

Amphetamine pretreatment accelerates the subsequent escalation of cocaine self-administration behavior

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Abstract It has been proposed that some neuroadaptations that underlie behavioral sensitization may play a role in the development and persistence of addiction. However, whether or not sensitization facilitates the development of symptoms specific to addiction, such as the escalation of drug intake, is not known. We examined, therefore, the effect of pretreatment with a sensitizing regimen of amphetamine on the escalation of subsequent drug intake in rats given the opportunity to self-administer cocaine. Amphetamine pretreatment produced psychomotor sensitization and also accelerated the subsequent escalation of cocaine intake. This suggests that the neural circuits that are altered as a consequence of repeated amphetamine treatment, and the induction of sensitization, may overlap with those responsible for the development of some addiction-like behaviors.

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1. Introduction

The repeated intermittent administration of psychostimulant drugs produces an enduring hypersensitivity to their psychomotor activating effects, a phenomenon known as psychomotor sensitization (Segal, 1975; Robinson and Becker, 1986). Psychomotor sensitization is associated with persistent neuroadaptations in mesocorticolimbic structures (Vanderschuren and Kalivas, 2000; Robinson and Kolb, 2004; Vezina, 2004), which are important in mediating the

incentive motivational properties of addictive drugs and of natural rewards (Wise and Bozarth, 1987; Kelley and Berridge, 2002). It is been proposed, therefore, that sensitization-related changes within this circuitry may alter the process of incentive motivation, and thus contribute to the development and persistence of addiction (Robinson and Berridge, 1993, 2003).

Consistent with this hypothesis, drug treatments that produce psychomotor sensitization facilitate the subsequent acquisition of drug self-administration behavior and a conditioned place preference for drug (Lett, 1989; Piazza et al., 1989; Horger et al., 1990; Vezina et al., 1999), and produce enhanced incentive motivation for drug (Mendrek et al., 1998; Deroche et al., 1999; Lorrain et al., 2000). However, these studies do not directly address whether or not treatments that induce psychomotor sensitization also

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facilitate the development of addiction. Addiction refers to a cluster of symptoms, including the compulsive pursuit of drugs, which are not necessarily reflected in self-administration behavior or a conditioned place preference. For this reason, there have been a number of attempts to develop animal models of addiction that better capture key behavioral symptoms of the disorder (Wolffgramm and Heyne, 1995; Ahmed and Koob, 1998; Heyne and Wolffgramm, 1998; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In one such model, animals allowed extended access to drug self-administration (6 h per session) develop several addiction-like behaviors that are not present, or are less pronounced, in animals given limited access to drug (1–3 h per session). For example, animals allowed extended access to cocaine self-administration gradually escalate their intake such that drug consumption within the first hour of a test session almost doubles relative to the intake of rats given more limited access (Ahmed and Koob, 1998). Also, compared to rats given limited access, rats given extended access, either by increasing daily drug availability or by making drug available for months, show other symptoms of addiction, including an increased motivation to obtain cocaine as assessed by break-point (Paterson and Markou, 2003; Deroche-Gamonet et al., 2004), continued pursuit of drug despite the risk of adverse consequences (Vanderschuren and Everitt, 2004) and enhanced cocaine-induced reinstatement of drug seeking (Ahmed and Cador, 2006).

We recently reported that extended access to cocaine self-administration not only results in escalated drug intake, but also produces especially robust psychomotor sensitization, compared to that produced by limited access self-administration (Ferrario et al., 2005). The association between psychomotor sensitization and escalated drug intake suggests that both may be due to related neuroadaptations in mesocorticolimbic systems. If this is true, then the induction of sensitization prior to being given the opportunity to self-administer cocaine may facilitate the development of addiction-like behaviors, including the escalation of drug intake. To address this hypothesis, we asked whether or not amphetamine pretreatment, resulting in robust psychomotor sensitization, would alter the escalation of subsequent cocaine self-administration behavior in rats given extended access to cocaine.

2. Experimental procedures

2.1. Experiment 1

2.1.1. Subjects

Male Wistar rats (Harlan, Indianapolis, IN) weighing 190–200 g at the start of the experiment were singly housed (14:10 reversed light/dark) and initially food and water were continually available. All testing was conducted during the dark phase of the light/dark cycle.

2.1.2. Amphetamine pretreatment

After acclimatization to the animal colony, two separate groups of rats were given i.p. injections of either saline (0.9%, 1 ml/kg, $N=25$) or an increasing dose regimen of d-amphetamine sulfate. One injection was given each day, 6 days per week, for a total of 13 injections in the following order: 0.5, 2, 3, 4, 5, 6, 0.5, 6, 6, 6, 6, 6 and 0.5 mg/kg (weight of salt, $N=9$). Injections were given in one of three places: activity monitors, plastic buckets or plastic cages (all similar in size).

Injections were administered in multiple environments in order to mitigate the development of context-specific sensitization.

On the first, seventh and last injection days, rats were placed in rectangular plastic activity monitors (41×25.4×20.3 cm) that contained a clear plastic insert in the cage center (23×6.3×20.3 cm). The insert formed a corridor along the perimeter of the cage that directed movements of the rat along the perimeter rather than across the center of the cage. The perimeter of the cages contained an array of photocell beams, and locomotor activity was indicated by the total number of photocell beam breaks per 5-min interval. During these test sessions, all rats were first allowed 1 h to habituate to the apparatus and were then given an i.p. injection of either amphetamine (0.5 mg/kg of d-amphetamine sulfate) or saline. Locomotor activity was recorded throughout the habituation period and for 2 h following injection.

2.1.3. Surgical procedures

Five days after the last amphetamine (or saline) injection, all rats were anesthetized using a mixture of ketamine and xylazine (100 + 10 mg/kg administered i.p.), and were outfitted with a catheter in the right jugular vein using procedures described previously (Weeks, 1972; Ferrario et al., 2005). Catheters were flushed once daily with 0.1 ml of gentamicin (50 mg/kg, in 0.9% sterile bacteriostatic saline) for 10 days following surgery.

2.1.4. Cocaine self-administration

Five days after surgery (and 10 days after their last drug exposure), all rats were food restricted to maintain them at ~85% of free-feeding body weight and cocaine self-administration training began. Self-administration training was conducted in standard operant chambers (25×27×30 cm) located within sound-attenuating cabinets (Med Associates, Georgia, VT). Each chamber contained two nose-poke ports, a red house light and a tone generator (2900 Hz). Infusion pumps were mounted on the outside doors of the sound-attenuating cabinets. At the start of each session the red house light was illuminated and remained on for the duration of the session. The red house light provides illumination so that the animals can be monitored via a video camera system. Responding in one nose-poke port (designated inactive) had no consequence, but was recorded. Responses in the other nose-poke port (designated active) resulted in the intravenous delivery of 0.4 mg/kg of cocaine HCl (weight of the salt) dissolved in 50 μ l of saline administered over 1.6 s. Drug delivery was accompanied by illumination of a light at the back of the active nose-poke port and presentation of the tone for 20 s. Cocaine was available on a fixed-ratio 1 (FR1) schedule of reinforcement with a time out of 20 s. All rats were trained during daily 1-h sessions for a total of three consecutive sessions.

After these initial training sessions, saline-pretreated rats were divided into two groups: limited access and extended access. These two groups were evenly balanced according to the number of infusions taken during training. The limited access-saline-pretreated group continued to have 1-h sessions of cocaine self-administration ($N=12$), whereas the extended access-saline-pretreated group was given access to self-administration for 6 h per session ($N=13$). All rats pretreated with amphetamine were given extended access to cocaine ($N=9$). For all self-administration groups, testing continued for 6 days per week (with 1 day/week off) for a total of 11 test sessions.

Catheter patency was tested by injecting the short acting barbiturate Pentothal® through the rat's catheter (thiopental sodium, 20 mg/ml in sterile water) on the 1 day per week when no self-administration session was conducted. Rats that did not become ataxic within 5 s underwent a second surgery during which a catheter was implanted into the left jugular vein. In addition, catheters were flushed with 0.9% sterile bacteriostatic saline before and after each self-administration session.

In Experiment 1, rats pretreated with amphetamine and given extended access to cocaine self-administration escalated their drug intake compared to both saline-pretreated groups. However, after 11

sessions of extended access, saline-pretreated rats had not escalated their drug intake, unlike what we had seen previously (Ferrario et al., 2005). Therefore, we replicated Experiment 1 using a separate group of animals.

2.2. Experiment 2

Procedures were identical to those described above with the exception that all rats were given extended access to cocaine self-administration after initial training ($N=9-13$).

2.3. Statistics

To assess whether or not drug pretreatment induced behavioral sensitization repeated measures ANOVA was used to compare the locomotor response across the three test injections (when 0.5 mg/kg amphetamine was given). Changes in self-administration across sessions and between groups were analyzed with mixed model ANOVA using the MIXED procedure in SPSS. This analysis has several advantages compared to other repeated measures analyses; it is particularly well suited to examine changes over time, allows for greater flexibility in modeling time effects than other repeated measures analyses, and is appropriate for examining data with inconsistent variability (Gueorguieva and Krystal, 2004). For this analysis, a Satterthwaite approximation for the denominator degrees of freedom was used, producing decimal places in these values. In order to assess escalation of drug intake, significant effects of session, group and significant group \times session interactions were followed by planned paired t -tests between the first and last self-administration test session. For Experiment 2, planned within group comparisons were made between baseline drug intake and the first hour of each subsequent extended access test session in order to identify the first test session in which drug intake increased significantly (escalated).

3. Results

3.1. Experiment 1

3.1.1. Psychomotor sensitization

There were no differences in beam breaks of drug-pretreated and saline-pretreated groups during habituation on any test day (data not shown). Fig. 1 shows the average number of beam breaks made after each amphetamine test injection (0.5 mg/kg) averaged across the first 20 min following injection. The amphetamine pretreatment regimen used here has been shown to induce robust and long-lasting psychomotor sensitization (Paulson et al., 1991) and associated neuroadaptations (Robinson and Kolb, 1997). As expected, we found a significant increase in the number of beam breaks made in response to 0.5 mg/kg dose of amphetamine across the three test injections, indicating the injection regimen produced behavioral sensitization (Fig. 1).

3.1.2. Cocaine self-administration

During the initial 3-day training period, all rats were given 1-h access to cocaine self-administration. As expected, there were no differences between the saline- and amphetamine-pretreated groups during these initial training sessions (Lorrain et al., 2000). In addition, the average number of responses in the active nose-poke port across the three training sessions was significantly greater than average responding in the inactive nose-poke port (mean difference = 33.88, $p < 0.001$). After training, saline-pretreated rats were divided into limited (continued 1-h access per session per day, $N = 12$) and extended

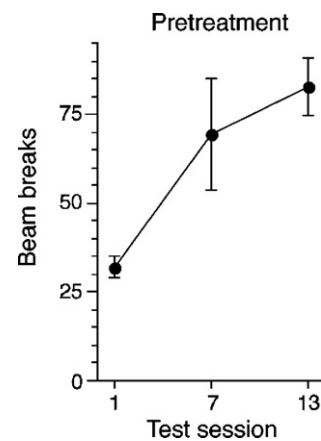


Figure 1 Mean (\pm S.E.M.) number of beam breaks made during the first 20 min after each test injection of 0.5 mg/kg amphetamine. There was a significant increase in the locomotor response to amphetamine across test sessions (repeated measures ANOVA, significant effect of session: $F_{(1,8)}=8.7$, $p < 0.01$).

access (6 h per session per day, $N=13$) self-administration groups balanced according to the number of infusions taken during training. All amphetamine-pretreated rats were given extended access to cocaine self-administration ($N=9$). Fig. 2 shows the number of cocaine infusions taken during the first hour of each test session (panel a) and during the first hour of the first and last test sessions (panel b) for all groups. Drug intake of animals pretreated with saline and given limited access to cocaine was stable, and did not differ between the first and last test sessions (Fig. 2b). Contrary to our expectations, for animals pretreated with saline and given extended access to cocaine, there was also no significant change in drug intake between the first and last test sessions, and drug intake of the two saline-pretreated groups did not differ from each other (Fig. 2b). However, amphetamine-pretreated animals did escalate their drug intake such that the number of infusions taken during the first hour of the last test session more than doubled relative to their intake during the first session (Fig. 2b). In addition, cocaine intake during the last test session was significantly greater for animals pretreated with amphetamine and given extended access than for either saline-pretreated group (Fig. 2b).

In this experiment, saline-pretreated rats given extended access to cocaine did not escalate their drug intake within 11 test sessions. Previous reports have shown that 11 sessions of extended access can produce escalated drug intake (Ahmed and Koob, 1998; Ferrario et al., 2005). There is, however, considerable variability in the number of sessions necessary for escalated drug intake to develop, from as few as 8 sessions (Ben-Shahar et al., 2004) to as many as 18 sessions (Ahmed et al., 2005). Therefore, we repeated this experiment using an identical procedure with the exception that all rats were given extended access to cocaine self-administration.

3.2. Experiment 2

3.2.1. Psychomotor sensitization

As expected, amphetamine pretreatment produced psychomotor sensitization, as indicated by a significant increase in

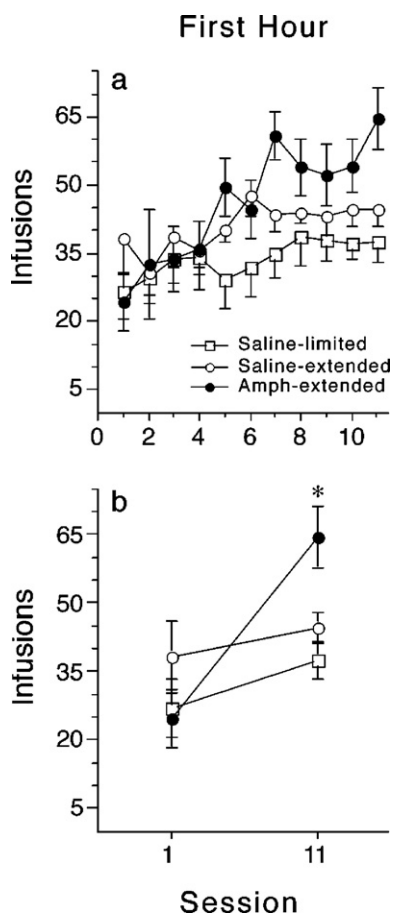


Figure 2 Mean (\pm S.E.M.) number of infusions taken during the first hour of each cocaine self-administration test session (panel a) and during the first hour of the first and last test sessions (panel b). The pattern of daily cocaine intake differed between the three groups tested (mixed model ANOVA: significant group \times session interaction: $F_{(2,317.9)}=7.17$, $p<0.02$). Cocaine intake across sessions did not differ between saline pretreated animals given extended versus limited access to drug nor did intake change across test sessions (mixed model ANOVA: effect of group: $F_{(1,66.7)}=1.2$, $p>0.05$; effect of session: $F_{(1,87.8)}=3.66$, $p>0.05$; group \times session interaction: $F_{(1,87.9)}=0.01$, $p>0.05$). The pattern of drug intake of the amphetamine pretreated group given extended access to cocaine was significantly different from both saline pretreated groups (mixed model ANOVA: Amph-extended vs. Saline-extended: significant group \times session interaction: $F_{(77.32)}=6.18$, $p<0.02$; Amph-extended vs. Saline-limited: significant group \times session interaction: $F_{(1,194.42)}=11.87$, $p<0.02$). Furthermore, animals pretreated with amphetamine and given extended access showed a significant increase (escalation) of drug intake between the first and last test session (panel b, indicated with an asterisk; paired t -test, $t_{(8)}=-4.20$, $p<0.01$).

the locomotor response to the last versus first 0.5 mg/kg injection of drug (Fig. 3).

3.2.2. Cocaine self-administration

During the initial 3-day training period, all rats were given 1-h access to cocaine self-administration. As before, responding was stable and no differences between saline- ($N=9$)

and amphetamine- ($N=13$) pretreated groups were observed during these initial training sessions. Furthermore, the average number of responses in the active nose-poke port across the three training sessions was significantly greater than average responding in the inactive nose-poke port (mean difference=25.16, $p<0.01$).

After training, all rats were allowed extended access to cocaine self-administration for a total of 11 sessions. During the first hour of the first extended access session drug intake deviated from that seen in the initial training sessions due to the behavior of one saline-pretreated animal. Thus, in order to establish a more reliable baseline that accurately represented basal levels of drug intake, baseline was determined by averaging across the first three training sessions and the first hour of test session one. Fig. 4 shows the average number of infusions taken during the first hour of baseline and on each subsequent extended access test session. Both saline- and amphetamine-pretreated groups showed a significant increase in drug intake between the first and last test sessions (Fig. 4). However, rats pretreated with amphetamine escalated their drug intake more rapidly than rats pretreated with saline (drug intake of the amphetamine-pretreated-extended access group differed from baseline by day 2), whereas intake the saline-pretreated group did not differ from baseline until the fifth extended access sessions (Fig. 4).

4. Discussion

It has been suggested that neuroadaptations within the mesocorticolimbic system that underlie psychomotor sensitization contribute to the development and persistence of addiction (Robinson and Berridge, 1993, 2003). Here we asked whether or not pretreatment with amphetamine, resulting in psychomotor sensitization, would facilitate the subsequent development of escalated drug intake, a common symptom of addiction. We found that, when given the opportunity to self-administer cocaine for 6 h per

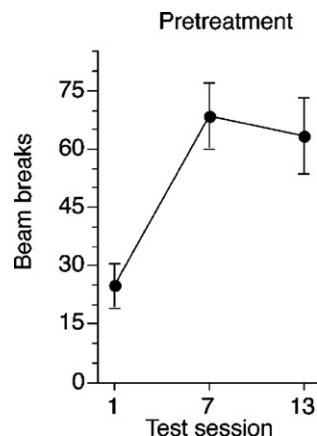


Figure 3 Mean (\pm S.E.M.) number of beam breaks made during the first 20 min after each test injection of 0.5 mg/kg amphetamine. There was a significant increase in the locomotor response to amphetamine across test sessions (repeated measures ANOVA, significant effect of session: $F_{(1,13)}=19.5$, $p<0.001$).

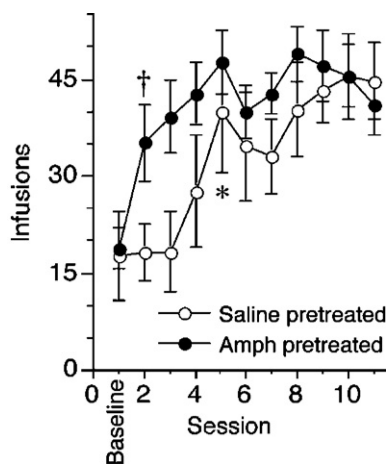


Figure 4 Mean (\pm S.E.M.) number of infusions taken during the first hour of each cocaine self-administration test session. Baseline shows the average number of infusions taken during three training sessions and during the first hour of test session 1. Drug intake of both groups escalated across test sessions (mixed model ANOVA, significant effect of session: $F_{(1,152.5)}=3.7$, $p<0.001$; paired t -tests first versus last test session, saline pretreated: $t_{(8)}=-3.46$, $p<0.01$; amphetamine pretreated: $t_{(13)}=-5.26$, $p<0.001$). However, there was a significant difference in the pattern of drug intake between saline and amphetamine pretreated groups (mixed model ANOVA, significant effect of group: $F_{(1,152.48)}=3.69$, $p<0.001$; significant effect of session: $F_{(1,152.5)}=3.7$, $p<0.001$; group \times session interaction: $F_{(1,152.48)}=0.83$, $p>0.05$). Specifically, drug intake of animals pretreated with amphetamine increased significantly after just one extended access test session (indicated by a dagger; paired sample t -test baseline vs. test session 2: $t_{(13)}=-2.79$, 2: $p<0.02$). In contrast, drug intake of the group pretreated with saline gradually increased and was not significantly greater than baseline until test session 5 (indicated by an asterisk; paired sample t -test baseline vs. test session 5: $t_{(8)}=-2.29$, 2: $p=0.05$).

session, animals previously sensitized to the psychomotor activating effects of amphetamine showed accelerated escalation of cocaine intake compared to saline-pretreated controls. Furthermore, in the second experiment, the amphetamine-pretreated group showed escalated drug intake after just one extended access session. These data suggest that at least some drug-induced neuroadaptations that accompany psychomotor sensitization may play a role in the development of escalated drug intake, and perhaps other addiction-like behaviors as well.

Although amphetamine-pretreated rats given extended access to cocaine escalated their drug intake in both experiments, saline-pretreated rats given extended access failed to escalate their drug intake in Experiment 1. The reason for the difference between the control groups in Experiments 1 and 2 is unknown. Previous studies using procedures similar to those used here have found that drug intake can escalate after as few as 8 tests sessions (Ben-Shahar et al., 2004), whereas in other experiments from the same group as many as 18 sessions were required (Ahmed et al., 2005); so, there is clearly considerable variation in the time necessary for escalation to develop. This variation may be due to pre-

existing individual differences. For example, Deroche-Gamonet et al. (2004) have shown that, even when the history of drug intake is identical, only a subset of rats develop escalated drug intake and other symptoms of addiction (Deroche-Gamonet et al., 2004). Thus, the development of addiction-like behaviors may be the result of an interaction between extended drug access and individual vulnerability.

In both Experiments 1 and 2 of the current study amphetamine pretreatment, using a dose regimen that produces robust sensitization, accelerated the escalation of cocaine intake when animals were allowed extended access to cocaine. The exact process responsible for this effect is not clear, but one possibility is that it is due to an enduring hypersensitivity to the incentive motivational properties of psychostimulant drugs produced by the amphetamine pretreatment. Previous studies have shown that pretreatment with a regimen that produces psychomotor sensitization enhances the motivation to obtain both cocaine (Horger et al., 1990; Deroche et al., 1999; Vezina et al., 1999) and amphetamine (Vezina et al., 2002) when limited access procedures are used. This may be due to adaptations in dopamine systems because blockade of D1 receptors attenuates the induction of psychomotor sensitization, abolishes the sensitized release of dopamine in the nucleus accumbens and blocks the enhancement of drug self-administration that is normally observed after systemic drug pretreatment (Vezina, 1996; Pierre and Vezina, 1998). Furthermore, dopaminergic projections to the nucleus accumbens are known to be important for mediating the motivational impact of Pavlovian conditioned stimuli on behavior (Cardinal et al., 2002), and repeated exposure to psychostimulant drugs can sensitize Pavlovian conditioned motivational processes (Harmer and Phillips, 1998; Wyvell and Berridge, 2001). Thus, exposing rats to a sensitizing regimen of amphetamine prior to extended access cocaine self-administration may have also rendered them hypersensitive to the incentive motivational properties of cocaine, accelerating the escalation of their drug intake.

Although much is known about the neuroadaptations that accompany psychomotor sensitization, relatively little is known about neuroadaptations that accompany the escalation of drug intake or other addiction-like behaviors. We recently showed that extended access to cocaine self-administration, leading to escalation of drug intake, is associated not only with robust psychomotor sensitization but also with an increase in the density of dendritic spines on medium spiny neurons in the core of the nucleus accumbens (Ferrario et al., 2005). It is possible, therefore, that a reorganization of accumbens (core) circuitry contributes to both the especially robust psychomotor sensitization and some addiction-like behaviors that develop as a result of extended access to psychostimulant drugs. Of course, more research is required in order to determine whether or not this is the case but the critical role of this brain region in motivated behavior suggests that it should be a target of future investigations (Cardinal et al., 2002). In conclusion, the current study suggests that the neural circuits that are altered as a consequence of repeated drug exposure, and that accompany psychomotor sensitization, may overlap with the neuroadaptations that underlie the development of addiction-like behaviors.

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