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Repeated Cocaine Experience Facilitates Sucrose-Reinforced Operant Responding in Enriched and Isolated Rats

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Abstract

The purpose of the present experiment was to determine whether repeated cocaine exposure differentially affects sucrose-reinforced operant responding in rats raised in an enriched condition (EC) or an isolated condition (IC). Specifically, the performance of EC and IC rats pressing a lever for sucrose under a high fixed-ratio schedule (FR 30) prior to and after 10 days of exposure to cocaine (15 mg/kg, i.p.) or saline was compared. Regardless of rearing condition, rats repeatedly exposed to cocaine had shorter reacquisition latencies to complete a sucrose-reinforced FR 30 task than saline controls. The results suggest that cocaine exposure may have cross-sensitized both EC and IC rats to the reinforcing effects of sucrose or sucrose-associated cues, thus facilitating reacquisition of operant responding.

Keywords

Cocaine; Environmental Enrichment; Fixed Ratio; Locomotor; Sensitization; Sucrose

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It has been suggested that there is a common pathway within the brain that mediates the incentive motivation for rewards (Wise, 1998). This reward system appears to be activated by natural rewards such as food and sex, as well as by unnatural rewards such as drugs. Repeated exposure to drugs of abuse may lead to long lasting changes in the neural circuitry involved with learning, pleasure, and motivation (Robinson & Berridge, 1993, 2003). Although the exact role of these changes in subsequent drug use is unknown, it has been suggested that drug-related neuroadaptations lead to incentive sensitization. According to incentive-sensitization theory, drug sensitization enhances the incentive salience of drugs and drug-related cues (Robinson & Berridge, 1993, 2001). This increase in incentive salience increases the attractiveness of drug-related cues, thereby increasing their ability to “grab” attention. In this way, once an organism is sensitized, formally neutral stimuli

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become salient incentives that trigger compulsive behavior to seek the drug, thus increasing vulnerability to relapse.

Evidence for incentive-sensitization theory comes from studies demonstrating a relationship between drug sensitization and subsequent drug-seeking behavior. For example, studies have shown that previous exposure to amphetamine increased the “breakpoint” for rats self-administering amphetamine using a progressive ratio schedule of reinforcement (Lorrain, Arnold, & Vezina, 2000; Mendrek, Blaha, & Phillips, 1998). Additional studies have found that cocaine self-administration enhances rats’ subsequent motivation to seek cocaine in a runway apparatus as measured by running speed (Deroche, Le Moal, & Piazza, 1999) and that sensitization can increase drug-induced CPP (Lett 1989a; Shippenberg & Heidbreder, 1995; Shippenberg, Heidbreder, & Lefevour, 1996). Thus, it appears that drug-induced changes in the reward pathway sensitize reactions to subsequent administrations of that drug. These same changes may also produce cross-sensitization to other similar drugs (Lett, 1989; Horger, Giles, & Schenk, 1992). Additionally, since the neural circuitry mediating natural rewards overlaps with the circuitry mediating drug reward (see Kelley & Berridge, 2002), it is also possible that exposure to drugs can produce cross-sensitization with natural reinforcers such as sex and food.

Indeed, evidence for cross sensitization between amphetamine and sex has been found in male rats (Fiorino & Phillips, 1999; Nocjar & Panksepp, 2002) and between cocaine and sex in male Japanese quail (Levens & Akins, 2004). In these studies, animals that exhibited behavioral sensitization to the drug exhibited more appetitive sexual behaviors than saline controls, despite the fact that they were in a drug free state at the time of testing.

Recent evidence also suggests that amphetamine sensitization increases the locomotor response to sucrose, an effect indicative of cross-sensitization to food (Avena & Hoebel, 2003a; see also Gosnell, 2005 for a similar effect with cocaine). Further, when the amphetamine sensitized rats were subsequently given access to a 10% sucrose solution for 1 hour in their home cages, they drank significantly more sucrose solution than saline treated rats (Avena & Hoebel, 2003a). These results suggest that amphetamine and sucrose activate a common brain mechanism and that sensitization to amphetamine increases the rewarding property of sucrose.

In a follow-up study, Avena & Hoebel (2003b) also found that rats maintained on a high sucrose diet displayed increased locomotor sensitization to amphetamine compared to rats reared on a standard laboratory diet. Similarly, it has been found that free access to a 32% sucrose solution enhances subsequent amphetamine CPP in rats (Vitale, Chen, & Kanarek, 2003). Thus, evidence exists that amphetamine-induced changes in the reward pathway also sensitize reactions to other natural stimuli such as food, and vice-versa. However, none of these studies have determined if repeated exposure to drugs directly alters the motivation to work for a palatable reward.

Another factor that has not been investigated systematically in the relationship between drug and non-drug cross-sensitization is the role of environmental rearing experiences. Previous research has shown that social or enriched housing attenuates the development of amphetamine sensitization (Ahmed, Stimus, Le Moal, & Candor, 1995; Bardo et al., 1995), but it is unclear whether the results generalize to cocaine or natural rewards. Environmental enrichment also appears to reduce the propensity to self-administer drugs and work for non-drug reinforcers. For example, research has shown that rats raised in an enriched condition (EC) self-administer less amphetamine at low doses relative to rats raised in an isolated condition (IC), as indicated by their persistence on a progressive ratio schedule (Bardo Klebaur, Valone, & Deaton, 2001). In addition, environmental enrichment appears to alter

responding for non-drug reinforcers with EC rats make fewer lever presses than IC rats for novel light flashes (Bardo & Dwoskin, 2004).

Therefore, the purpose of the current experiment was two-fold. First, the experiment examined whether repeated exposure to cocaine would alter subsequent motivation to work for sucrose. If cocaine exposure enhances motivation for sucrose, rats treated with repeated cocaine should exhibit shorter latencies to complete sessions of sucrose-reinforced responding compared to saline-control rats. Second, the experiment sought to determine whether repeated cocaine exposure would affect operant responding for sucrose in EC and IC rats differentially. Specifically, EC and IC rats were trained to respond for sucrose on a FR 30 schedule and then exposed to cocaine treatment on 10 consecutive days. One week after their last cocaine injection, sucrose responding was reassessed on an FR 30 schedule while the rats were in a drug-free state. Although cocaine sensitization has not been systematically studied in EC and IC rats, because IC rats show more robust amphetamine sensitization, it was hypothesized that any cocaine and sucrose cross-sensitization would be greater in IC rats.

Method

Subjects

Thirty-six male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) were weaned on postnatal day 20 and were delivered to the colony at 21 days of age. Upon arrival, rats were assigned randomly to either an EC or IC home cage condition for the duration of the study. EC rats ($n = 18$) were housed in a large metal cage ($60 \times 120 \times 45$ cm) with cohorts (8–10 per cage). The environment contained 14 novel hard plastic objects (commercially available toys and containers). Rats were removed briefly each day so that 7 of the objects could be replaced; the remaining objects were rearranged into a novel configuration. IC rats ($n = 18$) were housed individually in a standard hanging cage with wire mesh floor and front panel ($17 \times 24 \times 20$ cm), and solid metal sides, back and top. IC rats were not handled during the exposure period (21–51 days of age).

All animals had free access to food and water, except during periods of restricted access to food as described below. The animal colony was on a 12:12 hr light:dark cycle, with lights on at 7:00 A.M. All experimental procedures took place during the light portion of the cycle. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Kentucky and were in compliance with NIH's *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington D.C, 1996).

Apparatus

Operant chambers—Rats were trained and tested in standard two-lever operant conditioning chambers (ENV-007; Med Associates, St. Albans, VT). Each chamber measured $28 \times 21 \times 21$ cm with a metal rod floor. One panel of the chamber contained two response levers, one on each side of a recessed food tray. There was a white cue light positioned above each lever. A personal computer using Med-PC software (Med Associates, St Albans, VT, USA) recorded responses and delivered sucrose pellets (Noyes; 45 mg).

Locomotor activity chambers—Locomotor activity was assessed in a wooden rectangular activity box (24.5×28 cm) outfitted with two infrared beams 2 cm above a wire grid floor. The interior walls were painted white and pine bedding was placed under the grid floor. The beams were oriented at 90° from each other and centered on each wall. Infrared detectors were linked to a personal computer and photobeam interruptions were recorded in

5-min bins. The activity chambers were located in an isolated test room with normal overhead illumination and ambient white noise (~60 dB).

Drug

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Bethesda, MD) and was mixed with saline (0.9%) at a concentration of 15 mg/ml. Cocaine was injected intraperitoneally (i.p.) in a volume of 1 ml/kg body weight.

Procedure

Acquisition of Sucrose-Reinforced Responding—Beginning at 51 days of age, rats were maintained on restricted access to food over a period of 6 days in order to reach body weights of approximately 85% of their free-feed body weights. During this period, access to food was restricted to 60 min daily. EC rats were separated from cohorts during the feeding period. During the last three days of restricted food access, rats were allowed to eat sucrose pellets to alleviate neophobia during training.

Training in the operant conditioning chamber began at 57 days of age. To orient rats to the recessed food tray, they were given one session in the chambers where sucrose pellets were given with no lever response contingency. To keep procedures consistent with subsequent training, pellet delivery was signaled by a sequence of light cues. The sequence began with illumination of one cue light (counterbalanced among rats) for 0.5 sec. For the second step of the sequence, the first cue light was turned off and the other cue light was illuminated for the same duration. For the third step of the sequence, both cue lights were illuminated. After the third step, both cue lights were turned off and a pellet was delivered to the food tray. The total time between onset of the first cue light and delivery of the sucrose was 1.5 sec and the interval between pellets was varied randomly from 10 – 35 sec. Rats received a total of 32 pellets over a 15 min period.

Once the rats were successfully trained to eat from the food tray, they were shaped to press a lever to earn sucrose pellets on a continuous schedule (FR 1) of reinforcement. For this session, depression of the active lever (counterbalanced within rearing condition) initiated a fixed cue-light sequence identical to that used in pretraining; except that each signal duration was 1 sec. Rats were allowed to earn 80 pellets before being removed from the chamber. After this training session, rats were allowed free access to food and water to regain 100% of their free-feed body weight.

During the sessions that followed initial FR 1 training, the rats were progressively shaped (by increasing the FR requirement by 3) to FR 30. Because we were concerned that the rats would have difficulty completing the high FR requirement, we used the cue lights to signal proximity to reinforcement. Therefore, all FR training trials began with illumination of the cue light over the active lever. After the rat had completed one-third of the FR requirement, the first light was extinguished and the other cue light was illuminated. Once the rat had completed two-thirds of the FR requirement, both lights were illuminated. Finally, once the FR requirement had been met, both lights turned off and a sucrose pellet was delivered. Rats were allowed a maximum of 150 min to complete 15 trials. Rats were shifted to a higher FR requirement when they finished all 15 trials within 35 min.

It was apparent by Session 11 that EC and IC rats were showing different rates of acquisition under the free-feed condition, with IC rats progressing toward the FR 30 requirement faster than EC rats. Therefore, we attempted to equalize acquisition of FR responding by restricting access to food to increase hunger motivation. After Session 11, all rats were limited to 90 min access to food each day. Food access occurred after each daily

session so that rats were food deprived for at least 20 hr before each session. Although the limited food access equalized responding to some degree, an EC/IC difference in responding remained, again with IC rats completing sessions and moving to higher FR requirements faster than EC rats. Therefore, beginning on Session 22, the magnitude of sucrose reward for completion of each trial was increased from 1 pellet to 3 for the remainder of the study. In this way, rats were able to earn 45 pellets per session.

Rats were considered fully trained once they completed five consecutive sessions at FR 30 within an average of 40 min or less. Regardless of when the acquisition criterion was met, each rat continued to participate in FR training sessions so that all rats experienced an equal number of training sessions. Despite the measures taken to equalize responding, three EC rats failed to reach the final response contingency of FR 30 within 45 sessions; one rat stabilized at FR 18, and one stabilized at FR 24. The third EC rat failed to stabilize at any FR value. For the one rat that failed to stabilize at any FR value, the operant training and reacquisition data were not included in the final analyses (although locomotor data from this rat was used). All other rats exhibited stabilized responding after 46 sessions of FR training. After Session 46, rats were given free access to food to regain 100% of their free feed body weight. Rats were rested in their home cages for a total of 15 days before commencement of locomotor assessment.

Repeated Cocaine Treatment and Locomotor Activity—After 15 days under free-feed conditions following operant training, EC and IC rats were randomly assigned to either a saline or cocaine treatment, with the stipulation that mean latency to complete an FR 30 session at criterion (first five consecutive sessions at FR 30 within an average of 40 min or less) not differ significantly between dose groups within each rearing condition (see Figure 1). Rats were injected with either saline or cocaine HCl (15 mg/kg, i.p., in a volume of 1 ml/kg) and were placed in the locomotor activity chamber for 30 min immediately following injection. This procedure was repeated for 10 consecutive days. Rats were then given a 3-day drug-free rest period with free access to food in their EC or IC cages. Another three days of food restriction (90 min access to food per day) were implemented before reassessing operant responding.

Reacquisition of Sucrose-Reinforced Responding—Seven days after their last locomotor assessment session, rats were returned to the operant chambers to reassess operant responding for five sessions on the same FR 30 schedule used previously (with the exception of the two EC rats that stabilized at FR 18 and FR 24; they were reassessed an FR 18 and FR 24 respectively). As in training, rats received 3 sucrose pellets per trial and cues lights were used to signal proximity to reinforcement. During reassessment, any rat failing to complete 15 trials within 150 min was assigned a latency of 150 min for that session. The number of lever presses made to the active and inactive lever was recorded for each session. Rats were restricted to 90-min access to food daily after each session of reacquisition.

Data Analysis

Data were analyzed using analysis of variance (ANOVA) with Rearing Condition and Drug as between-subject factors and Day (locomotor assessment) or Session (sucrose reinforced responding) as within-subject factors. Results were deemed statistically significant at $p < .05$.

Results

Acquisition and Maintenance of Sucrose-Reinforced Responding

Despite efforts to equalize responding, the IC rats reached criterion in fewer sessions ($M = 30.83$, $SEM = .41$) than EC rats ($M = 34.94$, $SEM = 1.52$). A one-way ANOVA comparing the mean number of days to criterion for each rearing condition (IC vs. EC) indicated that the difference in acquisition was significant, $F(1,33) = 7.17$, $p < .05$. A baseline latency-to-session-completion score was also calculated for each rat. Baseline latencies were calculated by averaging the time (in minutes) it took to complete a session over the five criterion sessions (a session was defined as completion of 15 trials at the final response contingency). A one-way ANOVA conducted on the baseline latencies was significant, $F(1,33) = 11.34$, $p < .01$, with IC rats finishing criterion sessions faster ($M = 14.83$, $SEM = 1.11$) than EC rats ($M = 21.48$, $SEM = 1.65$). However, this difference diminished with continued training and a subsequent one-way ANOVA conducted on the latency to complete the last training session (Session 46) was not significant, $F(1,33) = 2.36$, $p = .13$, with IC rats ($M = 10.01$, $SEM = .817$) and EC rats ($M = 12.77$, $SEM = 1.63$) completing the session at a similar rate.

Cocaine-Induced Locomotor Activity

Although there was considerable day-to-day variability, cocaine-treated rats were more active than saline-treated rats across sessions (Figure 2). A $2 \times 2 \times 10$ (Drug $\times$ Rearing Condition $\times$ Session) repeated measures ANOVA performed on the activity scores revealed a main effect of Drug [$F(1,32) = 61.43$, $p < .0001$], with cocaine-treated rats being more active than saline treated rats. There was also a main effect of Rearing Condition [$F(1,32) = 5.02$, $p < .05$], with IC rats displaying more locomotor activity than EC rats. However, there was no significant Rearing Condition $\times$ Drug interaction [$F(1,32) = 1.63$, $p = .21$]. There was a significant effect of Day, [$F(9, 288) = 7.85$, $p < .0001$], as well as a Drug $\times$ Day interaction [$F(9, 288) = 5.745$, $p < .0001$].

An independent sample t -test conducted on Session 1 data found that IC rats receiving cocaine ($M = 379.14$, $SEM = 25.23$) displayed more locomotor activity than IC rats receiving saline ($M = 261.37$, $SEM = 16.97$), $t(16) = 3.87$, $p < .001$. However, an independent sample t -test comparing Session 1 data for EC rats receiving cocaine ($M = 225.75$, $SEM = 44.12$) with EC rats receiving saline ($M = 197.43$, $SEM = 33.67$) was not significant [$t < 1$]. As indicated by the ANOVA, both IC and EC rats receiving cocaine displayed more locomotor activity than saline controls during Sessions 2–10.

Although cocaine increased locomotor activity relative to saline, there was no clear evidence for cocaine sensitization. Paired sample t -tests comparing Session 1 and 10 were conducted for each group. The t -tests for the IC Cocaine [$t(8) = 1.94$, $p = .09$] and EC Cocaine [$t(8) = -1.22$, $p = .26$] groups were not significant. However the t -tests for the IC Saline [$t(8) = 3.99$, $p < .01$] and EC Saline [$t(8) = 2.50$, $p < .05$] groups were significant, thus demonstrating habituation in both saline treatment groups.

Reassessment of Sucrose-Reinforced Responding

A $2 \times 2 \times 5$ (Rearing Condition $\times$ Drug $\times$ Session) mixed factor ANOVA conducted on the reacquisition data revealed no significant effect of Rearing Condition, $F < 1$, nor were there any significant interactions involving Rearing Condition (all F s < 1); thus, the results presented in Figure 2 were collapsed across EC and IC rats. There was a main effect of Session [$F(4,124) = 20.18$, $p < .0001$], with all groups decreasing their latencies across reacquisition sessions. There was also a significant main effect of Drug [$F(1,31) = 5.36$, $p < .05$], with rats that received cocaine during the locomotor portion of the study exhibiting overall shorter latencies than rats that received saline (Figure 3). Although the effect of

cocaine dissipated across sessions, there was no significant Drug $\times$ Session interaction [$F(4,124) = 2.04, p = .09$].

An additional $2 \times 2 \times 5$ mixed factor ANOVA was conducted on the number of inactive lever presses made during reacquisition to examine general activity within the operant chambers. The main effect of Session approached, but did not reach significance [$F(4,124) = 2.36, p = .057$], with the number of inactive bar presses decreasing across sessions. There was no significant main effect of Rearing Condition [$F < 1$] or Drug [$F(1,31) = 1.29, p = .26$]. Further, none of the interactions were significant. The mean number of inactive bar presses made during each reacquisition session is shown in Figure 4.

Discussion

The most important finding in the current study was that rats repeatedly exposed to cocaine showed shorter latencies to complete sessions during reacquisition of a previously acquired sucrose-reinforced FR 30 task than rats that received saline. Because there were no significant differences in inactive lever pressing, this effect cannot be attributed to a general increase in activity. Interestingly, contrary to our initial hypothesis, this cocaine-induced increase in reacquisition performance did not differ significantly between EC and IC rats.

However, the current study did find that EC rats are less sensitive than IC rats to the locomotor stimulant effect of acute cocaine administration. Previous work has shown that EC rats are less sensitive than IC rats to the hyperactivity observed following acute nicotine (Green, Cain, Thompson, & Bardo, 2003) or acute morphine (Bardo, Robinet, & Hammer, 1997), but not following acute amphetamine (Bowling & Bardo, 1994). Taken together, these results indicate that the effect of environmental enrichment on the psychostimulant effect of drugs is pharmacologically specific. Consistent with current literature (e.g., Varty, Paulus, Braff, & Geyer, 2000), regardless of drug treatment, the current results also revealed a significant difference in locomotor activity across rearing conditions, with EC rats consistently exhibiting less locomotor activity than IC rats.

Although the current experiment is the only known study investigating cocaine and sucrose cross-sensitization with a fixed ratio operant task, several studies have been conducted with amphetamine and sucrose or food. One study (Barr & Phillips, 1999) found that rats repeatedly exposed to *d*-amphetamine demonstrated an initial reduction in motivation to obtain a sucrose solution compared to saline controls using a progressive ratio schedule of reinforcement. However, it is important to note that assessment of operant responding began one day after drug termination (when sensitization is not generally observed) and that the reduction in motivation was seen only during the first four days of amphetamine withdrawal. Other studies, using different conditioning procedures, have found evidence for cross-sensitization between amphetamine and natural rewards such as food (Nocjar & Penksepp, 2002), salt (Clark & Bernstein, 2004), sucrose (Avena & Hoebel, 2003a, 2003b; Wyvell & Berridge, 2001) and sex (Fiorino & Phillips, 1999; Levens & Akins, 2004) 7–21 days after drug termination.

Two studies conducted with humans found a relationship between cocaine exposure and preference for sweet solutions. In the first study, infants exposed to cocaine just prior to birth, sucked more on a sweet nipple and less frequently on a non-sweet nipple than control infants (Moane, Mattes, Beauchamp, 1992). The second study found that hospital inpatients with a history of cocaine abuse indicated a preference for high concentration sweet solutions compared to inpatient controls (Janowsky, Pucilowski, Buyinza, 2003). Thus, there is increasing evidence that repeated exposure to psychostimulants can increase the incentive salience of natural rewards in both human and non-human animals. The current study

contributes to this evidence by demonstrating that repeated exposure to cocaine increases the incentive salience of sucrose and that this effect is obtained even when subjects are exposed to enriching stimulation during development.

It should be mentioned that although the procedure in Experiment 1 is described as a FR 30 schedule, it could also be considered a second-order schedule because proximity to reward was signaled with distinct changes in the cue lights occurring one-third and two-thirds through the response requirement. Therefore it may be that repeated exposure to cocaine increased the salience or reward value of the cue light (rather than the sucrose), thereby facilitating reacquisition. This idea is consistent with previous experiments by Harmer and Phillips (1998, 1999; see also Wyvell & Berridge, 2001), who found that rats sensitized to *d*-amphetamine show enhanced appetitive conditioning and enhanced conditioned inhibition to sucrose-paired cues. It is especially relevant to note that as in the current study, the measure of enhanced conditioning in Harmer and Phillips' experiments was enhanced acquisition as measured by latencies, rather than the number of actual responses. Second order cues are known to exert powerful effects on drug-self administration in rats and monkeys (see Everitt & Robbins, 2000) and while the exact role the cue lights played in the current study is unknown, future studies could investigate specifically whether predictive cues contribute to the development of facilitated responding in drug exposed animals.

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Figure 1. Mean latency ($\pm$ SEM) to complete first five acquisition criterion sessions for IC and EC rats that subsequently received cocaine or saline.

Figure 2. Mean number of activity counts ($\pm$ SEM) across 10 sessions of locomotor assessment in EC and IC rats.

Figure 3.
Mean latency ($\pm$ SEM) to complete reassessment sessions (collapsed across rearing condition).

Figure 4. Mean number of inactive bar presses ($\pm$ SEM) during each reassessment session (collapsed across rearing condition).