

Research Article

Profile of MDMA Self-Administration from a Large Cohort of Rats: MDMA Develops a Profile of Dependence with Extended Testing

Susan Schenk, Joyce Colussi-Mas, Jennifer Do, and Judith Bird

*School of Psychology, Victoria University of Wellington, P.O. Box 600, Wellington, New Zealand
Address correspondence to Susan Schenk, susan.schenk@vuw.ac.nz*

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Abstract The present study provides a profile of acquisition and maintenance of self-administration of +/-3,4-methylenedioxymethamphetamine (MDMA) obtained from a large cohort of rats tested during a 2 year period. Of the 128 rats, 49% self-administered 1.0 mg/kg/infusion MDMA to an initial criterion within a 25 day cut-off period. The number of test sessions required to meet this initial criterion was normally distributed around an average of 15.9 days and responding increased in a compensatory manner when the dose was decreased. In a subgroup of rats that self-administered MDMA for an additional 14 days intake increased from 8.5 to 15.25 mg/kg/day. Thus, under these conditions, MDMA is a reliable reinforcer for about half of a large sample of rats, responding is dose-dependent and acquisition of self-administration for these sensitive rats requires more test sessions than is typically used for studies examining self-administration of other drugs of abuse.

Keywords MDMA; self-administration; drug dependence

1 Introduction

The use of +/-3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") has been increasing across the globe and a number of studies indicate that some Ecstasy users consume large quantities with high frequency [15,17,18,41,43]. While many ecstasy users limit use and indulge infrequently, some consume a large number of pills on each occasion, use frequently and meet criteria for dependence and/or abuse [10,16,24,44].

A number of studies have reported MDMA self-administration by laboratory monkeys, baboons, rats, and mice (see [34] for review) but most of these studies have shown moderate intake compared to others with more prototypical drugs of abuse. In direct comparisons, fewer rats self-administered MDMA than cocaine [39] and MDMA was a lower efficacy reinforcer than cocaine in rats [14,39], monkeys [2,25], and baboons [22]. Thus, despite the evidence of abuse and dependence, laboratory studies in animals have not often demonstrated high rates of self-administration.

Acute exposure to MDMA preferentially increases synaptic serotonin (5HT) via uptake inhibition and stimulated release [8]. In direct comparisons using *in vivo* microdialysis, MDMA-produced increases in 5HT are generally about twice the increases in dopamine (see, e.g., [3]). We have suggested that the development of MDMA self-administration is initially limited by the drugs preferential effects on 5HT neurotransmission [34,35]. Indeed, 5HTergic agonists are not effective reinforcers and are not self-administered [19,20,27,46] and the potency of amphetamine or cocaine analogues as reinforcers was decreased for drugs that had greater binding affinity at the 5HT transporter [21,26,32,33]. Further, the ability of amphetamine or cocaine to maintain self-administration was substantially decreased by the addition of the 5HT releasing stimulant, fenfluramine [47], by pretreatment with 5HT uptake inhibitors [11,28], including MDMA [7] or by manipulations that increased central 5HT [6,23,29,31,42]. These findings all suggest that a preferential 5HT agonist, like MDMA, would not support high rates of self-administration and the pronounced increase in synaptic 5HT might limit intake during the early days of self-administration for most of the rats [45].

For some rats, however, there is an escalation of self-administration with repeated testing and eventually some self-administer as much as 20.0 mg/kg or more of MDMA per day [36,38,39]. High levels of self-administration are accompanied by decreased 5HT transporter binding [39] and decreased tissue levels of 5HT [37]. At the same time, microdialysis revealed a sensitized dopamine response in the dorsal striatum to MDMA during tests of drug-seeking following self-administration [9]. It is important, however, that the development of high rates in self-administration occurs following a protracted period of testing. In this respect, MDMA self-administration is initially qualitatively as well as quantitatively different from self-administration of other drugs. These differences become less apparent, however, as testing continues.

In early 2008, we began to control the intake of some of our MDMA self-administering rats so that we could determine neurochemical and behavioral consequences of self-administration following self-administration according to a defined schedule. All rats self-administered the same amount of MDMA, although the number of test days required to reach our criterion varied markedly across subjects. We implemented a procedure that was based on our earlier findings of reliable self-administration of a relatively high dose of MDMA (1.0 mg/kg/infusion) during daily 2-h sessions. Following self-administration of 90 infusions of this dose, about 50–60% of the rats demonstrated a preference for a lever that resulted in the delivery of MDMA over an inactive lever and the number of responses was higher than when saline served as the reinforcer [9]. When the dose was subsequently decreased by one half, active lever responding increased in a compensatory fashion and when MDMA was replaced with vehicle solution responding decreased [36]. Our neurochemical and behavioral tests were often conducted after 150 infusions of this dose had been self-administered [9,37]. Thus, each rat received a total of 165 mg/kg MDMA. Some of the rats met this criterion relatively quickly, others met the criterion more slowly, and others failed to meet the criterion within a cutoff of 25 daily sessions [9,35]. Since we started implementing this standard protocol, a large cohort of rats has been tested, allowing us to document the pattern of self-administration under these conditions. In this paper, we report the results of analyses on these rats.

2 Material and methods

2.1 Subjects

Data from rats that were tested in our laboratory during approximately a 2-year period from April 2008 to April 2010 were used. Some of these rats were subsequently tested for drug-seeking following MDMA self-administration [9, 35] or for tests of effects of MDMA self-administration on learning [37]. Others are being used to assess changes in tissue levels of monoamines or other neurochemical changes following self-administration.

Male Sprague-Dawley rats ($n = 128$) weighing about 300 gms at the start of the study were bred in the vivarium at Victoria University of Wellington. The rats were housed in groups of 3–4 until surgery, after which they were housed singly in standard polycarbonate hanging cages. Food and water were available ad libitum at all times except during testing. The rats were housed in a temperature- (21 °C) and humidity- (55%) controlled colony maintained on a 12-h light/dark cycle with lights on at 0700 h.

2.2 Self-administration

For all rats reported here various outcome measures were obtained but the procedure for acquisition of self-administration was identical. Chronic indwelling intrajugular

catheters were implanted under deep anaesthesia induced by an intraperitoneal injection of a mixture of ketamine (90 mg/kg) and xylazine (9 mg/kg). Prior to the surgery, the anti-inflammatory analgesic, Carprofen (5 mg/kg, Pfizer Animal Health), was administered subcutaneously (SC). The silastic tubing was inserted into the vein and the distal end was passed subcutaneously to the skull where it was secured using acrylic dental cement adhering to 4 small jeweler's screws. A compound sodium lactate solution (Hartmann's solution, 2 × 6 mL, SC) was then administered to restore electrolyte balance.

Carprofen (5 mg/kg, SC) was administered on each of the two days following surgery. On each of the 5 days following surgery the catheters were flushed with 0.2 mL of a sterile 0.9% saline solution, containing heparin (30 IU/mL) and penicillin G potassium (250,000 IU/mL). At the start of the testing period, and every seven days thereafter, catheter patency was tested with a 0.1 mL infusion of sodium pentobarbital (5.0 mg/kg, IV). Catheter patency was confirmed by immediate loss of the righting reflex. Data from rats that failed the patency test at any time point are not included in any analyses.

Testing began 5–7 days following surgery. Each day following surgery the catheters were infused with 0.1 mL of a sterile saline solution containing heparin (30.0 IU/mL), penicillin G potassium (250,000 IU/mL), and streptokinase (8000 IU/mL) to maintain catheter patency and to prevent infection and the formation of clots and fibroids.

Self-administration tests were conducted in operant conditioning chambers (Med Associates, ENV-001) equipped with two levers. The testing room was temperature- (19–21 °C) and humidity- (55%) controlled. Depression of one lever (the “active” lever) resulted in a 12.0 s intravenous infusion (0.1 mL) of MDMA. Depression of the other lever (the “inactive” lever) was without programmed consequence. Coincident with drug infusions was the illumination of a stimulus light located above the active lever.

Rats were maintained in their home cages in the animal facility until testing. Immediately prior to each daily test session, the catheters were flushed with 0.1 mL of the heparin-penicillin-streptokinase solution and the exposed stainless steel tubing was attached to a length of microbore tubing that was connected through a swivel apparatus to a 20 mL syringe housed in a mechanical pump (Razel, Model A with 1 rpm motor). Drug delivery and data acquisition were controlled by a microcomputer using Med Associates software.

Daily test sessions were 2-h duration on Monday-Saturday. Each session began with an experimenter-administered infusion of the dose of MDMA that was available for self-administration. This infusion functioned to clear the line of the saline solution. Thereafter, infusions were delivered according to a fixed ratio 1 schedule of reinforcement.

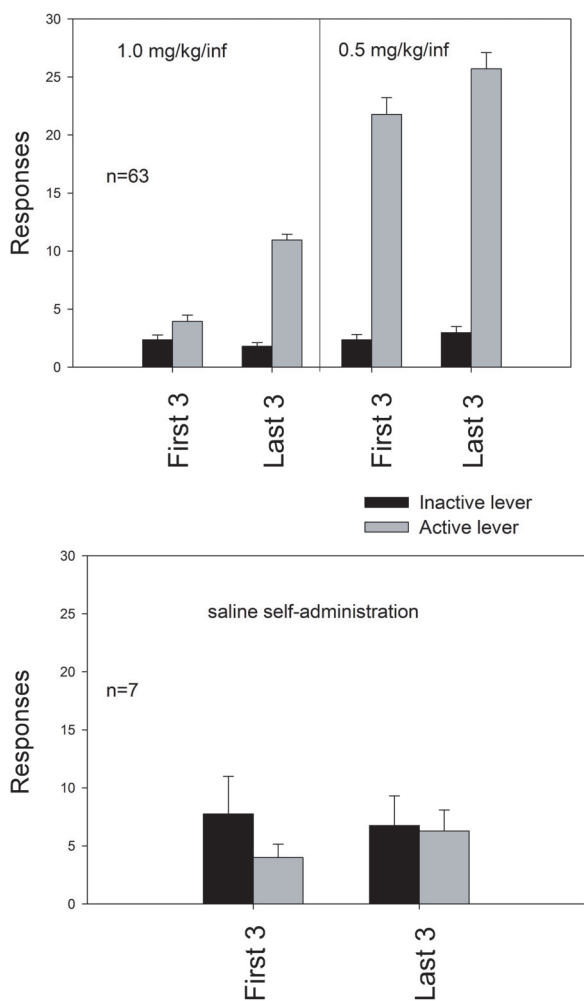


Figure 1: Mean number of active and inactive responses (+SEM) during the first and last 3 days of 1.0 or 0.5 mg/kg/infusion MDMA (top panel) or saline (bottom panel) self-administration.

Initially, responding was reinforced by delivery of 1.0 mg/kg/infusion MDMA during a maximum of 25 test days. The day after 90 infusions of this dose was self-administered; the dose was reduced to 0.5 mg/kg/infusion until additional 150 infusions were self-administered. Rats that failed to self-administer 90 infusions within the 25 day cut-off were considered to have not acquired self-administration and further testing was not conducted. Of the 128 rats reported here, 63 (49%) met this criterion for acquisition. Some of the rats ($n = 11$) received additional days of self-administration of 0.5 mg/kg/infusion MDMA which allowed us to determine whether there was an escalation of intake with repeated testing. An additional group of rats ($n = 7$) were tested as above but instead of receiving MDMA during daily self-administration trials, active lever responding was reinforced with an infusion of the saline vehicle.

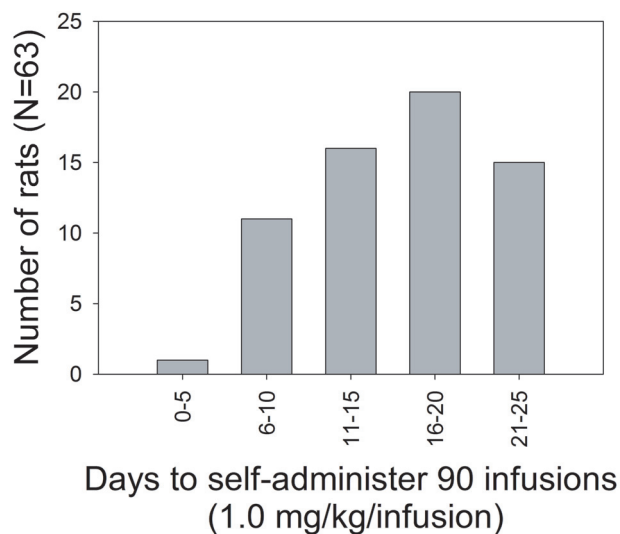


Figure 2: Frequency distribution of number of rats that met the criterion of 90 self-administered infusions of 1.0 mg/kg/infusion MDMA as function of days of testing.

3 Results

Figure 1 (top) shows the mean number of responses produced during the first and last 3 days of self-administration of 1.0 or 0.5 mg/kg/infusion MDMA. For all conditions, active lever responses were greater than inactive lever responses $t(62) = 2.423$ (first 3 days of 1.0 mg/kg/infusion); 19.267 (last 3 days of 1.0 mg/kg/infusion); 15.218 (first 3 days of 0.5 mg/kg/infusion); 17.592 (last 3 days of 0.5 mg/kg/infusion; all $P < .05$). A two-way ANOVA (Drug dose X test day) revealed that active lever responding increased as a function of test day ($F(1,62) = 10.27$, $P < .01$) and drug dose ($F(1,62) = 198.17$, $P < .01$).

Figure 1 (bottom) shows the mean number of responses produced during the first and last 3 days of self-administration of the saline vehicle. Active lever responses were not higher than inactive lever responses during either the first or last 3 days of testing.

Figure 2 shows a frequency distribution of the number of days required to self-administer the initial 90 infusions of 1.0 mg/kg/infusion MDMA for the 63 rats. The distribution shows that a small number of the rats met the criterion within 10 days (12/63) but extended testing was required for the remaining rats to meet the criterion. The average number of days to meet the criterion was $15.9 (\pm \text{SEM } 0.7)$.

Figure 3 shows the relationship between the average MDMA self-administered during the last 3 days of 1.0 mg/kg/infusion and the first 3 days of 0.5 mg/kg/infusion. Regardless of the amount of time required to meet the initial criterion of 90 infusions of 1.0 mg/kg/infusion MDMA, when the dose of MDMA was decreased responding increased in a compensatory manner ($r = 0.757$, $P < .001$).

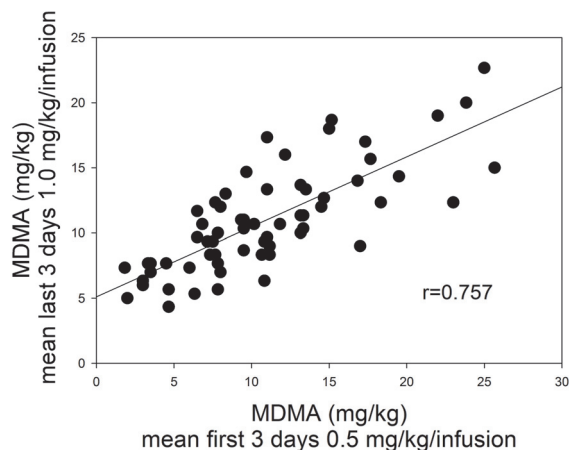


Figure 3: Regression analysis of mean intake during the last 3 days of self-administration of 1.0 mg/kg/infusion MDMA and the first 3 days of self-administration of 0.5 mg/kg/infusion MDMA.

Some rats were tested for a longer period of time during self-administration of 0.5 mg/kg/infusion. All of these rats met the initial criterion of 150 infusions of the 0.5 mg/kg/infusion dose of MDMA (range = 4–9 days) and daily tests were continued for 14 days. The mean number of lever responses as a function of test day is shown in Figure 4. There was an escalation of intake over days for these 11 rats from about 8.5 mg/kg on day 1 to 15.25 mg/kg on day 14. ANOVA (day \times lever) revealed a main effect of day ($F(13, 130) = 3.308, P < .01$), lever ($F(1, 10) = 103.228, P < .001$), and the interaction approached significance ($F(13, 130) = 1.770, P = .054$). A one-way ANOVA on the active lever responses revealed a significant effect of day ($F(13, 130) = 3.36, P < .001$) and simple contrasts indicated that responses produced on each day following day 8 were significantly higher than responses produced on day 1 ($P < .05$).

4 Discussion

In this paper, we provide data from a large cohort of rats that self-administered MDMA during a 2-year period. We present acquisition and maintenance data using a protocol that we have developed and that yields reliable self-administration in 40–60% of the rats. Our infusion times are relatively long (12.0 s), our infusion volumes are relatively large (100 μ L), and we do not have a time-out period following each infusion. These parameters are exactly the same as we have been using for cocaine self-administration but differ somewhat from parameters that are often used by other laboratories that generally administer shorter infusions, smaller volumes and often insert a time out of 30–60 s following each infusion. The extent to which these differences contribute to differences in the reinforcing efficacy of MDMA is unknown.

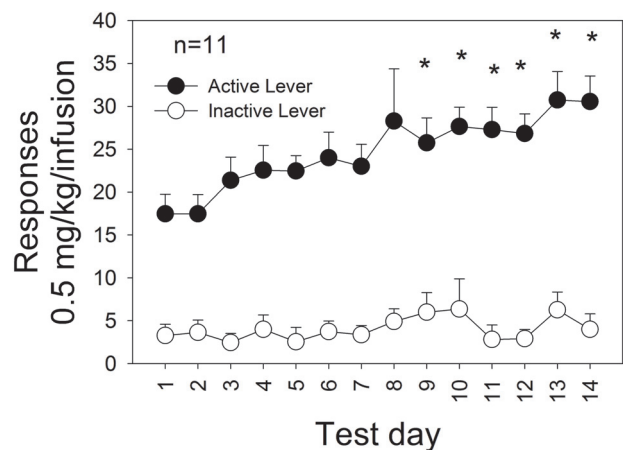


Figure 4: Mean number of active and inactive responses (+SEM) produced as a function of test day during extended testing of 14 days of MDMA self-administration (0.5 mg/kg/infusion). * $P < .05$ relative to responding on day 1.

It is apparent, however, that MDMA does not initially reinforce a large number of responses but that extended testing is required in order for MDMA to become an efficacious reinforcer. Our data suggest that only about half the rats self-administer MDMA to our criterion within the 25 day cutoff. Anecdotally, there are some rats that eventually meet the criterion with extended testing [38]. It is clear, however, that MDMA self-administration is acquired with much longer latencies than has been reported by our group and others for self-administration of cocaine [5, 39, 40] and therefore it is necessary to test these rats for a longer period of time. We have suggested that neuroadaptations in dopamine and/or 5HT contribute to the eventual acquisition of high rates of self-administration [34, 35]. Following low levels of self-administration (0.0 mg/kg, total intake) MDMA-produced 5HT was decreased but MDMA-produced DA was unchanged [30]. With more extended testing, however, MDMA-produced DA was increased [9].

Once acquired, all rats met the second criterion of 150 infusions but there are some rats that meet the second criterion quite rapidly, usually within 10 days. Other rats also required extended testing to meet this second criterion. These rats tend to have taken almost the maximum number of sessions (25) to meet the initial criterion and the number of responses produced by these rats remained low. Regardless, the number of responses produced was increased when the dose was decreased and there was a high and significant correlation between drug intake during the last days of self-administration of 1.0 mg/kg/infusion and the first days of 0.5 mg/kg/infusion MDMA. Thus, once acquired self-administration rates were sensitive to manipulations of dose, as we have previously reported [13, 36]. The amount self-administered MDMA was, however, still substantially lower than what we have

reported previously [36,38,39]. In those previous studies, self-administration continued for several additional weeks and there was an escalation of intake that is usually observed following extended self-administration of other drugs [1]. In a small subsample of rats from the present study that were tested for additional 2 weeks, we also observed an escalation of intake over days and following this two-week period, about 15.25 mg/kg/day was self-administered. When tested following more extensive self-administration experience, rats exhibit drug-seeking in response to drug primes or to cues that had been associated with self-administered MDMA [35,38] and MDMA self-administration is sensitive to pharmacological manipulations of dopamine D1- and D2-like receptors [4, 12]. Thus, we believe that neuroadaptations following extended exposure to self-administered MDMA underlie the development of high rates of responding and we have suggested that these neuroadaptations relate to tolerance to the serotonergic properties and/or sensitization to the dopaminergic properties of MDMA [34,35].

5 Conclusions

This manuscript characterizes various aspects of MDMA self-administration for a large cohort of rats tested during a 2-year period. The data suggest some unique aspects of MDMA self-administration; a relatively low percentage of rats acquire self-administration and a protracted period of acquisition training is required. With repeated testing, however, a pattern of self-administration that is comparable to patterns produced by other self-administered drugs emerges. The results show that some rats develop high levels of MDMA self-administration and that there is an escalation of intake with repeated daily testing. Coupled with our other data showing reinstatement of drug-seeking produced by either drug primes or stimuli that had been associated with self-administered MDMA, these findings are consistent with the data from users and suggest that a subsample of rats also demonstrate self-administration behavior that is consistent with MDMA dependence. This demonstration of acquisition and maintenance profiles of MDMA self-administration provide the procedures for further studies aimed at identifying relevant mechanisms of the different stages of MDMA self-administration.

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