Psychopharmacology (1998) 135:416–422

RAPID COMMUNICATION

Adrianna Mendrek · Charles D. Blaha
Anthony G. Phillips

Pre-exposure of rats to amphetamine sensitizes self-administration of this drug under a progressive ratio schedule

Received: 16 July 1997 / Final version: 22 October 1997

Abstract Two groups of male rats were tested to determine whether pre-exposure to *d*-amphetamine would enhance the motivation to self-administer the drug under a progressive ratio schedule of reinforcement. In the first phase of the experiment, one group of rats received *d*-amphetamine (2 mg/kg IP), while a second group received saline on alternate days for a total of ten injections. Following a 21-day drug withdrawal period, behavioral sensitization was confirmed by a significant increase in amphetamine-induced stereotypy in the *d*-amphetamine-pretreated group, relative to the saline-pretreated group. In the second phase of the study, all rats were implanted with chronic jugular catheters and trained to self-administer *d*-amphetamine (0.2 mg/kg per infusion) under a fixed-ratio schedule of reinforcement. The progressive ratio paradigm was then imposed for 7 consecutive days; *d*-amphetamine-pretreated rats attained significantly higher break points than saline-pretreated animals. These data suggest that pre-exposure to *d*-amphetamine may enhance the motivation to self-administer this drug.

Key words Sensitization · *d*-Amphetamine · Drug self-administration · Progressive ratio · Incentive motivation

Introduction

The repeated intermittent exposure to psychomotor stimulants, such as *d*-amphetamine or cocaine, can result in a progressive and enduring enhancement in many stimulant-induced behaviors, a phenomenon known as behavioral sensitization (Robinson and Becker 1986). The development of behavioral sensitization to psychomotor stimulants is thought to arise from increased synaptic transmission in the mesolimbic dopamine system (Robinson and Becker 1986; Kalivas and Stewart 1991), which has cell bodies in the ventral tegmental area (VTA) and axon terminals in the nucleus accumbens septi (NAS) and other limbic structures (Swanson 1982). Activity in the mesolimbic dopamine system has been strongly associated with the rewarding properties of many psychoactive drugs (Wise and Bozarth 1987), and it has been conjectured that repeated administration of psychomotor stimulants may sensitize this neurotransmitter system and thereby enhance the motivation to self-administer these drugs (Robinson and Berridge 1993). This hypothesis was tested in the present study.

A number of recent studies, using either conditioned place preference (CPP) or drug self-administration procedures, suggest that prior exposure to drugs of abuse may sensitize the subject to the rewarding effects of these drugs. Lett (1989) has found that pretreatment of rats with either *d*-amphetamine, morphine, or cocaine enhanced the rewarding effects of these drugs as measured by CPP. Cross-sensitization has been also reported using this paradigm; pre-exposure to *d*-amphetamine increased the rewarding effects of morphine, and pre-exposure to morphine increased the rewarding effects of *d*-amphetamine and cocaine (Lett 1989).

Much of the evidence consistent with sensitization of the rewarding properties of addictive drugs comes from drug self-administration studies. In one of the earliest drug self-administration studies to examine sensitization, a relatively low dose of methamphetamine supported lever pressing in rhesus monkeys after chronic pretreatment with this drug, but not before (Woolverton et al. 1984). Thus, the pre-exposure to methamphetamine lowered the apparent threshold dose for maintaining lever pressing, suggesting an increased sensitivity to the rewarding effects of the drug. Subsequent studies investigating this phenomenon revealed that rats pretreated with either cocaine, *d*-amphetamine, or nicotine acquired cocaine self-administration at drug doses that did not sustain self-administration in drug-naive animals (Horger et al. 1990, 1992). Moreover, it was demonstrated that repeated treatment with either *d*-amphetamine or with tail-

A. Mendrek · C.D. Blaha · A.G. Phillips (✉)
University of British Columbia, Department of Psychology,
2136 West Mall, Vancouver BC, Canada V6T 1Z4

pinch produced increased locomotion as well as greater *d*-amphetamine intake during the acquisition phase of self-administration, as compared to control animals (Piazza et al. 1990).

It has been suggested that sensitization to the rewarding properties of psychomotor stimulants occurs only when relatively low doses of *d*-amphetamine or cocaine are available for self-injection. In comparison, when higher doses of psychomotor stimulants are utilized in self-administration studies, rats with a history of drug pretreatment do not acquire self-administration habit more quickly than saline-pre-exposed animals (Li et al. 1994). Moreover, a chronic regimen with relatively high doses of cocaine increased the rate of cocaine intake in rats trained to self-administer this drug under a fixed ratio (FR) schedule of reinforcement (Emmett-Oglesby and Lane 1992), and decreased break point values in rats trained to self-administer cocaine under a progressive ratio (PR) schedule of reinforcement (Li et al. 1994). Overall, these findings suggest that, in contrast to sensitization, tolerance to the reinforcing effects of psychomotor stimulants may develop as a consequence of stimulant pre-exposure, and that the development of behavioral sensitization is dose-dependent and cannot be generalized across a range of psychomotor stimulant doses (Li et al. 1994).

The present study was carefully designed in an effort to resolve some of the issues discussed above. First, we employed a PR schedule of drug reinforcement, rather than an FR schedule, because of several advantages associated with its use in the study of motivated behavior (for review, see Roberts and Richardson 1992). In a PR schedule of reinforcement, the number of responses required for each successive drug infusion is systematically increased until the subject fails to receive the reinforcer within a set criterion period of time. The last performance ratio value successfully completed is defined as the break point. This value reflects the maximal effort that the subject expends in order to receive a single drug infusion, thus serving as a measure of incentive motivation and drug craving (Markou et al. 1993; Arnold and Roberts 1997). Second, in the present experiment we utilized a drug treatment schedule that has been shown to produce robust behavioral sensitization (Paulson and Robinson 1995). Third, as previous reports of drug-reward sensitization have been criticized for the use of relatively low doses of *d*-amphetamine or cocaine in the IV self-administration paradigm, in the present study we used a relatively high dose of *d*-amphetamine (0.2 mg/kg per infusion).

With these methodological considerations taken into account, the present study tested the hypothesis that repeated intermittent exposure to *d*-amphetamine produces sensitization to the motivation to self-administer this drug, as indicated by an increase in break point under a PR schedule of reinforcement.

Materials and methods

The following experiments were conducted in accordance with the standards of the Canadian Council on Animal Care.

Animals

Twenty-two male Long-Evans rats (Charles River, Quebec, weighing 300–350 g at the beginning of the experiment) were housed individually in stainless steel wire cages prior to surgery and in plastic cages with Sanicel bedding after surgery in a temperature-controlled animal colony, with lights on between 0700 and 1900 hours. They were handled daily for 5 days before the start of the experiment. Food and water were available ad libitum, except during testing. The animals were tested in the light phase of the light-dark cycle.

Behavioral sensitization

Animals were divided into two groups. The experimental group (n=11) received IP injections of *d*-amphetamine sulfate (2.0 mg/kg salt weight), whereas the control group (n=11) received saline vehicle (0.9% w/v). The injections were administered in the colony once every other day for a total of ten injections. Behavioral sensitization has been shown to be more pronounced 21 days following cessation of intermittent treatment with psychomotor stimulants (Paulson and Robinson 1995); therefore a similar period of drug withdrawal was used in the present study. On day 21 of the withdrawal period, animals were transported to the testing room, weighed, and placed in split-level Plexiglas boxes (51×60.5×15 cm) which served as activity testing chambers (Mendelson and Gorzalka 1987). A platform 30.5 cm in length centered and set 28 cm above the floor divided the chamber into two levels. Animals were able to move freely from one level to the other because of a set of ramps with Plexiglas strips to provide footholds, and a narrow landing at each end of the interior of the box. The floor of each level was lined with Sanicel and covered with a metal grid. After 1 h of habituation to the chambers, all rats were administered a single injection of *d*-amphetamine (2.0 mg/kg, IP). Their behavior was videotaped for subsequent detailed analysis performed by the experimenter, unaware of the rats' group designation. Before each session, the activity boxes were cleaned with a dilute Windex solution to minimize the influence of residual odors remaining from preceding groups.

Both locomotor activity and stereotyped behaviors were assessed "blindly" for 2 h following the challenge injection of *d*-amphetamine. To quantify locomotion a score of one was assigned for crossing either the top or bottom floor of the split-level chamber (horizontal activity), for changing levels from the floor to one of the two landings located in between the levels (vertical activity), and one score for rearing. Activity counts were then added and averaged at 10-min intervals. Stereotypy was rated for 1-min periods at 10-min intervals according to the rating scale developed by MacLennan and Maier (1983).

Surgery

Two days after the activity tests, rats were implanted with chronic indwelling IV catheters. Immediately prior to surgery, all instruments were cold sterilized with 0.15% alkylbenzyldimethylammonium chloride (EMI Industries) for about 20 min, followed by 70% ethanol for 5 min. Animals were given garamycin (8 mg IM) and ampicillin (50 mg IM), and then were anesthetized with separate injections of ketamine hydrochloride (100 mg/kg IP; MTC Pharmaceuticals, Cambridge, Ontario) and xylazine (7 mg/kg IP, Rompun, Etobicoke, Ontario). A Silastic catheter was inserted into the right jugular vein and its distal end was guided SC to an exposed portion of the skull and secured in place with dental acrylic to stainless steel screws. Two rats, one from the control and one

from the experimental group, died during the surgery and the data from these animals were not included in the final analysis. Each day following surgery and later, before and after each rat was placed in the IV self-administration chamber, the catheters were flushed with sterile saline solution containing 10 IU/ml heparin.

d-Amphetamine self-administration

Seven days following surgery animals began training under an FR2 schedule of reinforcement with *d*-amphetamine sulfate (0.2 mg/kg per infusion) serving as a drug reinforcer. Self-administration tests were conducted in six Plexiglas chambers (32×32×41 cm) enclosed in sound- and light-attenuating black wooden boxes. Each chamber was equipped with a stainless steel operant lever (7 cm×3 cm) and a white cue light (28 V, 170 mA; Spectra) located directly above the lever. The floor of the chamber was lined with Sanicel and covered with a metal grid. Tygon tubing was attached to the head-mounted connector and extended through the wooden box to an infusion pump (Sage Apparatus, model 341 equipped with 20 ml syringe) mounted on the top of the box. Drug delivery and data collection were controlled by MANX software (Gilbert and Rice 1979). All self-administration sessions were initiated with a "free" priming injection of 0.2 mg/kg per infusion of *d*-amphetamine or with saline (for the extinction session, see below). This dose of the drug was available throughout the session. The house lights remained on during the sessions except after each drug infusion, when the lights flashed for 5 s, followed by a 30-s time-out period during which the lights were turned off and responding on the lever had no programmed consequences. The FR2 sessions lasted either until nine drug infusions were self-administered (a total of ten injections including the priming dose) or until 5 h had elapsed. Only those animals that reached this criterion during 2 days of training advanced to the second phase of the study in which they responded to *d*-amphetamine under a PR schedule of reinforcement. Three subjects, two *d*-amphetamine-pre-exposed (experimental) and one saline-pre-exposed (control), did not attain this criterion.

Daily PR sessions also started with a priming infusion and illumination of the house lights. The progression in the number of responses (ratio) required for each successive injection of *d*-amphetamine was similar to that described by Roberts and Richardson (1992) and subsequently modified by Depoortere et al. (1993) to produce the following sequence: 3, 6, 10, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, etc. A maximum of 60 min was allowed for completion of each ratio. Testing with *d*-amphetamine under this PR schedule continued for 7 days and was followed by 2 days of extinction during which responding under the PR schedule resulted in the infusion of saline.

Drugs

d-Amphetamine sulfate was obtained from Smith-Kline Beecham, Oakville, Ontario. For IP injections, the drug was dissolved as the salt weight in 0.9% sterile physiological saline, and for IV self-administration it was mixed fresh daily in 1 IU/ml heparin solution of sterile physiological saline (0.9% w/v). All antibiotics and anesthetics were purchased as sterile solutions from local distributors.

Data analyses

The locomotion and stereotypy data were analyzed separately using a two-way analysis of variance (ANOVA) with repeated measures; Pretreatment Condition served as a between-group factor, whereas Time was a within-group factor. Spjotvoll and Stoline (1973) multiple comparisons for groups with unequal *n's* were used for post hoc analysis. For the analysis of self-administration under the PR schedule, the number of infusions obtained, rather than the final ratio completed, was used as a dependent variable because the final ratios were derived from an escalating exponential function and thus violated ANOVAs assumption of the homogeneity of variance. The number of reinforcers, on the other hand, was a natural logarithmic function of the ratio value and was therefore amenable to parametric analysis (Roberts and Richardson 1992). Thus, similar to behavioral sensitization, self-administration data were subjected to a two-way ANOVA analysis (Pretreatment Condition×Test Day) and to Spjotvoll and Stoline (1973) post hoc multiple comparisons.

Results

Figure 1 illustrates the effects of the *d*-amphetamine challenge on the stereotyped behaviors in both saline- and *d*-amphetamine-pretreated animals. While the control group displayed relatively low and stable ratings of stereotyped behaviors during 2 h of testing, the experimental group exhibited intense stereotypy, reaching a maximum mean score of 4.89, that lasted throughout the session. There was a statistically significant interaction between Pretreatment Condition and Time [$F(11,165)=4.8$; $P<0.01$], and Spjotvoll and Stoline multiple comparison procedures showed that the two groups differed significantly across time ($P<0.05$), except for the first 5 and last 15 min of the session.

The mean activity counts in response to challenge injections of *d*-amphetamine (2.0 mg/kg IP) are shown in Fig. 2. Locomotion scores increased in saline-pretreated animals but decreased in the *d*-amphetamine-pretreated group. A two-way ANOVA on the locomotor activity scores yielded a significant main effect of the Pretreatment Condition [$F(1,15)=8.1$; $P<0.05$] and a significant interaction between Pretreatment Condition and Time [$F(11,165)=10.9$; $P<0.01$]. Subsequent post hoc compar-

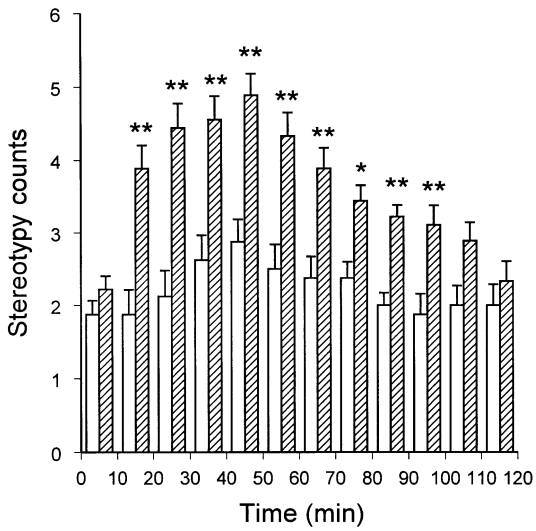

Fig. 1 The effects of *d*-amphetamine challenge injections (2.0 mg/kg IP) on stereotypy in rats that had received ten previous injections of either *d*-amphetamine (n=8; *striped*) or saline (n=9; *open*). The histograms represent the mean (±SEM) stereotypy scores during 1-min sampling periods, at 10-min intervals following *d*-amphetamine administration. The *star*s indicate a significant difference (* $P<0.05$; ** $P<0.01$) between the two groups at a given time interval

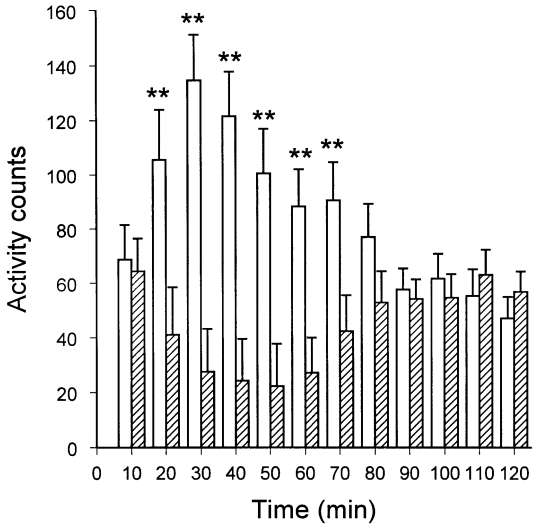

Fig. 2 The effects of *d*-amphetamine challenge injections (2.0 mg/kg IP) on locomotion in rats pretreated with ten injections of either *d*-amphetamine (*n*=8; *striped*) or saline (*n*=9; *open*). The histograms represent the mean (±SEM) locomotor counts during the 2 h following *d*-amphetamine administration. The *stars* indicate a significant difference ($P<0.01$) between the two groups at a given time interval

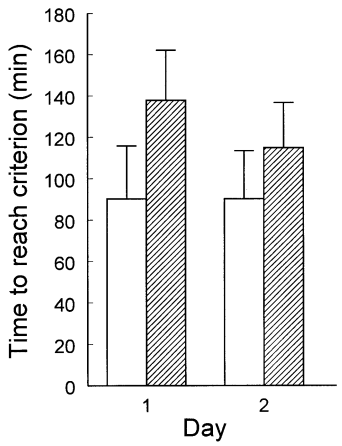

Fig. 3 The mean (±SEM) time per session to reach the self-administration criterion of nine *d*-amphetamine infusions (0.2 mg/kg per infusion) under an FR2 schedule of reinforcement, in rats given prior exposure to *d*-amphetamine (*n*=8; *striped bars*) or saline (*n*=9; *open bars*)

isons revealed that the saline-pretreated rats were significantly more active between 20 and 70 min post-injection ($P<0.01$).

The two groups of rats did not differ in terms of the time to reach a criterion of nine self-infusions of *d*-amphetamine over 2 days of training under a FR2 schedule of reinforcement [$F(1,15)=1.3$, NS; Fig. 3]. However, the analysis of *d*-amphetamine self-administration under the PR schedule revealed a main effect of Pretreatment Condition [$F(1,15)=4.9$; $P<0.05$], a main effect of Test Day [$F(8,120)=17.1$; $P<0.01$], and a significant interaction between these two factors [$F(8,120)=3.6$; $P<0.01$; Fig. 4]. The groups differed significantly on Test Day 2–7. *d*-Amphetamine-pretreated animals exhibited break points (range from 10.89 to 14.22 *d*-amphetamine reinforcers) corresponding to 77–145 bar presses for the last *d*-amphetamine infusion. Saline-pre-exposed rats achieved lower break points (range from 5.87 to 8.13 *d*-amphetamine reinforcers) corresponding to 25–40 bar presses for the last *d*-amphetamine infusion, on days 2–7 ($P<0.05$). The groups did not differ during the two extinction trials (Fig. 4).

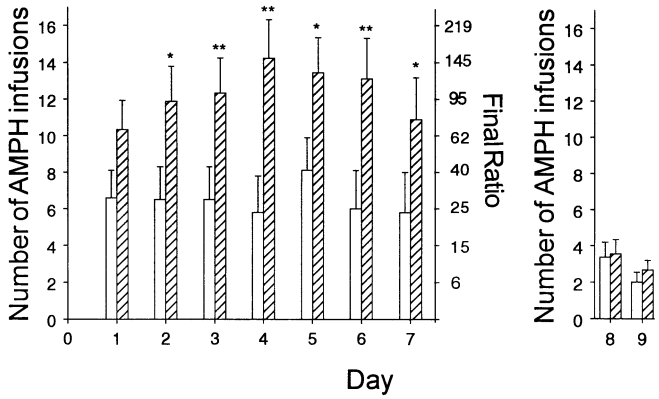

Fig. 4 The mean break point (±SEM) as defined by the number of obtained infusions of *d*-amphetamine (AMPH, 0.2 mg/kg per infusion) on seven daily self-administration test sessions. Responding on 2 days of extinction is also shown. Pre-exposure to *d*-amphetamine (*n*=8; *striped bars*) or to saline (*n*=9; *open bars*). The *stars* indicate a significant difference (* $P<0.05$; ** $P<0.01$) between the two groups at a given time interval

Discussion

Sensitization of motor responses was established in the present study after a 3-week withdrawal period, as evidenced by a significant increase in *d*-amphetamine-induced stereotypy in the *d*-amphetamine-pretreated group of rats, as compared to the saline-pretreated group. It is well established that lower doses of psychomotor stimulants promote prolonged periods of increased locomotion, whereas higher doses elicit stereotyped behaviors (Segal and Kuczenski 1994). Accordingly, augmented stereotypy and decline in locomotor activity, exhibited by the animals pretreated with *d*-amphetamine in the present experiment, parallel the type of changes that occur as a function of increasing doses of *d*-amphetamine, and thus reflect behavioral sensitization.

Subsequent tests confirmed that this *d*-amphetamine-induced behavioral sensitization was accompanied by enhanced lever pressing for intravenous self-administration of the drug. The fact that stereotyped behaviors were augmented in *d*-amphetamine-pretreated animals raises the possibility that increased drug self-administration observed in this group was due to stereotyped, perseverative lever pressing (see, e.g. Miczek and Mutschler, 1996). However, the relatively low bar pressing rate per minute (ranging from 1.2 to 4.3) does not consti-

tute intense focused stereotypy and therefore it is unlikely that the increase in break point values is attributed to perseverative lever pressing. Together, these data support the hypothesis that repeated intermittent treatment with *d*-amphetamine results in sensitization of both motor behaviors and the motivation to seek drug reinforcement.

The most significant finding of the present study is the fact that pre-exposure to *d*-amphetamine resulted in enhanced responding for the drug as indicated by an increase in break points, relative to saline-pretreated animals. Significant increases in break points on a PR schedule of reinforcement have been interpreted as an increase in motivation (Arnold and Roberts 1997). Specifically, an increase in the break point may reflect sensitization of the rewarding properties of *d*-amphetamine, which in turn may increase the motivation to obtain subsequent infusions of the drug. Previous studies have shown that repeated intermittent treatments with psychomotor stimulants produce higher rates of responding during the acquisition phase of drug self-administration under an FR schedule of reinforcement (e.g., Horger et al. 1990; Piazza et al. 1990). Data obtained here during the FR2 training trials, in which subjects were limited to nine drug infusions, did not reveal significant effects of sensitization. This may have been a consequence of the brief test session or relatively high dose of *d*-amphetamine available for self-administration. Interestingly, even though enhanced motivation was evident during self-administration of *d*-amphetamine under a PR schedule of reinforcement, there was no difference between the two groups of rats during two extinction sessions when saline was available for self-administration. This pattern of results suggests that drug-seeking in the absence of incentive stimuli predictive of drug reward is not facilitated by sensitization. This is consistent with previous findings of Stewart and colleagues (e.g., Stewart and Vezina 1988; Stewart and Wise 1992), which showed that reinstatement of drug taking is primed by involuntary administration of drugs that increase mesolimbic dopamine levels, implying that stimulation of this system reinitiates drug-seeking. In the light of these findings, it would be interesting in future studies to examine *d*-amphetamine self-administration in behaviorally sensitized rats that would be primed with the drug and then given access to saline.

The present results complement some earlier findings (e.g., Horger et al. 1990; Piazza et al. 1990), but they differ significantly from a recent report showing tolerance to the reinforcing effects of cocaine under a PR schedule of reinforcement (Li et al. 1994). Specifically, chronic treatment with cocaine (18 mg/kg, given once every 8 h for 7 days) produced a subsequent decrement in break point values under a PR schedule of reinforcement. This effect abated following a 5-day withdrawal from cocaine self-administration. On the basis of these results, Li and colleagues argued that the rewarding properties of cocaine undergo tolerance rather than sensitization following pre-exposure. It should be emphasized at this point that the dosing regimen plays a critical role in the development of sensitization. For example, repeated single daily injections of cocaine have been shown to induce sensitization of behavioral responses accompanied by a functional subsensitivity of DA autoreceptors, whereas continuous infusion of the drug results in tolerance, accompanied by autoreceptor supersensitivity (Jones et al. 1996). Moreover, animals pretreated with escalating doses of *d*-amphetamine exhibit drug sensitization in the form of enhanced behavioral responses and *d*-amphetamine-stimulated dopamine efflux in the NAS and dorsolateral striatum after 21, but not 3 or 7, days of drug withdrawal (Paulson and Robinson 1995). Therefore, it is conceivable that tolerance to the reinforcing effects of cocaine predominates over sensitization with a regimen of high drug doses administered closely together in time, and in the absence of an extended withdrawal period (Li et al. 1994).

Recent theories of drug reward have conjectured that it may consist of two separate components: subjective pleasure (hedonic effects) and incentive salience (craving) (Robinson and Berridge 1993). New evidence suggests that a PR schedule of reinforcement measures incentive salience, while an FR schedule is more sensitive to the hedonic, pleasure-inducing properties of addictive drugs. In a recent experiment, intracerebral injections of the dopamine D_1 receptor antagonist SCH 23390, either into the amygdala or the striatum, produced an increase in the rate of cocaine self-administration under an FR schedule of reinforcement but had no effect on break point values under a PR paradigm (McGregor and Roberts 1993). In contrast, injections of SCH 23390 into the NAS and medial prefrontal cortex produced an enhancement in the rate of responding for cocaine infusions and a decrement in break point values (McGregor and Roberts 1995). Thus, it was concluded that the two schedules of reinforcement measure different aspects of psychomotor stimulant self-administration. The rate of drug intake, as measured by an FR paradigm, is particularly sensitive to factors that interfere with the interoceptive stimulus qualities of a given drug, and hence may reflect the subjective experience of that drug. In contrast, the break point values measured by a PR procedure, may reflect the incentive value of the anticipated drug infusion, and thus measure drug craving or incentive salience (McGregor and Roberts 1995). In light of these studies, the present data suggest that pre-exposure to psychomotor stimulants, such as *d*-amphetamine, may increase drug craving without necessarily affecting the subjective euphoric properties of the drug.

Although we favor the interpretation that the enhancement of the rewarding properties of *d*-amphetamine is the most likely explanation of the results obtained under a PR schedule of reinforcement, we cannot rule out alternative explanations of the present data. Recently, Miczek and Mutschler (1996) showed that the exposure to social stress in rats resulted in increased response rates for IV cocaine self-administration under an FR schedule of reinforcement. This increase seemed to be induced by stereotyped response perseveration rather than sensitization

to the rewarding effects of cocaine (Miczek and Mutschler 1996). It is conceivable that in the present study, *d*-amphetamine-pretreated rats, which exhibited significantly greater stereotypy during tests for behavioral sensitization than saline-pretreated animals, attained higher break points under the PR schedule of reinforcement because of similar stereotyped perseverative lever pressing.

The mesolimbic dopamine system has been implicated in the development of both behavioral sensitization and the efficacy of drug reward (Robinson and Berridge 1993). Accordingly, enhanced mesolimbic dopamine transmission could be responsible for both the development of sensitization of motor behaviors and increased motivation to self-administer addictive drugs. It must be noted, however, that the locomotor activating effects of psychomotor stimulants and their reinforcing properties might be mediated by separate, independent neuronal systems. Thus, the locomotor activating effect of cocaine was enhanced following *d*-amphetamine, but not nicotine, pretreatment (Schenk et al. 1991), whereas in other studies both *d*-amphetamine- and nicotine-pretreated rats showed elevated rates of cocaine self-administration during the acquisition phase (Horger et al. 1992). Moreover, *d*-amphetamine pre-exposure induced behavioral sensitization as measured by increased motor activity, whereas the rewarding efficacy of *d*-amphetamine as measured by an intracranial self-stimulation paradigm was unaffected (Wise and Munn 1993).

Overall, the present study supports the hypothesis that repeated intermittent exposure to drugs of abuse may induce sensitization to the rewarding properties of these drugs (Robinson and Berridge 1993). When coupled with the fact that cross-sensitization may occur between drugs of the same class (e.g., *d*-amphetamine and cocaine), and between drugs of different classes (e.g., stimulants and opioids; Kalivas and Stewart 1991), as well as environmental stressors (Antelman et al. 1980), these findings emphasize that sensitization and associated changes in central neural systems may play a critical role in the development of human addictive behaviors.

Acknowledgements This work was supported by a Group Grant (PG-12808) from the Medical Research Council of Canada. The assistance of P. Di Ciano and F. G. LePiane is gratefully acknowledged.

References

Antelman SM, Eichler AJ, Black CA, Kocan D (1980) Interchangeability of stress and amphetamine in sensitization. Science 207: 329–331

Arnold JM, Roberts DCS (1997) A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement. Pharmacol Biochem Behav 57: 441–448

Depoortere RY, Li DH, Lane JD, Emmett-Oglesby MW (1993) Parameters of self- administration of cocaine in rats under a progressive-ratio schedule. Pharmacol Biochem Behav 45: 539–548

Emmett-Oglesby MW, Lane JD (1992) Tolerance to the reinforcing effects of cocaine. Behav Pharmacol 3: 193–200

Gilbert SG, Rice DC (1979) NOVA SKED II: a behavioral notation language utilizing the Data General Corporation real-time operating system. Behav Res Meth Instr 11: 71–73

Horger BA, Shelton K, Schenk S (1990) Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol Biochem Behav 37: 707–711

Horger BA, Giles MK, Schenk S (1992) Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology 107: 271–276

Jones SR, Lee TH, Wightman RM, Ellinwood EH (1996) Effects of intermittent and continuous cocaine administration on dopamine release and uptake regulation in the striatum: in vitro voltammetric assessment. Psychopharmacology 126: 331–338

Kalivas PW, Stewart J (1991) Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev 16: 223–244

Lett BT (1989) Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine and cocaine. Psychopharmacology 98: 357–362

Li D-H, Depoortere RY, Emmett-Oglesby MW (1994) Tolerance to the reinforcing effects of cocaine in a progressive ratio paradigm. Psychopharmacology 116: 326–332

Markou A, Weiss F, Gold LH, Caine B, Schulteis G, Koob GF (1993) Animal models of drug craving. Psychopharmacology 112: 163–182

MacLennan AJ, Maier SF (1983) Coping and stress-induced potentiation of stimulant stereotypy in the rat. Science 219: 1091–1093

McGregor A, Roberts DCS (1993) Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement. Brain Res 624: 245–252

McGregor A, Roberts DCS (1995) Effects of medial prefrontal cortex injections of SCH 23390 on intravenous cocaine self-administration under both a fixed and progressive ratio schedule of reinforcement. Behav Brain Res 67: 75–80

Mendelson SD, Gorzalka BB (1987) An improved chamber for the observation and analysis of the sexual behavior of the female rat. Physiol Behav 39: 67–71

Miczek KA, Mutschler NH (1996) Activational effects of social stress on IV cocaine self-administration in rats. Psychopharmacology 128: 256–264

Paulson PE, Robinson TE (1995) Amphetamine-induced time-dependent sensitization of dopamine neurotransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. Synapse 19: 56–65

Piazza PV, Deminiere JM, Le Moal M, Simon H (1990) Stress and pharmacologically induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res 514: 22–26

Roberts DCS, Richardson NR (1992) Self-administration of psychomotor stimulants using progressive ratio schedule of reinforcement. In: Boulton A, Becker G, Wu PH (eds) Animal models of drug addiction. Humana Press, Clifton, N.J, pp 233–269

Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res Rev 396: 157–198

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive sensitization theory of addiction. Brain Res Rev 18: 247–291

Schenk S, Snow S, Horger BA (1991) Pre-exposure to amphetamine but not nicotine sensitizes rats to the motor activating effects of cocaine. Psychopharmacology 103: 62–66

Segal DS, Kuczenski R (1994) Behavioral pharmacology of amphetamine. In: Cho AK, Segal DS (eds) Amphetamine and its analogs. Academic Press, San Diego, pp 115–150

Spjotvoll E, Stoline MR (1973) An extension of the T-method of multiple comparisons to include the cases with unequal sample sizes. J Am Statist Assoc 68: 975–978

Stewart J, Vezina P (1988) A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. Brain Res 457: 287–294

Stewart J, Wise RA (1992) Reinstatement of heroin self-administration habits: morphine prompts and naltrexone discourages renewed responding after extinction. Psychopharmacology 108: 79–84

Swanson LW (1982) The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull 9: 321–353

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94: 469–492

Wise RA, Munn E (1993) Effects of repeated amphetamine injections on lateral hypothalamic brain stimulation reward and subsequent locomotion. Behav Brain Res 55: 195–201

Woolverton WL, Cervo L, Johanson CE (1984) Effects of repeated methamphetamine administration on methamphetamine self-administration in rhesus monkeys. Pharmacol Biochem Behav 16: 293–302