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Passive exposure to a contextual discriminative stimulus reinstates cocaine-seeking behavior in rats

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Abstract

A significant problem in treating cocaine dependence is craving-induced relapse elicited by inadvertent (i.e., passive) exposure to cocaine-paired stimuli. Extinction/reinstatement of cocaine-seeking behavior in animals has been used to investigate this phenomenon. Most studies using this model have examined reinstatement by response-contingent exposure to discrete cocaine-paired stimuli. The present study expanded this research by examining passive (i.e., not contingent upon an operant response) exposure to a contextual cocaine-paired stimulus to better model craving elicited by inadvertent exposure to cocaine-associated environmental stimuli. Rats underwent daily cocaine and saline self-administration sessions that were identical to each other except for a discriminative stimulus (scented bedding) signaling cocaine availability (S+) or nonavailability (S−). Subsequently, they were placed into the self-administration chambers in the presence of neutral bedding. Reinforcement was not available and cocaine-seeking behavior (i.e., nonreinforced operant responses) was extinguished across days. Rats were then reintroduced to the S+ and S− stimuli. Presentation of the S+, but not the S−, elicited significant reinstatement of cocaine-seeking behavior. The results demonstrate that passive exposure to a contextual discriminative stimulus reinstates extinguished cocaine-seeking behavior. Furthermore, we suggest that reinstatement of cocaine-seeking behavior by passive exposure to cocaine-paired stimuli may provide a model of craving-induced relapse elicited by inadvertent exposure to a cocaine-associated environment.

Keywords: Drug abuse; Cocaine; Relapse; Cocaine-conditioned; Reinstatement; Extinction; Cocaine-paired cue; Discriminative stimulus; Contextual stimulus; Rat

1. Introduction

Laboratory studies have demonstrated that stimuli associated with cocaine use can acquire the ability to elicit physiological responses that correspond with self-reports of craving for cocaine (Childress et al., 1988; Ehrman et al., 1992; O'Brien et al., 1990). This conditioned craving phenomenon is thought to interfere with recovery from cocaine dependence since inadvertent exposure to cocaine-paired stimuli is a frequent occurrence and may lead to relapse. In one study of 35 habitual cocaine users who relapsed after detoxification, 34% reported that cue-induced craving led to their relapse (Wallace, 1989). Similar reports exist for other drugs of abuse (Heather et al., 1991; O'Brien, 1975; Wikler, 1977).

An animal model that has been developed to study this phenomenon is extinction/reinstatement. In this model, animals are trained to self-administer cocaine, and stimuli are paired with cocaine infusions. Subsequently, animals undergo a period of extinction, during which operant responding has no programmed consequences. Cocaine-seeking behavior (i.e., nonreinforced lever pressing) diminishes during extinction. However, reintroduction of the cocaine-paired stimuli can reinstate cocaine-seeking behavior, and the number of responses the stimuli generate can serve as an index of stimuli-elicited incentive motivation for cocaine (Fuchs et al., 1998; Markou et al., 1993).

The extinction/reinstatement model typically utilizes stimuli with discrete onsets and offsets that were previously paired directly with each cocaine infusion to reinstate cocaine-seeking behavior. Few studies have examined the effects of cocaine-paired contextual stimuli (i.e., stimuli that are components of the conditioning environment) on reinstatement of cocaine-seeking behav-

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ior. However, a recent study in humans has demonstrated that contextual stimuli paired with cocaine self-administration acquire conditioned craving and/or reinforcing effects (Foltin and Haney, 2000). Since studies on learning and memory have shown that contextual and discrete stimuli may be processed via different neural mechanisms (Desmedt et al., 1998; Rawlins et al., 1998; Selden et al., 1991), it is important to examine both discrete and contextual cocaine-paired stimuli in the extinction/reinstatement model.

Another important parameter to investigate is mode of stimulus presentation since different presentation modes may model different aspects of stimulus-elicited cocaine-seeking behavior. Reinstatement of cocaine-seeking behavior by cocaine-paired stimuli can be accomplished by presenting the stimuli either response-contingently or passively (i.e., not contingent upon the animal's responding). Response-contingent stimulus presentation yields higher levels of responding than does passive cue presentation (Grimm et al., 2000) and is, therefore, generally the preferred mode of stimulus presentation. However, the behaviors involved in actively seeking out stimulus exposure and passively receiving stimulus exposure differ considerably and may involve different neural mechanisms (Ito et al., 2000). This difference might parallel the distinction in humans between the following two behaviors: "needle-freaking," in which heroin abusers inject water into their veins to obtain a "rush" (Meyer and Mirin, 1979), and cue-elicited relapse, in which inadvertent exposure to drug-associated stimuli leads to craving and drug use. In developing pharmacotherapies for drug abuse, it would be beneficial to understand how a manipulation affects each of these different behaviors. Animal models for examining reinstatement via response-contingent cue presentation are well established. However, it is also important to develop animal models in which drug-paired stimuli are only presented passively.

The present study modified procedures used previously (McFarland and Ettenberg, 1997; Weiss et al., 2000) in order to examine reinstatement of cocaine-seeking behavior by passive presentation of a contextual discriminative stimulus for cocaine availability.

2. Methods

2.1. Animals

Male Sprague–Dawley rats (final $N = 7$), weighing 200–250 g at the beginning of the experiment, were housed individually in a climate-controlled facility with a 12-h light/dark cycle (lights off at 0630 h). The housing conditions and care of the animals were consistent with those specified in the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Science, National Research Council, 1996). Animals were acclimated to handling for at least 5 days prior to surgery.

2.2. Surgery

Rats were anesthetized with sodium pentobarbital (50 mg/kg, ip; Sigma, St. Louis, MO) given in conjunction with atropine sulfate (10 mg/kg, ip; Sigma, St. Louis, MO). Silastic catheters were implanted into the right jugular vein of each animal as described by Neisewander et al. (2000). Throughout the experiment, the catheters were flushed daily with a solution of 0.1 ml bacteriostatic saline containing heparin sodium (10 U/ml; Elkins-Sinn, Cherry Hills, NJ), streptokinase (0.67 mg/ml; Astra Pharmaceutical Products, Westerborough, MA), and ampicillin sodium (66.7 mg/ml; Bristol-Myers Squibb, Princeton, NJ) in order to maintain catheter patency. Patency was verified periodically throughout the experiment by administering 0.8 mg methohexital sodium (Eli Lilly, Indianapolis, IN), a dose that anesthetizes the animals briefly only when administered intravenously.

2.3. Cocaine self-administration and discrimination training

After at least 5 days of recovery from surgery, rats were trained to press a lever for cocaine reinforcement (0.75 mg/kg/0.1 ml, iv) in operant chambers equipped with a lever and a house light, mounted on opposite walls of the chamber. Each rat was exposed to only one operant conditioning chamber throughout the experiment. To facilitate acquisition of cocaine self-administration (Carroll et al., 1981), rats were restricted to approximately 17 g of food/day beginning 2 days prior to training. They remained food restricted until they met a criterion of seven infusions per hour on a fixed ratio (FR) 1 schedule of reinforcement. After meeting the criterion, rats were given free access to food in the home cage for the remainder of the experiment. Schedule completions resulted in the simultaneous activation of the house light and the infusion pump for the intravenous administration of 0.1 ml cocaine over a 6-s period. The house light remained activated during a subsequent 20-s time-out period, during which lever presses had no scheduled consequences. Upon meeting the criterion of seven infusions per hour, the rats advanced from an FR 1 to a variable ratio (VR) 2, VR 5, and VR 10 schedule of reinforcement.

Initially, rats were trained during daily 2-h sessions, 6 days/week. On the third day of self-administration training, an odor stimulus signaling the availability of cocaine (S+) was introduced into the operant chamber. Operant conditioning chambers were housed in two separate rooms located off of different corridors. Each room was randomly assigned to have either cedar- or pine-scented bedding as the S+ and half of the rats were assigned to be trained in each room. This permitted both a counterbalanced design and the separation of odors during a given training session. Bedding

was placed in a metal tray beneath the rod floor of the operant chambers approximately 5 min prior to each session. Approximately 20 g of cedar and 30 g of pine bedding was used. Less cedar than pine bedding was used since its odor is much stronger. After all rats had demonstrated stable cocaine self-administration on the VR 10 schedule (variability of cocaine infusions < 15% across three consecutive days), the 2-h session was divided into two 1-h sessions. These two sessions were separated by a 60-min period during which the rats were returned to the colony room in their home cages. After 2 days of adapting to this new schedule of cocaine self-administration, an additional 1-h saline self-administration session was added, accompanied by presentation of the S− stimulus (pine- or cedar-scented bedding) signaling the nonavailability of cocaine. For the remainder of discrimination training, rats underwent two cocaine self-administration sessions and one saline self-administration session daily, 6 days/week. The sessions were separated by 60 min and presented in a random order. All aspects of the cocaine and saline sessions were identical to each other except for the presence of the discriminative stimulus (S+ or S−) and the availability of cocaine. During the 60-min intersession period, all bedding was removed from the testing rooms. The operant chambers were cleaned with a mild-scented disinfectant spray (diluted Cidexplus; Johnson & Johnson Medical, Arlington, TX) 15–20 min prior to the start of each session. This served to mask traces of the S odor that might have remained in the room from the previous session.

2.4. Test for discrimination

After a minimum of 14 days of discrimination training, rats underwent two 30-min probe trials, separated by 60 min, during which lever presses had no programmed consequences. These probe trials examined cocaine-seeking behavior in the presence of both the S+ and S−, which were presented in a counterbalanced order. Since it was conceivable that the rats' discrimination responding was based on the first infusion of each self-administration session, either saline or cocaine, these probe trials were conducted to ensure that responding was indeed under the control of the S+ and S−. Rats underwent at least three additional days of discrimination training following the probe trial.

2.5. Extinction training

Following discrimination training, rats underwent extinction during daily 1-h sessions, 7 days/week. The purpose of this extinction training was to extinguish incentive motivational effects of stimuli, other than the bedding, that are part of the self-administration environment (i.e., the lever, bar floor, etc.). Rats were placed into the operant chambers in the presence of their home cage bedding, and lever presses had no programmed consequences (i.e., did not activate the infusion pump or the time-out cue). Extinction continued until responding declined to a predetermined extinction criterion (i.e., 25% of a rat's highest number of responses during the saline self-administration sessions for at least three consecutive extinction sessions).

2.6. Reinstatement of cocaine-seeking behavior

Following the last day of extinction training, rats received a 3-day rest period, during which they were not exposed to the operant conditioning room. Animals were then tested for stimulus-reinstatement in two 30-min sessions separated by 60 min. Each animal was placed in the operant chamber with either the S+ or S− bedding to examine whether the S+ stimulus and/or the S− stimulus would reinstate cocaine-seeking behavior. The S+ and S− sessions were counterbalanced for order. Lever presses were recorded, but did not activate the infusion pump or the time-out stimulus. The rats were tested for stimulus reinstatement on four separate days. Rats received a 3-day rest period between test days 1 and 2, a 6-day rest period between test days 2 and 3, and a 6-day rest period between test days 3 and 4.

3. Results

3.1. Self-administration and discrimination training

Rats underwent 24.14 ± 0.83 (mean ± S.E.M.) cocaine self-administration sessions prior to the initiation of discrimination training. Subsequently, rats underwent 23.14 ± 1.84 (mean ± S.E.M.) days of discrimination training. The daily intake of cocaine across self-administration and discrimination training was 15.06 ± 2.71 mg/kg (mean ± S.E.M.).

Fig. 1 demonstrates the rats' discrimination learning by comparing infusions per hour, as well as responses per hour, during cocaine and saline SA sessions for the first 3 and last 3 days of training. Data were analyzed using three-factor within-subjects ANOVAs with two levels of stimulus (S+ or S−), two levels of phase (beginning and end of training), and three levels of day. These analyses revealed significant Stimulus × Phase interactions [infusions: $F(1,6) = 17.05$, $P < .01$; responses: $F(1,6) = 10.73$, $P < .05$]. Post hoc analyses revealed a simple main effect of phase for S− only [infusions: $F(1,6) = 33.43$, $P < .005$; responses: $F(1,6) = 19.66$, $P < .005$], signifying a decrease in infusions and responding during S− sessions across time but no change during S+ sessions. Further analyses revealed a simple main effect of stimulus during the second phase for infusions [$F(1,6) = 18.72$, $P < .01$] and a strong trend for responses [$F(1,6) = 5.58$, $P = .056$], but no effect was found during the first phase. This demonstrates that animals received fewer infusions and likely performed fewer responses in S− sessions than in S+ sessions at the end of training.

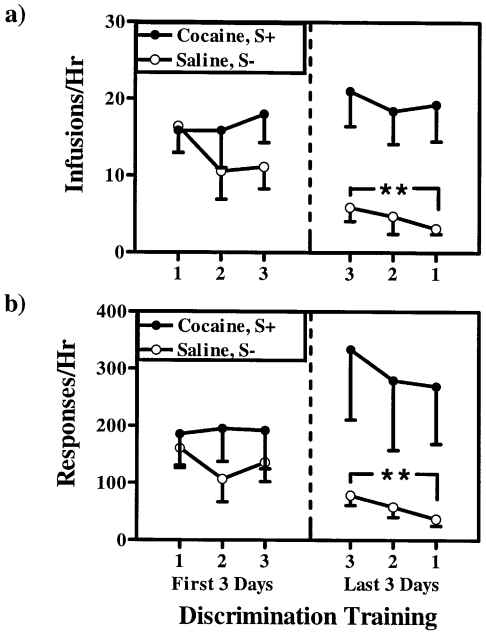

Fig. 1. (a) Infusions per hour (±S.E.M.) and (b) responses per hour (±S.E.M.) for the first 3 days and the last 3 days of discrimination training. The two daily cocaine self-administration sessions were averaged to obtain the mean responses and infusions per 1-h session. ** Significant difference from first 3 days of training: $P<.005$, simple main effects.

3.2. Test for discrimination

To determine whether the scented bedding had gained stimulus control over responding, 30-min probe trials were conducted as described above. Cocaine-seeking behavior, measured as nonreinforced lever presses, was analyzed using a mixed-factor ANOVA with stimulus (S+ or S−) as the within-subjects factor and odor assigned as the S+ (cedar or pine) as the between-subjects factor. This analysis revealed a significant main effect of stimulus [$F(1,6)=7.86$, $P<.05$], but no significant odor effect or Stimulus × Odor interaction. The rats exhibited more cocaine-seeking behavior in the presence of the S+ odor stimulus (mean±S.E.M.: 43.29±10.49) than in the presence of the S− odor stimulus (mean±S.E.M.: 14.86±2.44), regardless of the particular odor serving as the S+.

3.3. Extinction

In addition to the odor S+, other contextual stimuli in the operant chamber, such as the lever, house light, etc., also initially served as predictors of cocaine availability. Extinction of cocaine-seeking behavior elicited by these other stimuli began with the saline self-administration sessions during discrimination training since rats did not receive cocaine reinforcement during these sessions. Thus, to assess extinction of cocaine-seeking behavior elicited by stimuli in the operant chamber other than S+ bedding, we examined responding/session across the first three saline self-administration sessions (first panel, Fig. 1), the first three extinction sessions (first panel, Fig. 2), and the last three extinction sessions (second panel, Fig. 2). We chose to analyze our data in this manner because rats underwent different amounts of extinction training, ranging from 30 to 56 sessions (mean±S.E.M.: 47.86±3.12). Cocaine-seeking behavior was analyzed using a two-factor within-subjects ANOVA with three levels of session blocks (i.e., responding during initial saline self-administration, initial extinction training, and final extinction training) and three sessions in each block. This analysis revealed a significant main effect of phase [$F(2,6)=22.03$, $P<.001$], but no effect of session within the phase. Rats exhibited significantly less responding in each phase relative to the previous phase ($P<.05$, paired samples t test), demonstrating extinction of cocaine-seeking behavior elicited by contextual stimuli other than the odor cue.

3.4. Test for stimulus reinstatement

Nonreinforced responding during each 30-min S+ and S− test session was analyzed using a three-factor within-subjects ANOVA with two levels of stimulus (S+ or S−) and four levels of day. This analysis revealed a main effect of stimulus [$F(1,6)=11.36$, $P<.05$] and a significant Stimulus × Day interaction [$F(3,18)=5.05$, $P<.01$; see Fig. 2]. Post hoc comparisons revealed a significant difference in cocaine-seeking behavior between the S+ test session and the S− test session on the first and third reinstatement test days ($P<.05$, paired samples t test). Responding decreased across days only in the presence of the S+. Specifically, responding on test day 4 was significantly less than responding on test day 1 ($P<.05$, paired samples t test). Responding during baseline and S+ and S− test sessions was examined with separate one-factor within-subjects ANOVAs with five levels of day (four S+ test sessions and baseline or four S− test sessions and baseline). The ANOVA was significant for S+ responding [$F(4,24)=5.45$, $P<.005$], but not for S− responding. Post

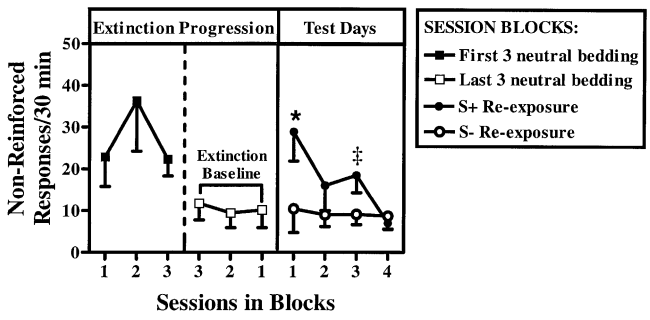

Fig. 2. Cocaine-seeking behavior expressed as nonreinforced responses (±S.E.M.) during the initial 30 min of the first and last 3 days of extinction training and the four reinstatement test days. Test days 1 and 2 were preceded by 3-day rest periods and test days 3 and 4 were preceded by 6-day rest periods. * Significant difference from S− test session and from baseline. ‡ Significant difference from S− test session only: $P<.05$, paired sample t tests.

hoc comparisons between baseline and the four S+ test sessions revealed a significant difference only on the first test day ($P < .05$, paired samples t test), suggesting that the S+ no longer reinstated cocaine-seeking behavior after the first test session.

4. Discussion

The present study demonstrated that passive presentation of a contextual discriminative stimulus for cocaine availability reinstates extinguished cocaine-seeking behavior in rats. However, this effect was not maintained across repeated test days. In fact, our findings suggest that the incentive motivational effects of the S+ may have extinguished during the first test session. We also examined whether spontaneous recovery of stimulus reinstatement would occur by increasing the intertest interval from 3 to 6 days for the third and fourth test sessions. Although a 6-day interval between the second and third reinstatement tests produced a significant increase in responding during the S+ test session relative to the S− test session, responding during the two sessions was the same again on the fourth test day.

While the discriminative stimulus model as applied in this study did not maintain stimulus reinstatement across repeated tests, a similar procedure used by Weiss et al. (2000) did achieve significant stimulus reinstatement in the same animals across eight test days. One key difference in the procedure applied by Weiss et al. that may account for the stability of their effect was that, in addition to the discriminative stimulus for cocaine availability presented passively during reinstatement testing, the animals also received response-contingent presentation of a discrete stimulus that had signaled time-out during self-administration training. Because this stimulus presentation overlapped with cocaine infusions and only occurred during cocaine self-administration sessions, and not during saline self-administration sessions, it may have acquired and maintained conditioned reinforcing effects. As Grimm et al. (2000) have shown, response-contingent presentation of cocaine-paired stimuli enhances stimulus-reinstated responding. Rats in the present study only received passive stimulus presentation during testing. A recent study in our laboratory has also demonstrated that animals show stable stimulus reinstatement across at least five test days when cocaine-paired stimuli are presented response-contingently (Alleweireldt et al., 2000). However, it has yet to be shown that passive presentation of a cocaine-paired stimulus can elicit stable stimulus-reinstatement of extinguished cocaine-seeking behavior across repeated tests. There are at least two possible explanations for the difficulty in establishing stable reinstatement by passive stimulus presentation. First, it is possible that stimulus-elicited incentive motivation for cocaine does occur across repeated test days, but animals cease responding because they have learned that responding no longer leads to reinforcement. In contrast, during response-contingent reinstatement of cocaine-seeking behavior, responding continues to elicit conditioned reinforcement, which likely helps to maintain responding across repeated tests. Second, it is possible that stronger conditioning is required for the cocaine-paired stimuli to sustain conditioned incentive effects across repeated tests following passive stimulus presentation relative to response-contingent stimulus presentation.

The procedure applied in the present study could be modified in several ways to achieve a stronger association between cocaine and the cocaine-paired stimulus, which might in turn improve the stability of stimulus reinstatement across repeated test days. First, in the present study, the animals could smell the odor stimulus upon entering the room prior to being placed in the self-administration chamber. Since previous research has demonstrated that optimal drug conditioning is achieved with simultaneous US−CS presentation (Bardo and Neisewander, 1986), conditioning using the present procedure might be enhanced by presenting stimulus onset and offset simultaneously with onset and offset of cocaine availability. Second, the intersession interval during discrimination training could be lengthened. On a given day, animals only received a 1-h rest period between saline and cocaine self-administration sessions. Given the half-life of cocaine in rats (18−20 min) (Barbieri et al., 1992), the animals may have still been affected by a previous cocaine session during a saline session. Thus, the animals may have experienced the daily saline self-administration sessions differently depending on whether the session was administered before, between, or after the two daily cocaine self-administration sessions. Indeed, in the present study, animals responded more when a saline self-administration session was between rather than before or after, the cocaine self-administration sessions (significant quadratic trend, $P < .01$). This varying state of the animals in the presence of the S− may have weakened the salience of both discriminative stimuli as predictors of cocaine availability or nonavailability, thereby weakening the stimulus control. Third, it may have been better to use a less demanding schedule of reinforcement during training. The VR 10 schedule was utilized in the present study with the intention of yielding high levels of responding during reinstatement testing since partial reinforcement schedules are associated with increased resistance to extinction (Mowrer and Jones, 1945). However, contrary to our prediction, this partial reinforcement schedule did not appear to enhance levels of responding relative to that reported previously using a continuous reinforcement schedule. Furthermore, use of the VR 10 schedule likely prolonged the extinction-training phase of the experiment. During this time, the memory of the association of the S+ with cocaine reinforcement may have diminished, resulting in weaker and less reliable reinstatement relative to that observed with a stronger memory of the S+−cocaine association (Gleitman, 1971). In addition to the discrimi-

native stimulus procedure, another modification of the extinction/reinstatement model that enhances reinstatement is compounding stimuli across sensory modalities. For example, passive presentation of a compound light/tone stimulus produces more robust reinstatement of cocaine-seeking behavior than does passive presentation of either the light or tone stimulus alone (Panlilio et al., 1996). Future research is needed to examine the ability of passively presented discrete and/or contextual compound stimuli to elicit reinstatement of cocaine-seeking behavior in the same animals across repeated test days.

The extinction/reinstatement model is a valuable tool for studying stimulus-elicited incentive motivation for cocaine. However, the complexity of this phenomenon in humans requires increased sophistication in the corresponding animal model. Specifically, research is needed to investigate passive versus response-contingent and discrete versus contextual stimulus presentation since each of these procedures may involve different neural mechanisms.

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