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Effect of SCH 23390 on (±)-3,4-methylenedioxymethamphetamine hyperactivity and self-administration in rats

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Abstract

Recently, we demonstrated that (±)-3,4-methylenedioxymethamphetamine (MDMA; ecstasy) was reliably and dose-dependently self-administered by previously drug-naïve laboratory rats. The neurochemical basis of MDMA self-administration has not, however, been extensively studied. The present study investigated the role of dopamine in MDMA self-administration and hyperactivity. Pretreatment with the D1-like antagonist, SCH 23390 (0.01–0.08 mg/kg) produced a dose-dependent attenuation of MDMA (20.0 mg/kg)-produced hyperactivity. In self-administration tests, the baseline rate of responding maintained by intravenous infusions varied inversely with MDMA dose; as the dose available was changed, responding also changed so that about 10.0 mg/kg MDMA was self-administered during each daily 2-h session. Pretreatment with SCH 23390 (0.02 mg/kg) produced a rightward shift in the MDMA dose–response curve. These findings suggest that MDMA self-administration, like self-administration of other drugs of abuse, is dependent on the activation of dopaminergic substrates.

Keywords: MDMA; Dopamine; SCH 23390; Self-administration; Hyperactivity

1. Introduction

Self-administration of psychoactive substances by laboratory animals has been widely used to investigate factors that contribute to drug taking. Virtually all drugs of abuse are self-administered by laboratory animals and the pattern of self-administration is comparable to the pattern exhibited by humans (Griffiths et al., 1978; Spealman and Goldberg, 1978; Deneau et al., 1969; Schuster and Thompson, 1969). There has been a massive increase in the use of (±)-3,4-methylenedioxymethamphetamine (MDMA) and the drug clearly has abuse potential because a high percentage of users met DSM-IV criteria for either dependence or abuse (Cottler et al., 2001). In contrast to other self-administered drugs, however, only a paucity of studies in laboratory animals has examined the positively reinforcing effects of MDMA (Schenk et al., 2003a,b; Braida and Sala, 2002; Fantegrossi et al., 2002; Ratzenboeck et al., 2001; Lamb and Griffiths, 1987; Beardsley et al., 1986). MDMA was reliably self-administered by drug-experienced (Fantegrossi et al., 2002; Lamb and Griffiths, 1987; Beardsley et al., 1986) as well as by initially drug-naïve (Schenk et al., 2003a,b; Braida and Sala, 2002; Ratzenboeck et al., 2001) animals, but little is known about the underlying mechanisms.

MDMA interacts with a number of neurochemical systems but most studies have focused on the role of serotonergic mechanisms and its behavioral effects (Bankson and Cunningham, 2001, 2002; Iravani et al., 2000). The discriminative stimulus (Baker and Makhay, 1996; Schechter, 1991; Nichols et al., 1990), motor-activating (Bankson and Cunningham, 2001; Kehne et al., 1996; Callaway and Geyer, 1992; Callaway et al., 1990), conditioned-reinforcing (Fletcher et al., 2002b; Bilsky and Reid, 1991) and anxiogenic (Scearce-Levie et al., 1999) effects of MDMA have been attributed to its ability to increase synaptic levels of serotonin (Cole and Sumnall, 2003).

MDMA also increases synaptic levels of dopamine via direct inhibition of the dopamine transporter (Iravani et al., 2000; White et al., 1996; Nash and Brodkin, 1991; Yamamoto and Spanos, 1988) and secondary to its ability to increase synaptic serotonin (Bankson and Cunningham, 2001; Koch and Galloway, 1997; McCreary et al., 1999; Obradovic et al., 1996; Schmidt et al., 1994). The ability to increase synaptic levels of dopamine is a common characteristic of drugs of abuse (Di Chiara, 1999) and self-administration is sensitive to manipulations of dopaminergic systems (Bergman et al., 1990; Watkins et al., 1999;

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Beninger and Miller, 1988; Caine and Koob, 1994; Phillips et al., 1994; Corrigall and Coen, 1991; Hubner and Moreton, 1991; Benniger et al., 1989; Corrigall and Vaccarino, 1988; Koob et al., 1984, 1987; Pilotto et al., 1984; Hanson et al., 1979; Yokel and Wise, 1976). In order to determine whether dopaminergic mechanisms also mediate the reinforcing effects of MDMA, the present study examined the effects of the D1-like receptor antagonist, SCH 23390, on MDMA self-administration and compared them to effects on MDMA-produced hyperactivity.

2. Methods

2.1. Subjects

Subjects were male Sprague–Dawley rats bred in the vivarium at Victoria University of Wellington. Rats for the self-administration experiments were initially housed in hanging polycarbonate cages in groups of four to six per cage, but once they reached weights of 250–275 g, they were individually housed. Rats used in the locomotion studies were initially housed in pairs but were separated on the day prior to testing. The humidity- (74%) and temperature (21 °C)-controlled animal colony was maintained on a 12:12-h light cycle with lights on at 0700 h. Food and water were freely available except during testing. All procedures were approved by the Animal Ethics Committee of Victoria University of Wellington.

2.2. Surgery

A Silastic catheter was implanted in the right jugular vein under deep anesthesia produced by separate injections of ketamine (60.0 mg/kg ip) and sodium pentobarbital (20.0 mg/kg ip). Briefly, the external jugular vein was isolated, the catheter inserted, and the distal end (22-gauge stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were flushed with 0.1 ml of a sterile saline solution containing heparin (30.0 U/ml) and ampicillin (250,000 U/ml) to prevent infection and the formation of clots. Behavioral testing began following at least 5 days recovery.

2.3. Apparatus

2.3.1. Locomotor activity

Locomotor activity was measured in eight Perspex-lined open-field chambers (50 × 50 × 20 cm). Each chamber was equipped with a bank of eight LEDS on each wall (5 cm apart, 5 cm above the base). The chambers were interfaced with a computer that recorded each beam interruption. Testing was conducted in the dark between 0900 and 1700 h. Immediately prior to each test, the boxes were wiped down with Virkon S (Antec International).

2.3.2. Self-administration

Self-administration testing was conducted in a humidity- (74%) and temperature (21 °C)-controlled laboratory. Each of the 24 operant chambers was equipped with two levers and a stimulus light (Med Associates, ENV 001) and was enclosed in a sound-attenuating closet. Depression of one lever (the 'active' lever) resulted in a drug infusion. Depression of the other lever (the 'inactive' lever) was without programmed consequence. Infusions were in a volume of 0.1 ml delivered over 12.0 s via Razel pumps equipped with 1.0 rpm motors and 20.0 ml syringes. Coincident with each infusion was the illumination of a stimulus light located above the active lever.

2.4. Procedure

2.4.1. Locomotion

Initial tests measured the effects of SCH 23390 on MDMA-produced hyperactivity. Preliminary studies (unpublished) indicated that MDMA-produced hyperactivity (5.0–20.0 mg/kg) was dose-dependent and that higher doses produced adverse effects in a number of rats. In order to allow observation of a dose-dependent reduction in activity following administration of the antagonist, the present study examined the effects of SCH 23390 on hyperactivity produced by 20.00 mg/kg MDMA. Separate groups of rats ($n = 6$/group) were injected with SCH 23390 (0.01–0.08 mg/kg sc), or the saline vehicle and were immediately placed in the activity boxes. After a 15-min period, they received an injection of MDMA (20 mg/kg ip) and activity counts were measured for an additional 60 min.

Additional groups of rats were tested to determine the effects of SCH 23390 on baseline levels of activity. For these tests, rats ($n = 8$/group) received an injection of SCH 23390 (0.02 mg/kg sc) or the saline vehicle immediately prior to being placed in the activity boxes. Activity counts were measured at 5-min intervals during a 60-min postinjection period. This dose of SCH 23390 attenuated MDMA-produced hyperactivity (see Results) and these additional groups were therefore tested to determine whether the attenuation reflected a generalized decrease in motor activity.

2.4.2. Self-administration training

MDMA (1.0 mg/kg/infusion) was available for self-administration during daily 2-h training sessions. This dose of MDMA was chosen based on our previous findings of acquisition of self-administration within approximately 10 test days (Schenk et al., 2003a,b). Each session began with an experimenter-administered infusion of MDMA. Thereafter, infusions were delivered according to an FR-1 schedule of reinforcement by depression of the active lever. Depressions on the inactive lever were recorded but had no programmed consequence. Self-administration was considered acquired when during a session, (1) at least 10 active lever responses were produced, and (2) the ratio of active/

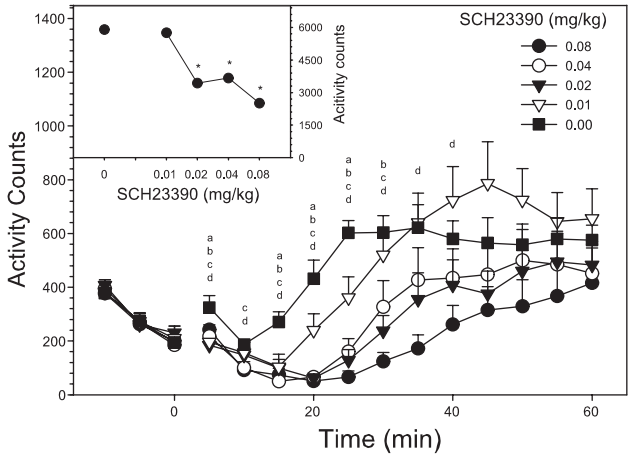

Fig. 1. Effects of SCH 23390 (0.08–0.00 mg/kg) on MDMA-induced locomotion. SCH 23390 was injected at time 15 min and MDMA was injected at time 0 min. Symbols represent the mean number of activity counts (± S.E.M.) as a function of SCH 23390 dose and time. Insert: total activity counts during the 60-min period following the injection of MDMA as a function of SCH 23390 dose. * Indicates significant ($P < .05$) decrease in activity relative to the vehicle (0.0 mg/kg) condition. (a) 0.01 mg/kg, (b) 0.02 mg/kg, (c) 0.04 mg/kg, (d) 0.08 mg/kg.

inactive lever responses was at least 2:1. When these criteria were met for at least three consecutive days with less than 20% variation in active lever responses across days, the MDMA dose was reduced to 0.5 mg/kg/infusion. Training continued until there was less than 20% variability in the number of responses produced across three consecutive testing days.

2.4.3. Effect of SCH 23390

Once self-administration responding was stable, tests were conducted to assess the effect of the dopamine D1-like antagonist, SCH 23390 (0.02 mg/kg sc) on responding, maintained by a range of MDMA (0.25–2.0 mg/kg/infusion) doses. This dose of SCH 23390 was chosen based on the results of the hyperactivity tests because it produced minimal effects on baseline activity but attenuated MDMA-produced hyperactivity.

A recurring series comprised of baseline and test days were used. At least 2 days of baseline testing were interspersed between tests of the antagonist effect. SCH 23390 was administered only when there were at least two prior and consecutive baseline tests during which the number of responses did not vary by more than 20%.

Initially, the dose of MDMA available for self-administration was 0.5 mg/kg/infusion. Once the effect of SCH 23390 on responding maintained by this dose of MDMA was determined, the MDMA dose was either increased or decreased for individual subjects and the effect of the antagonist on responding maintained by this new dose of MDMA was assessed. The effect of SCH 23390 on responding maintained by 0.5, 1.0 and 2.0 mg/kg/infusion MDMA was assessed in all rats ($n = 6$) and the effect on responding maintained by 0.25 mg/kg/infusion MDMA was determined in a subset of these rats ($n = 5$).

2.5. Drugs

Racemic MDMA HCl (ESR, Porirua, New Zealand) was dissolved in a sterile 0.9% saline solution containing 3 U/ml heparin. SCH 23390 (NIDA, USA) was dissolved in 0.9% saline. Intravenous infusions were in a volume of 0.1 ml and subcutaneous or intraperitoneal injections were in a volume of 1 ml/kg. All drug doses refer to the salt.

2.6. Data analysis

Activity data were analyzed using a repeated-measures ANOVA (Antagonist Dose × Time). The self-administration data were analyzed using a two-way ANOVA to determine the effect of antagonist dose on responses maintained by various doses of MDMA. Analyses were conducted using the SPSS statistical package (SPSS) version 11.0 for Windows 2000.

3. Results

Fig. 1 shows the effect of SCH 23390 on MDMA-produced hyperactivity as a function of dose and time. The insert shows the total counts during the 60-min period following the MDMA injection for groups that received various doses of the antagonist. SCH 23390 produced a dose-dependent decrease in MDMA-produced hyperactivity [$F(4,16) = 4.274$, $P < .05$]. Post hoc analyses revealed that decreases produced by doses equal to or greater than 0.02 mg/kg SCH 23390 were significant ($P < .05$). The interaction between dose and time was also significant [$F(44,253) = 2.457$, $P < .001$] and post hoc analyses revealed that the

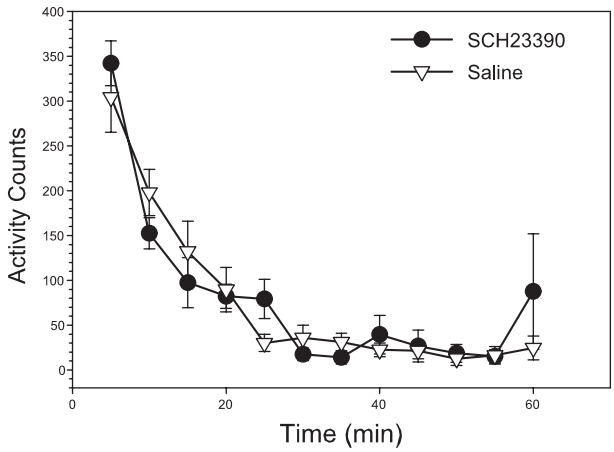

Fig. 2. Effects of SCH 23390 (0.02 mg/kg) on baseline locomotor activity. SCH 23390 or the saline vehicle was administered at time 0 min. Symbols represent the mean activity count (± S.E.M.).

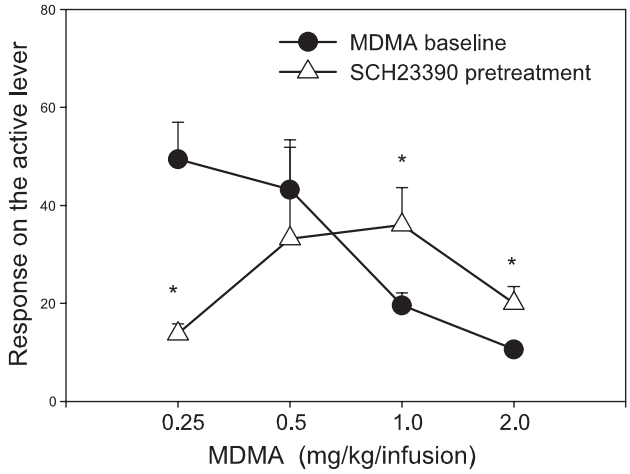

Fig. 3. Effects of SCH 23390 (0.02 mg/kg) on responding maintained by various doses of MDMA. Symbols represent the mean number of responses (± S.E.M.). * Indicates significant difference ($P < .05$) from baseline rate of responding.

decreases were produced primarily during the first 30 min following the injection of MDMA ($P < .05$).

Fig. 2 shows the effect of SCH 23390 (0.02 mg/kg) or the saline vehicle on baseline activity levels. For both groups, activity levels are initially high and decrease progressively throughout the session. Activity levels of the SCH 23390 group were comparable to activity levels of the control group and there was no significant decrease as a result of antagonist treatment [$F(1,14) = 0.105$, NS].

Fig. 3 shows the effect of SCH 23390 (0.02 mg/kg) on active lever responding maintained by a range of self-administered MDMA doses. Inactive lever responding remained low for all treatment conditions and for clarity, these data are not presented. ANOVA revealed a significant interaction between MDMA and SCH 23390 dose [$F(3,19) = 5.051$, $P < .01$]. Simple analyses revealed that responding maintained by 0.25 mg/kg/infusion MDMA was attenuated by SCH 23390 [$F(1,4) = 9.153$, $P < .05$], whereas responding maintained by 1.0 mg/kg/infusion MDMA [$F(1,5) = 13.811$, $P < .05$] and 2.0 mg/kg/infusion MDMA [$F(1,5) = 23.616$, $P < .005$] was increased by SCH 23390.

4. Discussion

MDMA-produced hyperactivity was attenuated in a dose-dependent manner by pretreatment with SCH 23390. Effective doses of SCH 23390 were lower than those required to produce a general disruption of motor activity (present results; Millan et al., 2001; Meyer et al., 1993; Piggins and Merali, 1989), suggesting a specific effect and supporting the hypothesis that dopaminergic mechanisms underlie MDMA-produced hyperactivity (Gold et al., 1989; Kehne et al., 1996).

The reinforcing effects of MDMA were also attenuated by pretreatment with a low dose of the D1-like antagonist. Pretreatment with SCH 23390 produced a rightward shift in the dose–response curve for MDMA self-administration. The development and maintenance of drug-taking in humans can be predicted on the basis of self-administration by laboratory animals. Therefore, these findings suggest that use and abuse of MDMA should also be dependent on dopaminergic mechanisms. Consistent with this hypothesis, drug-produced well-being and euphoria were decreased by pretreatment with the dopamine D2-like antagonist, haloperidol (Liechti and Vollenweider, 2000).

During self-administration training and testing, rats received substantial exposure to MDMA. Repeated exposure to MDMA produces effects on brain chemistry that might play a role in the ability of MDMA to increase synaptic dopamine and produce positively reinforcing effects that maintain self-administration. It is well documented that exposure to MDMA produces toxicity in central serotonergic systems (Reneman et al., 2001; Ricaurte et al., 2000; Schmidt and Kehne, 1990; Battaglia et al., 1988; Schenk et al., 2003a,b). There are complex interactions between serotonin and dopamine but several studies have shown that self-administration of cocaine (Czoty et al., 2002; Fletcher et al., 2002a; Loh and Roberts, 1990), morphine (Dworkin et al., 1988) and amphetamine (Leccese and Lyness, 1984) was altered following serotonin depletion, presumably as a result of decreased serotonin modulation of dopamine.

It has also been reported that exposure to MDMA produced a persistent decrease in the density of 5-HT2c receptors (McGregor et al., 2003). This might also contribute to the ability of MDMA to increase synaptic dopamine because activation of 5-HT2c receptors decreased dopamine release (Filip and Cunningham, 2002; Blackburn et al., 2002; Bonaccorso et al., 2002; Di Giovanni et al., 2000). Following acute MDMA administration, increases in 5-HT and the resulting activation of 5-HT2c receptors (Gudelsky et al., 1994) might be expected to limit MDMA-produced increased dopamine. Following repeated exposure, however, this inhibitory effect might be less influential because of decreased 5-HT2c receptor densities. The resulting disinhibition would explain the sensitized dopamine response produced following repeated MDMA exposures (Kalivas et al., 1998). This sensitized neurochemical response would be expected to maintain MDMA self-administration and produce cross-sensitization in the behavioral effects of MDMA and other indirect dopamine agonists (Cole et al., 2003; Itzhak et al., 2003; Schenk et al., 2003a,b; Fletcher et al., 2001; Kalivas et al., 1998; Morgan et al., 1997; Callaway and Geyer, 1992).

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