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Chronic cocaine pretreatment facilitates Pavlovian sexual conditioning in male Japanese quail

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Abstract

Repeated drug exposure that results in behavioral sensitization has been shown to enhance sex-seeking behaviors in rats as well as facilitate Pavlovian excitatory and inhibitory conditioning. In the present experiment, male Japanese quail were given repeated presentations of cocaine (10 mg/kg, i.p.) that resulted in increased locomotor activity relative to saline. After a 10-day withdrawal period, subjects received sexual conditioning trials that consisted of presentation of an object conditioned stimulus (CS) followed by sexual reinforcement. Results showed that birds that previously received chronic cocaine demonstrated more conditioned approach behavior to the CS object, a shorter latency to copulate with a female, and made more cloacal contacts (copulatory behavior) during sexual reinforcement than saline-treated birds. The findings suggest that chronic cocaine later facilitates Pavlovian conditioning in a sexual behavior paradigm. This may be the result of cocaine facilitating learning via the dopaminergic system. The findings are discussed in the context of the incentive sensitization theory and possible neuronal mechanisms.

Keywords: Chronic cocaine; Pavlovian conditioning; Learning; Avian; Behavioral sensitization; Birds; Sexual conditioning; Sexual behavior

1. Introduction

An important phenomenon associated with psychostimulant-induced locomotor activity is behavioral sensitization. Expression of behavioral sensitization suggests that underlying neural adaptations are occurring in response to drug (Robinson and Kolb, 1997). Some adaptations due to sensitization occur in dopaminergic mesolimbic brain areas (Robinson and Becker, 1986; Kalivas and Stewart, 1991; Stewart and Badiani, 1993) and sensitization is believed to be at least partly due to increased extracellular levels of dopamine (DA) in these areas (Wise and Bozarth, 1987; Kalivas and Stewart, 1991; Koob, 1992).

A theory of drug abuse related to behavioral sensitization is the incentive-sensitization theory (Robinson and Berridge, 1993, 2000). Incentive sensitization proposes that prolonged use of certain drugs creates neural adaptations in the mesolimbic DA system that are expressed as behavioral sensitization. Sensitization of these neural circuits is believed to be responsible for increasing the incentive salience of drug-related stimuli, leading to increased drug craving and drug seeking. Sensitization then "primes" the addict to engage in appetitive and consummatory behaviors designed around obtaining and consuming the drug, respectively. Presumably, the adaptations that lead to sensitization are a product of an increase in release of the neurotransmitter DA.

Evidence for incentive sensitization comes from studies demonstrating a relationship between drug-seeking behavior and drug sensitization in animals. For example, previous exposure to amphetamine enhances subsequent amphetamine self-administration (Valdez and Schenk, 1994; Pierre and Vezina, 1998). In addition, cocaine self-administration increases cocaine-seeking

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behavior in a runway apparatus (Deroche et al., 1999). Vezina et al. (2002) found a relationship between drug sensitization, dopaminergic activity, and self-administration. Amphetamine sensitization (induced systemically or intra-VTA) of midbrain DA neuron reactivity led to increased self-administration of amphetamine.

Incentive sensitization may also occur when drug sensitization later facilitates responding to other classes of naturally rewarding stimuli, a process referred to as cross-sensitization. Animals preexposed to a sensitization drug regimen have been found to demonstrate increases in sucrose seeking (Wyvell and Berridge, 2001) as well as enhanced sex-seeking behaviors (Mitchell and Stewart, 1990; Fiorino and Phillips, 1999a,b; Nocjar and Panksepp, 2002). Although the neural mechanism(s) that induces these effects is not fully understood, presumably the same system that regulates drug craving also regulates incentive salience of non-drug naturally rewarding stimuli (Robinson and Berridge, 1993).

Repeated drug exposure may also facilitate learning. For example, Harmer and Phillips (1999) demonstrated that prior repeated exposure to amphetamine facilitated both excitatory and inhibitory Pavlovian conditioning. Rats were sensitized to amphetamine (six daily injections at 3 mg/kg, i.p.) and trained to lever press for sucrose pellets. After reaching response criterion, rats were trained with either a stimulus that immediately preceded sucrose (A+; excitatory conditioning), or that same stimulus plus a new one (AB) that was not followed by sucrose (inhibitory conditioning). Not only did amphetamine-sensitized rats show greater sucrose responding during excitatory conditioning than control rats, they also showed reduced levels of responding during inhibitory conditioning. Thus, Pavlovian conditioning appears to be enhanced by drug sensitization.

In the present study, the notion that cocaine sensitization may influence sexual behavior by enhancing learning was investigated. Male Japanese quail served as subjects in the experiment because there is an extensive body of knowledge concerning Pavlovian conditioning of sexual behavior in this species (see Mills et al., 1997, for review). A well-studied sexual conditioning paradigm (e.g., Domjan et al., 1986) that involves assessing the amount of approach behavior to an object that has been paired with copulatory experience with a female bird was used. In this paradigm, males that receive these pairings typically increase the amount of time they spend near the object across conditioning trials and they spend more time near the object than males receiving the object and copulation in an unpaired fashion, thus demonstrating learning. In the present experiment, conditioning was either preceded by chronic cocaine or saline administration. It was hypothesized that males with a cocaine history would exhibit more learning/sexual conditioning than males that had a saline history.

2. Method

2.1. Animals

Subjects were 24 adult male Japanese quail (*Coturnix japonica*), 2–18 months old. Birds (eggs from GQF Manufacturing, Savannah, GA) were obtained from a colony at the University of Kentucky where they were hatched, raised, and kept in mixed-sex groups in brooders until 4–5 weeks of age. Afterwards, birds were housed individually in wire-mesh cages (GQF Manufacturing). All quail were drug and sexually naive prior to experimentation. Nine live female quail and three taxidermic female models served as copulation partners during sexual conditioning trials. To ensure that male quail copulated during the study, they were pretested for sexual behavior. A female quail was introduced into the male's home cage for 5 min. Only males who copulated during pretesting were used in the present experiment. Male quail that do not copulate within 5 min are unlikely to do so (Schein et al., 1972).

Lights were kept on in the colony room from 0600 to 2200 h to maintain the quail in reproductive readiness. Food and water were available ad libitum. Animals were cared for, and the experimental procedures conducted under the guidelines of the Institutional Animal Use and Care Committee at the University of Kentucky.

2.2. Apparatus

During cocaine administration, locomotor activity was measured in six locomotor activity chambers, each 26.7 cm (long)×22.9 cm (wide)×43.2 cm (deep). The chambers had white plywood walls with wire-mesh floors and ceilings, and were bisected into four equal quadrants by two photobeams placed 3.81 cm above the floor. Each time a subject broke a beam, a computer program (prepared by Larry Hull, Lexington, KY) recorded it. The frequency of photobeam breaks was used as an index of locomotor activity. The computer program had a 0.2-s filter on the photobeams, so that if a subject stood in a beam, only one break was counted.

Pavlovian conditioning trials occurred in a large Plexiglas test cage (91.4 cm wide×61.0 cm deep×30.5 cm tall) with a wire mesh floor. The sides, back, and ceiling of the cage were covered with white paper while the front door was clear. Attached to one end of the cage was a smaller Plexiglas side cage (30.5 cm wide×61.0 cm deep×27.9 cm tall). The side cage that housed a female had clear walls and ceiling (except the common wall with the larger test cage that was opaque) and a brown paper floor. A door (17.8 cm tall×11.4 cm wide) connecting the two cages was accessible to the experimenter for placement of a male subject into the female's cage. The door between the two cages was covered with white paper so that males were unable to see the female. Lowering a red

Styrofoam block (12.7 cm long×7.62 cm wide×3.81 cm tall) to the floor served as the conditioned stimulus (CS). When not in use, the CS was raised to the ceiling via a pulley system. During conditioning, the CS was lowered to the floor where it rested 10.2 cm in front of the door to the side cage. The floor area that contained the CS (35.6×30.5 cm) was marked off by white rope and this was referred to as the CS zone.

Locomotor activity chambers, sexual conditioning test cages, and home cages were located in separate rooms. Over the course of the experiment, subjects were housed in their individual home cages and were only placed in locomotor activity chambers or test cages during testing.

2.3. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Bethesda, MD) was dissolved in physiological saline (0.9% NaCl) at a concentration of 5 mg/ml and injected intraperitoneally (i.p.) at a volume of 2-ml/kg body weight for a dose of 10 mg/kg.

2.4. Procedure

Subjects were randomly assigned to one of four groups: Paired Cocaine (n=6), Unpaired Cocaine (n=6), Paired Saline (n=6), or Unpaired Saline (n=6). Cocaine group subjects received a daily intraperitoneal (i.p.) injection of cocaine (10 mg/kg), once a day for 6 consecutive days and saline groups received an ip injection of saline once a day for 6 days. At approximately 1100 h each day, subjects were brought into the running room, injected, and immediately placed into a locomotor chamber. Locomotor activity was recorded for 30 min, after which time subjects were promptly removed and returned to their home cage. This procedure and dose has previously resulted in behavioral sensitization in male Japanese quail (Levens and Akins, 2001).

Following a 10-day withdrawal period, 10 sexual conditioning trials were conducted, one per day between approximately 1100 and 0300 h. During each trial, paired subjects were introduced into the test cage for a 30-s baseline period. The CS was then lowered from the ceiling of the cage, and the amount of time subjects spent in the CS zone was recorded. After 30 s, the CS was raised and the door to the female's side cage was opened. Once males entered the cage, the door was closed, and they were given 5 min to interact with the female (US), after which, they were removed from the side cage and returned to their home cage. Thus, males spent approximately 1 min in the test cage and 5 min in the side cage during each trial. During the last 5 conditioning trials, a taxidermically prepared model of a female bird was presented behind the door as the US rather than the live female bird. This was done to reduce the likelihood of the female's behavior influencing the male's ability to copulate. Previous research has demonstrated that sexually experienced males will readily copulate with taxidermic models of females (e.g., Crawford and Akins, 1993).

During the 5-min interaction period with the US, the frequency of cloacal contacts made toward the US was recorded. Cloacal contact in avian species is generally the terminus of copulation and is typically when ejaculation occurs. In male Japanese quail, the copulatory sequence consists of the male grabbing the back of the female's head or neck feathers, mounting the female, then arching its back so as to bring its cloaca in contact with that of the female (Wilson and Bermant, 1972). Cloacal contact typically ends with the male spreading its wings and falling off the back of the female. Therefore, cloacal contact as described here is easily identifiable. In the current experiment, the frequency of cloacal contacts was recorded live during each trial and trials were videotaped.

Unpaired subjects received similar treatment as paired subjects except that they were given 5 min to interact with the female bird or taxidermic model of a female (US) 3 h prior to their CS trial, in an unpaired fashion. During US presentations, unpaired subjects were placed into the side cage of the test compartment that contained the US through a rear door and given 5 min to interact with the US. The door connecting the side cage with the test cage was not opened for the unpaired subjects. Afterwards, males were removed and returned to their home cages. Approximately 3 h later, subjects were placed in the test cage and given a 30-s baseline period, followed by 30-s CS exposure. After 30 s, the CS was raised and the subjects were removed from the test cage and returned to their home cage.

During sexual conditioning trials, in addition to the frequency of cloacal contacts for both paired and unpaired subjects, the latency to copulate was recorded for saline- and cocaine-treated paired subjects. Latency to copulate was collected with a stopwatch immediately after the door between the test cage and the side cage was raised, after the CS presentation. Since unpaired subjects were placed in the side cage during their US presentation rather than going through the door that separated the male's test cage and the side cage, latency to copulate was not collected for them.

2.5. Statistical analyses

A repeated-measures ANOVA was performed on the locomotor activity data. A 2 (drug treatment−cocaine versus saline)×2 (pairing−paired versus unpaired)×10 (trials) repeated-measures ANOVA was performed on the time spent in the CS zone and the frequency of cloacal contacts made toward the female or model. A repeated measures ANOVA was used to compare latency to copulate between cocaine paired and saline paired subjects. Where appropriate, simple main effect tests were used for further analysis.

3. Results

3.1. Locomotor activity

Fig. 1 represents mean photobeam breaks during the 30 min locomotor activity trials. Subjects receiving cocaine (M=561.18 breaks, S.E.M.=39.01) had significantly greater locomotor activity than those receiving saline (M=244.22 breaks, S.E.M.=19.56) during the 30 min locomotor trials. There were significant main effects of drug treatment [$F(1, 22)=10.45$, $P=0.004$] and trials [$F(5, 110)=6.36$, $P=0.0001$], but no drug treatment×trials interaction, [$F(5, 110)=1.52$, $P>0.05$]. Simple main effects analyses yielded significant differences between drug treatments on all of the trials [F's(1, 22)>5.53, P's<0.02].

3.2. Conditioning—approach

Fig. 2 illustrates mean time spent in the CS zone during the 30-s CS presentation of the sexual conditioning trials. Groups Paired Cocaine, Paired Saline, and Unpaired Cocaine increased the amount of time they spent in the CS zone across the first 4 trials, whereas Group Unpaired Saline did not. Group Paired Cocaine also had increased responding on trials 6 and 8, whereas Group Paired Saline generally maintained responding but showed no increases after trial 5. Although Group Unpaired Cocaine demonstrated an increase in responding, the magnitude was much lower than that of Groups Paired Saline and Cocaine. Overall, Group Paired Cocaine spent more time (s) in the CS zone (M=17.05, S.E.M.=1.321) compared to Groups Paired Saline (M=8.04, S.E.M.=1.231), Unpaired Cocaine (M=1.77, S.E.M.=0.451), and Unpaired Saline (M=1.32, S.E.M.=0.305). There were

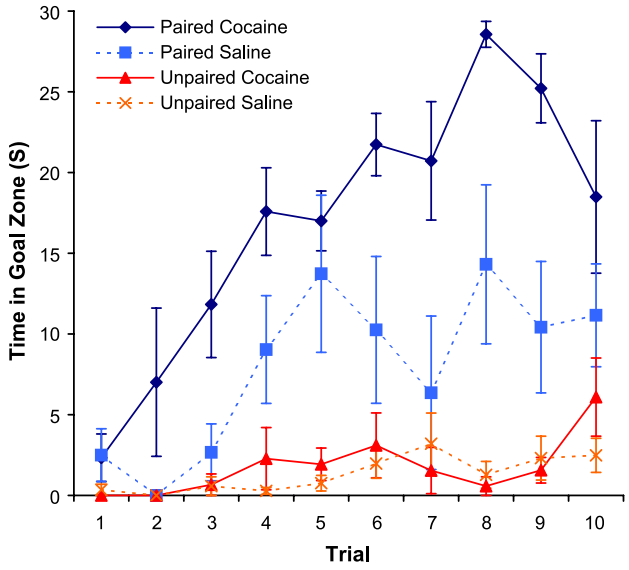

Fig. 2. Time (s) spent in the CS zone (±S.E.M.) during the 30 s presentation of the CS across sexual conditioning trials.

significant main effects of drug treatment [$F(1, 20)=13.37$, $P=0.002$], pairing, [$F(1, 20)=72.3$, $P=0.0001$], and trials [$F(9, 180)=9.52$, $P=0.0001$]. There was also a significant pairing×drug treatment interaction [$F(1, 20)=10.93$, $P=0.004$], and a significant pairing×trials interaction [$F(9, 180)=6.13$, $P=0.0001$]. A one-way ANOVA performed on the data for each group showed that the increase in time spent in the CS zone across trials was significant for Group Paired Cocaine [$F(9, 45)=7.942$, $P=0.0001$], Group Paired Saline [$F(9, 45)=2.402$, $P=0.02$], and Group Unpaired Cocaine [$F(9, 45)=2.409$, $P=0.02$]. Approach behavior for Group

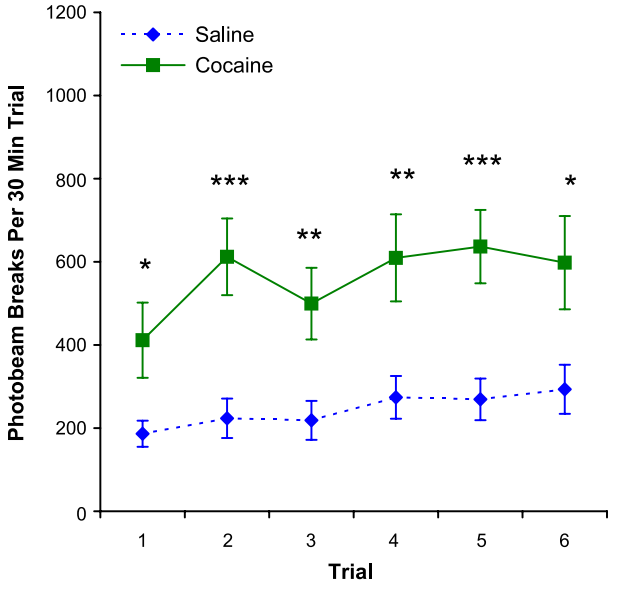

Fig. 1. Photobeam breaks across six 30 min trials for birds injected with cocaine (10 mg/kg, i.p.) or saline vehicle. *P<0.05; **P<0.01; ***P<0.0001, vs. saline.

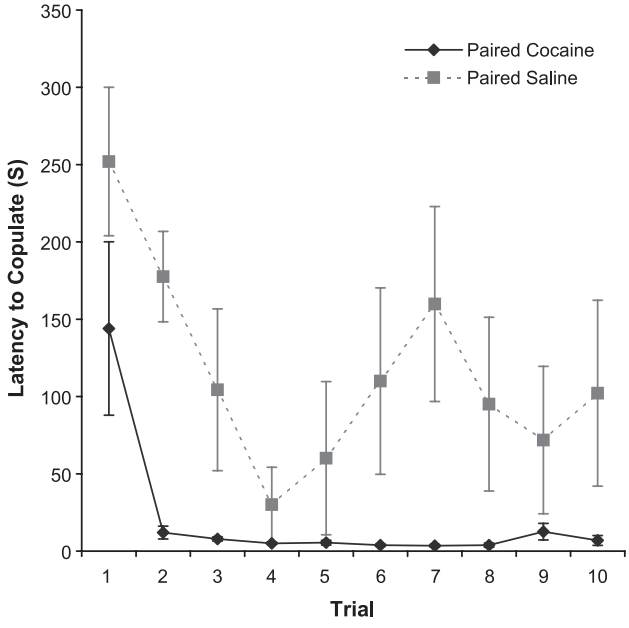

Fig. 3. Latency (s) to copulate (±S.E.M.) during a 5-min test for paired subjects that received a CS followed by copulatory opportunity across sexual conditioning trials.

Unpaired Saline did not change across trials [$F(9, 45)=1.522$, $P=0.17$].

3.3. Conditioning—latency to copulate

Because of differences in how paired and unpaired subjects received the female US (i.e., a door was opened to the side cage allowing paired subjects access to the US, whereas unpaired subjects were placed in the side cage with the US, through an exterior door), comparisons for latency to copulate were only performed in paired subjects. Fig. 3 represents mean latency to copulate with the US for the paired groups across conditioning trials. Latency to copulate (s) decreased across trials for both paired groups, however Group Paired Cocaine ($M=20.51$, S.E.M.=7.49) had a shorter overall latency than Group Paired Saline ($M=116.30$, S.E.M.=16.74). This resulted in significant main effects of drug treatment [$F(1, 10)=6.04$, $P=0.03$] and trials [$F(9, 90)=6.77$, $P=0.0001$], but no significant drug treatment×trials interaction [$F(9, 90)=1.239$, $P=0.28$].

3.4. Conditioning—cloacal contacts

Mean frequency of cloacal contacts with the US during the 5-min US period across conditioning trials is presented in Fig. 4. Although, these data appear to be highly variable at each trial, overall, Group Paired Cocaine ($M=7.28$, S.E.M.=0.71) made more cloacal contacts than Groups Paired Saline ($M=3.12$, S.E.M.=0.43), Unpaired Saline ($M=4.650$, S.E.M.=0.4), and Group Unpaired Cocaine ($M=5.02$, S.E.M.=0.46). The ANOVA revealed a significant pairing×drug treatment interaction [$F(1, 20)=4.7$, $P=0.04$].

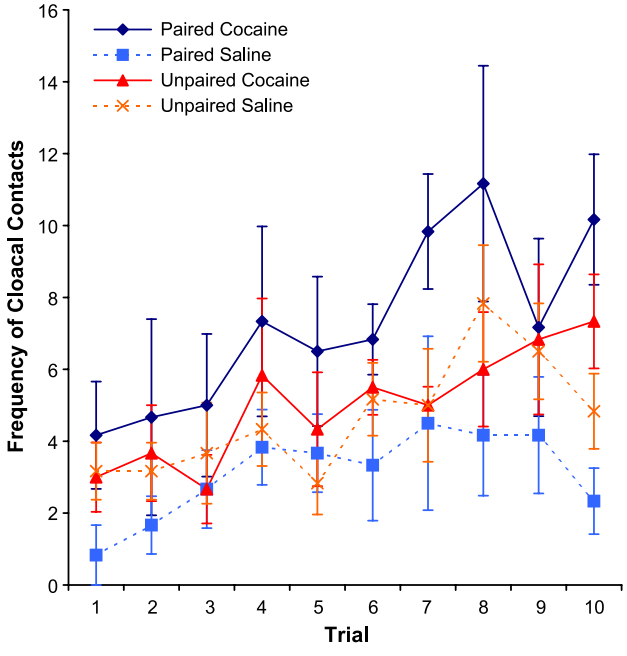

Fig. 4. Frequency of cloacal contacts (±S.E.M.) made during 5 min with a live female or taxidermic female model across sexual conditioning trials.

In addition, cocaine group subjects made more cloacal contacts toward the female or model than the saline groups, as indicated by a significant main effect of drug treatment [$F(1, 20)=6.7$, $P=0.02$]. There was also a significant main effect of trials [$F(9, 180)=4.43$, $P=0.0001$].

4. Discussion

Subjects that received cocaine had increased locomotor activity relative to saline subjects. Although cocaine-induced activity increased across trials, it is difficult to say whether this was behavioral sensitization as there was no significant drug treatment×trials interaction (due to saline subjects' increasing activity across trials). Upon subsequent Pavlovian sexual conditioning, subjects in paired groups demonstrated learned approach behavior. Across trials, they increased time spent in a zone that contained a CS that predicted sexual reinforcement. Overall, paired subjects engaged in more approach behavior than unpaired subjects. Of greater importance, Group Paired Cocaine spent more time near the CS than Group Paired Saline. Therefore, even though both paired groups appeared to learn the CS–US association, cocaine seemed to facilitate this learning. In addition, cocaine may have also facilitated copulatory responding. This was evident in paired cocaine subjects that demonstrated a shorter latency to copulate, and more cloacal contacts than paired saline subjects. Furthermore, that cocaine facilitated sexual conditioning 10 days after cessation of cocaine injections suggests that cocaine may have induced long-term CNS modifications (e.g., Robinson and Kolb, 1997).

The most important finding from this experiment was that cocaine appeared to facilitate learning about stimuli associated with sexual behavior. Similarly, Harmer and Phillips (1998, 1999) found that amphetamine sensitization in rats facilitated subsequent acquisition of Pavlovian conditioned responding to a stimulus that predicted sucrose solution. Likewise, amphetamine sensitization facilitated anticipatory behavior when male rats were placed in an environment that predicted a receptive female (Fiorino and Phillips, 1999a). Together, these results suggest that chronic psychostimulant exposure may enhance future Pavlovian learning.

Alternatively, it is possible that cocaine did not directly influence learning but rather affected the incentive salience or enhancement of the US. In the present experiment, paired cocaine birds had shorter latencies to copulate and made more cloacal contact than paired saline birds suggesting a possible cocaine-induced enhancement of the US or an increase in the incentive salience of the US. Further support that cocaine may have facilitated unconditioned sexual behavior in this study is that unpaired cocaine subjects also demonstrated an increase in cloacal contacts across trials. This is in agreement with previous literature demonstrating that in rats, cocaine may enhance male copulatory behavior,

independent of learning effects (Fiorino and Phillips, 1999a). However, that unpaired cocaine subjects demonstrated fewer cloacal contacts than the paired cocaine subjects suggests that in addition to influencing unconditioned sexual responding, cocaine may have also influenced learning in this particular paradigm.

In humans, cocaine has been associated with high risk sexual behaviors including having unprotected sex, sex with multiple partners, and sex with injecting drug users (Kolar et al., 1990; Condelli et al., 1991; Hoffman et al., 2000). In addition, treatment for drug abuse has been linked with a decrease in the number of incidents of risky sexual behavior among drug users. For example, drug treatment has been reported to decrease the number of sex partners and increase condom use among former addicts (Grella et al., 1996; Longshore and Hsieh, 1998; Woody et al., 2003). Although many factors may contribute to the relationship between drug taking behavior and risky sexual behaviors and its unclear whether the relationship is due to cross sensitization, the present findings and others like it (e.g., Fiorino and Phillips, 1999a) suggest that chronic psychostimulant administration may facilitate sexual behavior and sexual conditioning, and may thereby contribute to a drug facilitated increase in sexual activity.

The present findings may provide evidence for cross-sensitization between cocaine and sexual behavior. The CS object that was predictive of copulatory opportunity may have added incentive salience for subjects with a cocaine history. The incentive-sensitization theory proposes that sensitization of dopaminergic brain areas leads to attribution of incentive salience to stimuli associated with drug, causing increased drug craving and drug seeking (Robinson and Berridge, 1993). Thus, sensitization primes the addict to engage in appetitive and consummatory activities designed around obtaining and consuming the drug, respectively. It is possible that in the present experiment, cocaine sensitized the learning processes that facilitated sexual conditioning. Therefore, it may be that the sensitization of dopaminergic reward areas that lead to attribution of incentive salience may also involve the sensitization of learning processes. When these learning processes become sensitized, stronger Pavlovian associations between drug and drug-related stimuli may be formed, thereby, increasing the likelihood of drug cues to induce craving and relapse in addicted individuals. Further research is needed to assess this possibility.

Neuronal mechanisms involving dopaminergic/glutamatergic interactions may be responsible for this psychostimulant-induced facilitation of learning. Li et al. (2003) found that amphetamine sensitization produced long-term increases in dendritic spine density of medium spiny neurons in the nucleus accumbens (Nac) and caudate-putamen. These increases in density occurred at distal dendrites where DA and glutamate synapses interact, suggesting that amphetamine could be altering DA-glutamate signaling. Furthermore, there are glutamatergic neurons within the mesolimbic area and learning and long-term potentiation (LTP) involve glutamatergic transmission (Pennartz et al., 2000). LTP has been documented in mesolimbic areas, including the ventral tegmental area (VTA; Bonci and Malenka, 1999; Overton et al., 1999). Cocaine facilitates glutamate release within the VTA (Kalivas and Duffy, 1995) and cocaine exposure transiently increases the responsiveness of AMPA receptors on VTA DA neurons (Zhang et al., 1997). In addition, one exposure to cocaine has been found to induce LTP of AMPA-receptor mediated currents at excitatory synapses onto VTA DA neurons (Ungless et al., 2001). Therefore, psychostimulants appear to influence glutamatergic mechanisms within brain reward areas.

Glutamate receptors also may help mediate cocaine-related phenomenon. Glutamate antagonists administered systemically attenuate cocaine-induced locomotor sensitization (Karler et al., 1994; Kim et al., 1996) and CPP (Cervo and Samanin, 1995; Kim et al., 1996). However, glutamate antagonists only block cocaine CPP when administered within but not outside the VTA via microinjection (Harris and Aston-Jones, 2003). Harris and Aston-Jones suggested that VTA glutamatergic activity may be important for learning of Pavlovian associations between environmental cues and cocaine exposure. Furthermore, it appears that the neural substrates for Pavlovian conditioning may depend on increased expression of glutamatergic AMPA receptors (Lledo et al., 1998; Nayak et al., 1998). Therefore, it is possible that chronic cocaine exposure sensitizes mesolimbic glutamatergic neurons that are responsible for LTP. Sensitization of these neurons may then facilitate learning of associations between appetitive stimuli and cues predictive of those stimuli. Thus, in the present experiment, although speculative, cocaine administration may have enhanced glutamate activity within the VTA and this facilitated sexual Pavlovian conditioning.

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