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Initiation, maintenance and extinction of cocaine self-administration with and without conditioned reward

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Abstract Relapse prevention in abstinent cocaine addicts remains a major focus of drug addiction therapy. We used a rat model of cocaine addiction that focused on cocaine-seeking behavior elicited interoceptively and by conditioned stimuli. Each of 18 rats could self-administer a maximum of 20 intravenous cocaine injections (1.5 mg/kg) per session per day. To prevent initiation of responding by cocaine itself priming injections were never administered. Although cocaine was available beginning every session the rats displayed a self-imposed period of abstinence followed by a period of rapid consumption. The abstinence period was variable among rats but consistent for individual rats. In experiment 1 we studied the contribution of a CS^+ (stimulus light and lever retraction) to the motivation to initiate and maintain a cocaine self-administration episode. We compared the number of responses the rats emitted to receive the first and subsequent injections of the day between a group responding on a fixed-ratio (FR) schedule (n=6) and a group responding on a second-order (SO) schedule (n=5) of reinforcement. For all rats the number of responses per injection was raised daily until a rat failed to consume more than four injections. The SO group was able to emit approximately four times as many responses as the FR group to obtain their first and subsequent injections. In experiment 2 (n=7) responses during extinction were counted with and without the CS^+. Responding was greater in the presence of the CS^+ than in its absence. The present model demonstrates that the motivation to self-administer cocaine is variable and greatly enhanced by conditioned stimuli.

Key words Rats · Second-order schedule · Reinforcement · Reward · Conditioned reinforcement · Conditioned reward · Conditioned stimulus · Cocaine · Abstinence · Self-administration

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Introduction

Psychostimulant abuse in humans is characterized by alternating between "binges" and periods of abstinence (Gawin and Kleber 1986; Kleber and Gawin 1987; Gawin 1991). Following binge episodes, the motivation to use cocaine fluctuates, and depends on such variables as the length of time since the last dosage and the presence or absence of conditioned stimuli associated with drug use. The probability of cocaine seeking behavior is low following a binge but increases during periods of abstinence. With time, the likelihood of relapse becomes extremely high and constitutes a substantial problem in the treatment of drug addiction (Jaffe 1990).

Non-human primates and rats also display cycles of intake when given unlimited access to cocaine (Deneau et al. 1969; Johanson et al. 1976; Bozarth and Wise 1985). During abstinent periods a non-contingent drug injection can serve to "prime" an animal and reinstate self-administration behavior (de Wit and Stewart 1981). This may be equivalent to "cocaine-induced cocaine craving" observed in human addicts (Jaffe et al. 1989). Therefore, it seems that in both humans and rats, the effects of cocaine carry over from one administration to the next and serve to maintain the motivation to continue a binge.

The conditions in effect during most self-administration experiments using rats as subjects are analogous to drug taking behavior during a binge. Typically, animals are given a "priming" injection so that even initial responding is influenced by the effects of cocaine. The effects of each cocaine injection carry-over to influence subsequent responding and the results are necessarily influenced by the drug levels that accumulate during the test session. While these studies contribute to our understanding of the mechanisms that sustain drug taking behavior, they cannot address the factors that influence relapse to drug use.

In an effort to model the initiation phase of drug seeking behavior, Fitch and Roberts (1993) employed a discrete trials procedure to minimize the carry-over effects

of repeated injections. By lengthening the inter-trial interval (ITI), different patterns of drug self-administration emerged. A 15-min ITI produced a binge/abstinence pattern of intake, with animals self-injecting during consecutive trials for 24–36 h. A longer ITI (30 or 60 min), however, produced a very different pattern. Rats demonstrated a clear circadian pattern of drug intake, showing dramatically reduced drug intake during the light (inactive) phase of the light/dark cycle, while displaying reliable patterns of cocaine self-administration during the active phase. The fact that animals initiate drug taking at predictable times can be used advantageously to examine the effects of potential therapeutics on the initiation of self-administration.

The discrete trials procedure has been effective in demonstrating that the motivation to self-administer cocaine fluctuates over time; however, the paradigm offers no information concerning the magnitude of the motivation to initiate a cocaine self-administration episode. In the present experiments, we sought to investigate the motivational factors involved in the initiation as well as maintenance of a self-administration episode. The magnitude of the motivation to initiate and maintain a self-administration episode was examined by assessing the maximum number of responses emitted in order to obtain the first and subsequent injections of cocaine. In the absence of a "priming" injection, the value of a fixed-ratio (FR) schedule of reinforcement was systematically increased each day until levels of responding failed to exceed a set criterion.

Stimuli that are associated with drug injections can motivate and direct drug seeking behavior, although isolating these stimuli for study can be difficult. In most self-administration experiments, animals are housed in one environment and tested in another. A multitude of stimuli could influence self-administration behavior when animals are transported and introduced into a distinct test chamber. These stimuli were minimized in the present experiments by housing the rats in the test environment. Specific stimuli were systematically associated with cocaine injections through the use of a second-order (SO) schedule of reinforcement (Kelleher 1966; Mackintosh 1974). Whether such stimuli would affect motivation to initiate and maintain a self-administration episode was examined by comparing levels of responding between groups of rats trained with and without conditioned stimuli.

Materials and methods

Subjects

Male Wistar rats (n=18), obtained from Charles River Canada and weighing between 275 and 300 g upon arrival, were housed in pairs in clear plastic cages with metal grid roofs. The rats had access to food (Purina Rat Chow) and water ad libitum (except during food training during which time food was rationed) and were maintained on a reversed 12-h light/dark cycle (lights-on at 9:30 p.m.) in a temperature controlled holding environment (21°C). During the course of the cocaine self-administration experiments, the rats were housed individually in operant chambers. Treatment of the rats in the present study was in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care and relevant University policy and was approved by the Carleton University Animal Care Committee.

Lever-response training

One week following their arrival from the supplier the rats were placed in operant chambers and trained to depress a lever for food reward on a FR1 schedule of reinforcement. Starting 1 day before and continuing throughout the lever-response training period the rats' free-feeding time was restricted to 1 h per day (in their home cages) following each lever-response training session. After learning this response, the rats regained access to food ad libitum and were surgically prepared for the self-administration of cocaine experiments.

Surgery

Each rat was deeply anaesthetized with sodium pentobarbital (65 mg/ml) and two incisions were made; one on the back at the mid-scapular level and the other on the chest just above the position of the right jugular vein. A chronically indwelling silastic jugular cannula was implanted such that it exited from the animal's back (Roberts and Goeders 1989). Following cannulation, rats were placed in an operant chamber and left to recover for 1 day before starting training on cocaine self-administration.

Apparatus

Each rat was individually housed in a Plexiglas operant chamber [50×50×40 cm (h)], one wall of which was equipped with a retractable lever on the right side and a yellow light stimulus which served as a conditioned stimulus (CS) in the middle of the wall. Each chamber also was equipped with one water bottle. The cannula was mounted on a counterbalanced fluid swivel apparatus which allowed unrestricted movement within the operant chamber.

Procedure

Rats were given access to the response lever at 9:30 a.m. (the onset of the dark phase). Each lever response activated an injection pump (refilled when necessary) delivering 0.13 ml of saline solution containing 0.6 mg of cocaine HCl (NIDA in Rockville, Md., dissolved in 0.9% saline at a concentration of 5 mg/ml) over a 5-s period. Concurrent with the start of the injection the light was activated and the lever retracted serving as a compound CS. The CS lasted 20 s. The maximum number of injections that any rat could consume on any day was set to 20. At the end of the 20th injection the lever remained retracted for the remainder of the session. After the 20th injection the stimulus light turned off and remained off for the remainder of the session. None of the rats ever received priming injections. Rats that self-administered 20 injections during two consecutive daily sessions entered one of the following experiments. Eighteen rats fulfilled this criterion.

Experiment 1

The behavior of animals responding on either a simple FR schedule (n=6) or a second-order (SO) schedule (n=5) of reinforcement were compared. The response requirements for the FR group increased by a value of 2 on day 2 and 3 on each of the remaining days (FR1, FR3, FR6 and so on). The SO schedule consisted of two FR components arranged hierarchically. Thus, the CS was presented after a fixed number of responses and the CS plus cocaine-injection combination after a fixed number of CS presentations. For the SO group the schedule was increased each day according to the follow-

ing progression where the first value represents the number of responses required for each CS presentation and the second value the number of CS presentations required for each CS plus cocaine-injection combination: FR1:FR1, FR1:FR3, FR2:FR3, FR3:FR3, FR3:FR4, FR4:FR4, FR5:FR4, FR6:FR4, FR6:FR5, FR6:FR6, FR6:FR7, FR6:FR8, FR6:FR9 and so on. When animals failed to self-administer more than four injections during the 24-h test period they were removed from the experiment.

The data to be analyzed consisted of the values representing the highest number of responses emitted for each injection during the session before the one in which they failed to consume more than four injections. This value was defined as the breaking point (BP). A one-tailed *t*-test between these data from the FR and SO groups was performed to determine whether these groups showed significantly different BP values.

Experiment 2

The effect of conditioned reward on the initiation of cocaine-seeking behavior was evaluated by comparing the number of responses emitted during extinction tests with and without the presentation of the CS+. After a rat had self-administered 20 injections on two consecutive sessions, a second-order (SO) schedule was imposed. Following each session during which all 20 injections were self-administered, the SO schedule requirements for the next session were incremented according to the following progression: FR1:FR1, FR1:FR2, FR2:FR2, FR2:FR3, FR3:FR3, FR3:FR4, FR4:FR4, FR4:FR5, FR5:FR5, FR6:FR6, FR6:FR7 and FR6:FR8. Extinction testing was initiated after three consecutive FR6:FR8 sessions during which 20 injections were self-administered. Between the extinction sessions the rats were placed back to a FR6:FR4 schedule and this schedule was increased daily until the rats again self-administered 20 injections on three consecutive FR6:FR8 sessions. During extinction sessions the cocaine-filled syringes were removed from their pumps and rats responded on a FR6:FR8 schedule with or without the CS^+. For some rats the first extinction session was conducted with CS^+ and the second without and for other rats the reverse order was the case. Due to loss of catheter viability or to sickness, some rats did not participate in both types of extinction sessions.

The dependent measure was the total number of responses emitted during each extinction session.

Results

Rats exhibited a cyclical pattern of responding for cocaine injections. The onset of responding varied among rats but tended to remain consistent for individual rats. Figure 1 is a representative cumulative record of a rat responding on the SO schedule and shows that the behavioral profile produced by this paradigm consisted of three phases. The first phase was characterized by negligible levels of responding. During the second phase responding commenced, although prior to receiving an injection of cocaine response rates were low. A third phase began after the first few injections of cocaine were self-administered. It was characterized by a high rate of responding until an injection was obtained followed by a post-reinforcement pause. This cycle was repeated for the duration of the session (see Fig. 1).

Experiment 1

Figure 2 illustrates the number of injections self-administered as a function of response cost. The data indicate that these demand curves consisted of two segments. The first segment was characterized by a static horizontal line during which increases in response-requirements appeared to have no effect on the consumption of at least 20 injections of cocaine. This segment is referred to as the inelastic segment of the demand curve (DeGrandpre et al. 1992; Bickel et al. 1993). The second

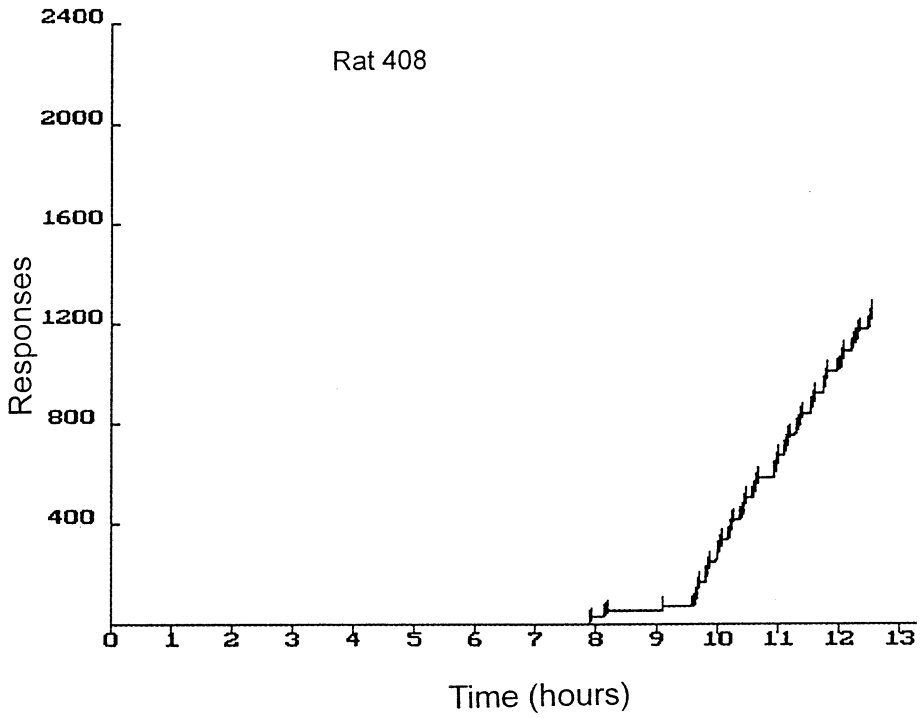

Fig. 1 A representative cumulative record of a rat responding on a second-order schedule of reinforcement. This record was taken during baseline training and illustrates the typical phases of responding for cocaine injections (1.5 mg/kg). All rats exhibited three phases of responding. Phase 1 appeared to be a self-imposed period of non-responding (0–8 h in the figure). Phase 2 consisted of a period during which responding was low and occurred in the absence of cocaine (8–9.5 h in the figure). Phase 3 was characterized by a period of high responding during which all available cocaine injections were consumed (9.5–12.5 h in the figure)

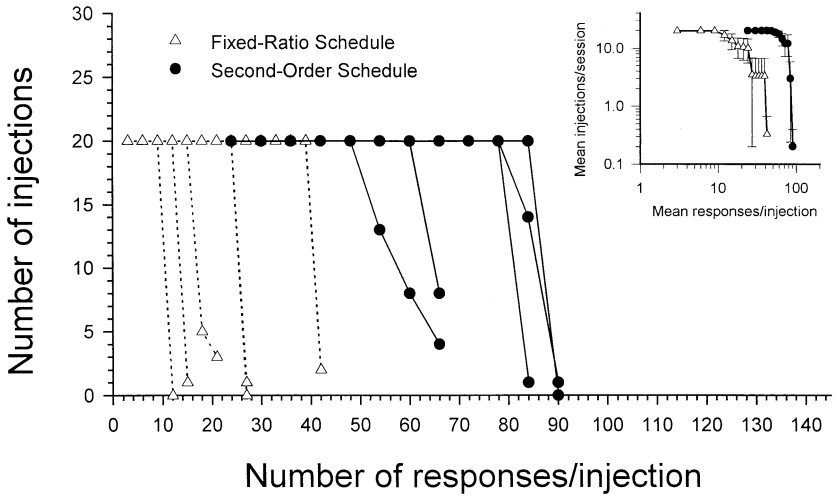

Fig. 2 Demand curves for each rat in experiment 1. Each demand curve illustrates the number of cocaine injections consumed (maximum of 20) for each response-requirement and demonstrates the breaking points at which consumption dropped below four injections. The inset is a plot of the average cocaine consumption (y-axis) as a function of response-requirement (x-axis) for the FR and SO groups

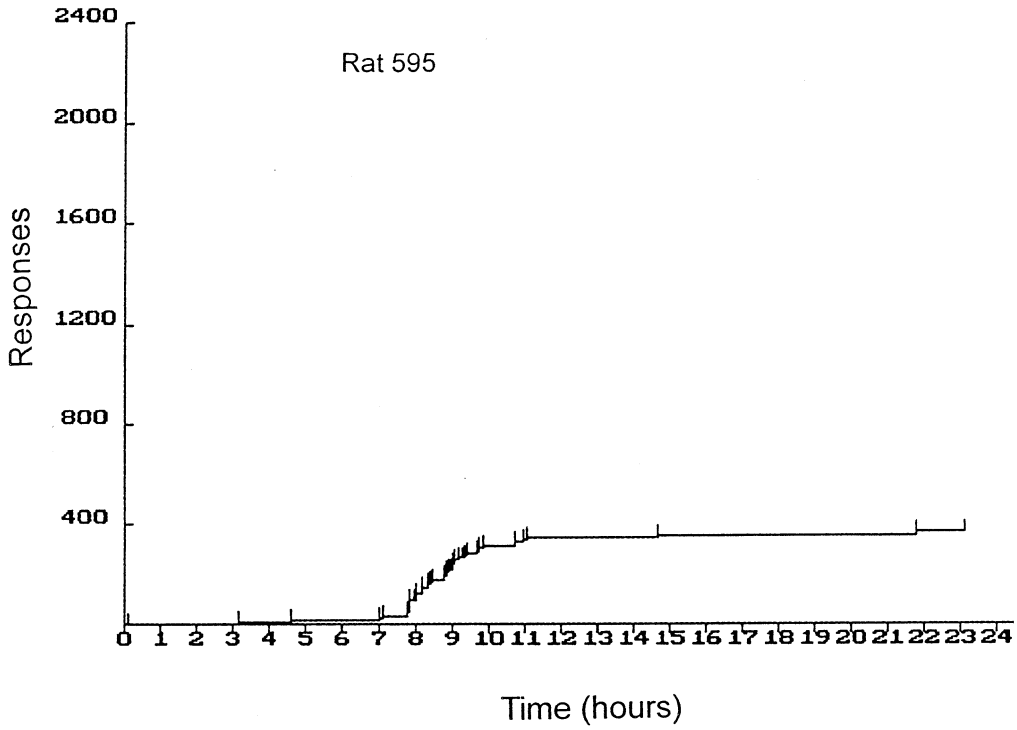

Fig. 3 A representative cumulative record taken during an extinction session in which the CS^+ was presented in the same SO schedule as during training. All rats responding in a CS^+-extinction session displayed three phases. In phase 1 there occurred relatively little or no responding at all. Phase 2 was characterized by high rates of responding in the absence of cocaine. Phase 3 consisted of little or no responding

segment was characterized by a dynamic, rapidly decelerating curve during which small increases in response-requirements produced large decreases in cocaine consumption. This segment is referred to as the elastic segment of the demand curve (Bickel et al. 1993; DeGrandpre et al. 1992).

Figure 2 also illustrates that the rats reinforced on a SO schedule responded to higher BPs than the rats reinforced on an FR schedule. Thus, the inelastic segment of the demand curves for the SO rats was longer than for the FR rats (see inset in Fig. 2). A *t*-test revealed significantly greater BP values in the SO group than in the FR group [$t(9)=8.86$, $P<0.001$].

Experiment 2

The contribution to responding by a CS^+ during extinction was evaluated. Figure 3 depicts a representative cumulative record for a rat responding during extinction in which it received CS^+ presentations according to the same SO schedule as during training sessions. The data demonstrate that the behavioral profile during these sessions consisted of three phases. Phase 1 was characterized by relatively little or no responding. Phase 2 consisted of high rates of responding in the absence of cocaine injections. This phase tended to begin at the same time of day during which high responding for cocaine occurred in training sessions. This phase was followed by a third phase during which little or no responding occurred.

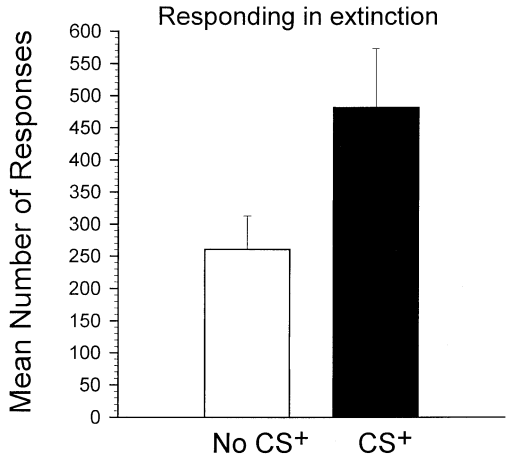

Fig. 4 Mean number of responses emitted during extinction sessions either receiving CS^+ presentations or not. All rats were trained to respond on a FR6:FR8 (total of 48 responses/injection) second-order schedule of reinforcement before testing. *Vertical bars* represent the standard error of the mean (SEM)

Figure 4 compares the mean (SEM) total number of responses between extinction sessions with and without CS^+ presentations for all rats in experiment 2. Clearly, the addition of CS^+ presentations contributed positively to responding. A one-tailed *t*-test revealed that a significantly greater number of responses [$t(9)=2.18$, $P<0.05$] occurred when the CS^+ was presented.

Discussion

The present model of cocaine-seeking behavior revealed a sequence of behavioral patterns consisting of self-imposed non-responding followed by initiation of responding followed by rapid consumption of cocaine. The model revealed that the motivation to self-administer cocaine is variable and that the presence of a CS^+ greatly enhances the motivation to initiate and maintain a cocaine self-administration episode.

Without a "priming" injection, rats often failed to respond for many hours. These periods of non-responding presumably indicate that the motivation to self-administer cocaine was low, even though cocaine was readily available. Inspection of the rats during the abstinence periods revealed that they were engaged in normal waking activities such as grooming and eating and were usually away from the lever area. This suggests that cocaine availability is not necessarily a strong trigger of relapse in the experienced rat. The fact that these rats began responding for cocaine late in the session, in the absence of priming injections, and at roughly the same time each day (data not shown) suggests that the motivation to initiate a cocaine self-administration episode may be partly triggered and controlled by interoceptive factors.

The observation of periods of abstinence is consistent with similar findings of Fitch and Roberts (1993). In that study, discrete (10-min) trials were offered throughout the 24-h cycle. When four trials per hour were presented, a binge pattern of cocaine intake was observed, with animals responding for consecutive injections for upward of 24 h. However, when the number of trials was reduced to one or two trials/h, so that the carry over effects of each injection were reduced, a stable circadian pattern of intake developed. In general, animals were most likely to self-administer cocaine during the last half of the active (dark) phase of the light/dark cycle. It is apparent from these data that there were periods of non-responding or "abstinence" each day. Animals were observed to be awake and active, often eating or grooming, when a signaled trial began, yet animals would decline to initiate self-administration behavior until late in the dark cycle. These results clearly illustrate that rats alternate between cycles of drug-taking behavior and periods of abstinence, given that the appropriate experimental parameters are in place.

The sequence of behavioral patterns revealed by this model may be used to gain insight into the drug addiction cycle. The cues signaling the availability of the drug were present during all periods of self-imposed non-responding That the animals were not engaged in drug-seeking behavior suggests a "voluntary restraint" from doing so in a way that may be analogous to some aspects of abstinence practiced by human addicts. In the present model responding for cocaine was initiated in a drug-free state and without any apparent initializing external stimuli (the CS^+ required at least one lever-press from the rat). This suggests that internal stimuli acted to increase the motivation for cocaine. These interoceptive stimuli may be analogous to those that human addicts describe as "craving". In the present model the motivation for cocaine rose to the point where the animals' behavior changed from abstinence to drug-seeking. This sequence of behavior may represent some aspects of the abstinence to relapse cycle observed in human addicts, although the abstinence period in this model might be considered relatively short. In this respect, the present model might be useful in investigating behavioral and neurobiological mechanisms involved in abstinence and relapse.

Other rat models of the addiction cycle have been developed. In some models animals are trained to perform an operant response that results in an intravenous infusion of a drug. Then the operant response is extinguished by replacing the drug with saline over the course of several hours or days. Once extinguished, responding can be initiated by various manipulations. These "reinstatement" models have revealed that response-reinstatement can be achieved with priming injections of the training drug (Smith and Davis 1973; Gerber and Stretch 1975; de Wit and Stewart 1981; Slikker Jr et al. 1984; Shaham and Stewart 1995) or another rewarding drug (Slikker Jr et al. 1984; Wise et al. 1990; Worley et al. 1994), exposure to stress (Shaham and Stewart 1995) or food deprivation (Carroll 1985). Conditioning studies have shown that response-reinstatement occurs with a contingent CS^+ (Smith and Davis 1973; Davis and Smith 1974, 1976) or a priming CS^+(de Wit and Stewart 1981).

There are some differences between the present model and reinstatement models. In the present model responding fails to occur in the presence of the response-maintaining drug. In reinstatement models responding fails to occur only after the response-maintaining drug is withdrawn and the animals experience a sufficient period of non-reward for a previously rewarded response. Most human addicts in abstinence have not experienced a period of non-reward with each consecutive drug intake but are prolonging abstinence by *refraining* to perform drug-taking or drug-related behavior. Thus, the difference in drug-seeking behavior that is initiated between after a period of abstinence and after extinction may be important in understanding and preventing relapse. In this respect, the present model can be used to understand certain aspects of the abstinence-relapse cycle.

The systematic pairing of the CS^+ with cocaine injections in a SO schedule resulted in the CS^+ acquiring the ability to significantly affect responding. First, the CS^+ acquired the ability to increase the number of responses that rats would emit to obtain their first and subsequent cocaine injections. Second, when responding in extinction, the presentations of the CS^+ increased the total number of responses that were emitted. These data indicate that the CS^+ presentations increased the motivation to initiate and maintain a cocaine self-administration episode.

The increased breaking points and responding during extinction seen with SO schedules suggest that the CS^+ acquired rewarding properties of its own and acted as a *conditioned reward* (Bindra 1974; Beninger and Ranaldi 1994). It appears that the initiation and maintenance of cocaine-seeking behavior is positively influenced by environmental stimuli that are historically associated with cocaine consumption. In studies with humans it has been reported that exposure to cocaine-associated stimuli can reliably elicit strong craving (motivation) for cocaine (Gawin and Kleber 1986; O'Brien et al. 1988; Kilgus and Pumariega 1994; Satel et al. 1995) which often results in relapse to cocaine use (Gawin 1991). Similarly, in the present study, the CS^+, by acting as a conditioned reward, enhanced the motivation to initiate and maintain a self-administration episode. These results underscore the strong role played by conditioned reward derived from cocaine-associated stimuli in the drug addiction cycle.

The acquisition of rewarding properties by a conditioned stimulus after repeated pairings with a rewarding drug has been shown in previous self-administration studies. Schuster and Woods (1968) demonstrated that rhesus monkeys trained to self-administer morphine responded more in extinction sessions during which the presentation of the CS^+ was a consequence of lever-pressing than in extinction sessions during which the CS^+ was absent. Davis, Smith and their colleagues extended these findings to rats and to other rewarding drugs. In a series of experiments these investigators showed that contingent (Smith and Davis 1973; Davis and Smith 1974) or non-contingent (Crowder et al. 1972) pairings of a CS^+ with morphine or amphetamine resulted in the acquisition of conditioned rewarding properties by the CS^+. This effect was demonstrated by the acquisition of a new response (lever-pressing) based on the CS^+ (Crowder et al. 1972) or the reinstatement of an extinguished response when the CS+ was made a consequence of that response (Smith and Davis 1973; Davis and Smith 1974; see Davis and Smith 1976). Our findings extend this previous work to show that stimuli associated with cocaine self-administration also can acquire conditioned rewarding properties.

Second-order schedules of reinforcement have been used previously in studies where primates were trained to self-administer cocaine or opiates (Goldberg et al. 1979, 1981; Johanson 1982; Bergman et al. 1989; Spealman et al. 1991; Spear and Katz 1991; Spear et al. 1991). Goldberg and colleagues (1976, 1977) trained rhesus and squirrel monkeys to respond on a SO schedule of morphine or cocaine reward. The completion of every FR schedule during a fixed interval of 60 min (FI:60) produced a CS^+ (light) and the first completion of the FR schedule after the FI:60 elapsed resulted in a CS^+ plus drug-injection pairing and the end of the session. Although the drug injection became available only after a 60-min period the trained animals began responding at high rates that accelerated during the session, indicating that the CS^+ gained control of responding (drug-seeking behavior) and acted as a conditioned reward. This type of control of responding by the CS^+ could be predicted from behavioral theories (see Kelleher 1966 and Mackintosh 1974). In general, the rates and patterns of responding were positively related to the presence of the CS^+. Interestingly, the monkeys in these studies did not display periods of self-imposed abstinence as was seen in our rats. This is likely due to the different procedures employed. The rats in the present studies lived in the self-administration chambers and, as a consequence, stimuli that signaled the start of the session were limited. By contrast, the monkeys were transported to the self-administration chambers before each session and, therefore, experienced many cues in the process. Perhaps these conditioned stimuli "primed" the monkeys to initiate self-administration behavior.

In the present experiments we used a SO schedule nested within a progressive-ratio schedule, where the latter schedule progressed between sessions. Spear and Katz (1991) tested the effects of conditioned reward on monkeys responding for cocaine on a SO schedule nested in a progressive-ratio schedule that progressed after each reward, within a session. Thus every FR completed during a FI resulted in the presentation of the CS^+. Every FR completed after the FI had elapsed resulted in a CS^+ plus cocaine-injection pairing. After every reward the value of the FR increased until a breaking point was reached. They found that breaking point decreased when the CS^+ was omitted, confirming that a CS^+ paired with cocaine on a SO schedule acquires conditioned rewarding properties. Interestingly, Spear and Katz (1991) also found that breaking point increased as a function of co-

caine dose, suggesting that in our paradigm dose of cocaine also might play a role in the between sessions breaking point.

The present model can be exploited to investigate the neural mechanisms underlying the control over relapse behavior by conditioned reward (CS^+). There is now strong evidence that the presentation of rewarding stimuli, including cocaine consumption, causes elevations in extracellular dopamine levels (Hernandez and Hoebel 1988; Radhakishun et al. 1988; Gratton et al. 1989; Joseph et al. 1989; Phillips et al. 1989; Kiyatkin et al. 1993) as measured by in vivo techniques. Several psychopharmacological investigations have suggested that dopamine plays an important role in the ability of conditioned reward to control behavior (Robbins 1975; Robbins et al. 1983; Beninger and Ranaldi 1992; Ranaldi and Beninger 1993, 1995; Ranaldi et al. 1995). Together with the present results, such findings suggest that it may be possible to affect the influence of conditioned reward on the initiation and maintenance of cocaine-seeking behavior through the administration of dopaminergic and/or other types of pharmacological compounds.

In summary, we report here the results of a unique relapse model of self-administration in rats that focuses on the motivation to initiate and maintain a cocaine self-administration episode. The results show that the motivation to self-administer cocaine is variable and is enhanced by a CS^+. These characteristics can be exploited to explore the neural mechanisms underlying the motivation to initiate and maintain a cocaine self-administration episode and the control of a CS^+ over these behaviors. A better understanding of these neural mechanisms will lead to more effective relapse-prevention therapies.

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