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ORIGINAL INVESTIGATION

Alasdair M. Barr · Anthony G. Phillips

Withdrawal following repeated exposure to *d*-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement

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Abstract Numerous studies have shown that withdrawal from sustained high doses of psychostimulant drugs such as cocaine or *d*-amphetamine produces depressive-like symptoms in both rats and humans. The majority of experiments with rodents have assessed the effects of amphetamine withdrawal on reinforcing electrical self-stimulation in different brain regions, but relatively few have examined effects on responding for natural reinforcers. In the present study, two groups of mildly food and water deprived male rats were trained to respond on a lever for a 4% sucrose solution under a progressive ratio schedule of reinforcement. One group was subsequently administered a 4-day regimen of injections of increasing doses of *d*-amphetamine based on a schedule shown previously to reduce self-stimulation behaviour. Break points were significantly reduced for up to 4 days after the termination of drug administration, suggesting a decreased motivation to obtain the natural reward. A further experiment demonstrated that the identical drug regimen produced no effect upon consumption of the 4% sucrose solution when it was freely available. These results demonstrate that the progressive ratio procedure may be a useful technique for evaluating changes in motivation for natural reinforcing stimuli following withdrawal from psychostimulant drugs.

Key words Anhedonia · Amphetamine · Depression · Progressive ratio · Psychostimulant · Rat · Sucrose solution · Withdrawal

A.M. Barr · A.G. Phillips (✉)
Department of Psychology,
University of British Columbia,
Vancouver, B.C., Canada V6T 1Z4
Fax: +1-604-822-6923

Introduction

For more than 20 years, the psychological effects of drug withdrawal have been explained within the theoretical framework of an opponent-process theory of motivation (Solomon 1977; Koob et al. 1997). According to this theory, during withdrawal the previously pleasurable effects of a variety of different drugs of abuse are inevitably followed by emotional states opposite in affect, and of a longer duration, as the body seeks to restore its "hedonic equilibrium" (Solomon and Corbit 1974). Thus, drugs such as the psychostimulants cocaine and *d*-amphetamine, which produce the acute effects of euphoria, increased energy and self-confidence, generated a withdrawal syndrome characterized by dysphoria, lethargy and anxiety (Gawin and Kleber 1986). This psychostimulant-induced withdrawal syndrome bears a remarkable similarity to human endogenous depression, and indeed depression is one of the most commonly described side-effects of cocaine and amphetamine withdrawal in humans (Pathiraja et al. 1995). The resemblance of psychostimulant withdrawal to endogenous depression has therefore prompted its development as an isomorphic animal model of depression (Seltzer and Tonge 1975; Leith and Barrett 1980; Kokkinidis et al. 1986; Geyer and Markou 1995).

One major symptom common to both psychostimulant withdrawal and depression is anhedonia, which represents a decreased interest in and pleasure from normally rewarding activities (Willner 1991). A variety of behavioural measures has been used to evaluate drug withdrawal and anhedonia in rodents, including a range of operant schedules (Denoble and Begleiter 1976; Carroll and Lac 1987), but the most frequently applied technique is the assessment of drug withdrawal on intracranial self-stimulation (ICSS) response thresholds from electrodes placed in either the lateral hypothalamus (Simpson and Annau 1977; Markou and Koob 1991), substantia nigra (SN) (Borowski and

Kokkinidis 1992) or ventral tegmental area (VTA) (Frank et al. 1992). Typically, rats or mice administered (by self-administration or the experimenter) medium to high doses of either cocaine or amphetamines show an increase in the frequency or current intensity required to support ICSS, which is interpreted as a reduced responsiveness of the brain's reward systems (Phillips and Fibiger 1989; Wise 1996). These effects generally last from between 4 days and 2 weeks, and in agreement with psychostimulant withdrawal as a model of depression, are shown to be alleviated by tricyclic antidepressants (Kokkinidis et al. 1980; Markou et al. 1992).

As anhedonia in humans is assessed by its effects on natural rewards, it is of obvious interest to ascertain how psychostimulant withdrawal, as a model of anhedonia in animals, affects their motivation to respond for natural rewarding stimuli. Furthermore, while drug-induced modulations of ICSS responding return to normal within 2 weeks (Wise and Munn 1995), there are numerous reports of human cocaine addicts experiencing long-term periods of anhedonia during drug withdrawal (Gawin and Kleber 1986, 1988), which can reduce their interest in natural rewards for many months. If similar results were found in animal models of psychostimulant withdrawal, this would significantly increase the utility of psychostimulant withdrawal as an animal model of depression (Willner 1995).

The purpose of the present experiment was therefore to determine if a drug regimen of repeated administration of *d*-amphetamine, which had been shown previously to produce anhedonic effects on ICSS responding (Leith and Barrett 1976; Cassens et al. 1981), could induce a state of withdrawal which would also reduce an animal's responding for a natural reward (4% sucrose solution), as measured by a progressive ratio (PR) schedule. The PR schedule of reinforcement has seen widespread use as a sensitive technique to measure motivation to respond for a variety of different reinforcers, including sweet solutions (Hodos 1961), electrical brain stimulation (Hodos 1965) and drugs (Roberts et al. 1989; Markou et al. 1993; Mendrek et al. 1998). Under this schedule, subjects are required to increase their operant responding for a fixed reward until they reach a "break point" which determines the maximal amount of effort animals will expend to procure the desired rewarding stimulus, with the break point providing an objective measure of the subject's motivation (Hodos 1961).

Materials and methods

Subjects

Thirty male Long-Evans rats, (Charles River, Quebec, Canada) weighing 300–350 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 hours); all training and testing took place during the light phase. Three subjects failed to complete the experiment, two due to illness and one failing to meet training criteria, and so their data were not included. All experiments were conducted in accordance with the Canadian Council on Animal Care guidelines for work with laboratory animals.

Apparatus

Experiments were carried out in four Plexiglas test cages (25 × 25 × 25 cm) enclosed within sound and light attenuating chambers. Each test cage was fitted with a removable response lever, which projected 5 cm above the wire grid test cage floor; it was removed whenever subjects were tested for their free consumption of sucrose (experiment 2). All test cages were also fitted with a lick activated solenoid valve which provided rats with a drop of sucrose solution each time their tongue contacted the tip of the metal spout. The valve regulated the volume of the drops of sucrose to 0.01 ml, so that for the standard reinforcement of 0.50 ml sucrose solution, the animal was required to lick 50 times. A small light (2.8-W) fitted in the roof of the chamber was turned on to designate the start of each training session, which coincided with activation of both the response lever and lick-activated dispenser. The concentration of the sucrose solution was set at 4% (w/v) because previous experiments (Barr and Phillips 1998) had shown that this concentration was optimal for detecting slight shifts (either increases or decreases) in the reinforcing value of the sucrose reinforcer, when using a PR schedule.

Operant training

All subjects were given an initial 48-h exposure to the 4% sucrose solution in their home cages, while water and food were also available ad libitum. After 24 h, rats were given two 30-min habituation sessions in the test chambers, during which both the response lever and drinking spout were removed. The lick-activated fluid dispensers were returned to the test cages and subjects could freely consume the sucrose solution for 1 h on each of the next 4 days. The rats were then placed on an intermittent feeding schedule depriving them of food and water for 20 h before being placed in the test cages; following testing, subjects were returned to their home cage and given ad lib access to both food and water. Throughout the remainder of the experiment, rats were trained on alternate days. Response levers were introduced into the test cages and the rats were placed on a 1-h session fixed ratio (FR) schedule of responding as follows: 3 days at FR1/0.05 ml of 4% sucrose solution, 3 days at FR3/0.15 ml sucrose and 3 days at FR10/0.40 ml sucrose per reinforcement. A minimum of 100 responses per session was required at each level of training, and any rat that did not meet this criterion received additional training sessions until it performed to the required standard.

After completing FR training, subjects were placed on a PR schedule of reinforcement whereby successive reinforcements could be earned according to the following number of bar-presses: 1, 3, 6, 10, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145. The final ratio achieved represented the "break point" value, and the session ended when rats failed to reach the next bar-press criterion within 1 h. Each reinforcement was set at 0.50 ml of 4% sucrose solution, as this value sustained high levels of operant responding while minimizing any effects of satiety on the PR data. Subjects received eight PR sessions; levels of responding were generally stable (i.e. typically varying by less than ± 1 break point per session) by the fourth session. When training for all animals was completed, subjects were divided into two groups based on their average break points for the last four PR training sessions. One group served as controls ($n = 12$), while the other group ($n = 15$) was placed on a *d*-amphetamine drug administration schedule.

Drug administration

Escalating doses of the drug *d*-amphetamine sulfate (obtained from SmithKline-Beecham, Oakville, Ontario, Canada) were administered to one group ($n = 15$) of rats based on a schedule modified from one shown previously to affect thresholds of ICSS responding (Leith and Barrett 1976). In a pilot study, animals subjected to the level of food and water deprivation used in training were more vulnerable to the toxic effects of high doses of *d*-amphetamine, and thus the final day of drug administration was modified. In this modified schedule, rats were injected IP three times per day (9 a.m., 5 p.m., 12 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 day 4, subjects received one final dose (10 mg/kg) at 9 a.m.; animals therefore received a total of ten 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 behaviour, and thereafter exhibited increasing levels of stereotypy. The *d*-amphetamine was dissolved in isotonic saline (1 ml/kg), and subjects were weighed each morning before the 9 a.m. injection so that any decreases in body weight would be compensated for by adjusting the dose. Control subjects were injected with isotonic saline under the same schedule as rats in the *d*-amphetamine group.

Operant testing (post-treatment)

After the final dose of *d*-amphetamine, subjects in both groups were again deprived of food and water for 20 h before being tested on the PR schedule for the 4% sucrose solution reward, as described above. Thereafter, subjects were tested every subsequent 48 h for an additional five sessions.

Experiment 2: free sucrose consumption

A separate group of six male Long Evans rats (300–400 g) were given access to the 4% sucrose solution in their home cages, for 48 h. Following the familiarization period, subjects were given two 30-min sessions in the test cages with no access to sucrose, and then placed on the same 20-h food and water deprivation schedule as the operant-trained rats. Subjects received four 1-h free consumption sessions in order to obtain a baseline measure, and were then subjected to the same ten-dose drug or vehicle injection regimen. Animals were subsequently tested for their free consumption of 4% sucrose solution at both 1 and 3 days after the tenth injection.

Data analyses

Baseline operant response rates were averaged for subjects over their last four training sessions. The break point values obtained in the PR test sessions were subjected to a two-factor ANOVA. Body weights and inter-lick-intervals were also subjected to two-factor ANOVAs, while latency measures were compared using the Student's *t*-test. For experiment 2 (free sucrose consumption), data were analyzed by a within-subjects repeated measures ANOVA. Post-hoc comparisons, when appropriate, were made using a test of simple main effects.

Results

Experiment 1

Figure 1 shows the break point scores (mean ±SEM) for vehicle and *d*-amphetamine administered groups, from both pre-drug test sessions and during drug withdrawal. Administration of an escalating series of ten *d*-amphetamine injections over 4 days produced a significant decrease in the break point value of responding for a 4% sucrose solution, as measured by a PR schedule, during the period of initial withdrawal on post-drug test sessions 1 and 2 (i.e. 1–3 days). The break point values for the *d*-amphetamine group were a mean of 5.3 ± 0.5 and 4.9 ± 0.7 for the 1- and 3-day sessions, respectively. In contrast, the break point values for the vehicle control group were a mean of 8.7 ± 0.6 and 8.8 ± 0.8, respectively. Analysis of the data by a two-factor ANOVA indicated a significant Group effect ($F1,25 = 4.54$, $P < 0.05$), as well as a significant effect

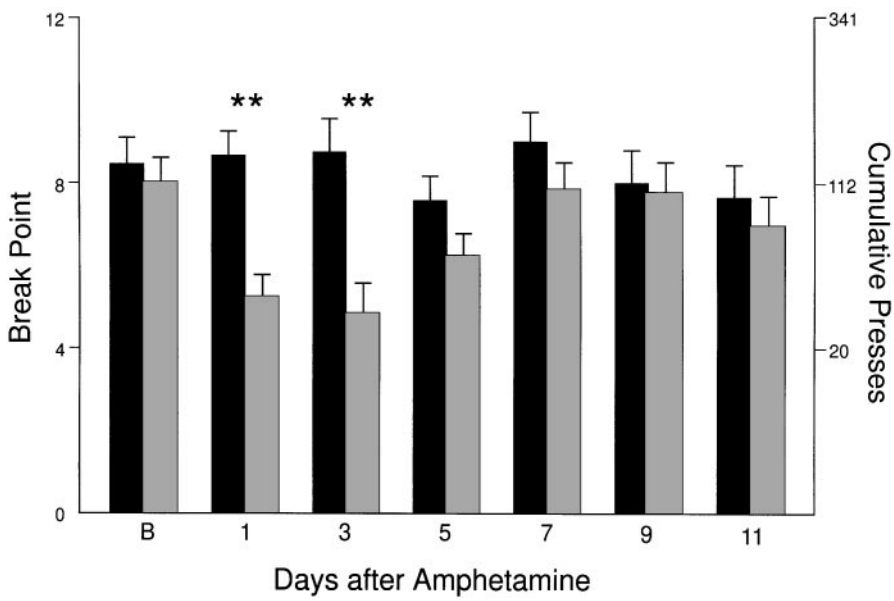

Fig. 1 The effect of *d*-amphetamine withdrawal on responding for a 4% sucrose solution under a progressive ratio schedule of reinforcement, across different test sessions. Values represent the break points (±SEM) and cumulative total responses of both groups [$n = 15$, drug (*grey bars*); $n = 12$, control (*black bars*)], during baseline condition (*B*) and after drug administration (*1–11* days). The *stars* indicate a significant difference between groups (**$P < 0.001$)

Table 1 The effect of *d*-amphetamine withdrawal upon the inter-lick-intervals taken by rats when consuming a 0.50 ml sucrose solution reinforcer (50 licks per reinforcement). Intervals, measured in seconds (s), are averaged with each rat for all reinforcements per session, and for all rats per group ($n = 15$, drug; $n = 12$, control). The *stars* denote a significant difference ($P < 0.10$)

Days after *d*-amphetamine	Drug (s)	Vehicle (s)
Pre-drug baseline	0.34 (0.04)	0.27 (0.05)
1	1.60 (0.92)*	0.28 (1.03)
3	1.74 (0.77)*	0.37 (0.86)
5	0.31 (0.04)	0.21 (0.05)
7	0.33 (0.07)	0.30 (0.08)
9	0.33 (0.08)	0.27 (0.07)
11	0.27 (0.04)	0.30 (0.04)

of Time of withdrawal ($F6,150 = 4.55$, $P < 0.001$) and an interaction of Group × Time ($F6,150 = 5.45$, $P < 0.001$). A simple main effects post-hoc comparison between groups revealed a significant difference between the two groups on the first two test post-drug sessions (1 and 3 days withdrawal). By the third post-drug test session (5 days withdrawal), the break point scores were no longer statistically significant.

Table 1 contains data on the average inter-lick interval (computed from 50 licks per reinforcement) when consuming the sucrose solution during the PR test sessions. Values were averaged across all reinforcements per test session for each rat, and analysis of the data by a two-factor ANOVA showed a trend towards a significant group effect ($F1,25 = 2.95$, $P < 0.10$) but no effect of time of withdrawal or interaction. Further analysis of these data revealed that the differences in inter-lick intervals between groups on the two test sessions following drug administration were due to pauses in consumption of the solution by animals treated previously with *d*-amphetamine rather than a consistent increase in the inter-lick interval.

Latencies to initiate operant responding following commencement of the test on the first two post-drug sessions differed significantly ($t14 = 6.99$, $P < 0.01$) between the *d*-amphetamine and vehicle-treated groups. The latency values, in seconds, were a mean of 148.1 ± 174 and a mean of 14.6 ± 9.6 for the *d*-amphetamine and vehicle groups, respectively. Latencies to begin responding for the next five reinforcements on post-drug test days 1 and 3, referred to as post-reinforcement pauses (Table 2), were not significantly different ($F4,88 < 1$, NS). Table 2 also includes the durations taken by each group to attain each of the first five reinforcements (representing the averaged break point value for the *d*-amphetamine treated group) on days 1 and 3 of withdrawal, and these data demonstrate that while rats treated with *d*-amphetamine achieved lower break points, they attained each reinforcement at approximately the same rate as vehicle treated rats ($F4,88 = 1.7$, NS).

The weights of animals during and after drug administration are shown in Fig. 2. These data were analyzed by a two-factor ANOVA which showed a significant between-group difference ($F1,25 = 8.22$, $P < 0.01$) as well as significant effects of Day ($F6,150 = 94.75$, $P < 0.001$) and Group × Day interaction ($F6,150 = 21.43$, $P < 0.001$). Administration of *d*-amphetamine therefore caused long lasting decreases in the weights of subjects, which were still evident when animals were weighed 3 weeks later ($t14 = 4.40$, $P < 0.01$).

Experiment 2

Figure 3 illustrates the mean volumes of 4% sucrose solution consumed by six rats in four pre-drug free consumption baseline tests, and in tests at 24 and 72 h following *d*-amphetamine administration. Analysis of these data by a repeated measures ANOVA indicated no treatment effect ($F1,30 = 0.81$, NS), confirming withdrawal following repeated injections of *d*-amphetamine had no effect on consumption of 4% sucrose when it was freely accessible.

Discussion

The present study investigated the effects of an escalating dose regimen of *d*-amphetamine administration (Leith and Barrett 1976) on rats' motivation to work for a natural reward in a post-drug withdrawal period that extended from 1 to 11 days. The main finding was that subjects pre-treated with the drug exhibited decreased break points on the first and third day post-drug tests when responding for a 4% sucrose solution on a PR schedule of reinforcement. These results indicate that the escalating dose drug regimen used in the current study which was chosen to represent a "binge-like" pattern (Segal and Kuczenski 1997), may

Table 2 The effects of drug treatment on both the post-reinforcement pause and the time to attain each reinforcement, for the first five reinforcements. Values represent the means (±SEM) of the combined average scores from post-drug test days 1 and 3. No significant effects were bserved

Response/ reinforcement ratio	Post-reinforcement pause (s)		Time to attain each reinforcement (s)	
	Drug	Vehicle	Drug	Vehicle
1	24.1 (5.5)	14.9 (6.0)	0.01	0.01
3	79.7 (45.9)	22.3 (49.5)	15.2 (5.5)	6.6 (6.0)
6	15.2 (4.2)	18.2 (4.4)	91.1 (34.1)	22.9 (36.9)
10	32.1 (5.6)	17.7 (5.6)	73.3 (24.3)	84.8 (25.3)
15	48.3 (11.7)	20.6 (10.6)	328.7 (95.1)	135.9 (95.0)

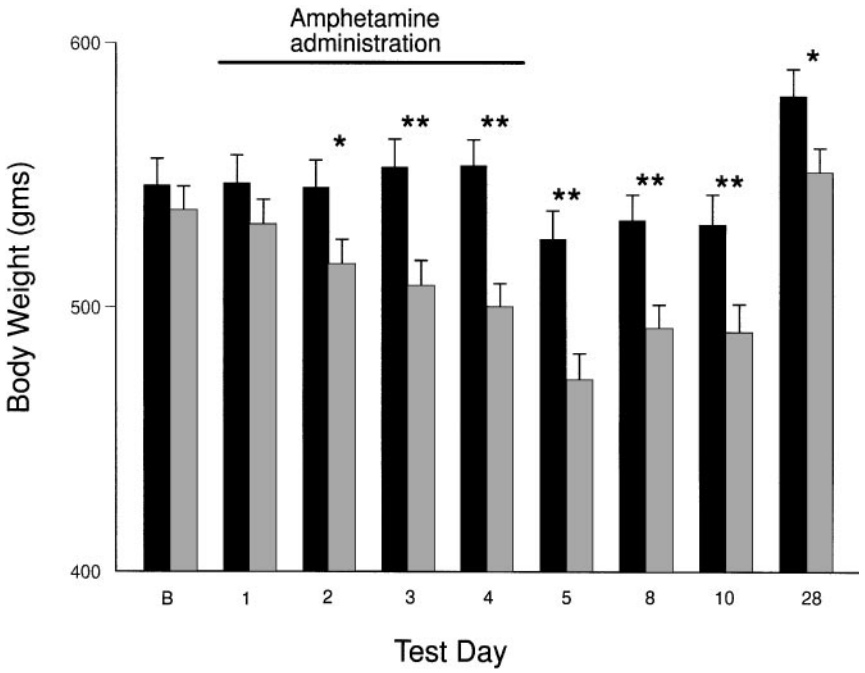

Fig. 2 Body weights of subjects in the drug [$n = 15$ (*grey bars*)] and vehicle control [$n = 12$ (*black bars*)] groups prior to *d*-amphetamine administration (*B*), during *d*-amphetamine administration (test days *1–4*), and for up to 3 weeks after *d*-amphetamine administration (test days *5–28*). Data are the body weights (±SEM) measured at 9 a.m. each morning. *Stars* indicate a significant difference ($*P < 0.01$, $**P < 0.001$)

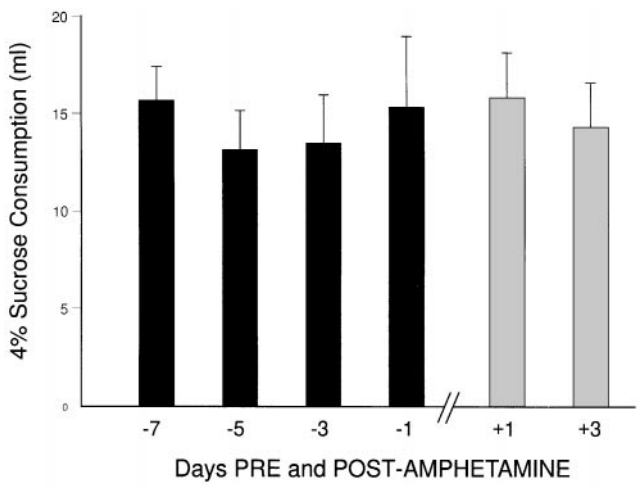

Fig. 3 The effect of *d*-amphetamine on free consumption of a 4% sucrose solution from a lickometer, including the four baseline sessions prior to drug administration. Each session lasted for 1h ($n = 6$). No significant differences were observed

subsequently produce a period of anhedonia which may reflect either a decrease the reinforcing properties of naturally rewarding stimuli or a reduction in motivation to obtain such rewards.

While the induction of a state of anhedonia represents the most likely explanation for the current findings, a number of alternative hypotheses need to be refuted. Firstly, it is unlikely that the reduced motivation shown by rats is due to the anorectic effects of the drug (Caul et al. 1988) causing a decrease in the motivational value of the sucrose, because experiment 2 failed to observe any effect of the same drug regimen on free consumption of a 4% sucrose solution. Secondly, it is also improbable that the reduction in break points of animals in the post-*d*-amphetamine condition represents a motoric deficit; although decreased levels of locomotor activity are commonly seen during psychostimulant withdrawal (Tonge 1974; Schreiber et al. 1976; Hitzemann et al. 1977; Paulson et al. 1991; Pulvirenti and Koob 1993; Schindler et al. 1994; but see Kokkinidis et al. 1986), numerous studies using ICSS protocols have elegantly demonstrated, through the use of rate-independent techniques, that operant responding for reinforcement during psychostimulant withdrawal is dependent on changes in reward value, rather than performance factors (Cassens et al. 1981; Markou and Koob 1992a,b). Furthermore, the increase in inter-lick intervals observed by animals during the first 3 days of drug withdrawal was characterised by short duration intervals interspersed with clear pauses (>3 s) in consumption of the sucrose solution: these results do not resemble the typical pattern of a uniform increase in inter-lick intervals, without pauses, seen in rats which are administered doses of neuroleptics sufficient to generate motor impairments (Fowler and Mortell 1992).

The decrease in break points observed in *d*-amphetamine-treated subjects in withdrawal may represent a reduction in energy allocation and operant response maintenance (anergia), as is observed following decreased function in the mesoaccumbens and mesostriatal dopamine systems (Salamone 1992). This explanation is unlikely for several reasons. Previous studies which have investigated the impact of different variables in PR paradigms have found that break points, in untreated rats, are far more sensitive to alterations in the reinforcing value of the food reward (such as

reward size) than changes in effort requirements (such as the height of the response lever) (Skjoldager et al. 1993). Additionally, a recent study by Sokolowski and Salamone (1998) has demonstrated that dopamine depletions in the nucleus accumbens only induce deficits in operant behaviour on schedules which generate high levels of responding, such as an FR5 schedule, but not in schedules producing moderate levels of responding, including a VI 30 schedule. Subjects in the present study had 1 h to attain each reinforcement, and break points in withdrawn rats were relatively low, suggesting that the current operant schedule placed only a low energy demand on subjects. Evidence from the present study also implies that rats were not anergic, because the *d*-amphetamine-treated rats did not show an increase in the post-reinforcement pause or a decrease in their rate of responding, as measured by latency to attain each successive reinforcement. Therefore these data indicate that the *d*-amphetamine-treated and control subjects responded with equal vigor. Other recent data from our laboratory have also shown that *d*-amphetamine withdrawal impaired certain motivational components of male rat sexual behaviour, whereas these rats displayed high levels of physically demanding copulatory activity for a 25-min period, consistent with an absence of either motoric or anergic deficits (Barr et al. 1998).

The PR procedure has been used previously in our laboratory to show that reductions of the concentration of the sucrose solution, or a decrease in the level of food and water deprivation, both produced corresponding decreases in break points (Barr and Phillips 1998). This procedure therefore provides a reliable technique for assessing changes in motivation to respond for a natural reward, and hence the present data strongly imply that following *d*-amphetamine withdrawal rats experience significant reductions in their motivation to obtain a previously preferred reward. This reduced motivation may correspond to what Berridge and his colleagues (Berridge and Valenstein 1991; Robinson and Berridge 1993; Berridge 1996) refer to as "wanting", as distinct from "liking", which is more closely related to alternative hedonic processes. Indeed, in a recent study (Potts et al. 1997), depressed patients with anhedonic symptoms showed the same ability to discriminate the sensory qualities of sweet solutions as non-depressed control subjects. In the present study, high levels of motivation were not required to maintain the reflexive lick response necessary to consume the freely available sucrose solution, whereas in the PR paradigm the motivation to attain the next reinforcement had to be maintained for up to 1 h. We interpret the lack of effect of drug withdrawal on the free consumption of sucrose as evidence for normal hedonic processes and attribute a motivational deficit to the finding that these rats were unable to maintain the level of responding required to maintain higher ratio reinforcements. Two other behavioural measures recorded during the experiment provide additional support for this hypothesis. The increase in latencies taken by subjects to begin responding once the test sessions had begun, as well as the pauses between bouts of licking, are consistent with a decrease in motivation to obtain the sucrose reward.

Previous experiments have examined the effects of a similar regimen of drug administration on ICSS responding and observed results consistent with those from this study. In an early study, Leith and Barrett (1976) demonstrated that amphetamine withdrawal depressed the facilitation of ICSS responding normally seen by low doses of *d*-amphetamine, and that this effect lasted for approximately 4 days. Similarly, Cassens et al. (1981) observed an increase in the current intensities required to sustain ICSS responding, with a return to baseline within 120 h after the final drug injection. Thus, there appears to be little difference between the effects of amphetamine withdrawal on ICSS responding and operant responding for naturally rewarding stimuli such as a sucrose solution. The present findings therefore provide additional support for the use of ICSS paradigms to investigate changes in the responsiveness of neural reward systems in models of drug withdrawal and depression (Vogel et al. 1990; Zacharko et al. 1991; Moreau et al. 1992; Geyer and Markou 1995; Koob 1995).

In a related study, Markou and Koob (1991) employed a drug self-administration procedure to establish post-cocaine anhedonia measured by a significant increase in ICSS current threshold. Current thresholds were elevated for 5 days post-drug treatment. Pretreatment with the tricyclic antidepressant desmethylimipramine returned ICSS thresholds to pre-drug values 12 h after cessation of cocaine self-administration.

The post-drug depression of ICSS responding associated with *d*-amphetamine withdrawal has also been shown to be responsive to the tricyclic antidepressants imipramine and amitriptyline. Kokkinidis et al. (1980) demonstrated a mitigation of the effects of a 10-day amphetamine regimen by these tricyclics, when ICSS responding at sites in the substantia nigra was measured. It is not known how effective other classes of antidepressant drugs, such as the selective serotonin reuptake inhibitors, or other antidepressant therapies [such as electro-convulsive therapy (White and Barrett 1981) or REM sleep deprivation] might be in animal models of psychostimulant withdrawal-induced anhedonia. It would therefore be of interest to examine the effects of antidepressant treatment on the suppressed 0responding for a sucrose solution, on a PR schedule, following the escalating dose of *d*-amphetamine protocol used in the present experiment.

One problem facing such research is the short duration of the anhedonic effects which are typically observed in animals. With most drug regimens producing observable effects for only a few days, and at most a couple of weeks, this may not allow for the

development of a theoretically viable model with which to examine the effects of many antidepressant treatments, which require a minimum of 2–3 weeks before changes in mood are seen in humans (Post et al. 1987) and certain animal models of depression (Willner et al. 1987).

Much important research has focused on individual differences in susceptibility to drugs of abuse (Piazza and LeMoal 1996; Nestler and Aghajanian 1997); however, to date, little has been done to identify factors which might predispose certain subjects to display more prolonged and severe psychostimulant withdrawal symptoms. Identification of such factors might lead to the development of an animal model of anhedonia in which the observable effects last for notably longer than in current models. Alternatively, repeated bingeing schedules such as those engaged in by human cocaine addicts (Gawin and Kleber 1986, 1988), or dosing with other types of psychostimulants [such as with MDMA, which has produced long-lasting deficits in monkeys on PR performance for natural rewards (Frederick et al. 1995)] may also provide opportunities for the generation of a longer duration animal model of anhedonia.

In conclusion, the present study has provided additional support for animal models of psychostimulant withdrawal-induced anhedonia by observing reductions in motivation for a natural reward by rats, as assessed by performance on a PR schedule of reinforcement. The duration of the effects, including measures of latency and inter-lick intervals, lasted approximately the same duration as previously reported alterations of ICSS responding, and so provide further support for ICSS techniques as a tool for the measurement of reinforcement. Further developments in the use of the PR paradigm as an instrument for assessing anhedonia in psychostimulant withdrawal may be related to its capacity to measure reversals of drug induced anhedonia by antidepressant treatments.

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