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Original Investigation

Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats

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Abstract

Rationale ±3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") use is increasing around the globe but there is a paucity of studies examining the abuse liability of this drug.

Objectives The ability of drugs to reinforce operant responding in laboratory animals is a valid and reliable predictor of abuse potential. MDMA is self-administered by humans, but there have been few reports of reliable self-administration by drug-naive laboratory animals. The present study sought to examine the acquisition and maintenance of MDMA self-administration by laboratory rats. The influence of prior training with cocaine self-administration on the acquisition of MDMA self-administration was also examined.

Methods MDMA self-administration (0.25–2.0 mg/kg per infusion) was examined in rats that were first trained to self-administer cocaine as well as by those that were drug-naive. The dose-dependency of MDMA self-administration and the temporal pattern of responding maintained by various doses of MDMA were examined. In some rats, self-administration of MDMA during a 24-h session was also examined.

Results MDMA was self-administered by laboratory rats that were experienced with self-administration of cocaine as well as by rats that were initially drug naive. For drug naive rats, the acquisition of MDMA self-administration (1.0 mg/kg per infusion) developed gradually during daily test sessions. The latency to acquisition of self-administration was shorter in cocaine-trained rats. Self-administration was dose-dependent, extinguished when saline was substituted for MDMA and, was reinstated when MDMA was reintroduced. During a 24-h self-administration session, a high rate of responding was produced during the first hour of the test session followed by a steady and lower rate of two to four responses per hour during subsequent hours of the test.

Conclusions These results suggest that prior experience with cocaine self-administration facilitates the acquisition of MDMA self-administration. The results also suggest that MDMA has abuse liability and that increased use of the drug should raise concern of a growing and widespread potential for chronic abuse.

Keywords MDMA - Self-administration - Ecstasy - Abuse

Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a ring substituted amphetamine that has become an increasingly popular illicit recreational drug. MDMA produces subjective effects that include feelings of well-being and euphoria (Liechti and Vollenweider *2000*, *2001*; Hernandez-Lopez et al. *2002*; Parrott *2002*), effects that might underlie its increasing popularity. Recently, it has been reported that MDMA use is on the rise and that the pattern is becoming consistent with that of other abused drugs (Schuster et al. *1998*; Pederson and Skrondal *1999*; Siliquini et al. *2001*; Pope et al. *2001*; Spruit *2001*).

Self-administration by laboratory animals is a valid and reliable index of abuse liability (Deneau et al. *1969*; Schuster

and Thompson *1969*; Fischman and Schuster *1978*). Amphetamine and other abused drugs are readily self-administered by laboratory animals, and a wealth of studies have indicated that self-administration is mediated by dopaminergic mechanisms (see Wise and Rompre *1989*; Kuhar et al. *1991*; Mello and Negus *1996*; Howell and Wilcox *2001*). MDMA increases synaptic levels of dopamine and serotonin (Nash and Brodkin *1991*; Rudnick and Wall *1992*; Gudelsky et al. *1994*; White et al. *1996*; Iravani et al. *2000*; Mayerhoffer et al. *2001*; Rothman et al. *2001*), but dopaminergic mechanisms have been suggested to underlie the increased positive mood following MDMA administration to humans (Liechti and Vollenweider *2000*, *2001*).

Only four studies, however, have reported MDMA self-administration in laboratory animals (Beardsley et al. *1986*; Lamb and Griffiths *1987*; Ratzenboeck et al. *2001*; Fantegrossi et al. *2002*). Three of these studies were carried out in primates that had received prior training with self-administration of other psychoactive compounds (cocaine or amphetamine). Under these conditions, MDMA maintained responding although it was a low efficacy reinforcer when compared with the training drug. Dose-dependent responding was produced by rhesus monkeys over a wide range of doses and the dose-effect curve for responding maintained by racemic MDMA was comparable to the curve for responding maintained by either the + or – isomers (Fantegrossi et al. *2002*).

Only one paper has reported self-administration of MDMA by laboratory rodents (Ratzenboeck et al. *2001*). Dose-effect curves were generated but responding was low with only two to four responses produced during a 2-h session. All rats had received prior training to lever press for food reinforcement and some received additional training with cocaine self-administration prior to MDMA self-administration sessions. The authors suggested that once acquired, MDMA self-administration was comparable regardless of whether the rats were cocaine-naive or cocaine-trained.

The failure to obtain a significant effect of cocaine training on MDMA self-administration was surprising, since pharmacological history has been shown to be an important determinant of sensitivity to the reinforcing effects of other psychostimulant drugs. Of particular relevance, pre-exposure to MDMA enhanced the reinforcing effects of cocaine as indicated by reduced latencies to the acquisition of self-administration (Fletcher et al. *2001*).

Acquisition of self-administration of low to moderate doses of psychostimulants occurs over a number of test sessions and the latency to acquisition is inversely related to the dose of drug that serves as the reinforcer (Schenk et al. *1991*, *1993*; Schenk and Partridge *2000*). Therefore, the decreased latency to acquisition of cocaine self-administration as a function of MDMA pre-treatment suggests a sensitization effect. The present study sought to examine the acquisition of MDMA self-administration and to determine whether cocaine pre-exposure sensitized rats to the reinforcing effect of MDMA. Additionally, the dose-response relationship and temporal characteristics of MDMA self-administration during short and long sessions were examined.

Materials and methods

Subjects

Subjects were male Sprague-Dawley rats bred in the vivarium at Victoria University of Wellington. They 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. The humidity (74%) and temperature (21°C) controlled animal colony was maintained on a 12:12-h light/dark cycle with lights on at 0700 hours. Food and water were freely available except during the short duration (2–6 h) self-administration tests described below.

Surgery

Rats were implanted with a Silastic catheter in the right jugular vein. The rats were deeply anesthetized with ketamine (60.0 mg/kg, IP) and pentobarbital (20.0 mg/kg, IP). The external jugular vein was isolated, the catheter was inserted and the distal end (22 ga 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 infused with 0.1 ml of a sterile saline solution containing heparin (30.0 IU/ml) and ampicillin (250,000 IU/ml) to prevent infection and the formation of clots. The rats were allowed 5 days post-surgery for recovery prior to behavioral testing.

Apparatus

Self-administration training and testing occurred in test chambers (Med Associates, ENV 001) enclosed in sound attenuating closets. The testing room containing the 24 test chambers was humidity (74%) and temperature (21°C) controlled. Each chamber was equipped with two levers and a stimulus light. Depression of one lever (the active lever)

resulted in an infusion of drug. 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. Each daily test began with an experimenter-delivered infusion of the dose of drug that was available for self-administration.

Procedure

The acquisition of MDMA self-administration in drug naive rats or rats that had received training with cocaine self-administration (0.5 mg/kg per infusion during 5–12 daily 2-h tests; *n*=4) was measured. Drug naive rats received 26 daily tests. During the first 11 days, the dose of MDMA available for self-administration during daily 2- (*n*=5) or 6- (*n*=6) h tests was 1.0 mg/kg per infusion. Most responses were produced during the initial hour of the test and so there was no difference in responding as a function of test duration. Therefore, data obtained during this initial 11 days of testing from the two groups were combined. The group of six rats that had been tested for 6 h daily received additional tests and during the next 8 days the dose available during the daily 6-h tests was 0.5 mg/kg per infusion. The test session was then reduced to 2 h duration and saline was substituted for MDMA during the next 2 test days. This was followed by 5 days of 2-h tests during which the dose of 0.5 mg/kg per infusion MDMA was available. Rats that were first trained with cocaine self-administration received 6 h tests of MDMA self-administration (1.0 mg/kg per infusion).

Eight rats received additional tests to examine further the dose-dependent nature of responding maintained by MDMA. For these tests, different doses of MDMA (0.25–2.0 mg/kg per infusion) were available for self-administration during 2-day blocks. Session length was 2 h. The starting dose for MDMA self-administration was 2.0 mg/kg per infusion and the dose was repeatedly reduced by one-half with each successive 2-day block. Data from the second day of each 2-day block were used for presentation.

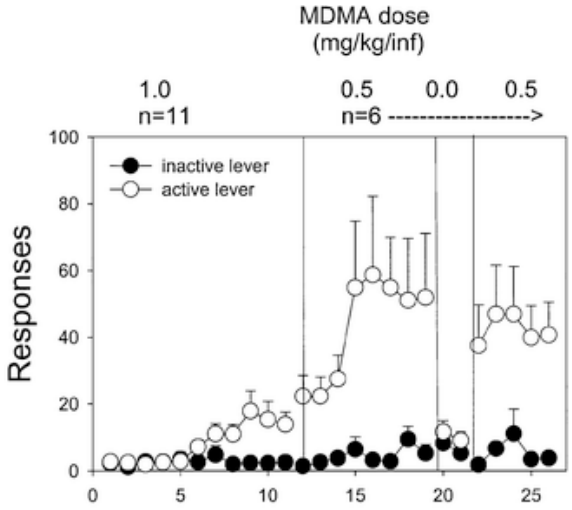
A final test measured responding maintained by MDMA (1.0 mg/kg per infusion) during a 24-h test. For these tests (*n*=8), the test chambers were equipped with a water bottle and food tray.

Drugs

Racemic MDMA HCl (ESR Ltd, Porirua, New Zealand) and cocaine HCl (Merck Pharmaceuticals, Palmerston North, New Zealand) were dissolved in physiological saline. MDMA purity was examined by gas chromatography/mass spectrometry and NMR, and assessed at greater than 98%. Drug doses refer to the salt.

Results

Figure 1 shows responding maintained by MDMA for rats that were initially drug naive. Responding on the inactive lever remained low throughout the 26 days of testing. During the first 6 days of testing when the dose of 1.0 mg/kg per infusion was available, responding on both the active and inactive lever remained low. Between days 7 and 11, responding maintained by this dose of MDMA increased and a preference for the active lever developed. When the dose of MDMA was decreased to 0.5 mg/kg per infusion between days 12 and 19, an increase in active lever responding and a marked preference for the active lever was produced. Saline substitution on days 20 and 21 resulted in a decrease in responding and responding was reinstated when MDMA was available again on days 21–26.



Day

Fig. 1. Acquisition of MDMA self-administration by drug naive rats. Mean responses (+SEM) on the active and inactive levers are presented as a function of day of testing and dose of MDMA

Figure 2 compares active and inactive lever responding maintained by MDMA (1.0 mg/kg per infusion) during the initial 6 days of testing for rats that were initially drug naive and received 6-h daily tests and for rats that received prior training with cocaine self-administration. Active lever responding for the cocaine trained rats was significantly higher [$F(1,8)=5.137$, $P=0.05$].

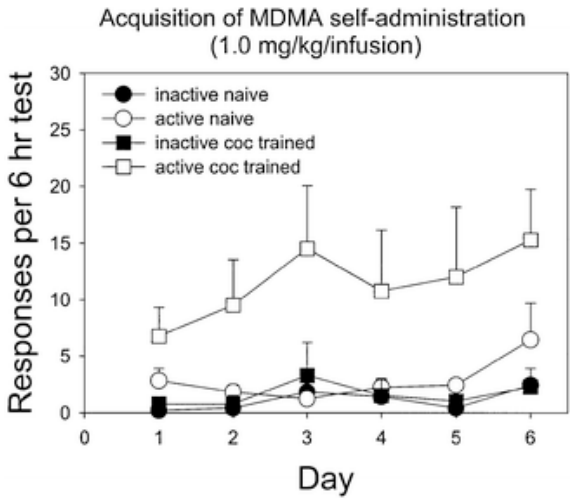


Fig. 2. Acquisition of MDMA self-administration for rats that received either cocaine self-administration ($n=4$) training prior to MDMA self-administration or no prior self-administration training ($n=6$) and were drug naive. Mean responses (+SEM) on the active and inactive levers are presented as a function of day of testing

MDMA self-administration was dose-dependent (Fig. 3). Decreasing the dose resulted in increased rates of responding [$F(4,28)=5.548$, $P<0.01$], as is commonly observed for self-administration of other psychostimulant drugs (Carroll and Lac *1997*). When saline was substituted for MDMA, responding decreased.

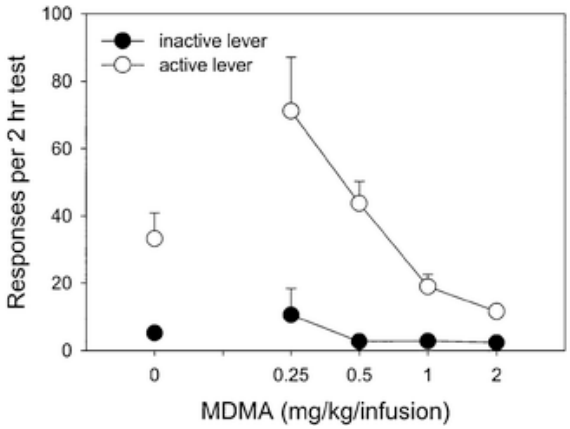


Fig. 3. Responding maintained by different doses of MDMA ($n=8$). Symbols represent the mean number of responses (+SEM) during daily 2-h sessions

Figure 4 shows the pattern of responding during each 2-h daily session for a representative rat. Higher doses of MDMA were self-administered primarily during the initial 30 min of the session. Self-administration of the lower dose (0.25 mg/kg per infusion) persisted throughout the 2-h session. The number of responses maintained by saline infusions was comparable to the number of infusions maintained by the highest doses of MDMA, but the pattern of saline self-administration differed from the pattern observed when MDMA was available.

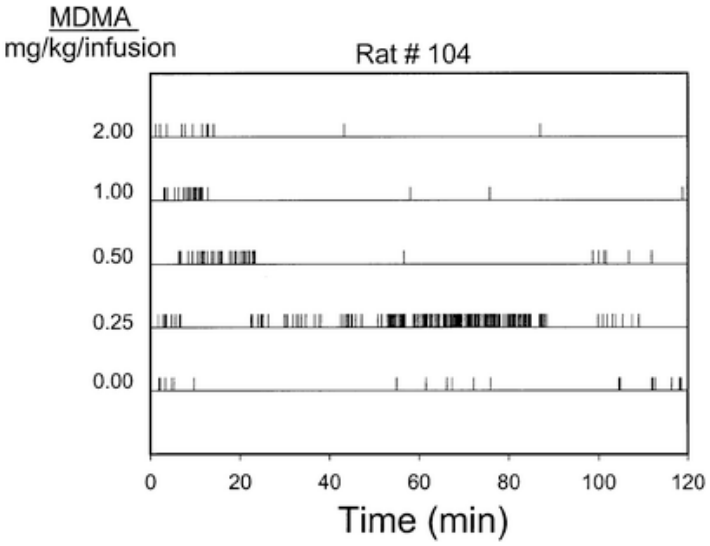


Fig. 4. Temporal pattern of responding during a 2-h session maintained by different doses of MDMA for a representative rat. Each *vertical line* represents an infusion of MDMA

Figure 5 shows the average number of active lever responses produced during each hour of the 24-h session. One of the eight rats died after approximately 11.5 h. During the initial hour, responding was high and during subsequent hours responding dropped off and was steady at two to four responses per hour except for during hour 20, when responding increased for one of the subjects. The insert in Fig. 5 shows the time course for responding during hour 1 of the 24-h session. The average number of responses during each of the 10-min periods was comparable.

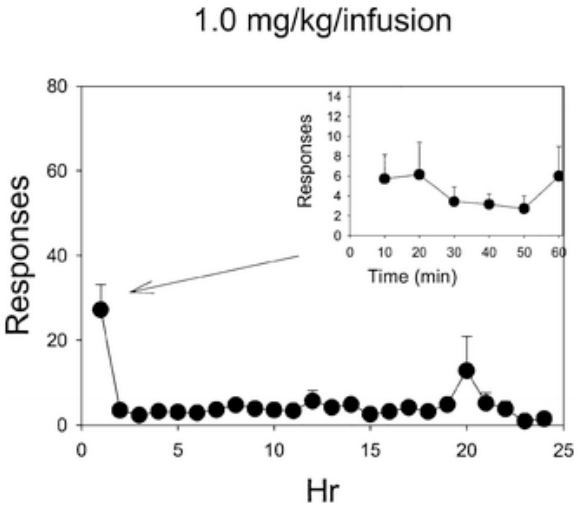


Fig. 5. Temporal pattern of responding maintained by MDMA (1.0 mg/kg per infusion) during a 24-h session (*n*=8). The average number of responses (+SEM) during each hour of the test is shown. One rat died after approximately 11.5 h of self-administration. The insert shows the average number of responses (+SEM) during each 10-min interval of the first hour of testing

Discussion

MDMA self-administration was gradually acquired with repeated daily tests in rats that had no prior self-administration training and were drug naive. These data are comparable to data obtained when the acquisition of self-administration of other psychostimulant drugs was measured. Acquisition of cocaine (Schenk et al. *1991*, *1993*; Schenk and Partridge *2000*) and amphetamine (Piazza et al. *1989*; Carroll and Lac *1997*; Pierre and Vezina *1997*) self-administration also occurs gradually over days and the gradual increase in the average number of responses as a function of test day results from the gradual increase in the number of subjects that reliably self-administer the drug.

A wealth of studies has indicated that pretreatment with psychostimulants sensitizes rats to the behavioral effects of subsequent injections (see Robinson and Becker *1986*; Kalivas and Stewart *1991*). Sensitization extends to the reinforcing properties of drugs, since latency to acquisition of self-administration was decreased by pretreating rats with either the to-be self-administered drug or a variety of other drugs (see Schenk and Partridge *1997*; Schenk *2002*). Behavioral sensitization has been attributed to sensitization in the ability of many drugs to increase synaptic dopamine levels (see Kalivas and Stewart *1991*).

Previous studies have indicated that some of the behavioral effects of MDMA are also susceptible to sensitization. For example, acute exposure to MDMA resulted in locomotor activation that became sensitized following repeated exposures (Spanos and Yamamoto *1989*; Kalivas et al. *1998*; McCreary et al. *1999*). Cross sensitization has also been demonstrated, and rats that received treatment with MDMA became more responsive to the locomotor activating effects of amphetamine (Callaway and Geyer *1992*) and cocaine (Kalivas et al. *1998*) as well as to the conditioned reinforcing effects of cocaine (Horan et al. *2000*). Of great interest, rats that were pretreated with MDMA subsequently acquired self-administration of a low dose of cocaine with shorter latencies than rats that received saline pretreatment (Fletcher et al. *2001*).

Previous self-administration studies have indicated that MDMA self-administration is readily produced in laboratory animals that had a prior history of cocaine self-administration (Beardsley et al. *1986*; Lamb and Griffiths *1987*; Ratzenboeck et al. *2001*; Fantegrossi et al. *2002*). Thus, in contrast to the acquisition data presented here, the ability of MDMA to substitute for cocaine suggests that the animals had become sensitized to MDMA's reinforcing effects. In the present study, sensitization to the reinforcing effects of MDMA was demonstrated in rats experienced with cocaine self-administration.

Following acquisition, responding maintained by MDMA was dose-dependent, extinguished when saline was substituted for the drug and was reinstated when MDMA was reintroduced. Following acquisition, responding maintained by different doses of MDMA was measured for a subgroup of rats. The number of responses was an inverse function of MDMA dose. There was almost perfect compensatory responding that maintained drug intake at about 20 mg/kg during daily sessions with different drug doses. When saline was substituted for MDMA, responding decreased for these more experienced rats. Saline-maintained responding was, however, higher than had been observed during acquisition and a preference for the active lever was demonstrated during these saline-reinforced trials. These findings suggest that these rats were more resistant to extinction as a result of a more extensive MDMA self-administration history.

The demonstration of reliable, dose-dependent self-administration is consistent with characteristics of a drug that possesses high abuse liability. This interpretation is strengthened by the finding that reliable self-administration persisted during a single 24-h session. MDMA self-administration during this long session differed from what we have previously reported for cocaine self-administration (Schenk and Partridge *1997*, *2001*). Responding maintained by cocaine infusions persisted at a high hourly rate during long sessions. The decrease in responding after the first hour of MDMA self-administration might reflect the long duration of action of MDMA and/or the accumulation of an active metabolite.

A primary mechanism of action of MDMA is the stimulated release and reuptake blockade of serotonin and acute administration produces massive increases in synaptic levels of this neurotransmitter (Kalant *2001*; Teter and Guthrie *2001*). Serotonergic mechanisms have been implicated in some of the behavioral effects of MDMA. For example, the discriminative stimulus properties of MDMA generalized to serotonin agonists (Baker et al. *1995*). Some effects of MDMA were attenuated by prior administration of serotonin uptake inhibitors (Callaway et al. *1990*; Hekmatpanah and Peroutka *1990*) or pharmacological manipulations of serotonergic systems (Marona-Lewicki et al. *1991*; McCreary et al. *1999*; Liechti and Vollenweider *2000*; Bankson and Cunningham *2002*). Serotonergic mechanisms have also been implicated in the positively reinforcing effects of MDMA, since pretreatment with the 5-HT_2 antagonist, ketanserin, decreased MDMA self-administration by rhesus monkeys without altering cocaine self-administration (Fantegrossi et al. *2002*).

Synaptic levels of dopamine are also increased following MDMA administration via direct inhibitory effects of MDMA on the dopamine transporter (Yamamoto and Spanos *1988*; Metzger et al. *1998*; Iravanai et al. *2000*; Hansen et al. *2002*). These effects of MDMA might underlie its reinforcing properties. MDMA effects on dopamine can also occur secondary to serotonin release. Serotonin neurons innervate dopaminergic systems that underlie the reinforcing effects of drugs of abuse (Herve et al. *1987*). Evidence is emerging that activation of some serotonin receptor subtypes facilitates dopamine effects (Schmidt et al. *1994*; De Deurwaerdere et al. *1997*; McCreary et al. *1999*; Ng et al. *1999*; Bankson and Cunningham *2001*; Yan and Yan *2001*). As a result, repeated MDMA-produced increases in serotonin might repeatedly activate reward-relevant dopaminergic substrates. This repeated activation of dopamine might be expected to lead to neurochemical sensitization that becomes expressed in reliable self-administration. This effect of repeated MDMA would also explain its ability to enhance the reinforcing and other behavioral effects of cocaine (Kalivas et al. *1998*; Horan et al. *2000*; Fletcher et al. *2001*), which has been attributed to sensitization of dopaminergic substrates.

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