasing diversity in the results of alcohol challenge studies. In the laboratory of the author and her colleagues (McCaul et

al. 1990*b*), findings indicated that FHP subjects reported significantly greater subjective effects of ethanol than FHN subjects. In the same study, the author and colleagues failed to find ethanol-induced differences in body sway between FHP and FHN subjects. Similar findings of increased or no difference in ethanol sensitivity for FHP subjects have been reported by other laboratories for a variety of measures including: body sway (Behar et al. 1983; Lipscomb et al. 1979; O'Malley and Maisto 1985), subjective ratings of ethanol effects (Behar et al. 1983; de Wit and McCracken 1990; Vogel-Sprott and Chipperfield 1987; Wilson and Nagoshi 1988); electrophysiological responses (Ehlers and Schuckit 1990; Pollock et al. 1983); heart rate (Wilson and Nagoshi 1988); facial flushing (Schuckit and Duby 1982); resting muscle-tension scores (Schuckit et al. 1981); psychomotor tasks (Vogel-Sprott and Chipperfield 1987; Wilson and Nagoshi 1988); and attenuation of stress response (Finn and Pihl 1987; Levenson et al. 1987). Thus, results from a number of laboratories have yielded conflicting evidence of the direction and magnitude of FHP versus FHN group differences following ethanol ingestion.

A number of studies have examined stress-response dampening in high-risk males (Finn and Pihl 1987; Levenson et al. 1987; Sher and Levenson 1982). Specifically, multigenerational FHP compared to FHN males have been shown to have increased cardiovascular, skin conductance, and muscular reactivity to aversive stimuli (e.g., unavoidable shock) when sober, and to have significantly larger decrements in reactivity to these stimuli following alcohol ingestion (Finn and Pihl 1987, 1988; Finn et al. 1990). Stewart and colleagues (1992) have shown this stress-dampening effect to be dose dependent, with heart rate decreases evident only at moderate to high alcohol doses in FHP subjects. Most recently, the specificity of alcohol stress-dampening effects was examined by comparing cardiovascular and muscular reactivity in two groups known to evidence cardiovascular reactivity to novel stimuli when sober—multi-generational FHP males and males with a family history of essential hypertension (HT) (Conrod et al. 1995). Importantly, results indicated that alcohol ingestion was associated with greater decreases in heart rate and muscle tension in FHP as compared with HT or FHN subjects. Pihl and colleagues (1990) hypothesized that increased responsivity to stimulation when sober coupled with large reductions in reactivity following alcohol ingestion may differentially negatively reinforce alcohol use in FHP males, thereby increasing their risk for development of alcoholism.

To date, only one laboratory study has examined ethanol self-administration in FHP and FHN youth. Using a relatively restrictive choice procedure that paced drinking behavior, this study found no difference in choices of ethanol drinks over placebo drinks, or in the amounts of ethanol consumed within choice sessions (de Wit and McCracken 1990).

Finally, despite many endocrine studies in alcoholics, little research has been published on the neuroendocrine axes as a marker for a familial predisposition for alcoholism. Schuckit and coworkers found that FHP males had blunted plasma ACTH, cortisol, and prolactin responses to an acute ethanol challenge compared to FHN subjects (Schuckit and Gold 1988; Schuckit et al. 1983, 1987*a*, 1987*b*); in contrast, Moss and coworkers (1989) reported comparable effects of ethanol on prolactin secretion in their sample of FHP and FHN males. In adolescents, Behar and coworkers (1983) did not demonstrate any differential cortisol response to ethanol as a function of family history. More recently, Gianoulakis and coworkers (1989) found that acute ethanol challenge produced a small but significant rise in plasma beta-endorphin (co-secreted with ACTH) in multigenerational FHP offspring compared to FHN subjects.

The Effects of Other Drug Challenges in Offspring of Alcoholics

As described earlier, differential responsiveness to ethanol is thought to be one potential mechanism for the observed differences in risk of alcoholism in FHP males. In order to better understand the nature of the risk conferred by a family history of alcoholism, it is important to determine whether FHP offspring show different dose-response relationships for drug classes other than alcohol, thereby suggesting increased risk for developing substance abuse disorders in general.

Recent studies in the author's laboratories used the alcohol challenge method to examine the pharmacological specificity to ethanol of FHP versus FHN response differences. Specifically, dose-effect functions for a variety of physiological, subjective, and psychomotor measures were established in FHP and matched FHN subjects for the short-acting barbiturate secobarbital. The well-documented cross-tolerance, similarity in intoxicating and withdrawal effects, and common mechanism of action at the GABA-benzodiazepine receptor complex between ethanol and barbiturates made this an interesting drug class for examining the sensitivity of FHP males to other drug classes. A single dose of ethanol was included in the design to allow for an explicit comparison of the magnitude of effect with

secobarbital. FHP subjects reported greater ethanol effects than FHN subjects on almost all subjective measures. Following the high dose of secobarbital, FHP but not FHN subjects showed elevated subjective effects, although these effects were less pronounced and evident in fewer measures than following ethanol. These findings suggest that family history differences partially generalize to another drug class that is cross-tolerant with alcohol and has a common mechanism of action.

Several drug challenge studies have been conducted comparing the effects of benzodiazepines in family history-positive and -negative subjects. Two studies have reported increased euphoric responses following alprazolam or diazepam administration as measured by the morphine benzedrine group (MBG) Scale of the Addiction Research Center Inventory (Ciraulo et al. 1989; Cowley et al. 1992; 1994). Also, Schuckit and colleagues (1991*b*) reported that intravenous (IV) diazepam administration significantly increased growth hormone in FHP as compared with FHN males; however, in the same study, no differences were observed in subjective effects, body sway, prolactin, or cortisol levels as a function of family history status (Schuckit et al. 1991*a*; 1991*b*). In contrast, Cowley and colleagues (1994) reported that FHP males evidenced less sensitivity to diazepam effects on two eye movement tasks (peak saccadic eye movement velocity and average smooth pursuit eye movement gain), self-rated sedation and memory (repetition, recall, and recognition).

A recent investigation examined the functional responsitivity of the GABA-benzodiazepine receptor complex as a function of familial alcoholism (Volkow et al. 1995). Specifically, effects of lorazepam were studied on regional brain glucose metabolism using positron emission tomography in subjects with and without a family history of alcoholism. Results indicated lower basal metabolic levels and a blunted drug response in the cerebellum of FHP subjects; no family history differences were observed in whole-brain glucose metabolism or in cortical or subcortical activity. FHP subjects also evidenced somewhat less motor impairment following lorazepam administration compared to FHN subjects, and impaired motor response following drug administration was found to be positively correlated with cerebellar metabolism. Overall, these findings suggest the involvement of the GABA-benzodiazepine receptor complex in sensitivity to alcohol and benzodiazepine effects.

Finally, using a self-administration paradigm, no significant differences were observed in frequency or amount of diazepam choices

by FHP and FHN males (de Wit 1991). Also, no differences were observed on ratings of drug liking, drug identification, Digit Symbol Substitution Test, or mood, although observer-rated signs of intoxication (e.g., slurred speech, trouble walking, talkativeness, drowsiness) were elevated following diazepam ingestion in FHP subjects only.

To date, there have been no alcohol or drug challenge studies in offspring of drug abusers.

MARKERS AS PREDICTORS OF SUBSTANCE ABUSE DEVELOPMENT

Several followup studies have been conducted to examine the predictive utility of the various measures that have been investigated as potential markers for alcoholism risk. Such work will be critical in determining the functional significance of the various differences that have been observed in behavioral and physiological studies of high-risk youth.

Schuckit (1994) reported findings from an 8- to-12-year followup of 223 men who participated in the alcohol challenge research conducted in his laboratory over the last decade. Remarkably, all subjects were located and only 1 percent of subjects declined participation in the followup interview. At the time of the followup interview, 34 percent of FHP subjects and 13 percent of FHN subjects had developed DSM-III-R alcohol abuse or dependence. Subjects who had developed alcohol abuse or dependence at followup had scored significantly lower on ratings of subjective high and had evidenced less body sway following alcohol administration in the earlier laboratory study; these effects were obtained independent of family history status. These findings suggest that decreased alcohol sensitivity may place individuals at increased risk for the subsequent development of alcoholism.

Berman and colleagues (1993) reported 4-year followup data on alcohol and drug use among FHP and FHN boys who had completed ERP assessment as preadolescents prior to substance exposure. A summary score of substance use was derived using an adolescent behavior questionnaire that elicited self-report data on use and/or effects of alcohol, tobacco, caffeine, marijuana, pills and other drugs, and on delinquency. Independent of family history status, P300s of lowest amplitude were associated with highest substance use scores at

followup. When corrected for subjects' age, there was a significant relationship between the combination of reduced amplitude and increased latency of target and nontarget P300 and substance use scores; however, the combination of these variables accounted for less than a quarter of the variance in the adolescent substance use measure. These findings suggest that while P300 measures may be predictive of subsequent development of substance use, other variables will need to be included in the model to more accurately predict risk.

Finally, the predictive utility of psychomotor sensitivity was examined using followup data from the Colorado Alcohol Research on Twins and Adoptees (CARTA) project (Rodriguez et al. 1993). Initial sensitivity on three psychomotor measures following alcohol ingestion was used to predict self-reported alcohol consumption collected annually over a 4-year period. For male subjects, decreased sensitivity to rail walking was associated with increased reports of alcohol use at year 2. For females, increased sensitivity on hand steadiness was associated with increased reports of alcohol use at year 2. The investigators suggested that overall results indicated at best a relatively weak relationship between psychomotor sensitivity and subsequent alcohol use since a relationship was observed for only one of three measures, at only one of four timepoints, and was opposite in direction for males and females.

METHODOLOGICAL LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

Refinements in Proband Ascertainment for High-Risk Studies

There has been considerable variation in the definitions of a positive family history of alcoholism used to recruit and characterize subjects across high-risk studies. For example, definitions have varied as to the proximity and extent of affected family members. In some early studies, probands were considered positive for a family history of alcoholism if a sibling had an alcohol problem; other more recent research has required that the proband's father, grandfather, and at least one other first- or second-degree relative meet diagnostic criteria for alcohol abuse/dependence. Further, there has been substantial variability in the rigor of the assessment methods and criteria for identifying a positive family history. Assessment strategies have included the Michigan Alcoholism Screening Test (Selzer 1971) (adapted to apply to the subject's mother or father), Family History-Research Diagnostic Criteria (Andreasen et al. 1977, 1986), Feighner

criteria (Feighner et al. 1972), or DSM-III-R criteria (American Psychiatric Association 1987). Such variability in subject selection criteria could certainly be expected to contribute to the discrepant findings across laboratory studies with FHP youth.

Genetic factors, as compared with environmental factors, are more likely to be major determinants of alcoholism in families with high-density patterns of alcoholism than in families with only one affected member. Thus, many of the study subjects that met criteria for participation in earlier research may not be genetically at risk for the disorder (Tarter 1988) or may differ in the degree of risk conferred by their familial alcoholism characteristics (Cloninger 1988). Indeed, this research is made even more challenging by the fact that even if a subject is FHP, he or she may not have inherited the marker or be at increased risk. It is important that only approximately 25 percent of FHP male offspring and fewer than 10 percent of FHP female offspring go on to develop substance use disorders as adults (Cloninger et al. 1981).

As described earlier, in a report by the author's research team (McCaul et al. 1990*a*), differences in self-reported alcohol and drug use patterns and associated problems were found as a function of extent of family alcoholism history. The greatest levels of alcohol and drug use were found for college students with a high density of alcoholism in their families (first- and second-degree affected relatives), an intermediate level for students with low alcoholism density families (first-degree affected relative(s) only), and the least in students with no affected relatives. Generally, students from high-density families reported greater use of alcohol, marijuana, sedatives, and cocaine; a younger age at first alcohol intoxication and first use of marijuana; and more experience with less commonly used drug classes such as opiates and hallucinogens. Finally, a greater percentage of these students reported personal alcohol- or drug-related problems as well as family mental health care. While similar findings have been reported in offspring of treated alcoholic probands (Merikangas et al. 1985), this was the first report of the significant role of density of familial alcoholism in determining the onset, amount, and broad extent of substance use in a diverse population of college males. These results are in line with earlier findings by Schuckit and Sweeney (1987) that men with a high density of familial alcoholism tended to report a higher frequency of drinking days, an earlier age of drinking onset, and more life problems than males with low density or unaffected families.

The importance of family density of alcoholism as a determinant of ethanol effects is further supported by a secondary analysis of alcohol challenge data from the author's laboratory (McCaul et al. 1991*b*). In general across physiological, psychomotor, and subjective measures, responses of subjects with a high density of familial alcoholism were significantly greater than either low-density or FHN subject responses; indeed, there were no differences between low-density and FHN subjects. Also, using laboratory methodology, Finn and Pihl (1987) demonstrated significant differences in resting heart rate and change in heart rate to a shock stressor for multigenerational family history-positive subjects as compared with low-density and FHN subjects, but no differences on these measures between low-density and FHN subjects. Thus, both epidemiological and laboratory studies have shown extent of familial alcoholism to be an important determinant of alcohol ingestion and effects.

While improved specification of family history status may be the most important subject selection criteria targeted for refinement, a number of other issues important in subject selection also should be addressed.

First, there needs to be increased restrictions on prior alcohol use of subjects enrolled in laboratory research. When subjects already have initiated use, the potential effects of differential prior exposure to alcohol/drugs on research outcomes cannot be ruled out. It is important to ensure that subjects have had no or only minimal prior alcohol exposure in research examining baseline differences between FHP and FHN subjects and that no symptoms of alcohol abuse or tolerance have developed in subjects included in alcohol challenge research.

A second area of consideration in subject selection is improved matching of FHP and FHN subjects. Investigators need to be sure to match on the variety of variables that may affect their results, including gender, race, typical and maximal alcohol use, other drug use, and, if administering a drug challenge, body composition.

Third, investigators need to consider the impact of the sociodemographic diversity in their subjects. In earlier research, many laboratories have recruited only college-enrolled subjects. In so doing, investigators may well be selecting individuals who are at reduced risk for problems compared to the general population. Finally, family history research would benefit from better characterization of subjects' personality characteristics, particularly

antiscoial personality (ASP) tendencies and symptoms. Such traits may be important determinants of baseline characteristics as well as alcohol/drug responses and should be characterized in the study sample.

Refinements in Laboratory Methods for High-Risk Studies

In addition to the suggested refinements in subject ascertainment, several methodological issues need consideration in designing laboratory research examining the effects of familial alcoholism.

First, several investigators have suggested that it is important to examine potential biphasic effects of alcohol in family history research. For example, Newlin and Thomson (1990) suggested that sons of alcoholics demonstrate greater acute sensitization during ascending blood alcohol levels and acute tolerance during descending blood alcohol levels as compared with sons of nonalcoholics. Given the rapid achievement of peak blood alcohol levels in many subjects, early and frequent collection of dependent measures would be necessary to detect such ascending blood alcohol effects. There is also evidence of family history differences in postsession "hangover" or withdrawal effects (McCaul et al. 1991*a*; Newlin and Pretorius 1990), suggesting the importance of extending data collection periods beyond the acute challenge session.

Second, this area of research could benefit from the inclusion of a range of biological and behavioral measures in the same studies. All too often, reports focus on either biological (e.g., hormonal or neurophysiological data) or behavioral-dependent measures, thus limiting the interpretation of study findings.

Third, investigators should consider increased standardization of procedures (e.g., alcohol/drug doses; timing of data collection procedures) and dependent measures (e.g., subjective report measures; hormonal measures; psychomotor tasks) to facilitate comparisons across studies.

Finally, as described earlier, it will be important in future research to evaluate subjects' long-term alcohol/drug use status to determine the predictive utility of proposed markers. Ultimately, laboratory measures that demonstrate significant differences as a function of family history will be informative only to the extent that they predict differences in alcohol and/or drug use patterns in adult FHP offspring.

SUMMARY

Epidemiological research has clearly demonstrated the importance of a family history as a determinant of future alcohol and, possibly, drug use in offspring of alcoholics. Laboratory studies have examined a wide range of potential markers both in the presence and absence of alcohol challenge, which may predict those subjects at high risk for the future development of alcoholism. While this body of research has yielded several replicable differences in FHP and FHN subjects, it also has been marked by many discrepancies in outcomes across studies. Future refinements in subject ascertainment and laboratory methodologies may help to bring greater procedural uniformity and consistency in study outcomes.

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Integrating Genetic and Behavioral Models in the Study of Substance Abuse Mechanisms

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INTRODUCTION

Over the past several years it has become broadly accepted that genetic factors play an important role in determining the robustness of certain drug-seeking behaviors. However, relatively little effort has been made to integrate the elegant methods established in behavioral genetics and the sophisticated techniques that form the basis for studying operant behavior. This chapter will hopefully serve to aid in this effort by reviewing some of the findings obtained in studies that have combined these approaches, and by illustrating how genetic methods can be used as a tool for achieving a greater understanding of the behavioral mechanisms of substance abuse.

A number of years ago the author and his colleagues began a series of studies that demonstrated genetic differences in the reinforcing effects of ethanol (EtOH) and other drugs. In the initial study, EtOH-reinforced behavior was examined in ALKO Alcohol-Accepting (AA) and Alcohol Non-Accepting (ANA) rats, animals that had been selectively bred for high versus low EtOH preference using a home cage, free access, two-bottle choice procedure, respectively (Ritz et al. 1986). It was found that, under a fixed ratio (FR) 1 schedule of reinforcement, AA rats would press a lever for 5.7 percent (w/v) EtOH more frequently than they would for water. Indeed, when water was substituted for the EtOH their operant behavior extinguished over a period of a few days, but was quickly reestablished when EtOH was reintroduced. This demonstrated that EtOH was functioning as a positive reinforcer in these animals. Conversely, the ANA rats showed no differences between responding for EtOH and water. While this was consistent with their low preference, this was the first demonstration that these two lines actually differed in positive reinforcement from EtOH.

That study and those which followed (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990; George 1987, 1990; Ritz et al. 1989*a*, 1989*b*; Suzuki et al. 1988) illustrate a number of important points. One is

the importance of control for genetic variability in experimental research. For example, it is rare to find an experiment in which the subjects consisted of one rhesus monkey, one beagle dog, and one rat. Control for species differences has been standard practice for many years, and represents a partial control of genetic variability. However, within a species, less attention has been given to further genetic definition and control. An important perspective on this is that using genetically undefined animals is akin to using an undefined "stimulant" drug. Scientists do not say subjects self-administered a stimulant; instead, they are very precise in defining the actual chemical used, such as cocaine-HCl. Similarly, researchers can exercise the same amount of experimental control over the tissue with which the drug is interacting by precisely controlling genotype, and using "reagent grade" subjects. To the extent that scientists are able to control for such variability, they should do so.

Second, a major advantage of genetic control and the use of genetically defined subject populations is that findings contribute to and become a part of an ever-growing database for use in correlational analyses. For example, the data that are obtained when using readily available inbred rodent strains add to the existing database for that genotype, and may be repeatedly used by the original investigator as well as by other investigators.

There are additional advantages to using genetic methods, but the two described above form a significant portion of the basis for incorporation of this genetic approach into behavioral research. The remainder of this chapter is devoted to describing some of the ways in which these genetic factors may be used to aid in understanding the behavioral as well as biochemical mechanisms of substance abuse.

REINFORCEMENT: A UNIQUE EFFECT OF CERTAIN DRUGS

One question that researchers have been interested in exploring is the relationship among different responses to drugs, such as reinforcing effects, depressant effects, stimulant effects, etc. This question can be approached in a systematic manner using a number of genetic methods. Through the use of genetic correlational analyses, genotypes that differ for a given trait can be used to test associations between that trait and any other traits hypothesized to be causally related. A lack of correlation indicates that the measures studied are not mechanistically related. A strong positive correlation, while not conclusive, provides supportive evidence that the measures are

causally related and mediated at least in part by common genetic mechanisms.

For example, in developing an effective animal model of drug taking, it is important to understand the degree of relationship among various methods of measuring alcohol or other drug intake. In the area of alcohol consumption, it is important to determine the degree to which homecage preference paradigms and operant drug reinforcement studies measure the same or similar phenomena, both behaviorally and biochemically. Animals that prefer EtOH when given a choice between a drug solution or water in a 24-hour access homecage testing situation may or may not work to a significant extent to obtain the drug under more rigorous and constrained operant chamber conditions. Similarly, lack of drinking in a preference paradigm may or may not suggest lack of reinforcement under other operant conditions.

Reinforcement Versus Preference

The relationship between reinforcement from EtOH and EtOH preference has been estimated by comparing EtOH-reinforced responding using operant procedures and EtOH preference scores from a number of rodent genotypes (George 1990; George and Ritz 1993). The results suggest a moderate but not significant positive relationship between these two measures of EtOH drinking (figure 1A). The most notable exceptions to a general positive relationship are Long Sleep (LS) mice, which show a high degree of reinforcement from EtOH but very low EtOH preference, and Non-Preferring (NP) rats, which are reinforced by EtOH even though they have been genetically selectively bred for having low EtOH preference.

Thus, while preference paradigms may provide a rapid method useful in initial screening of subjects, this model does not appear to be a good predictor of positive reinforcement from EtOH. There are a number of possible reasons for this lack of association. One is that preference studies typically are confounded by taste and prandial influences, since the measure of drinking is based upon consumption over time with food concurrently available. A second is that preference paradigms may not be sufficiently sensitive to detect intake of significant amounts of EtOH in animals whose absolute levels of intake are limited by neurosensitivity factors, such as the LS mice, but for which EtOH is reinforcing (Elmer et al. 1990). A third possible reason is that in preference studies that do not

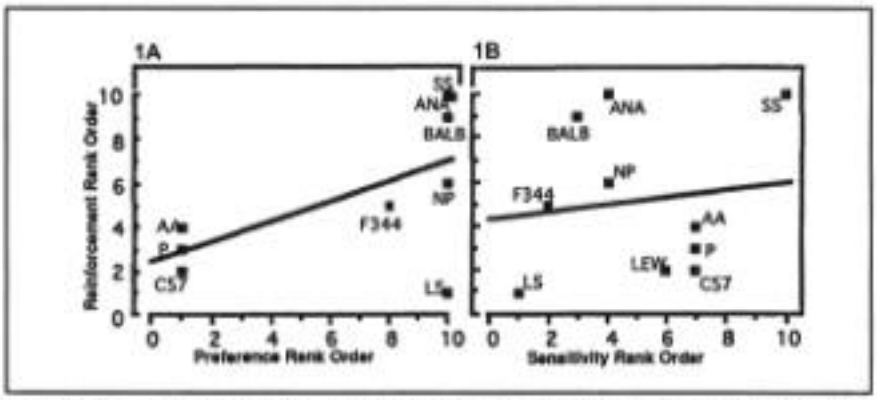

FIGURE 1. *Comparison of rank order for EtOH reinforcement versus EtOH preference (T=0.39) (1A) and EtOH reinforcement versus neurosensitivity to EtOH defined by duration of loss of the righting reflex (T = 0.12) (1B) for several rat and mouse genotypes. Linear regression lines are included for illustrative purposes. Concordance between measures is based upon Kendall's Tau coefficient (T) for rank-order correlations.*

SOURCE: George (1990).

incorporate exposure to significant amounts of the drug through some form of initial training, low preference may be due to avoidance of the drug solution for reasons related to taste or smell, resulting in a situation where consumption is too low for the animals ever to experience the postabsorptive interoceptive cues related to initiation of reinforcement. Thus, preference may be a permissive factor, particularly important for drug taking via the oral route, which allows the organism to consume significant amounts of a drug. Consumption of large doses over a sustained period of time may then result in association of the drug-taking behavior with its postabsorptive, presumably central effects, and the drug may then come to serve as a positive reinforcer. However, preference per se does not appear to be equatable with reinforcement.

Reinforcement Versus Neurosensitivity

The relationship between reinforcement from EtOH and neurosensitivity to EtOH has also been studied. In this context, neurosensitivity to EtOH is more specific than sensitivity to EtOH in a broad sense, in that differences in neurosensitivity implies a difference in some aspect of central nervous system (CNS) function, in the absence of any detectable pharmacokinetic or metabolic differences. For example, the highly neurosensitive LS and the

highly neuroinsensitive Short Sleep (SS) mice show extreme differences in response to the depressant effects of EtOH as measured by duration of loss of the righting reflex; yet, Elmer and colleagues (1990) showed that EtOH could readily function as a positive reinforcer in LS mice but not in SS mice. This outcome is the opposite of what would be expected if reduced neurosensitivity to EtOH was a primary factor in establishing EtOH as a reinforcer, and when combined with other findings (figure 1B) indicates that there appears to be virtually no relationship between propensity to self-administer EtOH and this measure of neurosensitivity to EtOH (George 1990). Thus, while neurosensitivity may be a limiting factor in terms of absolute intake of EtOH, neurosensitivity, at least as defined by the depressant effect of duration of loss of the righting reflex, does not appear to influence the ability of EtOH to function as a positive reinforcer.

Other recent findings suggest that reinforcement from EtOH also is not related to the severity of withdrawal from EtOH nor to the locomotor stimulant effects of EtOH. EtOH has a broad dose-response curve and produces many effects, any of which could be related to or predictive of drinking and/or reinforcement from EtOH. For example, neurosensi-tivity is important in determining the severity of EtOH withdrawal. A common measure of EtOH withdrawal is the occurrence of seizures, since many animals, including humans, exhibit seizures during EtOH withdrawal (McSwigan et al. 1984). These EtOH withdrawal convulsions are quantifiable and positively correlated with dose and duration of EtOH exposure (McSwigan et al. 1984). Interestingly, when LS and SS mice were tested for EtOH withdrawal severity, SS mice showed the most severe withdrawal seizures (Goldstein and Kakihana 1975). Since SS mice do not appear to prefer or be reinforced by EtOH, while LS mice are readily reinforced by this drug (Elmer et al. 1990), it is possible that genes related to severity of EtOH dependence or withdrawal reactions may be involved in mediating at least a portion of EtOH's rewarding effects.

Recently, mice have been selectively bred to be either Withdrawal Seizure Prone (WSP) or Withdrawal Seizure Resistant (WSR) to EtOH withdrawal as assessed by the extent of handling-induced convulsions following establishment of physical dependence on EtOH and subse-quent withdrawal of this drug (Crabbe et al. 1983). Currently, these WSP and WSR mice differ by some tenfold in severity of withdrawal seizures, and by implication, in their degree of physical dependence on EtOH (Kosobud and Crabbe 1986). It has also been shown that

differences between these lines with regard to CNS excitability are specific to EtOH (McSwigan et al. 1984).

The relationship between EtOH-reinforced behavior and physical dependence on EtOH as measured by withdrawal severity has been examined by using operant methodology to test for reinforcement within the WSP and WSR mice (Barbera et al. 1994). EtOH did not serve as a reinforcer for any of the groups. However, further analysis revealed individual differences in responding within each of the four groups (WSP1, WSP2, WSR1, WSR2), as at least one animal from each group did show EtOH-reinforced behavior. These individual differences did not show any systematic pattern within or between groups, suggesting that genes regulating the rewarding effects of EtOH are independent of genes mediating withdrawal severity and appear to be segregating randomly within and between groups. These findings indicate a lack of relationship between the traits of withdrawal severity and the reinforcing effects of EtOH and are consistent with a lack of association between propensity to develop physical dependence on EtOH and propensity to find this drug reinforcing. There are several possible reasons for the absence of group effects in this study. It is possible that there was a problem with the procedure or that animals were inappropriately trained. This seems unlikely since the procedure used is similar to that used successfully in several previous studies with mice (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990); similar studies were simultaneously being conducted in the author's laboratory in which robust reinforcement effects were found; and all animals showed elevated blood EtOH concentrations (BECs) during the training phase. A second possibility for the absence of robust reinforcing effects of EtOH is simply that none of the animals were in fact reinforced by EtOH. This also seems unlikely since some animals did achieve BECs above 100 mg/dL within a brief 30-minute session. These levels are typically associated with overt behavioral effects of EtOH, and were achieved in the absence of any prandial or postprandial confounds since food was not available prior to or during the test sessions. A third possible explanation appears correct based upon the findings obtained. The data indicate that some individual animals within each selection line were indeed positively reinforced by EtOH, but these individual animal data were masked by those of other animals within each selection line group, which were not reinforced. When combined as group averages, data from the reinforced and nonreinforced animals effectively canceled out one another, such that the group averages indicated an overall lack of positive reinforcement.

With the exception of those genes mediating EtOH withdrawal severity, the genotypes of the mice used in this study should represent a sample from a randomly segregating population with substantial heterogeneity. Since mice are capable of showing reinforcement from EtOH (Elmer et al. 1986, 1987*a*, 1987*b*, 1988, 1990), and since the WSP and WSR populations are derived from several inbred strains, which include EtOH drinkers and EtOH avoiders (Crabbe et al. 1983), some individual animals would likely show reinforcement, some might show avoidance, and some might show no effect, consistent with the third explanation for the lack of robust group effects in this study. If withdrawal severity is not indicated in EtOH reinforcement, then EtOH reinforcement becomes an independently segregating phenomenon and should be represented, in a random pattern, across all genotypes. While there are several factors that could contribute to this type of response distribution, the data are consistent with the conclusion that the genes mediating the reinforcing effects of EtOH are segregating independently of genes mediating the withdrawal effects of EtOH.

One further issue is whether animals selected for withdrawal seizure proneness or resistance must experience their selected phenotype to allow the genes mediating the phenotype to exert pleiotropic effects on other phenotypes, such as EtOH-reinforced behavior. However, if genes mediating withdrawal seizure severity are exerting pleiotropic effects on EtOH drinking or reinforcement, they should do so regardless of the experience or naivete of the subject with regard to the selection phenotype. Thus, the present findings suggest that there is little influence of withdrawal seizure genes, as opposed to withdrawal seizure experience, on drinking and reinforcement.

In another study (Sanchez et al. 1994), operant self-administration of EtOH was examined in mice selectively bred for high locomotor stimulation in response to EtOH injection (FAST mice) and mice selectively bred to produce little locomotor stimulation response to EtOH (SLOW mice). This study examined EtOH consumption and rein-forcement in replicate lines of mice that have been selectively bred for differential locomotor stimulation in response to EtOH. This particular genetic trait of the animals allows for a test of the relationship between locomotor stimulation and EtOH reward.

There were no differences between the selected lines in the extent to which the animals would self-administer EtOH. None of the groups of mice showed EtOH-reinforced behavior, although within each group there were both responders and nonresponders. These findings

provide initial evidence that the genes mediating locomotor stimulant effects of EtOH are distinct from those associated with the rewarding effects of this drug.

When combined with similar data from other drugs, evidence suggests that the reinforcing effects of drugs comprise a unique dimension of effect that is not the result of, nor due to, causal genetic relationships with other drug effects. Reinforcement appears to be a unique effect associated with a subset of psychoactive compounds, and determination of the causes of and controls for this effect requires direct study of drugs as reinforcers and not indirect implications of reinforcement based upon other possibly correlated measures.

REINFORCEMENT: COMPRISED OF MULTIPLE COMPONENTS

Research findings from several areas of research suggest that there exist several related but distinct dimensions of drug-seeking behavior, and that these dimensions can be separated for detailed analysis of their contributions to substance abuse. For example, studies of EtOH-reinforced behavior in animals genetically selected for high or low EtOH preference indicate that EtOH-reinforced behavior may be influenced by not only the intrinsic rewarding effects of the drug, but also factors that determine motivation to work for the drug (i.e., incentive value). AA rats, genetically selected for maximal EtOH consumption in a two-bottle choice paradigm, while reinforced by EtOH, will not exhibit prolonged responding in operant paradigms requiring learned sequences of behavior to gain access to EtOH solutions (Ritz et al. 1986, 1989*a*, 1989*b*). For these rats, as FR size increases above FR1, response rates decrease substantially, especially when compared to response rates of other "alcohol preferring" rats, such as the EtOH-Preferring (P) rat line. In similar recent experiments, EtOH-reinforced behavior was studied in EtOH P and High Alcohol Drinking (HAD) rats and NP and Low Alcohol Drinking (LAD) rats. Genetic differences in EtOH-reinforced behavior were observed. EtOH served as a strong positive reinforcer for P rats, a slightly less efficacious reinforcer for NP and HAD rats, and was not shown to be reinforcing for LAD rats (Ritz et al. 1994*a*, 1994*b*; Samson et al. 1988; Waller et al. 1984). These findings are consistent with results discussed earlier, indicating that EtOH drinking in a preference paradigm is not highly predictive of the reinforcing effects of EtOH. NP rats, like P rats, will exhibit EtOH-reinforced responding under operant conditions. Further, preferring HAD rats exhibit significantly fewer responses for EtOH under a range of

concentrations and FR sizes relative to their P rat counterparts, even though both lines have been genetically selected for EtOH preference using a home-cage, two-bottle choice paradigm, and rats from both lines consume similarly high quantities of EtOH on a gram/kilogram/day basis in a preference test.

In addition, these results illustrate genetic differences with regard to the propensity of animals to maintain EtOH-reinforced behaviors as work requirements were increased. As shown in table 1, P rats are high preferring, reinforced by EtOH, and show persistent responding under increasing workloads, while high preferring HAD rats are more modestly reinforced and show little persistence in responding for EtOH under conditions of high workloads. It is interesting to note that while the parental stocks for these two lines differed, the similar selection processes used produced rats that consume similar amounts of EtOH when tested in a two-bottle preference task. NP rats, on the other hand, are very low preferring, but show EtOH-reinforced responding for EtOH equivalent to that of the HAD rats when only one lever press was required. Interestingly, NP rats also show a moderate level of persistence in responding, and this persistence is much greater than that seen in HAD rats. Finally, the low preferring LAD rats are not reinforced by EtOH and show no significant persistence in responding for EtOH (Ritz et al. 1994*a*, 1994*b*).

Thus, although EtOH can be readily established as a reinforcer for AA, NP, and HAD rats, rats from these lines appear to lack specific motivational factors that would facilitate continued responding under conditions requiring higher workloads. These data suggest that continued chronic abuse of a drug requires not only specific reinforcing effects of a drug, but also motivational factors, which appear to vary independent of response to reinforcing effects. Taken together, the results suggest that reinforcing effects of EtOH may be due to the influence of multiple components, including: (1) an intrinsic permissive factor contributing to EtOH preference, (2) direct rewarding effects, and (3) motivational factors.

TABLE 1. *Qualitative expression of preference, reinforcement, and persistence for EtOH-seeking in rats selectively bred for high or low EtOH preference.*

Genotype	Preference		Reinforcement		Persistence
P	+++		+++		+++
NP	---		++		++
HAD	+++		++		-
LAD	---		---		---

KEY: + = relative degree of positive performance (e.g., P and HAD rats each have three plus symbols under the preference column to indicate highly similar preference tests results and to indicate higher preference than the other listed genotypes). å = relative degree of nondrinking or avoidance. These symbols indicate a qualitative relationship rather than an absolute quantitative one.

SOURCE: George and Ritz (1993).

REINFORCEMENT: A GENERALIZABLE EFFECT

Another important question in substance abuse that can be effectively addressed using genetic correlation methods is whether propensity to self-administer one drug, such as EtOH, shares common genetic control with the propensity to self-administer other drugs, such as cocaine or opiates. This "commonality" question can be addressed by measuring the extent to which animals from various inbred strains self-administer a variety of drugs. Researchers in the author's laboratory have begun to address this commonality question by examining operant self-administration of alcohol, cocaine, and opiates in several mouse and rat strains (George and Goldberg 1989). The potent opioid agonist etonitazene (ETZ) has been established as a reinforcer in Lewis rats and C57BL/6J mice, but not for F344 rats or DBA/2J mice. F344 rats and DBA mice in fact tend to avoid ETZ solutions. Similar results have been obtained with cocaine. Lever-press responding by Lewis rats and C57BL/6J mice was high for cocaine but low when only water was present as the reinforcer, whereas responding by F344 rats was minimal and occurred sporadically. Overall, the results suggest that a high degree of qualitative commonality exists across these genotypes and drugs, as summarized in table 2 (George 1991).

TABLE 2. *Summary of qualitative commonality.*

Genotype	Alcohol	Opiates	Cocaine
Rats			
LEW	+++	+++	++
F344	+å	åå	å
Mice			
C57BL/6J	+++	+++	+++
DBA/2J	åå	åå	NA

KEY: + = relative degree of positive reinforcement; å = relative degree of nonreinforcement or avoidance. Three symbols is maximum response relative to all genotypes tested. NA = Data not available.

SOURCE: George (1991).

These initial results from studies of drug self-administration across different drugs and genotypes suggest that genotypic patterns of reinforcement from EtOH may correlate highly with patterns of reinforcement from cocaine and opiates. Thus, drug-seeking behaviors maintained by EtOH, cocaine, and opiates may have at least some common biological determinants. The fact that this significant level of commonality or generalizability exists would suggest that reinforcement, while a unique drug effect, is a broad-based phenomenon defined by the responsivity of the individual organism to this effect, and may be generalizable across substances.

Thus, the integration of behavioral genetic and operant methodologies has potential for increasing researchers' understanding of the contributions and interactions of genetic and environmental factors in determining drug-seeking behavior, and in distinguishing between various aspects of reward and motivation as they contribute to substance abuse. Further, the demonstration of genetic differences in animal models of drug-seeking behavior suggests that there may exist human populations with differing degrees of biological risk for drug abuse.

Thus, reinforcement is a unique dimension of effect that occurs following administration of certain psychoactive drugs; it appears to be composed of multiple, distinct components; and there appears to

be a substantial degree of generalizability of reinforcement within a given genotype across drugs.

USING GENETIC METHODS TO DETERMINE ASSOCIATED BIOCHEMICAL CORRELATES OF DRUG-SEEKING BEHAVIOR

The density of serotonin (5HT) receptors and the influence of 5HT systems have been implicated in alcohol preference and reinforcement. The author has recently begun a systematic investigation into the role of 5HT systems in the operant reinforcing actions of EtOH. Through the use of mice from two genetically similar strains, which differ in their densities of 5HT receptors, genetic influences on alcohol-reinforced behavior that may be mediated by $5HT_2$ receptors have been shown. C57BL/6J mice have significantly lower $5HT_2$ receptor densities than do C57BL/6ByJ mice (figure 2). In order to explore differences in EtOH consumption between these two strains, operant conditioning studies were used to examine the self-administration of EtOH.

The purpose of experiment one was to determine if alcohol would serve as a reinforcer, and to what extent, for these genetically different but similar mouse strains. Subsequently, by increasing the number of lever presses needed to receive EtOH reinforcement, experiment two attempted to establish how much work the mice would be willing to perform in order to obtain access to a solution of 8 percent EtOH. The responses of the two strains at different EtOH concentrations were then examined.

Using standard food-induced training procedures, mice were exposed to a series of increasing EtOH concentrations (0, 2, 4, 5.7, and 8 percent w/v) in response to a lever press during repeated daily 30-minute test sessions. Subsequently, the amount of food received before each session was gradually reduced to zero. To determine if EtOH served as a reinforcer, the liquid consumed was alternated between 8 percent EtOH and vehicle (0 percent). To test if EtOH served as a reinforcer under

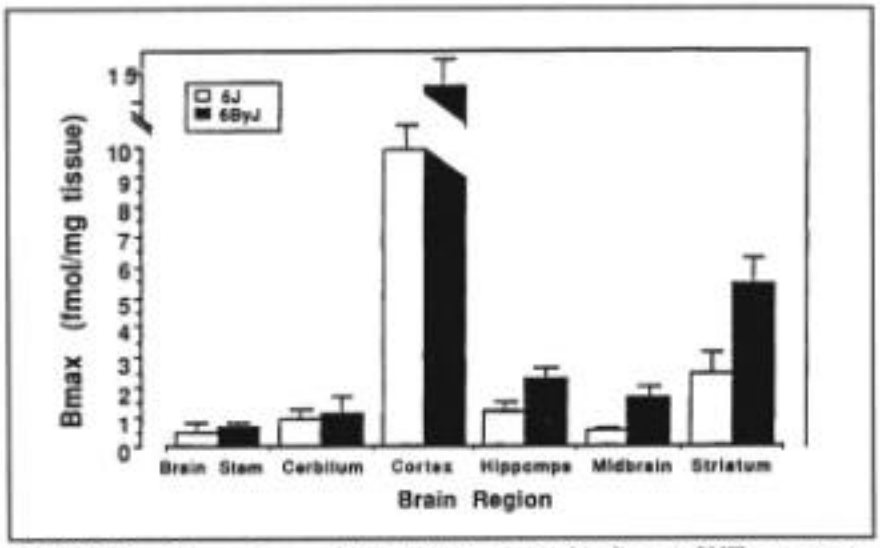

FIGURE 2. *Comparison of tritiated ketanserin binding at $5HT_2$ receptors across several brain regions in C57BL/6J and C57BL/6ByJ male mice. Cerbllum = cerebellum. Hippcmps = hippocampus. Differences significant ($p < 0.05$) in hippocampus, midbrain, and striatum.*

varying FR conditions, the number of lever presses required to obtain a reinforcement was increased in order from 1 to 2, 4, 8, 16, 32, 64, and 128. The concentration of EtOH was also manipulated in a subsequent experiment.

The differences in BECs and trials completed between the two strains were significant during training. The highest group BEC observed was 264 mg/dL in the C57BL/6J mice, and the highest group BEC observed for the C57BL/6ByJ mice was 150 mg/dL. None of the groups showed a pattern of responding consistent with extinction or the development of taste aversion. At FR1, the C57BL/6J (low $5HT_2$ receptor density) mice completed more trials (figure 3) and had higher BECs than the C57BL/6ByJ mice. Trials completed, BECs, and lever presses were all higher for the C57BL/6J (low $5HT_2$ receptor density) mice than for the C57BL/6ByJ mice in the FR conditions (figure 4). No differences were found between the groups when the EtOH concentration was varied.

The results of these experiments provide evidence that the density of 5HT receptors may influence the extent to which EtOH serves as a

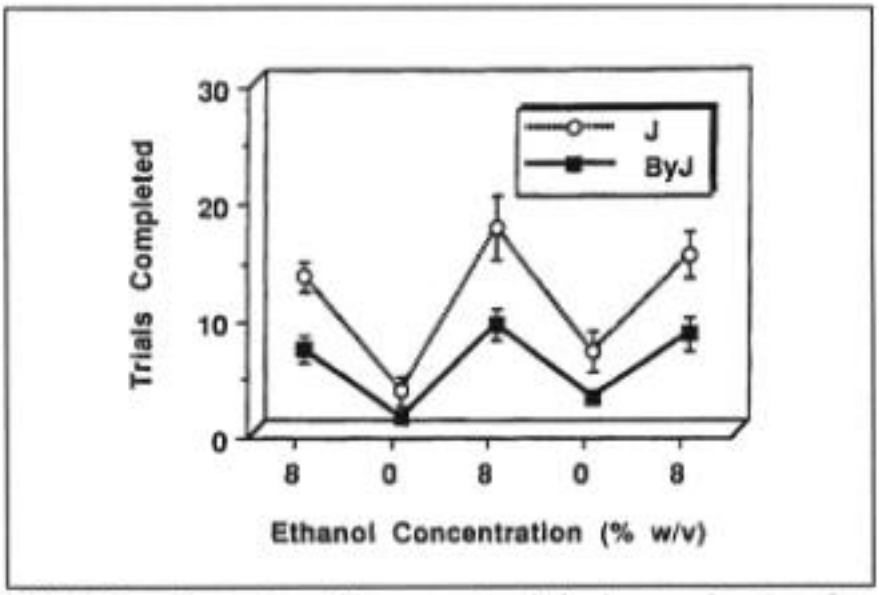

FIGURE 3. *Comparison of lever-pressing behavior as a function of EtOH or vehicle availability in C57BL/6J and C57BL/6ByJ male mice.*

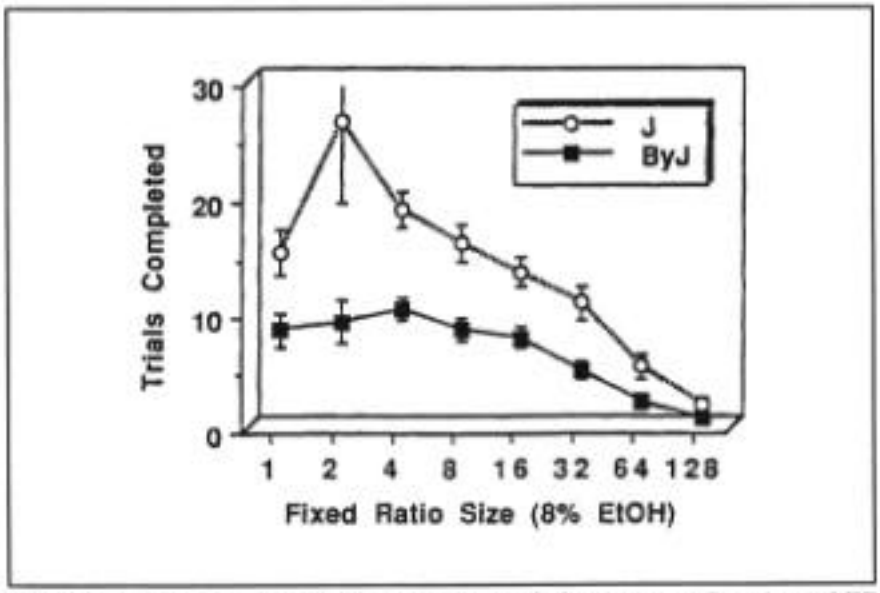

FIGURE 4. *Comparison of lever-pressing behavior as a function of FR size in C57BL/6J and C57BL/6ByJ male mice.*

reinforcer. The results of experiment one indicate that alcohol served as a reinforcer for both the C57BL/6J (low $5HT_2$ receptor density) and the C57BL/6ByJ mouse strains. The consumption of EtOH by the C57BL/6J mice, however, was in all instances significantly greater than alcohol consumption by the C57BL/6ByJ mice. The C57BL/6J mice appear to work harder in general than the C57BL/6ByJ mice for EtOH reinforcement.

Because these two strains of mice are so similar genetically and differ at only a few loci, the results suggest that the density of $5HT_2$ receptors present may influence motivational factors associated with the reinforcing properties of alcohol. Animals with greater densities of $5HT_2$ receptors showed less persistence in responding for EtOH, even though all animals were reinforced by EtOH to some extent. This conclusion supports the hypothesis that predisposition to alcohol abuse involves multiple genetic factors, and that some of those genetic factors may be related to $5HT_2$ receptor function.

CONCLUSIONS

For too long, geneticists have been studying the role of genetic factors in conveying susceptibility to drug abuse, while behavioral scientists have been dissecting the roles of learning and behavioral patterns in initiating and maintaining drug use, both with little recognition of the other's contributions to science. Much could be gained, however, by combining these fields into a more integrated view of the problem of addiction. Behavioral scientists could achieve improved control over variation and subsequent error in their studies by incorporating the use of better-defined subjects in terms of genetic heritage. For example, the use of Sprague-Dawley rats conveys little genetic control relative to the precise behavioral measurements used in most behavioral pharmacology experiments. Much better experimental control over subject variance could be easily obtained by choosing a more precisely defined experimental subject, such as a rat from a truly genetically inbred strain, such as the Lewis strain. By using genetically identical subjects, it should be readily apparent to the reader that any resulting variation in response to a drug or other experimental challenge would be the result of "environmental" variance and that it could be explored parametrically without the confounds of undefined "genetic" variance acting to increase the overall variation and "noise" in one's studies. Years ago, in the absence of evidence to the contrary, it was simple for behaviorists to state that any subject will respond to a positive reinforcer under the appropriate learning conditions. But it is now clear that this is not

the case, and that while the environmental conditions are important for the expression of a trait, there are also biological, i.e., genetic constraints that greatly affect the ability of subjects to perform even the most species-appropriate learned tasks.

Thus, genetic methods have great potential for increasing scientists' understanding of addictions, especially if these methods are integrated into other established approaches. The objectives of this integrative approach are to identify, at the molecular, cellular, and behavioral levels, those factors that maintain drug-taking behaviors. Issues such as the biochemical sites of drug reinforcement, the relationship between drug preference and drug reinforcement, and the commonality of self-administration behavior across drugs can be effectively addressed using behavioral genetic approaches. The use of genetic models in this area is not only improving researchers' understanding of genetic contributions to addiction, but can also aid in understanding the environmental factors involved in vulnerability to drug abuse.

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Disaggregating the Liability for Drug Abuse

Ralph E. Tarter, Howard Moss, Timothy Blackson, Michael Vanyukov, Janet Brigham, and Rolf Loeber

It is consensually accepted that the liability for developing a substance abuse disorder is not the same for all individuals in the population. Only marginal progress has been made, however, in determining the factors responsible for the variation in the liability to drug abuse, encompassing interacting biological, behavioral, and environmental processes. Since variation in the liability has a multifactorial basis, it is necessary, therefore, to identify the integral biobehavioral traits and to determine how a person's position on these traits (phenotypes) covaries with environmental influences to determine liability status. Once this can be accomplished, it will be possible to specify with a high level of precision the liability for developing a drug abuse disorder for each individual in the population.

At the outset, determining the factors contributing to the liability for drug abuse requires documentation of the pharmacological properties of compounds having abuse potential. From the multifactorial perspective of drug abuse etiology, pharmacological factors (including both kinetics and behavioral reactions), in concert with a host of other variables such as influences from family and friends, psychiatric status, drug availability, personality disposition, and beliefs about the effects of drugs, combine to determine the liability for a drug abuse disorder. This liability can be characterized as a continuous multidimensional trait ranging from a score of zero (no likelihood for the adverse outcome) to one (affected state of drug abuse disorder).

Because the liability has a multivariate basis, its distribution, as shown in figure 1, is normal in keeping with the theorem of central limits. To surpass the liability threshold for diagnosis, biochemical, physiological, and behavioral processes, through interaction with microenvironment (e.g., family) and macroenvironment (e.g., community) influences, shift or deflect the person's position (his or her liability phenotype) on the liability axis to the beyond-the-threshold region. The person is thereby deemed to be "affected" or to be a "case."

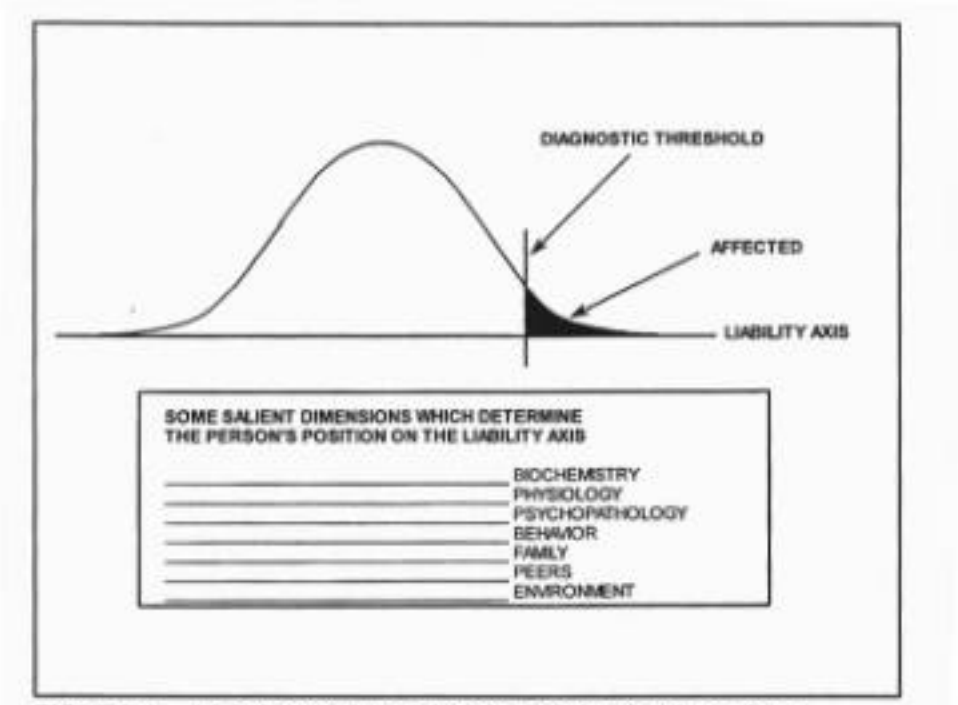

FIGURE 1. *Multifactorial model of the liability for drug abuse.*

Why does an individual's status change from noncase to case? This is the overarching question in research on drug abuse etiology. The theoretical framework guiding this line of research is discussed below.

THEORETICAL FRAMEWORK FOR DISAGGREGATING THE LIABILITY

A person's position on the liability axis is the product of the interaction between phenotypic variation on salient traits and environmental influences. As illustrated in figure 2, phenotypic variation (that is, the person's position on a trait) is the product of the interaction and covariation between genotypic variation for the trait in the population and two types of environmental influences. As the terms denote, *shared* and *unique* environments refer to aspects of the environment that are held in common with other family members or are specific to the individual. On continuous traits, there are, therefore, an infinite number of phenotypes.

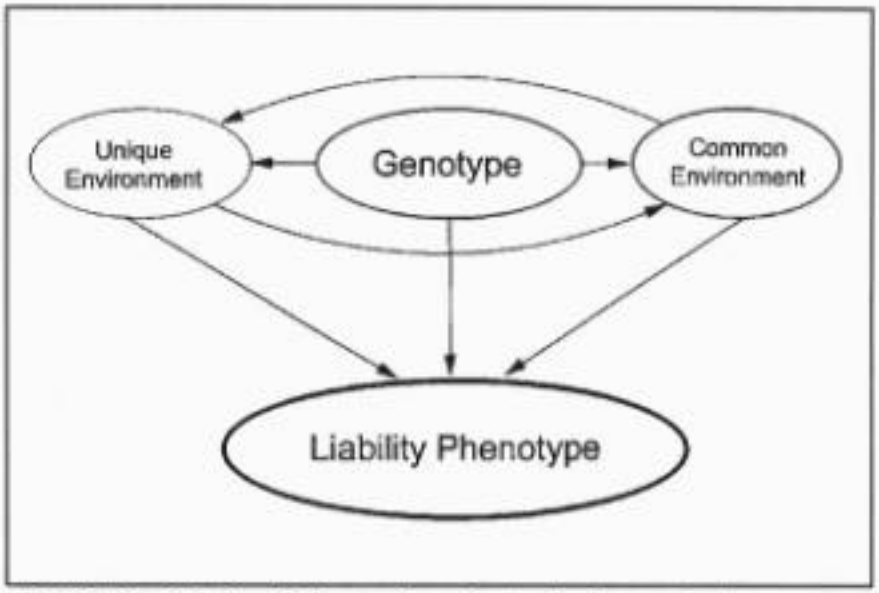

FIGURE 2. *Origins of phenotypic variation in the population.*

Inasmuch as numerous biobehavioral traits are associated with the liability to drug abuse (see figure 1), and because each trait has an infinite number of potential phenotypes, the etiological pathway to drug abuse is distinct for each affected individual. Elucidating the etiology of drug abuse thus requires determining how phenotypic individuality contributes to the outcome diagnosis of substance abuse/dependence. In other words, how are individual differences molded into a shared outcome phenotype, namely, the characteristics qualifying for diagnosis? To address this question, empirical research focuses on two main topics. First, investigations are directed at identifying the biological and behavioral traits that are salient to drug abuse liability. Second, research is conducted to determine how phenotypic variation on the putatively salient traits interact among each other so as to determine the person's position on the liability trait or axis.

Numerous biochemical, physiological, behavioral, and cognitive traits have been implicated to be associated with the liability for substance abuse/dependence. With respect to biochemical traits, neurochemical and endocrine mechanisms have been linked to the liability for substance abuse (Eskay and Linnoila 1991). Physiological evidence has been accrued pointing to the importance of intrinsic EEG rhythms and information-processing efficiency as measured by event-related potentials (Brigham et al. 1995). In addition, autonomic

reactivity has been observed to be associated with the liability for substance abuse (Finn et al. 1990). Numerous behavioral traits have also been implicated; the most frequently reported include sensation-seeking, impulsivity, coping style, and social skills. Finally, certain neuro-cognitive capacities as well as expectancies and beliefs about the effects of drugs appear to be associated with the liability for drug abuse (Hesselbrock et al. 1991). Clearly, many biobehavioral traits contribute to the variation in the liability. To date, comprehensive integrative research has not been conducted to delineate in quantitative fashion how phenotypes across multiple levels of biological organization interact to determine the person's position on the liability axis.

Research into the multifactorial determinants of the liability to substance abuse requires a developmental focus. Epidemiological research has demonstrated that the age at which a substance abuse diagnosis is first manifest is not equally distributed across the lifespan among the population of individuals who develop this disorder. This is not surprising since biological and behavioral processes change with age consequent to ongoing interactions with multiple environments (e.g., family, peers, work.). Consequently, the factors influencing one's position on the liability axis are not the same throughout life. For example, in youth, the factor of peer affiliation is likely to be a more important contributor to the liability for substance abuse than in adults, since adolescents are especially susceptible to the influence of friends. In contrast, among older adults, reactions to the pharmacological properties of analgesic and hypnotic drugs may be more important determinants of the liability because chronic pain and sleep disorders are uncommon in youth. It is thus important to research drug abuse etiology within a developmental framework inasmuch as the particular traits contributing to the liability and their constituent phenotypes change throughout the lifespan. Because the components of the liability change during life, the person's position on the liability axis fluctuates over time. Consequently, depending on the changing dynamic between phenotypes and environmental influences, a drug abuse disorder can occur at any time in life subsequent to initial drug exposure. As depicted in figure 1, the shift from nonaffected to affected status corresponds to the person surpassing the diagnostic threshold on the liability axis.

This lifespan perspective is illustrated in figure 3. It can be seen in the hypothetical developmental pathway that the person's position on the liability axis changes with age. At the moment of conception,

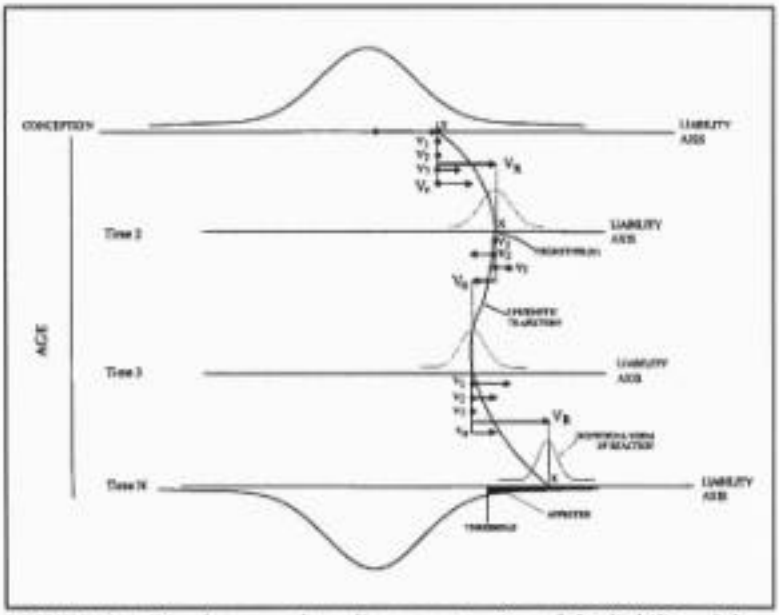

FIGURE 3. *Developmental nonlinear patterning of the liability of drug abuse.*

everybody's liability phenotype is subthreshold, as the whole age-specific liability distribution, reflecting predominantly genotypic variation, contains no substance abuse phenotypes. The mode of the age-specific liability distribution shifts to the right as age progresses. Concomitantly, the individual phenotype may change in its absolute value and with respect to its relative position within the liability distribution. The upper and lower limit of phenotypic change that is possible within a particular environment is genetically determined; this range is termed the norm of reaction. In effect, the potential for modification of behavior has limits which, in a given environment, is genetically determined. (For example, a baby's future height in adulthood, or for that matter any complex phenotype, has an upper and lower limit controlled by genetic factors; however, within that range environmental factors influence variation.) In the example shown (see figure 3), following a series of events occurring during the lifespan, the person satisfies criteria for a drug abuse diagnosis; this is shown by the person's position in the affected range on the liability axis in the distribution at the bottom of the figure. One of the cardinal issues in etiology research is to clarify the developmental trajectory linking the outset and outcome positions on the liability axis.

As previously discussed, one's liability phenotype is determined by the interaction among the phenotypes on salient traits spanning biobehavioral organization and shared and unique environmental influences. This is designated on the liability axis by $\underline{X}$ in figure 3. $\underline{X}$ is the product of the interaction of all phenotypes V_1, V_2, V_3...V_N on traits associated with the liability. Their resultant product is a vector designated V_R. This vector, consisting of all salient phenotypes and in the context of shared and unique environmental factors, influences the direction of the developmental trajectory toward either a good or poor outcome. In figure 3, this is manifest as a shift in the position on the liability axis toward either the normative (left side) or toward the affected (right side) segment of the population distribution.

Numerous factors operate during development that determine the course and direction of the trajectory. For example, changing environmental circumstances impact on the individual to change behavior and physiology, thereby either augmenting or decreasing the person's liability. Also, the acquisition of liability-enhancing or liability-attenuating behaviors is influenced strongly by prior behaviors. This process is referred to as epigenesis. The main point to be made, however, is that the developmental pathway to a drug abuse outcome is nonlinear, complex, and idiosyncratic.

Prevention interventions involve methods that shift one's liability position toward the left side of the liability axis. Treatment involves shifting an affected person toward the subthreshold side of the distribution. Whether the intervention is prevention or treatment, effectiveness depends on identifying and disaggregating the unique components of each person's liability and applying methods that are capable of deflecting the person's position toward the left side of the axis. Because no two individuals in the population have the same developmental history, composition of phenotypes, or environment, it follows that it is necessary to adopt an individualized approach to prevention and rehabilitation.

A lifespan developmental approach has potential for clarifying the etiology of substance abuse. This perspective emphasizes the influence of cumulative prior experience as the major determinant of the emergence of each successive phenotype. This epigenetic process allows understanding of the etiology of drug abuse in the context of an orderly process in which the outcome is the culmination of an ongoing developmental trajectory concomitant to person-environment interactions. It is important to note, however, that other outcomes (e.g., AIDS, criminality, dementia) can likewise be

investigated through continued monitoring of the trajectory across the lifespan. Thus, drug abuse is not necessarily the only or final outcome of interest but instead is commonly intermediary to other negative outcomes. The epigenetic approach enables, therefore, the integration and sequencing of adverse outcomes associated with drug abuse as well as quantitative analysis of the patterning of other outcomes.

In order to fully understand how a segment of the population succumbs to drug abuse/dependence, it is essential to characterize and be able to predict the course of both normal and deviant development. Upon completing this task, the liability to drug abuse will be elucidated; however, the magnitude of this task is daunting considering the manifold biobehavioral traits that appear to be salient components of the liability. For example, it is universally recognized that exposure to particular environments influences the liability. Equally important is the fact that individuals with particular phenotypic features seek out specific environments. For example, shy youth are less inclined to form the same social relationships as aggressive youth. Thus, to understand how the person's position on the liability axis shifts during development, a central task is to analyze the quality of person-environment interactions as an ongoing bidirectional process.

A developmental approach also provides the theoretical foundation for understanding termination of drug abuse. For example, it is well established that only a small segment of the drug-using population become "affected"; that is, develop a diagnostic disorder. Among those who qualify for a diagnosis of abuse/dependence, a substantial proportion spontaneously remit. In effect, their position on the liability axis shifts from the suprathreshold to subthreshold location (see figure 1). Understanding person-environment interactions during the lifespan affords the opportunity for researchers to determine which factors foster nontreatment-based recovery. By identifying the factors that facilitate the transition from a diagnostic disorder of substance abuse/dependence to nondrug abuse, it may be possible to devise more imaginative and effective therapies that encompass an understanding of liability-attenuating influences. By extension, the developmental approach is suitable for detecting the factors associated with resiliency and primary prevention.

The multifactorial perspective aligns with research directed at determining how individual variation interacts with variations in multiple environments (e.g., family, peers, school, work, retirement community, etc.). Investigations of drug and alcohol preference and

consumption patterns in animals are informative to the extent that the distinguishing characteristics among different strains studied comprise components of the liability in humans. For example, what is it about alcohol-preferring rodents, apart from a propensity to drink alcohol, that predisposes to developing a pattern of habitual consumption and its consequences (e.g., tolerance)? Obtaining this type of information from animal research is important in clarifying the liability to substance abuse in humans.

To date, systematic research has not been conducted to determine how phenotypic variation in animals covaries with specific facets of environmental variation to determine the liability for substance use. For example, temperament in subhuman primates and the opportunity during infancy to acquire affectional bonds with parents are critical determinants of future alcohol consumption when the monkeys are adolescents (Higley et al. 1987, 1988). Unfortunately, this interactional approach has not been widely adopted by researchers who use animal models to investigate drug abuse liability.

In summary, delineating the liability to drug abuse requires analysis of the covariation between salient phenotypes in the context of interaction with multiple environments. This interactional approach is well established in human-based research but has not yet been widely adopted by researchers who utilize animal models to elucidate the liability for drug abuse.

RESEARCH PARADIGM

The National Institute on Drug Abuse (NIDA)-funded Center for Education and Drug Abuse Research (CEDAR) has the primary mission of identifying the traits associated with the liability to drug abuse and delineating the covariation among phenotypes on these traits and environments during the period between late childhood and middle adulthood. Subjects are prospectively tracked and biannually reevaluated to characterize liability status. This longitudinal investigation thus enables discovering the determinants of the liability for substance abuse among youth prior to exposure to abusable compounds. Thereafter, the factors that contribute to first use, habitual use, and ultimately the affected condition of drug abuse or dependence can be elucidated.

Probands in this research are adult men who either do or do not have a lifetime diagnosis of drug abuse or dependence. It is well established

that the population of offspring of men with drug abuse are at higher than average risk to develop drug abuse or dependence. Hence, identifying and tracking boys whose fathers have a drug abuse disorder according to DSM-III-R or DSM-IV criteria provides an efficient method for accruing a sample in which the likelihood of experiencing the adverse outcome is higher than average. Contrasting these youth at high risk with children who do not have a parental history of drug abuse thereby enables detecting the discriminating factors that are influential determinants of the liability. And, by tracking these two groups of youth into adulthood, it is possible to ascertain the relative and potentially changing impact of these variables on developing a drug abuse disorder at different stages of life.

Figure 4 illustrates the paradigm. The comparison groups consist of children at high average risk and low average risk for drug abuse; both groups are drawn from the population in which the father is either affected (substance abuse/dependence) or nonaffected (normal). Importantly, it should be noted that this paradigm does not specify whether a particular individual in each group is at high or low risk; rather it is the group that is at higher or lower risk. For example, as can be seen in figure 4, it is possible that some offspring in the high-risk group, although having an affected father, are not at the high end on the axis of the liability distribution.

Employing this paradigm, one aspect of CEDAR's current activities focuses on the role of temperament as a key determinant of the liability to substance abuse or dependence. Researching the contribution of temperament is heuristic for several reasons. For instance, certain temperament phenotypes have been shown to distinguish prepubertal male offspring of alcoholics (Tarter et al. 1990*a*) and other types of drug abusers (Blackson 1994; Blackson et al. 1994) from children of normal fathers. Magnitude of deviation on temperament traits has also been shown to be associated with severity of substance use involvement among adolescents (Tarter et al. 1990*b*; Windle 1991).

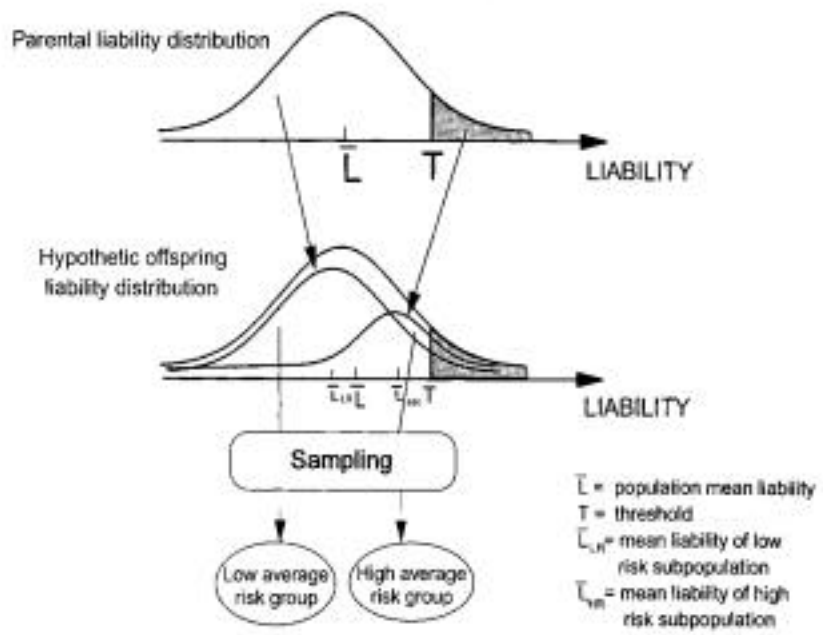

FIGURE 4. Sampling strategy in the high-risk paradigm.

In addition, several cogent theoretical reasons prompt investigating the contribution of temperament to the overall liability for drug abuse. First, phenotypic variation on temperament traits is determined to significant extent by genotypic variation in the population (Buss and Plomin 1975). These psychological propensities thus afford the opportunity to clarify the heritable contribution to the liability and provide the framework for linking genetic and behavioral processes. Second, temperament traits are reliably measurable within the first month or two after a child's birth (Buss and Plomin 1975). Hence, it is possible to initiate research into drug abuse etiology from the beginning point of the developmental trajectory. Third, a poor "fit" between the child's temperament and the environmental context substantially augments the risk for psycho-pathology and behavior disorder by late childhood (Thomas and Chess 1984). Thus, particular phenotypes are neither "normal" nor "abnormal" but rather are adaptive or nonadaptive depending on the environmental context. And fourth, temperament phenotypes tend to be temporally stable. In effect, temperament phenotypes reflect dispositional features of the individual, although the topography of expression changes during the lifespan. High emotionality in childhood, for example, is expressed in childhood as tantrums and intense, sudden crying spells. In adulthood, this same

temperament trait is usually (but not always) expressed differently. Typically, high emotionality is manifest as anxiety-spectrum reactions.

Temperament is measured at CEDAR using the revised Dimensions of Temperament Survey - Revised (DOTS-R) (Windle 1992). Youth and adult versions of the DOTS-R are administered to each child in the sibship and to each parent. The DOTS-R was selected to measure temperament because it has sound psychometric properties, and the traits measured are relevant for understanding the emergence of psycho-pathology and behavior disorder among youth and adolescents. The temperament traits evaluated are as follows: General Activity, Flexibility/Rigidity, Approach/Withdrawal, Mood Quality, Daily Rhythms, Eating Rhythms, Sleep Rhythms, Distractibility, and Persistence. In addition to these primary scales, the DOTS-R yields aggregate indices that multidimensionally characterize temperament makeup. Of particular interest is the constellation of traits referred to as the difficult temperament. This configuration consists of high scores on the primary traits measuring activity level and low scores on the traits measuring mood quality, rhythmicity, and sociability.

Consistent with the prospective paradigm, investigative efforts focus on clarifying the role of temperament in the development of drug abuse. However, rather than search for direct causal effects, the association between temperament and other putative risk factors with drug abuse liability is examined within a mediational framework. In this manner, the multifactorial liability for drug abuse can be decomposed into its components and the relative contribution of the constituent factors can be determined.

RESULTS

Figure 5 illustrates a structural path model depicting the relationship between difficult temperament, history of substance abuse disorder in the father, and socioeconomic status with three parameters reflecting nonnormative social behavior. These six variables were measured in 92 boys when they were 10 to 12 years of age. Alcohol and drug use was measured 2 years later when the boys were 12 to 14 years of age. The coefficients that are statistically significant are depicted by the

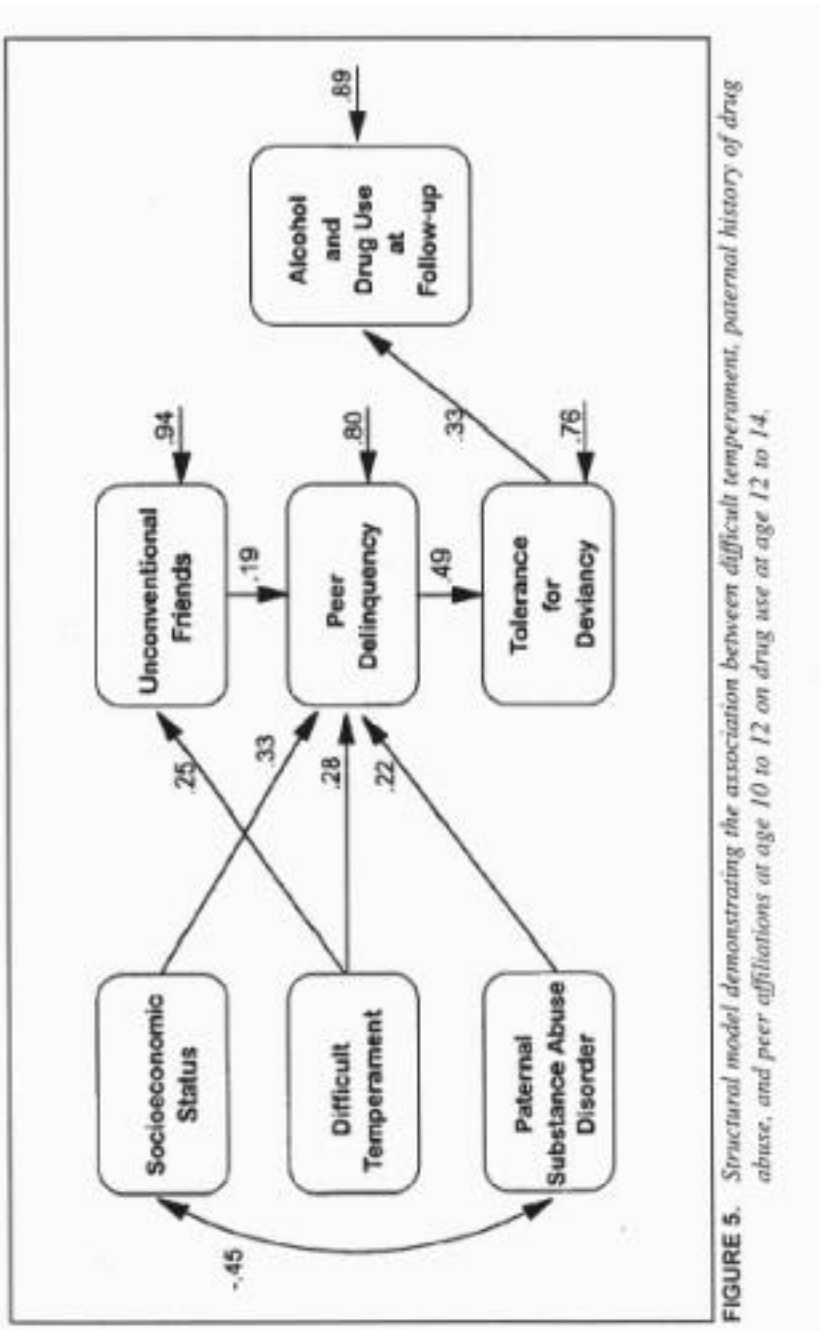

FIGURE 5. *Structural model demonstrating the association between difficult temperament, paternal history of drug abuse, and peer affiliations at age 10 to 12 on drug use at age 12 to 14.*

arrows connecting the variables. Nonsignificant pathways are not shown in order to illustrate only those relationships that are relevant to under-standing the association among the factors at age 10 to 12, which predict alcohol and drug use 2 years later.

Three aspects of the results are noteworthy. First, it can be seen from the significant path coefficients that difficult temperament is directly related to affiliation with unconventional friends and delinquency among peers. Second, these latter two variables are directly associated with tolerance for deviancy which, in turn, is the only factor that predicts alcohol and drug use at 2-year followup. Third, socioeconomic status mediates the relationship between paternal substance abuse disorder and delinquency in the child's peer network. The data fit this model quite well (chi-square with 11 degrees of freedom = 9.24 (p = 0.057). The goodness of fit index = 0.097. The normed fit index = 0.90.

From the analysis summarized in figure 5, difficult temperament, paternal history of substance abuse, and socioeconomic status are directly associated with level of delinquency among the boys' friends. However, this latter factor is not directly associated with drug and alcohol use 2 years later. Rather, delinquency among peers predisposes to acceptance or tolerance of deviancy that in turn leads to drug/alcohol use. Within the framework of this chapter, difficult temperament in the child is thus an important contributor to the initiation of alcohol/drug use by age 12 to 14; however, its influence is mediated by peer affiliation and tolerance of deviancy.

Biological Substrate of Temperament

As noted previously, phenotypic variation on temperament traits is explained to significant extent by genotypic variation in the population. A question having important ramifications for understanding the biological mechanisms underlying drug abuse liability pertains to whether biochemical or physiological processes can be detected that covary with temperament phenotype. Preliminary analyses conducted at CEDAR indicate that plasma GABA is unrelated to difficult temper-ament. Neither plasma homovillic acid (pHVA) nor MHPG, a dopamine metabolite, nor MHPG, a noradrenaline metabolite, correlates with difficult temperament in 10- to 12-year-old sons of substance-abusing fathers. Thus, the biochemical substrate of difficult temperament remains obscure.

RECOMMENDATIONS FOR FUTURE RESEARCH

Research employing animal subjects is informative to the extent that important questions about the liability to drug abuse can be addressed that are not otherwise amenable to investigation. In the context of the theoretical perspective discussed herein and the data presented, several innovative opportunities are noteworthy.

1. Recognizing that the focus of research on humans is to elucidate the covariation between organismic and environmental variables as determinants of the liability, it would appear important to conduct studies on animals in which phenotypes and environments are systematically manipulated. The advantage of using animal models is the opportunity to experimentally control the phenotypes and environments. In this manner, the conditions contributing to drug abuse liability in animals can be established, which then allows for confirmation in humans. Significantly, certain inbred strains of rodents have phenotypes that in humans have been linked to drug abuse liability. These phenotypes include behavior activity level, emotionality, and aggressivity. In addition to studies comparing inbred strains, it is potentially heuristic to investigate the role of liability-enhancing phenotypes in unselected animal subjects. The association between particular phenotypes and environmental factors that promote or mitigate drug self-administration can be measured. Each strategy provides the opportunity to systematize the relation-ship between specific phenotypes and specific environmental conditions underlying the liability for drug abuse.

2. As reported in this chapter, temperament traits are heuristic for elucidating certain of the early-age contributors to drug abuse liability. Research on animals allows for an objective determination of the role of temperament as a contributor to the liability because of the opportunity for rigorous control over environmental conditions. Significantly, several temperament phenotypes that are pertinent to the liability to drug abuse in humans have been inbred in rodent strains. Using these animals, the neurobiological substrate of temperament phenotypes can be determined.

3. Although research traditionally has aimed to exercise control over environmental conditions, it is dubious whether the range of environments that have been investigated in animals are relevant to understanding the liability for drug abuse in humans. For example, unlike animals maintained in the abnormal circumstance of social isolation, drug use by humans usually occurs in a social context. Research with animals could potentially make an important advance to understanding drug abuse liability by expanding the range of paradigms to include systematic manipulations of the social environment so as to delineate phenotype-environment covariation.

4. Prevention intervention is a powerful method for informing about etiology. For example, poor parent-child attachment augments the liability for drug abuse. A huge literature has developed in the past six decades regarding the importance of affectional bonding for normal development in humans and animals. Similarly, other well-established traits (e.g., aggression) are known to be associated with drug abuse liability. In effect, this line of research would be directed at modifying putative liability-enhancing phenotypes toward norma-tive expression and their determining whether this intervention alters drug preference.

5. It was argued in this discussion that the pharmacological properties of a given compound need to be considered in the framework of comprising a single liability factor, not as the main or only causal determinant. Hence, the importance of pharmacologic properties in relation to other liability enhancing and attenuating variables remains to be determined before there can be a comprehensive understanding of drug abuse etiology. Furthermore, broad-based research of this type needs to be undertaken within a lifespan perspective inasmuch as a compound's pharmacologic effects may not be constant throughout life. It is recommended, therefore, that researchers expand pharmacological investigations into the liability for drug abuse in humans and animals to also encompass the critical factor of age-specific pharmacologic effects as a contributor to drug abuse liability.

CONCLUSIONS

This chapter outlined the general theoretical framework for conducting research into the liability of substance abuse/dependence within a multifactorial perspective. The central research goal in this perspective is to determine how individual uniqueness is transformed through the course of ontogeny into a pattern of substance abuse or dependence. Because the liability is hypothesized to have multiple determinants, integrative research having a multidisciplinary focus is required. Investigations using animal models are necessary to test hypotheses not possible to test in humans. Drug abuse is invariably preceded by a period of no drug use and a stage of casual and often nonproblem use. This sequencing of increasing involvement and deleterious consequences argues for an ontogenetic perspective and, accordingly, for the use of longitudinal paradigms. A lifespan approach focusing on understanding changing person-environment interactions affords the opportunity to delineate the developmental trajectories to a substance abuse outcome. Once it is possible to disaggregate these interactions to reveal the determinants of the liability, empirically sound prevention and treatment will then be possible.

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