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

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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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