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Pre-Exposure to (±)3,4-methylenedioxy-methamphetamine (MDMA) Facilitates Acquisition of Intravenous Cocaine Self-Administration in Rats

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Pre-exposure to (±)3,4-methylenedioxymeth-amphetamine (MDMA) elevates locomotor activity and extracellular dopamine levels in the nucleus accumbens following a cocaine challenge. The present study determined whether MDMA-induced sensitization to the effects of cocaine could be demonstrated in rats self-administering cocaine. Three groups of rats were treated with saline (Sal), 5 mg/kg MDMA (once per day for 10 days; MDMA-5) or 20 mg/kg MDMA (twice per day for 4 days; MDMA-20). Subsequently, spontaneous acquisition of cocaine self-administration was measured in 12 daily 2-h sessions. During these test sessions, two response levers were present. Responses on one lever delivered infusions of 0.1 mg of cocaine; responses on the other lever had no programmed consequences. Group Sal showed a weak preference for the active lever; whereas, group MDMA-20 exhibited a stronger active lever preference. By day 12, the MDMA-20 group earned approximately twice the number of cocaine infusions as those in group SAL. At this time point, more than twice as many rats in group MDMA-20 were taking a minimum of 10 infusions per session, as compared to group Sal. Rats in group MDMA-5 did not seem to differ from group Sal in terms of lever discrimination, number of cocaine infusions, and percentage of rats obtaining a criterion of 10 infusions. These results indicate that pre-exposure to a high dose of MDMA may facilitate acquisition of cocaine self-administration. This dosing regimen of MDMA is likely to release DA and to be neurotoxic to 5-HT neurons. Either or both of these mechanisms could contribute to the ability of MDMA to facilitate cocaine self-administration.
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KEY WORDS: *MDMA; Cocaine; Sensitization; Drug abuse; Reinforcement; Rat*

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A large body of evidence indicates that the reinforcing effect of cocaine is dependent in part upon increased dopamine (DA) transmission, particularly within the mesolimbic DA pathway terminating in the nucleus accumbens. Neurochemical studies have shown that at self-administered doses, cocaine increases extracellular DA levels in the nucleus accumbens (Pettit and Justice 1991; Di Ciano et al. 1995). Lesion studies have demonstrated that depletion of DA within the nucleus accumbens abolishes self-administration of cocaine (Roberts et al. 1977, 1980; Pettit et al 1984). Similarly, pharmacologic studies indicate that injection of DA receptor antagonists in the nucleus accumbens increases intrave-

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nous self-administration of cocaine (Maldonado et al. 1993; Caine et al. 1995).

The response of the mesolimbic dopamine system to cocaine, or such other psychomotor stimulants as amphetamine, can be influenced by previous drug exposure. Repeated intermittent injections of either cocaine or amphetamine result in an augmentation of the behavioral effects of a subsequent challenge dose of cocaine or amphetamine. The development of such sensitization is accompanied by a variety of adaptations in the functioning of mesolimbic neurons, including an increase in the ability of psychomotor stimulants to elevate extracellular levels of dopamine in the nucleus accumbens (reviewed in Kalivas and Stewart 1991; Kalivas et al 1993; Pierce and Kalivas 1997). Although the behavioral manifestation of sensitization has been most thoroughly studied in the context of locomotor activity, a number of studies indicate that the acquisition of cocaine or amphetamine self-administration can be enhanced by previous experience with these drugs (Horger et al. 1990, 1992; Valadez and Schenk 1994; Pierre and Vezina 1997; Lorrain et al. 2000). The results of these studies suggest that the reinforcing effects of cocaine and amphetamine are increased in animals previously exposured to these drugs.

The amphetamine derivative (±)3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") shares some stimulant properties with both amphetamine and cocaine (Gold et al. 1989; Geyer and Callaway 1994; Green et al. 1995; White et al. 1996). One of these similarities is that rats treated with MDMA may subsequently show augmented responses to psychomotor stimulants. Repeated treatment with MDMA (20 mg/kg, twice a day for 4 days) augments the locomotor stimulant properties of amphetamine (Callaway and Geyer 1992) and of cocaine (Kalivas et al. 1998). Using the same treatment regimen, extracellular levels of dopamine in the nucleus accumbens were elevated in MDMA-treated rats following a cocaine challenge (Morgan et al. 1997), an effect similar to that observed in rats receiving a sensitizing regimen of cocaine itself (Pettit et al. 1990). These results provide strong evidence that MDMA apparently sensitizes rats in such a way that behavioral and neurochemical responses to cocaine are augmented. More recently, MDMA preexposure has been shown to increase the ability of cocaine to function as an uncon-ditioned stimulus in a conditioned place preference procedure (Horan et al. 2000). This result provides direct evidence of an increase in the rewarding properties of cocaine in rats pre-exposed to MDMA.

Both MDMA and cocaine are abused in humans, and MDMA augments the behavioral and neurochemical effects of cocaine. One implication of the latter findings in rats is that previous experience with MDMA could lead to an increased vulnerability to cocaine abuse. The purpose of the present experiment was to test this hypothesis using an animal model of drug-taking behavior. Specifically, we investigated the effects of repeated injections of MDMA on the acquisition of cocaine self-administration. This procedure involves allowing animals the opportunity to self-administer a low dose of cocaine that by itself promotes only weak self-administration in control animals. If MDMA pre-exposure sensitizes rats to the reinforcing effects of cocaine, we predicted that MDMA-treated rats would show a facilitated acquisition of self-administration.

METHODS

Animals

Adult male Sprague–Dawley rats, weighing 275 to 325 g at the start of the experiment were used. They were housed individually in hanging plastic cages with free access to food and water. The housing room was maintained at a constant temperature of 20 ± 2°C, on a 12:12 h reverse light–dark cycle; lights off at 8 AM. Experimental procedures and manipulations conformed to the guidelines laid down by the Canadian Council on Animal Care and were approved by the Animal Care Committee at the Centre for Addiction and Mental Health.

Drug Injections

Rats were divided into three groups matched for body weight. One group (MDMA-5) received 10 daily injections of 5 mg/kg MDMA ((±) 3,4-methylenedioxymethamphetamine HCl; NIDA Drug Supply Program); a second group (MDMA-20) received twice daily injections of 20 mg/kg MDMA for 4 days. Animals in the final group (Sal) received either 10 daily injections of saline (n = 9), or twice daily injections of saline for 4 days (n = 7). These saline-treated animals were subsequently combined into one group. MDMA was dissolved in 0.9% saline and injected subcutaneously.

Surgery

Approximately 1 week following the MDMA or saline injection regimen surgery was performed to implant a chronic indwelling intravenous catheter. The rats were anesthetized with sodium pentobarbital (Somnotol, 45–50 mg/kg IP). Catheters were constructed from two lengths of silastic tubing, differing in outer diameter, connected by a small piece of heat-shrunk tubing. The smaller diameter silastic tubing (0.025 o.d.) was inserted into the right jugular vein. The larger diameter tubing (0.046 o.d.) was connected to a length of 22-gauge stainless steel tubing cemented inside a nylon bolt. This terminal end of the catheter exited between

the scapulae and was anchored there by means of sutures and a small piece of Marlex mesh. Following surgery, animals were injected with 1 ml/kg Penlong. Catheters were flushed daily with 0.05 to 0.1 ml of a 0.9% saline solution containing 5 IU/ml heparin and 800 IU streptokinase to maintain patency.

Apparatus

Testing was conducted in 22 operant chambers measuring 28-cm long, 21-cm wide, and 21-cm high (Med. Associates Inc., St Albans, VT, USA). Each chamber contained two response levers 4.5-cm wide and 7 cm above the floor of the chamber and a stimulus light located 6 cm above each lever. A counterbalanced arm held a fluid swivel above the ceiling of the chamber. The swivel was attached at one end by Tygon tubing to a syringe mounted on a motor-driven syringe pump (Razel) located outside the chamber. At the other end of the swivel a length of Tygon tubing, encased in a stainless steel tether, connected the animal's catheter to the syringe via the swivel. Each chamber was illuminated by a house light and housed in a sound-attenuating box equipped with a ventilating fan. The apparatus was controlled, and the data were collected, by a 386-SX IBM-type computer.

Procedure

Six days after surgery, rats were tested for spontaneous acquisition of self-administration of a low dose of cocaine (0.1 mg in 0.1 ml saline per infusion) delivered over 5.5 s. This dose was chosen, because it falls below those that have been reported to maintain self-administration reliably (Horger et al. 1990). Each self-administration session began with a single priming infusion of cocaine. Subsequently, responses on the left lever delivered an infusion of cocaine according to a fixed ratio (FR-1) schedule. Infusions were accompanied by illumination of the left stimulus light. This light remained on for 20 s after the infusion; during this time, responses were recorded but had no programmed consequences. Responses on the right lever were also recorded but had no programmed consequences. Sessions were 2 h in duration and were conducted on 12 consecutive days. Following the last day of testing, all rats were administered a short-acting anesthetic agent, methohexital (0.1 ml of a 10% solution), to test for patency of the jugular catheters. Rats failing to lose muscle tone within 5 s were eliminated from the study. The final number of rats contributing data were 16, 14, and 19 for the Sal, MDMA-5, and MDMA-20 groups, respectively.

In each session, the numbers of active and inactive lever responses, as well as the number of earned infusions were recorded. In addition, a further criterion was used to determine the percentage of animals deemed to have exhibited self-administration during the course of the experiment. To meet this criterion, a rat had to earn a minimum of 10 cocaine infusions on each of 3 consecutive days. In practice, rats reaching this criterion earned considerably more than 10 infusions, and rats not reaching this criterion generally took fewer than 5 infusions. Given the temporal aspect of this criterion, the percentage of rats in each group reaching criterion could only be calculated from day 3 onward.

Neurochemical Analyses

Several days after the completion of the experiment, rats were sacrificed by decapitation and the brains removed. The time interval between completion of the experiment and sacrifice was either 7 or 10 days, with approximately half of each group being sacrificed on each of these days. The hippocampus, striatum, and nucleus accumbens were dissected on ice and then stored at −80°C until analysis. The levels of 5-HT, DA, noradrenaline, and their metabolites in these brain regions were measured using high-performance chromatography (HPLC) with electrochemical detection, following extraction in 0.1N perchloric acid containing 2μM sodium bisulphite as an antioxidant. The analytical system consisted of a Waters 600 Mutlisolvent Pump, an Hichrom 250 × 4.6 mm column with ODS2 5μm packing material, an ESA Coulochem 5100A detector with a 5020 Guard Cell and a 5011 Analytical Cell, a TSP AS3000 refrigerated autosampler, and a Spectra Physics SP4290 Integrator. The mobile phase comprised 0.822M acetic acid, 0.094M sodium acetate, 6% methanol, 0.8mM octane sulphonate, and 0.124 mM EDTA in purified distilled water filtered through a 0.22μm nylon filter.

Statistics

Data for lever responses were analyzed by three-way analysis of variance (ANOVA) using Group (Sal, MDMA-5, and MDMA-20) as a between-subjects factor and Lever (active versus inactive) and Days as within-subjects factors. The number of cocaine infusions was analyzed using a two-way ANOVA with Group and Days as factors. Post-hoc tests were made using Tukey's test for pairwise comparisons. Tests for significant differences between two proportions were used to compare the percentage of animals reaching criterion in the Sal and MDMA-20 groups (Bruning and Kintz 1997). Neurochemical data were analyzed using separate one-way analyses of variance for each monoamine (or metabolite) in each brain region, with treatment as the factor. Following a significant F-ratio, post-hoc comparisons were made using Dunnett's test for comparisons against a control mean.

RESULTS

Figure 1 illustrates the effects of pre-exposure to saline and MDMA on the number of responses on the active and inactive levers over the 12 days of testing. The three-way ANOVA revealed that responding was generally higher on the active versus the inactive lever [$F(1,46) = 27.34$, $p < .0001$] and increased over days [$F(11,506) = 7.47$, $p < .0001$]. The over-all three-way interaction was significant [$F(22,506) = 2.14$, $p < .002$]. This interaction reflects the observation that the difference in responding on the active versus inactive levers differed across groups and across days. Post-hoc testing showed that in the MDMA-20 group, active lever responses were significantly greater than inactive lever responses on days 7 to 12, but for the saline group, this difference only reached statistical significance on days 7, 8, and 9. In the MDMA-5 group, active lever responses were greater than inactive responses on days 11 and 12. Further post-hoc testing indicated an important difference between the saline and MDMA-20 groups in terms of active lever responses. Thus, on days 10, 11, and 12, MDMA-20 rats responded to a higher level on the active lever than did rats in the saline pre-exposed group. The total number of inactive lever presses did not differ between any of the groups.

Figure 2 shows the number of cocaine infusions earned by each of the groups of rats. The number of in-

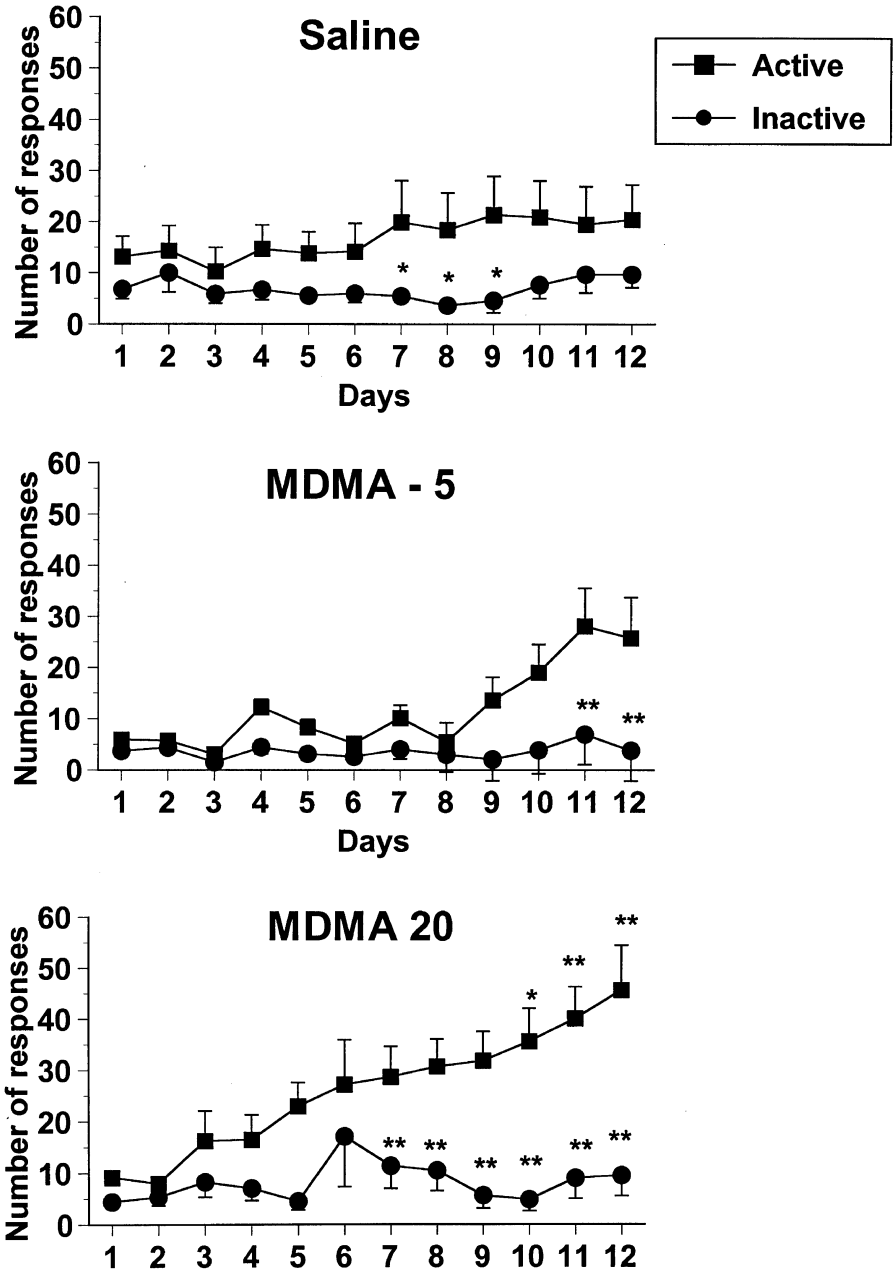

Figure 1. The mean (± SEM) number of responses on the active and inactive levers for rats pre-exposed to saline ($n = 16$), 5 mg/kg MDMA ($n = 14$) and 20 mg/kg MDMA ($n = 19$). Asterisks located between the symbols for the active and inactive levers denote a significant difference between responses on those levers within the pre-exposure condition (* $p < .05$, ** $p < .01$). Asterisks located above the symbols for active lever responses denote a significant difference as compared to responses in saline pre-exposed animals (** $p < .01$).

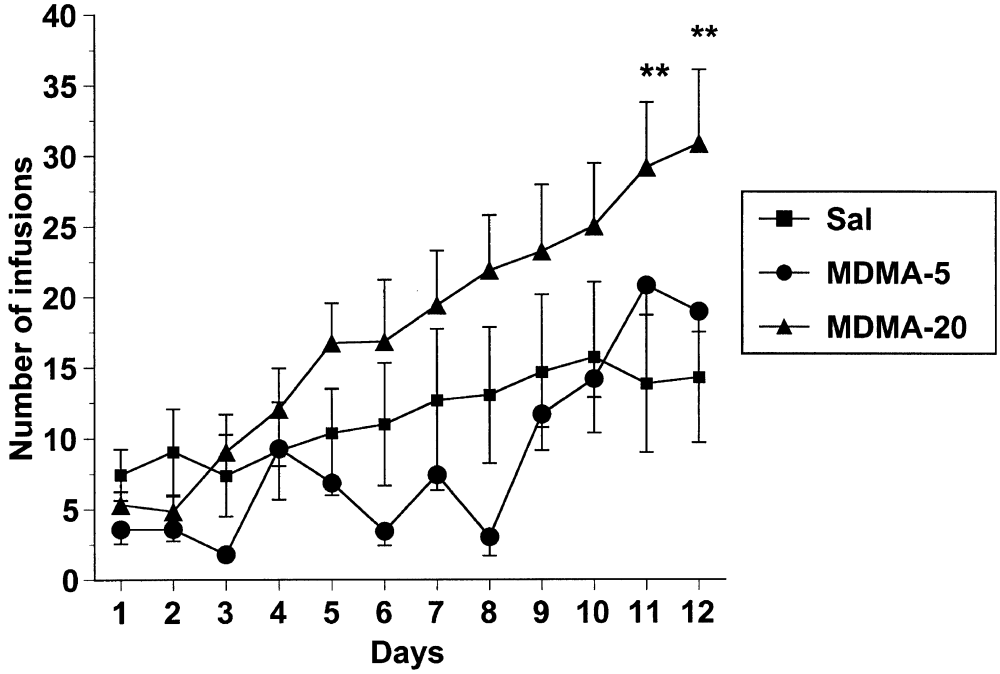

Figure 2. The mean (± SEM) number of infusions earned by rats in the saline, MDMA-5, and MDMA-20 groups on each of the 12 test days. ** $p < .01$ as compared to group Sal.

fusions increased over Days [F(11,506) = 19.47, $p < .0001$]. Although the main effect of Group was not significant [F(2,46) = 2.00 $p > .1$], a highly significant interaction between Group and Days [F(22,506) = 2.58, $p < .001$] was detected. Tukey's tests confirmed that this was attributable to a significant increase in the number of cocaine infusions earned by the MDMA-20 group on days 11 and 12, as compared to the saline group.

Tests for significance of a difference between the proportions of animals reaching criterion in the Sal and MDMA-20 groups indicated that a significantly higher proportion of rats in the MDMA-20 group reached criterion (greater than 10 infusions on 3 successive test days) on days 9 to 12 ($z > 1.96$, one-tailed test). For the MDMA-20 group, out of 19 rats, 11, 12, 12, and 15 rats reached this criterion on days 9 to 12, respectively; for rats in group Sal, out of 16 rats, 4 rats reached criterion on day 9, and 5 rats reached criterion on days 10 to 12. Thus, on day 12, 79% of group MDMA-20 rats reached criterion versus 31% of group Sal rats. Rats in group MDMA-5 did not differ from group Sal, with 6 of 14 rats (43%) reaching criterion on days 10 to 12.

Table 1 shows the effects of repeated treatment with MDMA on brain levels of 5-HT, 5-HIAA, DA, and NE in hippocampus, striatum, and nucleus accumbens. Rats in the MDMA-20 group showed significant depletions in content of 5-HT and 5-HIAA in all three brain regions. The levels of 5-HT were reduced by 44, 18, and 44% in hippocampus, nucleus accumbens, and striatum, respectively. Rats in group MDMA-5 did not show hippocampal depletions of 5-HT or 5-HIAA. However, these animals did exhibit small but statistically significant reductions in nucleus accumbens and striatum. Thus, levels of 5-HT were reduced by 14 and 15% in nucleus accumbens and striatum, respectively. No consistent

Table 1. Levels of 5-HT, 5-HIAA, DA, and NE in Selected Brain Regions of Rats Pre-Exposed to Saline (Sal), 5 mg/kg MDMA (MDMA-5) and 20 mg/kg MDMA (MDMA-20)

Region	Treatment	5-HT	5-HIAA	DA	NE
Hippocampus	Sal	0.3667 (0.06)	0.4012 (0.08)	na	0.4753 (0.06)
	MDMA-5	0.3785 (0.01)	0.5176 (0.06)	na	0.4517 (0.01)
	MDMA-20	0.2045** (0.01)	0.2174** (0.02)	na	0.4816 (0.02)
Nucleus accumbens	Sal	0.9432 (0.04)	0.5411 (0.02)	10.5602 (0.56)	0.6860 (0.07)
	MDMA-5	0.8099* (0.06)	0.3903** (0.02)	11.1796 (0.45)	0.4549 (0.05)
	MDMA-20	0.7245** (0.04)	0.3258** (0.01)	10.5456 (0.29)	0.6238 (0.045)
Striatum	Sal	0.7567 (0.04)	0.4493 (0.01)	11.3287 (0.35)	na
	MDMA-5	0.6393* (0.04)	0.3907* (0.01)	11.0088 (0.37)	na
	MDMA-20	0.4186** (0.04)	0.2668** (0.01)	11.0440 (0.41)	na

Values represent mean (± SEM) tissue levels expressed as ng/mg tissue.
*$p < .05$ compared to Sal.
**$p < .01$ compared to Sal.
na = not measured.

effects of MDMA on DA or NE content were observed. Correlational analyses showed that there were no significant relationships between 5-HT or 5-HIAA levels and either the number of active lever responses or the number of cocaine infusions on day 12 of testing (data not shown). This occurred regardless of whether the correlational analyses were conducted within each treatment group or on data collapsed across treatment groups.

DISCUSSION

The main finding of the present experiment is that rats pre-exposed to 20 mg/kg MDMA, twice a day for 4 days, showed evidence of enhanced acquisition of cocaine self-administration. As a group, rats pre-exposed to saline demonstrated only weak cocaine self-administration. These animals showed only a small discrimination between the cocaine lever and an inactive lever that was not consistent, in that it was only statistically significant on days 7 to 9 of testing. The apparent discrimination between levers exhibited by this group was driven by a minority of animals, with only approximately 30% of the animals showing consistent self-administration by the end of testing. In contrast, rats in group MDMA-20 showed a more consistent and marked preference for the cocaine lever. This active lever preference emerged at day 7 and was sustained over the remainder of the experiment. By the final day of testing, approximately 80% of the rats in this group showed evidence of reliable cocaine self-administration. Two further aspects of the results indicate a difference between the MDMA-20 and saline groups. First, responding on the cocaine lever by the MDMA-20 group was significantly higher than responding by the Sal group on days 10 to 12. Second, as would be expected from this latter effect, the number of cocaine infusions earned by the MDMA-20 group was significantly higher than the number earned by group Sal.

In contrast to the effect of 20 mg/kg MDMA, rats treated with 5 mg/kg MDMA did not show evidence of increased acquisition of cocaine self-administration. This extends the findings of Kalivas et al. (1998) who found that four daily injections of 5 mg/kg MDMA did not augment the locomotor stimulant effect of cocaine. On days 11 and 12, group MDMA-5 showed a significant active lever preference. However, this group was not significantly different from group Sal with respect to the number of active lever responses, the number of cocaine infusions earned, or the percentage of rats exhibiting self-administration. Comparing the effects of the two different treatment regimens of MDMA, it seems that the ability of MDMA to facilitate acquisition of cocaine self-administration is dose-dependent.

Responding for infusions of cocaine follows an inverted U-shaped dose-response function. The dose of 0.1 mg per infusion used in these experiments falls near a threshold value for self-administration, on the ascending limb of this curve (e.g., Horger et al. 1990). Therefore, the increase in responding for cocaine observed in the MDMA-20 group can be seen as congruent with an increase in the unit infusion dose of cocaine. Previous work has shown that previous repeated treatment with 20 mg/kg MDMA augments the locomotor stimulant effects of amphetamine (Callaway and Geyer 1992) and cocaine (Kalivas et al. 1998) as well as the ability of cocaine to support a conditioned place preference (Horan et al. 2000). Increased extracellular levels of dopamine in the nucleus accumbens, induced by cocaine, were also significantly increased in MDMA pre-exposed rats, as compared to saline pre-exposed rats (Morgan et al. 1997). This apparent sensitizing effect of MDMA on extracellular DA levels following a psychomotor stimulant challenge provides evidence of a neurochemical correlate for the enhanced acquisition of cocaine self-administration. Given the importance of dopamine in the nucleus accumbens in mediating the reinforcing effects of cocaine, all of these results provide a convergent body of evidence that pre-exposure to MDMA renders these animals more sensitive to the reinforcing effects of cocaine.

Two possible mechanisms related to the known effects of MDMA on 5-HT and dopamine function can be postulated to underlie the effect of MDMA to enhance acquisition of cocaine self-administration. MDMA stimulates release of both monoamines (Green et al. 1995; White et al. 1996) and is also neurotoxic to 5-HT neurons in rats and nonhuman primates (Commins et al. 1987; Insel et al. 1989; Ricaurte et al. 1988, 1992; Sabol et al. 1996; O'Shea et al. 1998). In the present experiment, group MDMA-20 exhibited substantial depletions of 5-HT and 5-HIAA, raising the possibility that 5-HT depletion contributes to the enhanced self-administration of cocaine observed in group MDMA-20. Additional support for this hypothesis derives from the observations that 5-HT depletion, induced by 5,7-dihydroxytryptamine, increases responding for cocaine maintained on a progressive ratio schedule of reinforcement (Loh and Roberts 1990), and enhances the acute locomotor response to a cocaine challenge (Morrow and Roth 1996). However, several other observations indicate that the effects of 5-HT depletion on cocaine-induced behaviors are not so clear cut. Thus, 5-HT depleting lesions that increase cocaine self-administration also increase responding for food (Roberts et al. 1994), suggesting a more generalized impact of 5-HT depletion on operant behavior. We have also shown that 5,7-DHT lesions fail to alter acquisition of amphetamine self-administration using a procedure similar to that employed in the present experiment (Fletcher et al. 1999). With regard to locomotor activity, one study has found that 5,7-DHT lesions transiently reduces the stimulant effect of cocaine (Sahni et al. 1993), a finding consistent with the observation that the tryptophan hydroxylase in-

hibitor PCPA diminishes the ability of cocaine to stimulate locomotion (Svingos and Hitzemann 1992).

In the context of the present experiment, two observations indicate that 5-HT depletion induced by MDMA may not be a primary mechanism by which MDMA facilitates cocaine self-administration. First, the levels of 5-HT or 5-HIAA in the brain regions assayed did not correlate with any measure of self-administration. Second, groups MDMA-5 and MDMA-20 exhibited similar, small reductions in 5-HT content in the DA-rich nucleus accumbens, yet only group MDMA-20 exhibited enhanced acquisition of cocaine self-administration. Thus, at the present time, the available evidence suggests that the neurotoxic effect of MDMA on 5-HT neurons may not contribute directly to the increased neurochemical and behavioral sensitivity of MDMA-treated rats to cocaine. However, without further direct experimentation, this mechanism cannot yet be ruled out.

A second mechanism by which MDMA may facilitate acquisition of cocaine self-administration relates to its action on dopamine neurons. As noted in the introductory section, a large body of evidence indicates that repeated treatment with psychomotor stimulants sensitizes the mesolimbic DA system. MDMA also stimulates DA release (Kankaanpaa et al. 1998) without any neurotoxic effect on DA neurons (O'Shea et al. 1998; Colado et al. 1999). Therefore, it is possible that for rats in the MDMA-20 group, repeated injection of MDMA sensitized the mesolimbic DA system by virtue of repeated release of DA. Such a sensitised DA system may then facilitate acquisition of self-administration in the face of a challenge by a weakly reinforcing dose of cocaine (Horger et al. 1990, 1992; Valadez and Schenk 1994; Pierre and Vezina 1997; Lorrain et al. 2000). Although this explanation could readily account for the effects observed in group MDMA-20, it is necessary to account for the failure of group MDMA-5 to show a sensitized response to cocaine. The DA-releasing effect of MDMA is dose-dependent, and a 5 mg/kg dose of MDMA is also likely to stimulate DA release (Kankaanpaa et al. 1998). However, the magnitude of DA release induced by this dose is likely to be less than that released by 20 mg/kg MDMA (Kankaanpaa et al. 1998). Thus, it is possible that the extent of DA release induced by 5 mg/kg MDMA is not sufficient to sensitize the DA system, but that the larger DA releasing effect of 20 mg/kg MDMA can sensitize the mesolimbic DA system.

As a final possible mechanism to account for MDMA-induced sensitization to the effect of cocaine the dual effect of MDMA on 5-HT and DA function should be considered. The differential effects of the two MDMA treatment regimens on 5-HT systems may have some bearing on the influence of MDMA on DA function. Although 5-HT and 5-HT agonists increase dopamine release in nucleus accumbens and striatum when these substances are administered via a microdialysis probe (Benloucif et al. 1993; Parsons and Justice 1993), behavioral work has generally shown quite consistent inhibitory effects of 5-HT on dopamine-dependent behaviors (e.g., Fletcher and Korth 1999), including cocaine and amphetamine self-administration (Richardson and Roberts 1991; Fletcher et al. 1999). Thus, it is possible that the DA-ergic effects of 5 mg/kg MDMA are countered by the simultaneous release of 5-HT. Consistent with this view, the locomotor stimulant effect of MDMA was enhanced in rats pretreated with the nonselective 5-HT receptor antagonist methysergide (Gold and Koob 1988). In the case of the MDMA-20 group, such an inhibitory influence of 5-HT would be less likely to occur, given that just a single administration of this dose of MDMA depletes 5-HT (O'Shea et al. 1998). This depletion, and the attendant neurotoxicity to 5-HT neurons, would essentially diminish the capacity of subsequent doses of MDMA to release 5-HT.

In summary, the present experiment demonstrates that pre-exposure to MDMA increases the acquisition of cocaine self-administration. Although the mechanisms responsible for this effect remain to be determined, the neurotoxic effect of MDMA on 5HT neurons, as well as the ability of MDMA to enhance extracellular levels of dopamine, are obvious candidates. Given the widespread recreational use of MDMA (Hegadoren et al. 1999), the present results raise the possibility that MDMA users may be at risk for developing subsequent psychomotor stimulant abuse. However, this conclusion must be tempered by an acknowledgement of the limitations in generalizing from rats to humans, not only in terms of the potential differences in dose and route of administration of MDMA, but also in terms of the quite differing complexities of the mechanisms involved in drug abuse in rats versus humans.

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