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ORIGINAL INVESTIGATION

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Influence of a conditioned light stimulus on cocaine self-administration in rats

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Abstract *Rationale:* A number of studies have suggested that the continued presentation of stimuli associated with cocaine may contribute to drug-seeking and drug-taking. The influence of conditioned stimuli on the maintenance of self-administration has not, however, been systematically investigated. *Objectives:* This study was designed to determine whether omission of a stimulus that had been paired with self-administered cocaine would influence the maintenance of cocaine self-administration and whether the effect was dependent on cocaine dose or session length. *Methods:* During self-administration training, self-administered cocaine infusions were always paired with the illumination of a light. On test days, self-administered cocaine was delivered either with or without the cocaine-associated cue. For one group of rats, responding maintained by cocaine (0.50 mg/kg per infusion) was measured during daily 18-h sessions. For other groups, responding maintained by additional doses of cocaine (0.125, 0.25, or 1.0 mg/kg per infusion) was measured during daily 8-h sessions. For a final group, daily test sessions (4–5 h) produced the dose-effect curve (0.015–1.0 mg/kg per infusion) by repeatedly reducing the cocaine dose from a starting dose of 1.0 mg/kg per infusion. *Results:* Removal of the light cue decreased cocaine self-administration. The magnitude of this effect was dependent on the dose of self-administered cocaine and on the test session duration. Greater decrements in responding were produced as session length increased or when low doses of cocaine were self-administered. *Conclusions:* These findings demonstrate that in the absence of a cocaine-associated stimulus, cocaine self-administration is attenuated and that maintenance of cocaine self-administration is maximally affected by the presence or absence of the conditioned stimulus when the self-administered dose is low and/or when session duration is long.

Keywords Cocaine · Self-administration · Conditioned stimulus · Drug abuse

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Introduction

Both clinical and preclinical efforts to develop effective preventative and therapeutic interventions for cocaine abuse have focused on identifying the factors that maintain drug-taking. Self-administration has often been attributed to the positive effects of the drug (Koob et al. 1994; Mello and Negus 1996) that serve to reinforce continued use. Following repeated exposure to cocaine, a transition from use to abuse occurs in some individuals and self-administration becomes compulsive and is characterized by a loss of control. Abusers reported an intense craving for more cocaine following exposure to a small priming (Jaffe et al. 1989) or self-administered (Fischman et al. 1985) dose of cocaine. Craving was also elicited by the presentation of videotaped sequences of cocaine use or cocaine-related paraphernalia (Ehrman et al. 1992; O'Brien et al. 1992; Childress et al. 1988), suggesting that exposure to these cues might play a role in cocaine self-administration by experienced cocaine users.

Preclinical studies have shown that cocaine-associated stimuli acquire the ability to control some aspects of behavior. For example, a preference develops for an environment that has been associated with cocaine (Schechter and Calcagnetti 1993, 1998; Bardo 1998 for reviews) and laboratory animals will acquire a new behavior in order to obtain a stimulus that had been previously paired with cocaine (Spear and Katz 1991; Ranaldi and Roberts 1996; Whitelaw et al. 1996; Weissenborn et al. 1997; Grimm and See 2000).

The strengthening of stimulus/reward associations through the repeated presentation of stimuli that have

been associated with self-administered cocaine might contribute to the acquisition and maintenance of cocaine self-administration. One possibility is that as cocaine-associated stimuli develop the ability to direct behavior and to lead to drug-seeking, their continued presentation serves to maintain drug-taking and to contribute to the compulsive cycle of drug-seeking and drug-taking that characterizes abuse.

It is well established that cocaine self-administration is facilitated by the continued presentation of cocaine-associated stimuli. Responding produced according to second-order schedules of reinforcement have provided elegant demonstrations of these facilitative effects (Goldberg et al. 1979; Panlilio et al. 1996; Ranaldi and Roberts 1996; Arroyo et al. 1998) and of the powerful ability of these stimuli to direct behavior. In other studies, the ability of the continued presentation of a cocaine-associated stimulus to delay extinction following the removal of cocaine has been demonstrated (Neisewander et al. 2000).

It is clear that cocaine-associated stimuli acquire the ability to direct behavior but the extent to which the continued presentation of these stimuli is *required* for cocaine self-administration has not been systematically investigated. If the development of compulsive use is, at least in part, a function of the ability of conditioned stimuli to maintain drug-seeking, then the influence on self-administration might become more apparent during long sessions. The magnitude of the influence of these stimuli on self-administration might also be a function of the dose of cocaine. Sensitization to cocaine's reinforcing effects is often reflected in an increase in the ability of low doses of cocaine to reinforce operant behavior (Schenk et al. 1991, 1993; Schenk and Partridge 2000). If sensitization is at least partly due to the development of stimulus/reward associations (Taylor and Horger 1999), then low dose self-administration might be influenced to the greatest extent by the inclusion or omission of a cocaine-associated stimulus. These hypotheses were tested in the present study by measuring self-administration of a range of cocaine doses following the removal of a stimulus that had been associated with self-administered cocaine infusions.

Materials and methods

Subjects

Male Sprague-Dawley rats (Harlan, Tex., USA) weighing 325–350 g were used. They were housed individually in hanging polycarbonate cages. The humidity and temperature were controlled and food and water were freely available except during testing. The colony was maintained in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care and all experiments were conducted in accordance with the guidelines of the University Laboratory Animal Care Committee of Texas A&M University.

Surgery

Rats were implanted with a Silastic catheter in the right jugular vein. Briefly, the rats were deeply anesthetized with ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated, the catheter was inserted, and the distal end (22 gauge stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (1.25 U/ml), penicillin G potassium (250,000 U/ml), and streptokinase (8,000 IU/ml, Kabikinase; Pharmacia Upjohn) to prevent infection and the formation of clots and fibroids. The rats were allowed 5 days postsurgery for recovery.

Apparatus

Self-administration testing was carried out in standard experimental chambers (Med Associates; ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in an intravenous infusion of cocaine HCl. Depression of the other lever (the inactive lever) was without programmed consequence.

Rats were maintained in the animal colony except during testing. Immediately prior to each daily test, the catheter lines were infused with 0.1 ml of the heparin-penicillin-streptokinase solution, and the portion of the catheter comprised of stainless steel tubing was connected to a length of microbore tubing that was connected to the syringe. At the end of each test, the lines were again infused with 0.1 ml of the heparin-penicillin-streptokinase solution, the stainless steel tubing was plugged, and the animal was returned to its home cage. Drug delivery and data acquisition were controlled by the OPN software program (Spencer and Emmett-Oglesby 1985). Cocaine deliveries were made via mechanical pumps (Razel; Model A with 1 rpm motor equipped with 20.0-ml syringes).

Procedure

Training

Acquisition of cocaine self-administration was monitored during daily 2-h sessions. Depression of the active lever produced automated cocaine infusions (0.5 mg/kg per infusion) according to an FR-1 schedule of reinforcement. The criterion for acquisition of cocaine self-administration consisted of at least 30 reinforced responses (15.0 mg/kg) during the 2-h session and a ratio of active:inactive lever responses of at least 2:1. Self-administration was considered acquired when these criteria were met for 3 consecutive days. Following acquisition, the response requirements were increased to FR-5. Daily 2-h sessions were conducted until there was less than 20% variation in responding on 3 consecutive days. During training, the cocaine infusion (12.0 s) was always paired with the illumination of a stimulus light (also 12.0 s) located directly above the active lever. All training and test sessions began with an experimenter-delivered infusion of the dose of cocaine that was available for self-administration.

Test

Once stable self-administration behavior was produced, the influence of the light stimulus on responding for a single dose of cocaine was determined for some groups. An initial group of rats (n=8), self-administered cocaine during an extended test of 18 h duration. On the 1st test day, responding on an FR-5 schedule was reinforced by an infusion of cocaine (0.5 mg/kg per infusion) and the light stimulus that had been paired with cocaine infusions during training. On a 2nd test day, the light stimulus that had been paired with cocaine infusions during training was omitted. Daily 2-h sessions were interspersed between tests 1 and 2 and the second test was conducted only when the criteria for stable responding, as indicated above, was obtained (3–5 test days). All rats were tested first with the light stimulus presented during each cocaine infusion. For this group, order effects were not controlled since there was concern that an initial test with the light stimulus omitted might impact the effect of reintroduction of the light in a later test. Order effects were controlled for in subsequent tests (see below).

Other groups of rats were tested in order to establish whether the influence of light condition on self-administration was dependent on the dose of cocaine available for self-administration. For one test, a between-groups design was used and separate groups of rats (n=4–5 per group) self-administered different doses of cocaine (1.0, 0.25, or 0.125 mg/kg per infusion) during an 8-h test. For these tests, there were six separate groups (three doses of cocaine × two light conditions) that were tested only once each.

For a second test, a within-groups design was used and the dose-effect curve for self-administration of seven doses of cocaine, plus the saline vehicle, was obtained in a single test session. For these tests, rats (n=6) received additional training (14–21 days) once stable self-administration was achieved under the FR-5 schedule. Daily sessions were divided into 30-min bins, each separated by a 10-min time-out. During each 30-min bin, a different dose of cocaine was available under the FR-5 schedule of reinforcement. The starting dose was 1.0 mg/kg per infusion and during each subsequent bin the dose of cocaine administered was reduced by one half. Reductions in dosage from the starting dose of 1.0 mg/kg per infusion to that of 0.125 mg/kg per infusion were achieved by reducing infusion time (12 s for 1.0 mg/kg per infusion, 6 s for 0.5 mg/kg per infusion, etc., to a minimum 1.5 s infusion time). At the start of each 30-min bin, rats received an experimenter-delivered priming injection of the dose of cocaine that would be available for that bin.

The concentration of cocaine used for these infusions was 10.0 mg/ml per kg. Delivery of doses lower than 0.125 mg/kg per infusion was achieved by decreasing the concentration of cocaine infused from 10.0 to 1.25 mg/ml per kg. The lines were flushed and refilled with this new concentration of cocaine. The 0.06 mg/kg per infusion dose was obtained using an infusion time of 6 s. Doses lower than 0.125 mg/kg per infusion were obtained by reducing infusion times (minimum time = 1.5 s). In this manner, the dose was repeatedly reduced until a dosage of 0.015 mg/kg per infusion was obtained. Thus, during these dose-effect determinations, responding maintained by all doses of cocaine (0.015–1.0 mg/kg per infusion) was studied during each session. A final 30-min test was conducted to measure responding when the cocaine solution was replaced with saline. For these tests, the lines were again flushed and refilled with saline. Responses on the active lever produced a 12-s infusion of saline.

Dose-effect curves were determined daily until stable self-administration behavior was achieved. The criteria for stability for each rat were: (1) the two doses defining the ascending phase of the dose-effect curve did not differ in three consecutive test sessions and (2) less than 20 responses were emitted in response to saline during the same three test sessions.

Once stable behavior was achieved, the influence of the stimulus lights paired with cocaine self-administration was determined as above. For these tests, the dose-effect curve for cocaine self-administration was determined in the presence of the light stimulus (“light 1”), in its absence (“no light”), and in its presence again (“light 2”). Cocaine infusions were accompanied by illumination of the light stimulus only during tests that measured responding maintained by cocaine and the associated light stimulus (tests 1 and 3); priming infusions were delivered without the light during test 2.

At the completion of each test, catheters were infused with sodium pentobarbital (20.0 mg/kg). An immediate loss of the righting reflex confirmed catheter patency.

Drugs

Cocaine HCl (National Institute of Drug Abuse) was dissolved in sterile physiological saline and heparin (3 U/ml). Intravenous infusions were in a volume of 12.5–100 µl. Drug weights refer to the salt.

Data analysis

For all experiments, the dependent measure of number of active lever responses was compared across conditions using ANOVAs.

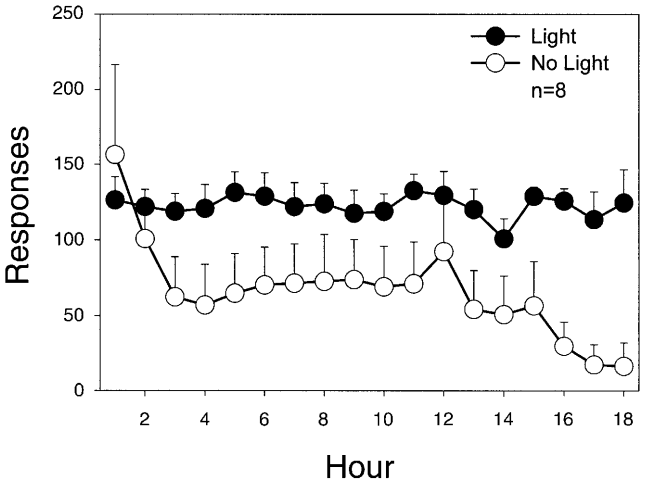

Fig. 1 Average number of responses (+ SEM) in rats working for cocaine (0.5 mg/kg per infusion) delivered according to an FR-5 schedule during each hour of an 18-h test. During training, self-administered cocaine infusions were always paired with the illumination of a light. On the test day, the light was either presented with the cocaine infusion (“light” group) or was omitted (“no light” group). Removal of the light stimulus produced a decrease in cocaine-reinforced responding

For data from the 8- and 18-h sessions, number of responses for each 60-min period and/or for the total session was analyzed as a function of light condition (hour×light condition). For data from the within-session dose-effect tests, responses on the active lever were analyzed during each 30-min bin. The number of responses produced as a function of cocaine dose for the “light 1” and “light 2” conditions as well as for the “light 1” and “no light” conditions were compared (light condition×cocaine dose). Significant main effects and interactions were further analyzed using Tukey post hoc tests for pairwise comparisons. All data are expressed as the average number of responses (+) SEM.

Results

Acquisition of cocaine self-administration was achieved within 5–10 days and stability on the FR-5 schedule of reinforcement was achieved within 5–10 additional days of training. Stability for dose-response responding measured using the within-session protocol required an additional 14–21 days of training.

Figure 1 shows the effect of light condition on responding for a single dose of cocaine (0.5 mg/kg per infusion) during each 60 min of the 18-h session. When tested with the light stimulus, responding is high and fairly consistent during each of the 60-min periods. When self-administration was measured without the light stimulus, the number of cocaine-reinforced responses decreased to about 50% by the third hour of testing and reached almost 0 by the end of the 18-h test. Of the eight rats tested, only one maintained a high level of responding throughout each hour of the 18-h test when the light stimulus was omitted. Responding of the other rats was reduced during the first and subsequent hours and for five of these subjects, 25 responses or less per hour were produced during the fifth and sixth hours of testing and

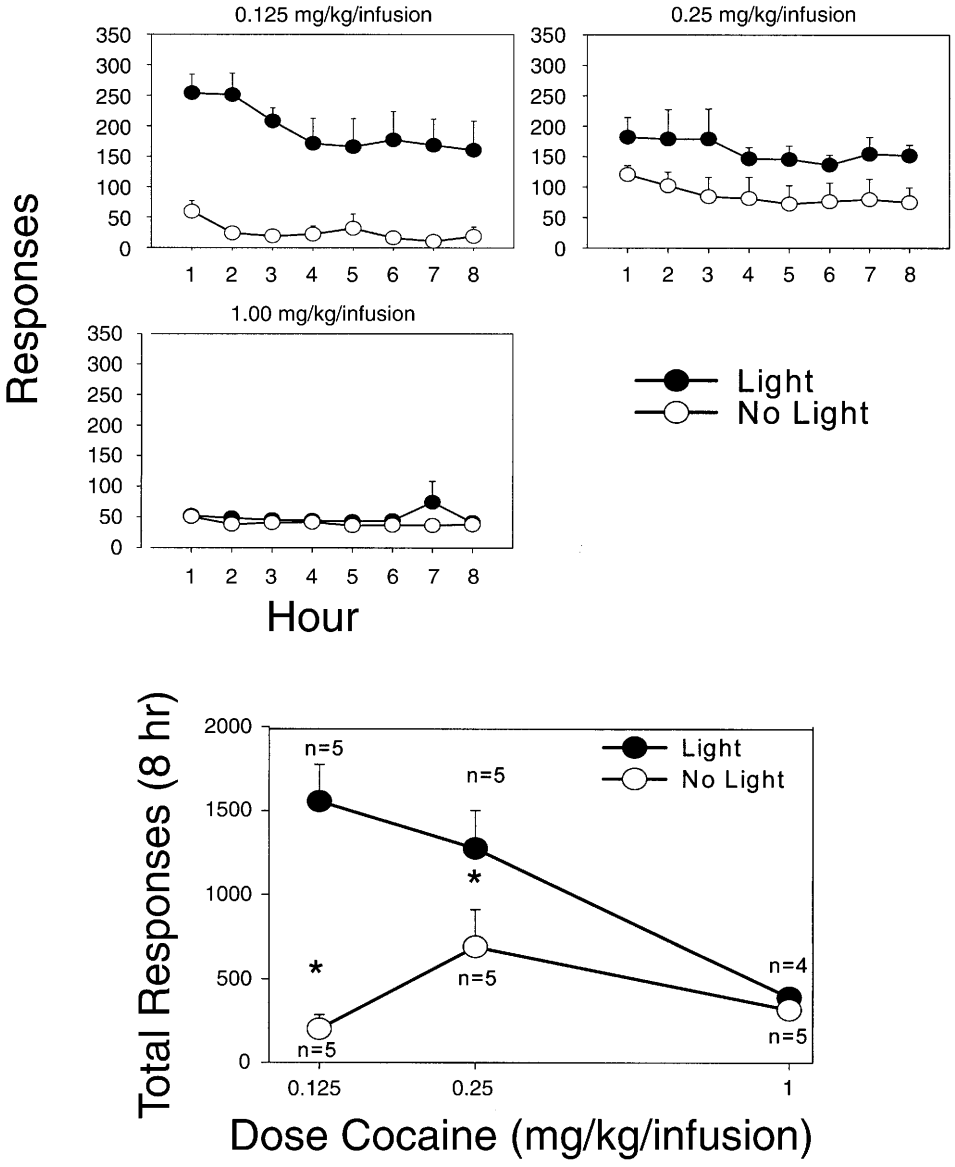

Fig. 2 *Top panels* : average number of responses (+ SEM) reinforced by cocaine (0.125, 0.25, or 1.0 mg/kg per infusion) during each hour of an 8-h test. Responding was reinforced according to an FR-5 schedule. During training, self-administered cocaine infusions were always paired with the illumination of a light. On the test day, the light was either presented with the cocaine infusion ("light" group) or was omitted ("no light" group). Responding maintained by 1.0 or 0.25 mg/kg per infusion cocaine was not significantly influenced by the presence of the light stimulus. However, removal of the light stimulus produced a decrease in responding maintained by 0.125 mg/kg per infusion cocaine. *Bottom panel* : total number of responses (+ SEM) reinforced by cocaine (0.125, 0.25, or 1.0 mg/kg per infusion). When the data are collapsed across hour, removal of the light stimulus decreased responding maintained by 0.25 and 0.125 mg/kg per infusion (* $P<0.05$)

less than 10 responses per hour were produced during subsequent hours of the test. The two other subjects maintained relatively high rates of responding until hour 16 of the test.

An ANOVA (light condition×time) revealed a main effect of light condition [$F(1,7)=11.851$, $P=0.011$] and a main effect of time [$F(17,119)=2.386$, $P=0.003$]. The interaction between these variables approached significance [$F(17,119)=1.693$, $P=0.053$]. Inactive lever responding (data not shown) remained low during these tests.

Figure 2 (top) shows the effect of light condition on responding maintained by each dose of cocaine during each hour of the 8-h tests. Responding maintained by the 1.0 mg/kg per infusion dose of cocaine was not influenced by the absence of the cocaine-associated light stimulus [$F(1,7)=0.841$, NS]. Although there was a tendency for the number of responses maintained by the 0.25 mg/kg per infusion dose of cocaine to be lower when the cocaine-associated light stimulus was omitted, this decrease in responding was not significant [$F(1,8)=3.396$, NS]. Of the five rats tested in the "no light" condition, responding remained high during each hour of the test for two of the subjects, was reduced during each hour of the test for one subject, and was initially high for two subjects but decreased to less than 20 responses per hour by the third hour of the test. The number of responses maintained by the 0.125 mg/kg per infusion dose of cocaine was significantly lower when the light stimulus was omitted [$F(1,8)=32.973$, $P<0.0001$]. Inactive lever responding (data not shown) remained low during these tests.

Figure 2 (bottom) shows the total number of responses produced during the 8-h session as a function of cocaine dose and light condition. When the data are collapsed across the time factor, the ANOVA revealed a significant effect of cocaine dose [$F(2,23)=7.569$, $P=0.003$], light condition [$F(1,23)=23.347$, $P<0.001$], and an interaction

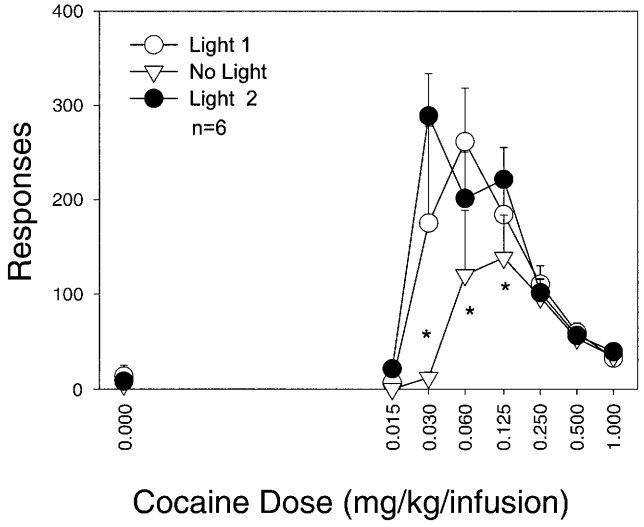

Fig. 3 Effect of the presence ("light 1", "light 2") or absence ("no light") of a cocaine-associated stimulus on responding maintained by a wide range of cocaine doses. The "light 1" test was conducted first, followed by the "no light" test and, finally, the "light 2" test. Each dose of cocaine was available during 30-min bins during a 4- to 5-h daily test. Doses of cocaine were tested in a descending order beginning with the 1.0 mg/kg per infusion dose. *Symbols* represent the average number of responses (+ SEM). Although there was no effect on responding maintained by the highest doses of cocaine, responding maintained by the 0.030, 0.060, and 0.125 mg/kg per infusion doses was significantly reduced in the "no light" group when compared to the "light 1" group (*=P<0.05)

[F(2,23)=7.117, P=0.004]. The number of responses produced in the "no light" groups was lower than in the "light" groups when cocaine doses of 0.25 and 0.125 mg/kg per infusion were self-administered (P<0.05).

Figure 3 shows the effect of light condition on responding maintained by cocaine during the within-session dose-effect test. During the first ("light 1") and third ("light 2") tests, the light stimulus was illuminated during each cocaine infusion. During the second test ("no light"), the light stimulus was omitted. Responding reinforced by cocaine initially increased as the dose of cocaine was decreased from the starting dose of 1.0 mg/kg per infusion. Maximum responding maintained in the "light 1" condition was obtained with the 0.06 mg/kg per infusion dose, with the 0.125 mg/kg per infusion dose in the "no light" condition, and with the 0.03 mg/kg per infusion dose in the "light 2" condition.

An ANOVA on the data produced during the two light conditions failed to reveal a significant effect of light condition [F(1,5)=3.019, NS]. ANOVA on the data from "light 1" and "no light" conditions (light condition× cocaine dose) revealed significant effects of cocaine dose [F(6,30)=6.350, P<0.0001] and light condition [F(1,5)=9.860, P=0.026] as well as an interaction [F(6,30)=3.030, P=0.020]. When the cue light was removed, responding for the 0.125, 0.06, and 0.03 mg/kg per infusion dose of cocaine was significantly reduced relative to the light condition (P<.05). Inactive lever responding (data not shown) remained low during these tests.

Discussion

These studies were designed to determine whether removal of a stimulus that had been paired with self-administered cocaine infusions produced changes in cocaine self-administration. Further, they examined the possibility that the influence of conditioned stimuli on responding might be related to cocaine dose and/or session length. During training, self-administered cocaine infusions were always paired with the illumination of a light stimulus. Removal of the light stimulus produced effects on self-administration that were dependent on both the dose of cocaine and the duration of the test session. The continued presentation of the light stimulus facilitated responding when the self-administered dose was low and/or when session length was long.

When responding was measured during the long sessions, removal of the light stimulus decreased responding maintained by doses of 0.5 mg/kg per infusion cocaine or less. When responding maintained by a range of cocaine doses was measured using the within-session dose-effect procedure, removal of the light stimulus decreased responding maintained by doses of 0.125 mg/kg per infusion or less of cocaine but responding maintained by the higher doses of 0.25 or 0.50 mg/kg per infusion cocaine was unaffected. These differences might reflect the influence of different training or testing procedures. One procedural difference is that rats received relatively high-dose exposures to cocaine during early components of the within-session dose-effect test when doses of 1.0 and 0.5 mg/kg per infusion cocaine were self-administered. Accordingly, when responding maintained by 0.5 or 0.25 mg/kg per infusion cocaine was measured in these tests, there was a significant amount of cocaine already "on board". This might explain why removal of the light stimulus failed to decrease responding maintained by these doses of cocaine under these test conditions.

The dose-dependent influence of the light stimulus on the maintenance of responding might explain why a previous study failed to obtain significant decreases in responding of a small sample of rats following removal of a cocaine-associated stimulus (Carelli and Ijames 2000). In that study, high-dose cocaine infusions (0.33 mg/infusion; approximately 1.0 mg/kg per infusion) were delivered according to an FR-1 schedule of reinforcement. In the present study, removal of the cocaine-associated stimulus was also ineffective in decreasing responding maintained by this high dose of cocaine.

The continued presentation of stimuli that have been paired with self-administered cocaine infusions appears to be critical to the maintenance of self-administration of some doses of cocaine. It is important to note, however, that self-administration is also acquired when a light stimulus is omitted and responding under these conditions is also maintained during long sessions (Schenk et al. 2000). Self-administration of rats that have been trained and tested without a salient cue associated with self-administered infusions, however, can be differentiated

from self-administration of rats that have been trained and tested with a salient cocaine-associated stimulus. For example, the acquisition of self-administration is delayed when a salient cue is omitted particularly when the cocaine dose is low (unpublished findings). Further, once self-administration has been acquired, pretreatment with the kappa-opioid receptor agonist, U69593, decreased responding of rats that had been trained to self-administer cocaine with an associated light stimulus, as in the present study (Schenk et al. 2000). Pretreatment with U69593 produced minimal effects on cocaine self-administration for rats that were trained and tested without the cocaine-associated light stimulus (Schenk et al. 2000). Thus, self-administration that has been associated with a salient stimulus may be differentiated from self-administration that has not been associated with a specific stimulus.

The development of conditioned reinforcing properties of cocaine-associated stimuli might explain the facilitative effects of these stimuli on self-administration. Other laboratories have demonstrated the ability of cocaine-associated stimuli to reinforce high rates of operant responding in the absence of cocaine (Weissenborn et al. 1997; Arroyo et al. 1998; Markou et al. 1999). Maintenance of high rates of responding under a second-order schedule was dependent on the continued presentation of these conditioned reinforcers (Arroyo et al. 1998). In the present study the possibility that the light stimulus acquired conditioned reinforcing properties that contributed to maintenance of self-administration was not systematically investigated; responding maintained by the light stimulus in the absence of cocaine was not measured during the 8- or 18-h self-administration sessions. The within-session dose-effect tests included a 30-min period of saline self-administration. The development of conditioning is minimized during these tests, however, due to the extensive training that repeatedly paired the light stimulus with saline as well as cocaine.

Additionally, it is possible that the light stimulus acquired cocaine-like physiological or neurochemical effects. It is well established that neurons in the nucleus accumbens are critical for cocaine self-administration (Wise 1984; Koob et al. 1994) and a number of studies have shown that individual nucleus accumbens cells respond to self-administered cocaine infusions (Carelli et al. 1993, 2000; Carelli and Deadwyler 1994; Peoples and West 1996; Peoples et al. 1997, 1998). Some of these cells respond prior to the delivery of cocaine and others respond following the presentation of self-administered cocaine. One cell type is specific to cocaine-reinforced responding and does not respond to alternate reinforcers (Carelli and Deadwyler 1994; Carelli et al. 2000). Recent data have suggested that the response of cells that exhibit changes in firing rate within seconds of the cocaine-reinforced response appears to become controlled, at least in part, by a cocaine-associated stimulus rather than by cocaine itself (Carelli 2000).

Consistent with this finding, dopamine overflow increased following exposure to cocaine-associated stimuli in rodents (Brown et al. 1992; Fontana et al. 1993; Kiyatkin and Stein 1996; Weiss and Ciccocioppo 1999) but not in rhesus monkeys (Bradberry et al. 2000). As suggested by the authors, it is possible that the response of primates and rodents differs. The present results offer an alternate interpretation. Since the influence of cocaine-associated cues on the efficacy of a reinforcer is greatest when the reinforcement potency is low, the failure to observe an increase in dopamine levels following exposure to the cocaine-associated stimulus might have been a function of cocaine dose.

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