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Increased successive negative contrast in rats withdrawn from an escalating-dose schedule of D-amphetamine

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Abstract

The exposure of humans and animals to high doses of psychostimulant drugs, followed by their withdrawal, leads to a number of aversive psychological symptoms. These symptoms include increased anxiety and anhedonia, and may be manifested behaviorally as a decreased interest in normally rewarding stimuli. In the present study, we determine the effects of withdrawal from an escalating-dose schedule of D-amphetamine on the consumption of a 4% sucrose solution under normal conditions, and after an incentive downshift. The downshift was induced by subjecting animals to a consumatory negative contrast paradigm, by switching them from a familiar 32% sucrose solution to a novel 4% solution. In unshifted animals, there was no effect of D-amphetamine withdrawal on consumption of the 4% solution. In contrast, drug-withdrawn animals displayed an exaggerated negative contrast effect, primarily reflected as a delayed recovery from the downshift lasting for at least 60 h. This effect is interpreted as a consequence of the increased emotionality of withdrawn animals, and may be related to disruption of normal search behaviors.

Keywords: Amphetamine; Anhedonia; Anxiety; Drug; Rat; Successive negative contrast; Withdrawal

1. Introduction

Both animals and humans are subject to the aversive affective states that arise from the discontinuation of high doses of psychostimulant drugs such as cocaine and D-amphetamine (Koob et al., 1997). Human drug abusers report dysphoric symptoms that include depression, psychomotor retardation and anxiety after excessive intake of drug (American Psychiatric Association, 1995; Coffey et al., 2000; Gawin and Kleber, 1986, 1988; Gillin et al., 1994; Pathiraja et al., 1995). Animal paradigms have been developed that allow the objective measurement of these dysphoric states. For example, rodents that have self-administered binge-like doses of cocaine exhibit high levels of postdrug anxiety, as measured by increased acoustic startle and distressful ultrasonic vocalizations (Barros and Miczek, 1996; Mutschler and Miczek, 1998). Similarly, animals given high doses of psychostimulants passively display increased anxiety during the postdrug withdrawal, when tested in tasks such as the elevated-plus maze and defensive burying (Basso et al., 1999; Sarnyai et al., 1995).

Evidence for a state of anhedonia in drug-withdrawn animals has been determined with the refined use of rodent models of reinforcement. The decreased hedonic capacity of rodents that are in postdrug withdrawal has been well characterized by reductions in their responding for rewarding electrical brain stimulation (Cassens et al., 1981; Kokkinidis et al., 1980; Leith and Barrett, 1976, 1980; Lin et al., 1999; Markou and Koob, 1991; Wise and Munn, 1995). In our laboratory, we have recently shown that rats will exhibit reduced motivation to obtain natural reinforcers, including a sucrose solution and access to a sexually receptive conspecific, for up to 5 days after the termination of an escalating-dose schedule of D-amphetamine administration (Barr and Phillips 1999; Barr et al., 1999). These results indicate that postdrug withdrawal may be typified by a reduction in the motivation to respond for normally rewarding stimuli. What remains unknown, however, is how animals that are in a state of anhedonia will

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respond for a rewarding stimulus when its incentive properties are devalued unexpectedly.

In the successive negative contrast paradigm, animals are trained to receive reliably a reward of a consistent value. If this reward is unexpectedly substituted with one of lesser value, animals normally consume lower levels of the reward than subjects that continue to receive the lesser reward. This phenomenon, referred to as a "successive negative contrast," has been widely demonstrated across different species, including rodents, primates and humans (Flaherty, 1982, 1996; Grigson et al., 1994; Schnorr and Myers, 1967; Specht and Twining, 1999). Numerous explanations have been provided to account for the expression of successive negative contrast, many of which are based on the induction of negative affective states. Prominent among these affect-based theories are the development of emotional constructs such as disappointment and frustration (Amsel, 1958; Crespi, 1942; Flaherty, 1982, 1996), as the animal fails to find the same reward expected on the basis of previous experience and instead finds one of a lesser value. These data are also consistent with the shift causing a decrease in the incentive salience of the lesser reward compared to its salience in unshifted animals (Berridge and Robinson, 1998), as "downshifted" animals not only consume less of the reward, but also decrease their running speed as they approach it (Crespi, 1942; Flaherty, 1982).

Given that rodents exhibit a state of anxiety and anhedonia after withdrawal from psychostimulant drugs, we were interested in determining the effect of a further downshift in the incentive value of a stimulus by subjecting D-amphetamine-withdrawn rats to a successive negative contrast effect. Hypothetically, the adverse affective state that accompanies psychostimulant withdrawal should render animals especially sensitive to the emotionally disruptive effects of successive negative contrast, as two stressful situations would be experienced coincidentally. The purpose of the present experiment was therefore to determine the effects of withdrawal from a binge-like regimen of D-amphetamine on the consumption of a 4% sucrose solution in rats that had been downshifted from prior experience with a 32% sucrose solution.

2. Materials and methods

2.1. Subjects

Thirty-two male Long–Evans rats (Charles River, Quebec), weighing 250–275 g at the beginning of the experiment, were housed individually in a temperature-regulated colony (21 ± 1 °C) under a 12-h light–dark cycle (lights on at 0700 h); training and testing occurred during the light phase. All procedures were conducted in accordance with the Canadian Council on Animal Care guidelines for work with laboratory animals. Water was always available ad libitum in the home cage.

2.2. Apparatus

Subjects were trained and tested in four Plexiglas test cages (25 × 25 × 25 cm) that were enclosed within sound- and light-attenuating chambers. Each test cage was fitted with a lick-activated solenoid valve that provided rats with a drop of sucrose solution each time their tongue contacted the tip of a metal drinking spout, located 6 cm above the chamber floor. The solenoid valve regulated the volume of the drops of sucrose to 0.01 ml. A small light (2.8 W) attached to the roof of the chamber was turned on to designate the start of each training and test session, and was turned off when the session finished; the activation/termination of the valve coincided with light onset/offset. Recording of lick data was computer-controlled, with a sampling frequency of 10 ms (100 Hz).

2.3. Training and testing

All animals were placed on a deprived feeding schedule in which food intake was limited to 21 g/day, which reduced body weight of the rats to approximately 85% of their free-feeding weight. After subjects had attained the desired body weight, they were randomly assigned into two different groups ($n = 16$ per group). One group of animals was subsequently exposed to and trained with a 32% sucrose solution, while the remaining group was exposed to and trained with a 4% sucrose solution. Initially, subjects were given two 1-h habituation sessions to the sucrose solutions in their home cages, on alternate days. Animals were then given access to their respective sucrose solutions for a 5-min period once per day in the testing apparatus. Daily training sessions continued for 10 days, by which time most of the rats had reached an asymptotic level of consumption of the sucrose solutions. At the conclusion of the 10th day of training, each of the two groups of animals was subdivided into two further groups ($n = 8$ per group), based upon a rank-ordered division of animals with respect to the number of licks that they exhibited in the final 5-min training session.

One group from each of the 4% and 32% sucrose solution exposed animals was then subjected to a 4-day regimen of D-amphetamine injections, while the remaining groups received injections with the vehicle solution. Following the conclusion of the drug regimen, all groups were tested for their consumption (measured as the number of licks) of a 4% sucrose solution for an additional 8 days, tested once per day. For the two groups of animals trained with the 32% sucrose solution, the presentation of the 4% solution represented an unexpected decrement in the rewarding value of the stimulus.

2.4. Drug administration

Escalating doses of the drug D-amphetamine sulfate (SmithKline-Beecham, Oakville, Ontario) were administered to two groups ($n = 8$ per group) of rats based on a

schedule modified from one that we have shown previously to affect motivated responding for rewarding stimuli (Barr and Phillips, 1999; Barr et al., 1999; Leith and Barrett, 1976). In this schedule, rats were injected intraperitoneally three times per day (9:00 a.m., 5:00 p.m., 12:00 p.m.), starting with a dose of 1 mg/kg and escalating by 1 mg/kg on each subsequent dose, for the first 3 days for nine doses. On the fourth day, subjects received three doses of 10 mg/kg; animals therefore received a total of 12 injections over the 4-day period. Subjects were not exposed to the test chambers at any time during administration of the drug. For the first day of injections, the rats generally displayed elevated locomotor activity and exploratory types of behavior, and thereafter exhibited increasing levels of stereotypy. D-Amphetamine was dissolved in isotonic saline (1 ml/kg), and subjects were weighed each morning before the 9:00 a.m. injection so that any decreases in body weight would be compensated for by adjusting the dose; body weights were also recorded the morning 1 day after drug termination and an additional 5 days later. As D-amphetamine-treated animals typically display a loss of body weight during the 4-day drug regimen, each drug-treated animal was "yoked" to a vehicle-treated animal, matched by body weight. The amount of food that each drug-treated animal consumed over 24 h (determined by measuring the amount of the original 21-g daily allowance that remained the following morning) was measured during the drug regimen and for an additional 4 days, and the yoked animal was limited to consume this amount. Control subjects were injected with isotonic saline under the same schedule as rats in the D-amphetamine group.

2.5. Data analysis

The lick and body weight data were analyzed by repeated-measures analysis of variance (ANOVA) in a three-factor design, with drug treatment (D-amphetamine vs. vehicle) and preshift sucrose solution (32% vs. 4%) as the two between-groups factors, and the test session as the within-subjects. When the ANOVA indicated the presence of a significant effect, further analysis was conducted with Fisher's LSD post hoc tests. For the lick data, results from only the predrug baseline and the first four test sessions after the drug regimen were analyzed, as the effect of reward downshift was no longer evident after this point. Body weights were recorded at baseline, the morning after each day of drug administration, and the mornings both 1 and 5 days following the termination of injections.

3. Results

Prior to drug administration, all animals exhibited high rates of licking for either the 32% or the 4% sucrose solution. Analysis of the data during the 84-h period following drug termination with the repeated-measures ANOVA indicated a significant main effect of drug treatment, $F(1,28) = 7.31$, $P < .05$, as animals that were shifted from the 32% to 4% solution after exposure to the escalating-dose regimen of D-amphetamine exhibited reduced consumption of the 4% sucrose solution, compared to vehicle-treated subjects. There was also a significant main effect of preshift sucrose solution, $F(1,28) = 4.38$, $P < .05$, whereby both groups of rats that were allowed to consume the 32% sucrose solution displayed dramatically reduced consumption of the 4% solution after the animals were downshifted to this new reward, confirming a negative contrast effect. The ANOVA also indicated a significant interaction of Drug Treatment × Preshift Solution × Test Session, $F(4,112) = 6.43$, $P < .001$.

The significant interaction was analyzed further with the use of post hoc tests (Fig. 1). These tests revealed that both of the downshifted groups (32% → 4%) displayed reduced consumption of the novel 4% sucrose solution compared to the unshifted (4% → 4%) groups during their first two exposures to the 4% solution. On the third exposure to the 4% solution, at 60 h after drug termination, the vehicle-treated group displayed an unexpected increase in consumption of the 4% solution, compared to both of the unshifted groups. This effect had diminished by the fourth test session, at which time there was no longer a significant difference between these groups. In comparison, the downshifted group that had been exposed to D-amphetamine displayed reduced levels of consumption of the 4% solution for three, as opposed to two, test sessions, and returned to control levels of consumption by the fourth test session. When the two downshifted groups were compared to each other, the D-amphetamine-treated group exhibited significantly lower levels of consumption across the first three test

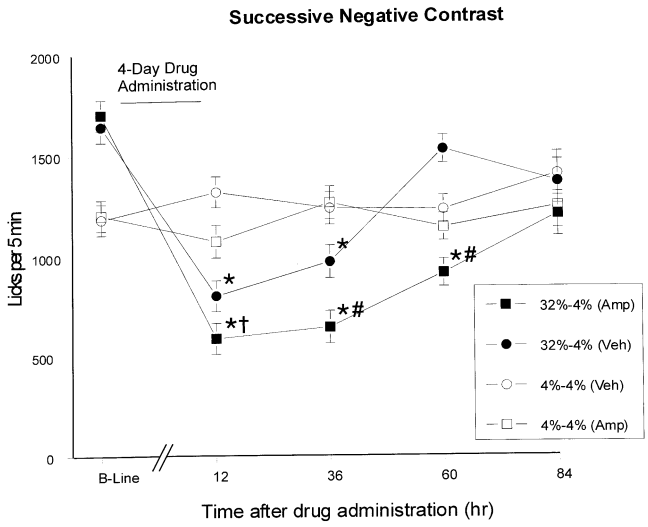

Fig. 1. Effects of withdrawal from a 4-day regimen of D-amphetamine, or vehicle, on number of licks for a 4% sucrose solution. Animals were given 5 min fluid consumption tests at different time points before (B-Line) and after withdrawal from drug administration. * Significantly different from 4% to 4% (VEH) group, $P < .05$. † Significantly different from 32% to 4% (VEH) group, $P < .10$. # Significantly different from 32% to 4% (VEH) group, $P < .05$.

Table 1
Body weights of rats recorded at baseline, the morning after each day of drug administration and the mornings 1 and 5 days following the termination of drug

Time (days)	Drug (g)	Vehicle (g)
Predrug baseline	415.3 (9.9)	417.0 (9.9)
1	402.0 (9.8)	408.6 (9.8)
2	385.8 (9.5)*	400.8 (9.5)
3	377.4 (9.1)#	387.9 (9.1)*
4	376.1 (8.8)#	389.9 (8.8)*
5	385.2 (9.2)*	400.8 (9.2)
10	408.4 (9.0)	423.2 (9.0)

Both groups of animals consumed the same quantity of food. Values represent group means ± (S.E.M.).
* Denotes significantly different weight from baseline ($P < .05$).
# Denotes significantly different weight from baseline ($P < .01$).

sessions, although this effect was only marginally significant on the first test day.

Analysis of the body weights of animals prior to, during and after drug or vehicle indicated no significant main effect of drug treatment, $F(1,28) = 0.67$, NS, or main effect of reward shift, $F(1,28) = 0.09$, NS. However, there was a highly significant effect of test session, $F(6,168) = 230.32$, $P < .001$, on body weight, as well as a significant Drug × Test Session interaction, $F(6,168) = 7.93$, $P < .001$, but no significant Drug × Shift × Test Session interaction, $F(6,168) = 0.45$, NS. With the absence of the three-way interaction, the data for both groups in each drug-treatment condition (i.e., shifted and unshifted animals) were collapsed and post hoc tests were conducted on the interaction between drug treatment and test sessions (Table 1). Body weights were significantly reduced compared to baseline values in D-amphetamine-treated rats following the second day of treatment, and were still significantly lower the morning following the first day of drug withdrawal. In contrast, body weights of rats in the vehicle-treated group were not significantly lower than baseline values until after the third day of treatment, and had recovered to levels that were not significantly different from baseline values by the morning following the first day of drug withdrawal. Differences in body weight between the groups were not due to differences in food consumption, as all animals were yoked in consumption during the drug regimen, and all animals consumed their full daily allowance of food following drug termination.

4. Discussion

In the present experiment, we have demonstrated that rats exhibit a greater consumatory negative contrast compared to control subjects when they are tested after withdrawal from an escalating-dose regimen of D-amphetamine. This effect was manifested initially as a marginally significant increase in the size of the contrast effect on the first day of exposure to the devalued sucrose solution. By the second day of exposure to the devalued stimulus, the magnitude of the contrast effect was substantially greater between the downshifted groups, as vehicle-treated animals showed a more rapid recovery from the exposure to the devalued stimulus. On the third day of exposure to the devalued sucrose solution, only the D-amphetamine-withdrawn animals continued to exhibit a contrast effect, indicating that withdrawal from a psychostimulant drug can perpetuate negative contrast effects in rodents.

A number of different hypotheses have been proposed to account for the phenomenon of negative contrast. One of the most influential of such theories postulates that contrast effects arise from associative generalization decrements (Capaldi, 1971; Flaherty, 1982; Spear and Spitzner, 1966), whereby changes in either the rewarding environment or the rewarding stimulus lead to a reduced association between the two, with a commensurate decrease in consumption of the reward. Although generalization decrements fail to account for several important aspects of contrast effects, such as the existence of positive contrast effects (Flaherty, 1982), it may be argued that in this case animals in the novel state of drug withdrawal would exhibit potent generalization decrements when exposed to the devalued stimulus for the first time (Grilly, 1975). This explanation is unlikely, however, as the animals in the group that received D-amphetamine and was not downshifted did not reduce their consumption of the 4% sucrose solution. It is also unlikely that the increased negative contrast observed in drug-withdrawn animals, measured by a decreased fluid consumption, is a reflection of psychomotor deficits that arise from the withdrawal of high doses of psychostimulant drugs. Although several studies have reported reduced locomotor activity by drug-withdrawn animals (Paulson et al., 1991; Persico et al., 1995; Pulvirenti and Koob, 1993), we have shown in previous experiments, using a similar regimen of drug administration, that animals are capable of vigorous physical activity during the withdrawal state when responding for naturally rewarding stimuli such as a sexually receptive conspecific or a sucrose solution (Barr and Phillips, 1999; Barr et al., 1999). In addition, psychomotor deficits should have affected the unshifted, D-amphetamine-treated group equally; for which there was no evidence. The protracted recovery from a downshift in reward in drug-treated animals is also unlikely to arise from residual anorectic effects of the amphetamine. The strongest evidence for this lies in the absence of altered consumption of 4% sucrose in the corresponding unshifted group following the termination of the drug regimen. Furthermore, using a similar dosing schedule of D-amphetamine, we have shown previously that withdrawal from the drug is associated with a decrease in the motivation to obtain a sucrose solution under the higher effort requirements of a progressive ratio schedule of reinforcement, but no effect of drug withdrawal is observed at lower ratios or when rats are allowed to consume the fluid freely (Barr and Phillips, 1999). It is, in addition, doubtful

that the difference in time taken to return to normal levels of consumption between shifted groups might reflect a more rapid recovery of the vehicle-treated animals rather than a delayed recovery in drug-withdrawn rats. It may be argued that in rats that are already food deprived, the additional involuntary food restriction imposed on vehicle-treated animals due to the yoking procedure used in the current study may make them more motivated to consume the solution (and hence accelerate their recovery from the downshift) than drug-treated animals that voluntarily consumed less food during the drug regimen. Several lines of evidence suggest that this hypothesis is unlikely; first, the vehicle-treated, unshifted animals did not consume more of the sucrose solution than the unshifted drug-treated animals, which might be expected to occur if they were hungrier or more motivated to consume. Second, as drug-treated animals consumed normal levels of food in the home cage on the days immediately following completion of the drug regimen, the yoked animals were not subjected to additional involuntary food restriction during the critical days of behavioral testing. Third, the body weights of drug-treated animals exhibited a more rapid decrease and remained below baseline values for significantly longer than vehicle-treated subjects after the termination of the drug regimen, implying a greater level of metabolic deprivation in D-amphetamine-treated rats. Finally, the period of the contrast effects observed in vehicle-treated animals was comparable to the duration observed in previous studies that have used a similar contrast protocol (Riley and Dunlap, 1979).

Alternate theories for the basis of negative contrast effects have focused on the role of psychological constructs such as "emotionality" and anxiety (Becker et al., 1984; Flaherty, 1982; Weinstein, 1972). The withdrawal from high doses of psychostimulant drugs in rodents has been shown reliably to provoke aversive affective states (Koob et al., 1997). In particular, two of the more commonly described sequelae of drug withdrawal are increased anxiety (Basso et al., 1999; Mutschler and Miczek, 1998) and anhedonia (Lin et al., 1999; Markou and Koob, 1991; Wise and Munn, 1995). With respect to anxiety, there is a substantial body of evidence that suggests that negative contrast effects may be mediated, in part, by increased levels of anxiety in subjects. The capacity of a wide range of anxiolytic drugs to ameliorate the effects of successive negative contrast (Flaherty, 1990; Morales et al., 1992), as well as the anticontrast effects of selective amygdaloid lesions (Becker et al., 1984; Salinas et al., 1996), indicates that anxiety-like processes may be involved in the expression of negative contrast effects. In addition, it was reported that Syracuse low-avoidance rats, which exhibit greater levels of anxiety (Brush et al., 1988), displayed increased levels of consumatory negative contrast when compared to the less emotionally reactive Syracuse high-avoidance strain (Flaherty et al., 1994). It is theoretically possible that the withdrawal from a binge-like dose of D-amphetamine could perpetuate the effects of negative contrast by sustaining high levels of anxiety in rats, and thus potentiate the weaker anxiogenic effects of the contrast paradigm in later exposures to the devalued stimulus. However, a recent study of consumatory negative contrast in humans failed to detect increases in anxiety when subjects were presented with a devalued sweet solution, despite perceptions of reduced absolute sweetness (Specht and Twining, 1999). Furthermore, rats that were selectively bred for high levels of consumatory negative contrast did not display an expected increase in anxiety-related behaviors when compared to the control animals (Flaherty and Rowan, 1989). These contrary findings suggest that, while anxiety may contribute in some measure to the expression of negative contrast effects, other psychological factors are clearly involved.

Flaherty (1990) and Mitchell and Flaherty (1998) have postulated that the expression of successive negative contrast involves a multistage process of distinct yet interacting cognitive and affective processes. One of the more important of these stages involves a pattern of search activity by the downshifted animal, after it detects and avoids the devalued stimulus and instead searches for the familiar high-reward stimulus. The existence of this component of Flaherty's multistage model is supported by the recent findings of Pecoraro et al. (1999), who observed that downshifted animals engaged in systematic investigative activity after detection of the devalued stimulus, presumably seeking the more rewarding stimulus. The effects of D-amphetamine withdrawal may be particularly disruptive at this point in the multistage process, for several reasons. Firstly, it has been shown that animals in a state of psychostimulant withdrawal exhibit a suppressed response towards novel stimuli (Persico et al., 1995). Secondly, and in a similar manner, psychostimulant withdrawal is associated with reduced investigative activity in rodents (Barr et al., 1999; Hitzemann et al., 1977; Meert, 1992). A suppressed response to the novel, downshifted reward, followed by inhibited seeking for the familiar high-reward stimulus, could in theory delay the sequence of recovery that is predicted by the multistage hypothesis of successive negative contrast, and account for the prolonged contrast effects that were observed in the present study. This hypothesis would also be consistent with the large body of evidence that has demonstrated that drug-withdrawn animals experience anhedonia (Cassens et al., 1981; Kokkinidis et al., 1980; Leith and Barrett, 1976, 1980; Lin et al., 1999; Markou and Koob, 1991; Wise and Munn, 1995). Anhedonic animals would be less interested in both the previous high-reward and the novel, downshifted reward, leading to a delayed return to consumption of the 4% sucrose solution. However, this hypothesis remains to be tested empirically, and future studies should measure search behaviors when animals are downshifted.

In conclusion, the results of the present study indicate that withdrawal from a psychostimulant drug is associated

with increased consumatory negative contrast effects, primarily reflected in a delayed recovery by these animals. The exact nature of the extended negative contrast effect remains unknown, but may be related to increased emotionality in withdrawn animals, and deficits in their exploratory activity. The contribution of different psychological constructs towards this phenomenon should be determined in future studies by the administration of psychoactive compounds, such as anxiolytics or drugs that alleviate anhedonia. In this regard, it will be of interest to test the effects of fast-acting antidepressant pharmacotherapies on enhanced negative contrast following withdrawal from D-amphetamine or cocaine.

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