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Interaction of noncontingent cocaine and contingent drug-paired stimuli on cocaine reinstatement

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Abstract

Both noncontingent cocaine and the presentation of cocaine-paired external stimuli will reinstate cocaine-appropriate operant responding. However, the interaction of noncontingent cocaine and cocaine-paired stimuli in producing reinstatement has not been extensively examined. In the present study, the ability of noncontingent cocaine alone, the combination of noncontingent cocaine + contingent cocaine-paired lights + tone and contingent lights + tone alone to produce reinstatement were examined. No cocaine dose (3, 10, 17 mg/kg) produced significant reinstatement in the absence of cocaine-paired lights + tone. When responding also resulted in lights + tone presentation, all doses of cocaine produced similar, significant reinstatement. Finally, when only response contingent lights + tone were presented, none of the groups showed significant reinstatement. These findings indicate that in isolation, noncontingent cocaine alone and cocaine-paired external stimuli may be insufficient to engender significant levels of reinstatement, but when presented together produce robust reinstatement. The results highlight the important interaction between drug administration and drug-paired environmental stimuli in the reinstatement model.
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Keywords: Cocaine; Reinstatement; Relapse; External stimulus

1. Introduction

Relapse to drug use following a period of abstinence is a major problem in drug abusers. Many detoxified drug abusers report that they relapsed due to craving induced by the environment that was previously associated with drug taking (O'Brien et al., 1977; Sideroff and Jarvik, 1980; Wallace, 1989). Other abstinent drug abusers report that craving followed exposure to the previously abused drug (McCaul et al., 1989; Chornock et al., 1992). Although both interoceptive and external environmental variables are believed to play significant roles in relapse, the interaction of the two is not well understood (Childress et al., 1993).

The drug reinstatement paradigm in animals is frequently used to explore the factors underlying relapse and has been theorized to model some aspects of human drug craving and relapse (Koob, 2000; Littleton, 2000). In reinstatement studies, operant responding resulting in drug injections is extinguished after a period of drug availability. Following extinction, noncontingent presentation of the previously self-administered drug or a pharmacologically similar drug will result in renewed responding on the manipulandum that previously produced drug injections (Shaham et al., 2002). The magnitude of drug-induced reinstatement has been shown to be dose-dependent, with low doses producing less robust reinstatement than moderate or high doses (Schenk and Partridge, 1999). External stimuli, typically light and/or tones that have been repeatedly paired with drug delivery, will also reinstate operant responding when presented response contingently, and to a lesser degree when presented noncontingently during reinstatement testing (Gerber and Stretch, 1975; Arroyo et al., 1998; Weiss et al., 2001). Exposure to a specific environment that has been intentionally paired with the opportunity to self-administer cocaine will also result in significant, albeit transient, reinstatement responding (Alleweireldt et al., 2001).

Few studies have explicitly examined the interaction between interoceptive drug effects and contingent drug-paired external stimuli on the magnitude of subsequent reinstatement. One experiment in squirrel monkeys found

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that drug-paired external stimuli combined with a noncontingent drug injection resulted in more pronounced reinstatement responding than either the external stimuli or drug alone (Spealman et al., 1999). A second study in cocaine-trained rats demonstrated that noncontingent presentation of drug-associated external stimuli in combination with an injection of D-amphetamine produced greater reinstatement and enhancement of dopamine efflux in the nucleus accumbens than D-amphetamine or noncontingent stimuli alone (Di Ciano et al., 2001).

The major goal of the present study was to determine the degree of interaction between noncontingent cocaine dose and response contingent drug-paired external stimuli on reinstatement. To examine this interaction, three different noncontingent cocaine doses were initially presented alone immediately prior to reinstatement testing. These same three doses of cocaine were subsequently presented in combination with response-contingent flashing lights + tone. Finally, only the response contingent flashing lights + tone were presented during reinstatement testing.

2. Materials and methods

2.1. Subjects

Subjects were 32 adult, male, experimentally naïve Sprague–Dawley (Charles River Laboratories, USA) rats. Animals were food-restricted to 15 g of rodent chow per day and had continuous access to water except during the experimental sessions. Rats weighed at least 275 g at the beginning of the study. The animals were individually housed in standard plastic rodent cages in a temperature-controlled (22° C) 12-h reversed light/dark cycle colony room. Studies were approved by the Institutional Animal Care and Use Committee of VCU and conformed with NIH Guidelines for Care and Use of Laboratory Animals.

2.2. Surgical procedure

Rats were pretreated with 2 mg/kg morphine as an analgesic and anesthetized with a combination of ketamine, acepromazine and pentobarbital. A tapered catheter constructed from 3.5 French polyurethane tubing (Access Technologies, USA) was then implanted into each rat's right jugular vein. The distal end of the catheter was passed subcutaneously to a cannula connector pedestal (Plastics One, USA) implanted subcutaneously in the mid-scapular region. The catheters were flushed with 0.2 ml heparinized normal saline before each experimental session. Following each self-administration session catheters were filled with 0.1 ml of a 50% glycerol/50% sterile saline solution to which was added 500 units/ml heparin, 250 mg/ml ticarcillin and 9 mg/ml clavulanic acid (Timentin, SmthKline Beecham, USA) to help maintain patency. Rats were permitted a minimum of 5 days of post-operative recovery before beginning self-administration training. If a catheter failed during cocaine self-administration training, it was removed, the left jugular vein was catheterized and the animal was returned to the study. If a catheter failed during reinstatement testing, the rat was excluded from the study and replaced with another animal.

2.3. Drugs

Cocaine HCl (National Institute on Drug Abuse, USA) was diluted in heparinized (5 units/ml) sterile saline for the intravenous self-administration solution. For i.p. drug reinstatement testing, cocaine HCl was diluted in sterile saline and administered at a volume of 1 ml/kg, i.p. 10 min prior to the test session.

2.4. Apparatus

Experiments were conducted in 24 operant conditioning chambers housed inside individually isolated and ventilated enclosures (Med Associates, USA). The front wall of each chamber was equipped with two retractable response levers with a white stimulus light above each lever. A 5-W house light and Sonalert tone generator were located in the rear wall of the chamber. During each session, infusion tubing, protected by a stainless steel spring tether, connected the back-mounted pedestal implanted in each rat to a balanced liquid swivel suspended above each chamber. Infusions were delivered by a syringe pump located outside each chamber. Schedule parameters were controlled by MED-PC IV software (Med Associates) running on IBM PC compatible computers.

2.5. Training and testing

Cocaine self-administration training sessions were conducted 5 days/week (M–F) for 2 h daily. Initially, each response (fixed ratio 1) on the active lever resulted in delivery of a 0.5 mg/kg cocaine infusion (0.18 ml/6 s). For the duration of the infusion, a 2900-Hz, 50-dB tone sounded and the stimulus lights above both levers flashed at 3 Hz. Active-lever responses during the infusion as well as all inactive lever responses were recorded, but had no scheduled consequences. Over days, the fixed-ratio (FR) requirement for each infusion was increased to FR5. Rats were eligible for extinction and reinstatement testing only after they received 15 or more cocaine infusions per session for four consecutive sessions at FR5.

Extinction sessions were identical to cocaine self-administration sessions, except that saline was delivered under the FR5 schedule and neither lights nor tones accompanied saline infusions. Two-hour extinction sessions were conducted once daily, 7 days/week, until the number of active-lever responses per session declined to less than 20% of the number of active-lever responses on the last day of FR 5 cocaine self-administration.

Following extinction, rats were assessed for cocaine alone, cocaine + contingent cocaine-paired external stimuli and contingent cocaine-paired external stimuli alone reinstatement of cocaine-appropriate responding in 12 consecutive 2-h test sessions. Rats ($n = 8$/group) were administered either saline, 3, 10, or 17 mg/kg i.p. cocaine, 10 min prior to reinstatement testing, for the first eight consecutive days. On days 1–4, completion of each FR5 during the test session resulted in a 0.18-ml infusion of saline, but neither tone nor stimulus light presentation (noncontingent cocaine alone). On days 5–8, each completed FR5 resulted in a saline infusion as well as 6 s of tone presentation and 3 Hz flashing illumination of both stimulus lights (cocaine + contingent cocaine-paired external stimuli). On days 9–12, all rats received i.p. saline injections, 10 min prior to reinstatement testing and completion of each FR5 resulted in a saline infusion as well as 6 s of tone presentation and 3 Hz flashing illumination of both stimulus lights (contingent cocaine-paired external stimuli alone).

2.6. Data analysis

Active- and inactive-lever responses and infusions were recorded for each subject daily. Statistical analysis was performed using SuperAnova (Abacus Concepts, USA). The effects of treatment days, cocaine dose and stimulus condition were compared using a three-way mixed analysis of variance (ANOVA). The effect of treatment day was not significant in this analysis, therefore the individual day data from each of the three stimulus conditions were collapsed into single mean values for each rat and a two-way mixed ANOVA was conducted using cocaine dose and stimulus condition as factors. Further analysis comparing individual cocaine pretreatment doses and stimulus conditions was conducted using Bonferroni post hoc tests only if main effects were significant.

3. Results

Rats readily acquired self-administration of 0.5 mg/kg/infusion cocaine. Averaged across rats, a mean of 15.9 (± 1.1) cocaine self-administration sessions were required to reach FR5 and meet criteria for beginning extinction. A mean of 29.4 (± 1.7) cocaine infusions were obtained on the last day of cocaine self-administration training. During extinction, an average of only 2.8 (± 0.3) days were required to reach reinstatement testing criteria. Neither total infusions on the final day of self-administration or days to reach reinstatement testing criteria differed significantly between groups. The effects of saline, 3, 10 or 17 mg/kg i.p. cocaine pretreatment alone, cocaine + contingent cocaine-paired external stimuli and contingent cocaine-paired external stimuli alone on active lever responding during reinstatement testing are shown in Fig. 1 ($n = 8$/group). There was no main effect of cocaine dose on reinstatement responding

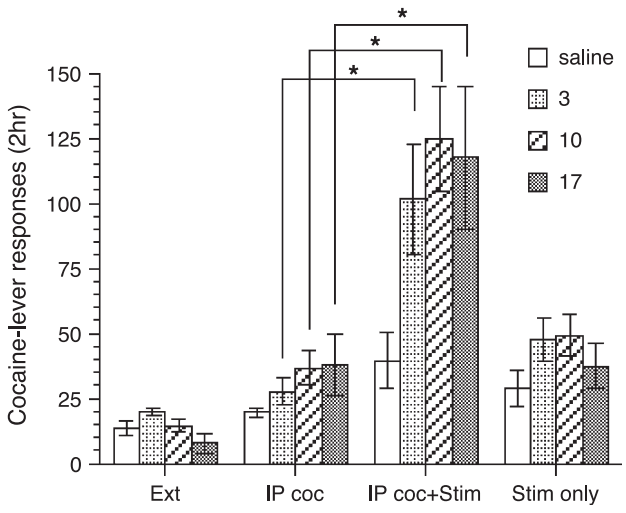

Fig. 1. Effects of saline, 3, 10 or 17 mg/kg noncontingent i.p. cocaine injections and contingent cocaine-paired external stimuli presentation on active-lever responding. Data depict 2 h mean (± S.E.M.) responses in each of three different stimuli presentation conditions. The first four bars (Ext) show mean (± S.E.M.) responses on the final day of saline extinction. The second group of four bars (IP coc) show mean (± S.E.M.) responses following noncontingent i.p. cocaine injection during reinstatement sessions in which responding did not result in presentation of cocaine-paired external stimuli. The third group of four bars (IP coc + Stim) show mean (± S.E.M.) responses during reinstatement sessions in which noncontingent i.p. cocaine was given prior to testing and responses-contingent external cocaine stimuli were presented under an FR5 schedule during testing. The last group of four bars (Stim only) show mean (± S.E.M.) responses during reinstatement sessions in which noncontingent i.p. saline was administered to all groups prior to reinstatement test sessions in which responding under an FR5 schedule resulted in presentation of cocaine-paired external stimuli. *Denote statistically significant effects ($p < 0.05$).

[$F(3,28) = 2.79$, $P = 0.0589$]. There was, however, a significant main effect of stimulus condition [$F(2,28) = 48.479$, $P = 0.0001$] and a significant cocaine dose × stimulus condition interaction [$F(6,28) = 3.341$, $P = 0.007$]. Post hoc Bonferroni tests indicated that none of the three doses of cocaine alone resulted in significantly greater active-lever responding than that in the saline pretreatment group, although there was a general trend for increased responding on the cocaine-lever as a function of cocaine pretreatment dose. Under the cocaine-alone condition, a maximum of 38 (± 11.7) responses were emitted on the active lever at the 17 mg/kg cocaine pretreatment dose. In contrast, when combined with contingent cocaine-paired external stimuli (6-s flashing stimulus lights and tone) following each completed FR5, all three doses of cocaine resulted in significantly greater active-lever responding than cocaine alone ($P < 0.05$). A maximum of 124 (± 20.3) responses were emitted at the 10 mg/kg cocaine pretreatment under these stimuli conditions.

The last four bars in Fig. 1 show the effect of contingent cocaine-paired external stimuli alone in combination with i.p. saline injection in all four groups. Responding significantly decreased in all three groups of rats previously given noncontingent cocaine as compared to the previous cocaine

+contingent cocaine-paired external stimuli condition. There were no significant differences resulting from prior exposure to noncontingent cocaine in the contingent cocaine-paired external stimuli test condition. Inactive-lever responding was extremely low in all reinstatement test conditions. The highest mean inactive-lever responses in any of the test conditions was nine (± 3.2) responses at the 3 mg/kg cocaine+contingent lights+tone test condition. There were no significant effects of drug or stimuli condition on inactive lever responding.

4. Discussion

The results in the present study show that under some conditions neither noncontingent cocaine nor contingent cocaine-paired external stimuli presentation may be effective in reinstating extinguished cocaine-reinforced behavior. However, their concurrent presentation may powerfully evoke such behavior beyond that expected by their individual contributions and do so repeatedly for several days. Although both noncontingent cocaine and contingent cocaine-paired external stimuli have been individually demonstrated to reinstate cocaine-appropriate responding, few previous studies have examined the unique contribution their interaction could provide.

In the present study, i.p. cocaine doses of 3, 10 and 17 mg/kg produced dose-depended increases in reinstatement responding, which neared but did not reach statistically significant levels when previously cocaine-paired external stimuli were omitted during extinction and subsequent reinstatement testing. Based on the trend for greater responding at increasing cocaine doses, it is possible that all three noncontingent cocaine doses (3, 10, 17 mg/kg) were too low to produce significant reinstatement or that the sample size was too low to show a significant reinstatement effect using our test procedure. Other studies have shown that cocaine doses of 10 and 20 mg/kg produce significant and reliable reinstatement in groups of similar size, making that interpretation possible, but less likely to be the sole reason for the ineffectiveness of cocaine alone as a reinstating stimulus (Worley et al., 1994; Schenk and Partridge, 1999; Erb et al., 2000).

A second possibility is that repeated testing over four consecutive days might have reduced the effectiveness of cocaine alone as a reinstating stimulus. If this were the case, the inability of noncontingent cocaine alone to produce significant reinstatement could have been due to collapsing the individual day data for each rat into four session means. To assess this possibility, we independently reanalyzed responding on the first cocaine alone reinstatement day (data not shown). In this analysis, even the first day of noncontingent cocaine administration failed to produce significant reinstatement, suggesting that repeated testing did not play a role in the lack of effects of noncontingent cocaine alone.

A third, and perhaps most likely hypothesis for the present finding is that omission of contingent cocaine-paired external stimuli during extinction and subsequent reinstatement testing decreased the effectiveness of noncontingent cocaine alone as a reinstating stimulus. In squirrel monkeys, noncontingent cocaine alone has been shown to produce reinstatement without presentation of extinguished drug-paired stimuli (Spealman et al., 1999). However, in the vast majority of published drug-induced reinstatement studies in rodents, cocaine-paired external stimuli were presented either contingently and/or noncontingently during both extinction and drug reinstatement testing (Shaham et al., 2002). Doubtless, the reinstating power of these stimuli is significantly attenuated by repeated presentation during extinction, but it is possible that they still possess some reinstating efficacy. The absence of cocaine-paired external stimuli, in any form, in the drug alone reinstatement condition in the present study might have played an important role in reducing the magnitude of the cocaine reinstatement effect to insignificant levels.

Cocaine-paired external stimuli have been reported to enhance the reinstating effectiveness of noncontingent cocaine administration in rats and monkeys previously trained under second-order schedules of drug reinforcement, (Spealman et al., 1999; Kantak et al., 2002a,b). In the present study, the combination of i.p. cocaine+contingent cocaine-paired external stimuli significantly reinstated responding, whereas cocaine alone did not produce significant reinstatement. It is interesting to note that the reinstatement responding produced by cocaine+contingent cocaine-paired external stimuli was not dose-responsive, with all three doses of cocaine producing similar, significant levels of reinstatement. Previous reports in the literature have shown that a positive, dose–response relationship exists between reinstating drug dose and the magnitude of reinstatement (Schenk and Partridge, 1999). Although there were a number of differences between the present study and those in the literature, the major difference was that in the present study the cocaine-paired external stimuli were not extinguished prior to reinstatement testing. It is therefore likely that these stimuli were more salient, perhaps enhancing their relative contribution to the reinstatement effect.

Several other differences also exist when the present results are compared to those reported previously that suggest an essential role of conditioned stimuli in producing reinstatement. Firstly, in previous studies combining cocaine-paired external stimuli and noncontingent drug administration, one set of external stimuli was explicitly paired with cocaine self-administration and a second set of stimuli explicitly paired with extinction (Spealman et al., 1999; Lee et al., 2003). The use of differential stimuli during self-administration and extinction has been shown to greatly enhance the reinstating effectiveness of the drug-paired conditioned stimuli, perhaps by enhancing their salience (Weiss et al., 2000, 2001). Secondly, in these prior studies,

second-order schedules of drug self-administration were employed. One of the important characteristics of second-order schedules is that the drug-paired external stimuli also come to serve as conditioned reinforcers, which themselves maintain behavior. Conditioned reinforcers can produce very prolonged periods of operant responding in the absence of the primary, drug reinforcer (Goldberg et al., 1977; Everitt and Robbins, 2000). In the present study, there were no explicit stimuli paired with extinction and the animals were trained under a simple FR5 schedule. Both of these manipulations could be expected to reduce the conditioned reinforcing effect of the drug-paired external stimuli, and in fact when presented alone they failed to significantly reinstate cocaine-appropriate responding. However, when presented in conjunction with noncontingent cocaine the combination resulted in very robust reinstatement.

Previous studies have noted that presentation of drug-paired external stimuli alone can produce reinstatement, but that the effect is typically less robust than reinstatement produced by noncontingent drug or footshock stressors (Fuchs et al., 1998; Tran-Nguyen et al., 1998). In the present study, contingent cocaine-paired external stimuli alone were ineffective in significantly reinstating cocaine-appropriate responding in the saline control group, which had not received any prior testing with drug cues, as well as in all three noncontingent cocaine reinstatement groups. Our negative findings with contingent cocaine-paired external stimuli alone may have been due to some critical difference in the experimental conditions between the present study and those in the literature. Many of the previous studies showing that cocaine-paired external stimuli alone were effective in reinstating responding presented them either contingently under an FR1 schedule, noncontingently throughout the sessions, or using some combination of contingent and noncontingent presentation. These conditions would be expected to insure some minimal exposure to the previously drug-paired external stimuli during the reinstatement session. In the present study, cocaine-paired external stimuli were presented on a relatively large FR5 schedule and never presented noncontingently, therefore since the animals were extinguished they would have received few light/tone stimuli presentations. This relative scarcity of stimuli delivery might have attenuated the ability of these stimuli alone to produce reinstatement. However, when responding was somewhat elevated by noncontingent cocaine injections, the previously cocaine-paired external stimuli would have been presented more frequently, perhaps contributing to the pronounced increase in reinstatement responding shown in the present results.

It is also possible that the order of test presentation could have had an impact upon our ability to show a significant reinstatement effect of contingent presentation of cocaine-paired external stimuli. Prior to the first external stimuli alone test, each of the three cocaine treatment groups had received four test days with noncontingent cocaine + contingent cocaine-paired stimuli. Since drug-paired stimuli alone have been shown to have only modest reinstating efficacy, it could have been the case that their ability to reinstate lever-pressing behavior was substantially diminished by the time external stimuli alone were tested for reinstating efficacy (Fuchs et al., 1998; Tran-Nguyen et al., 1998). However, although elevated, reinstatement responding in the saline treatment group was not statistically significant in the noncontingent cocaine + contingent external stimuli condition. These animals had not received any prior contingent external stimuli presentations, supporting the conclusion that testing order alone, while potentially a contributing factor, was not entirely responsible for the lack of reinstating efficacy of contingent cocaine-paired external stimuli.

Taken together with previous studies, the present data reinforce the hypothesis that drug-paired environmental stimuli are likely to have a major impact on relapse. Indeed, exposure to drug in the presence of drug-paired environmental stimuli may be a much more powerful promoter of relapse than might have previously been predicted. This data would also suggest that studies should be conducted to determine the effectiveness of relapse preventing medications or other relapse prevention treatments under conditions in which both drug and drug-paired external stimuli are presented as their robust combined reinstating ability may be extremely resistant to successful treatment.

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