

The threshold lowering effects of MDMA (ecstasy) on brain-stimulation reward

Carol B. Hubner*, Michael Bird, Stefanie Rassnick, and Conan Kornetsky

Boston University School of Medicine, Laboratory of Behavioral Pharmacology, 80 East Concord Street, Boston, MA 02118, USA

Abstract. 3,4-Methylenedioxymethamphetamine (MDMA) is a psychoactive phenylisopropylamine which is structurally similar to both amphetamine-related sympathomimetics and the hallucinogen, mescaline. MDMA produces pleasurable effects which include euphoria, and recent reports continue to demonstrate its widespread recreational use. The aim of the present study was to assess the effects of racemic MDMA on the threshold for rewarding intracranial self-stimulation, an animal model used to assess a drug's abuse liability in man. Rewarding electrical stimulation was delivered via electrodes stereotactically implanted in the medial forebrain bundle-lateral hypothalamic area of the rat brain. Thresholds were determined by means of a rate-independent psychophysical method. MDMA produced a dose-related lowering of the reward threshold in all four animals tested. Given that increased sensitivity for rewarding brain stimulation, measured as a lowering of the reward threshold, is an animal model of drug-induced euphoria these results suggest a similar mode of action for its reinforcing effects as other abused substances.

Key words: Racemic 3,4 MDMA – Self-stimulation – Reward – Abuse potential

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a psychoactive derivative of 3,4-methylenedioxyamphetamine (MDA). While MDA has both sympathomimetic and hallucinogenic activity (Anderson et al. 1978), several recent studies have demonstrated that MDMA produces qualitatively different psychoactive effects. Based on results obtained using the drug discrimination paradigm in which stimulus generalization was not found between racemic DOM, a hallucinogenic drug, and racemic MDMA (Glennon et al. 1982), it has been suggested that MDMA does not produce psychotomimetic effects. This interpretation is supported by clinical reports that MDMA produces altered states of consciousness, characterized by positive changes in attitude and self-confidence, without the concomitant production of hallucinogenic sensory distortions (Anderson et al. 1978; Shulgin and Nichols 1978; Greer and Strassman 1985). However, like MDA, it has been demonstrated that MDMA produces centrally mediated stimu-

lant effects. Generalization to racemic MDMA occurs in animals trained to discriminate (+)-amphetamine (Glennon and Young 1984) and sympathomimetic effects have been reported in man (Anderson et al. 1978; Shulgin and Nichols 1978).

While MDMA's psychoactive effects have led to the suggestion that it may serve as a useful adjunct to traditional psychotherapy (Greer 1983), the possibility that it may be subject to abuse and dependency has recently come under question. MDMA has been reported to produce feelings of euphoria (Greer and Strassman 1985) and there is evidence of extensive recreational use of this drug. There is also growing concern that MDMA may have irreversible neurotoxic effects, amid mounting evidence that chronic and acute treatments of MDMA produce long-lasting neurochemical and histochemical alterations of serotonergic neurons (Ricarte et al. 1987).

Drugs of abuse are believed to have their rewarding effects, and thus the potential for abuse, because of their actions on central reward pathways which subserve self-stimulation (Kornetsky et al. 1979). Increased sensitivity for rewarding brain stimulation has been used as an animal model for drug-induced euphoria and is thought to be predictive of abuse liability in man. Thus, the purpose of the present study was to determine if MDMA has similar effects on the threshold for rewarding brain stimulation in the rat as those of other substances of abuse.

Materials and methods

Subjects and surgical procedure. Four male albino rats of the F-344 strain (Charles River Laboratories, Inc., Wilmington, MA) weighing approximately 300 g were anesthetized with Chloropent[®] (0.3 ml/100 g body weight) and bipolar stainless steel electrodes (0.13 mm in diameter and insulated except at the tips) (Plastic Products, Roanoke, VA) were stereotactically implanted into the lateral hypothalamic region of the medial forebrain bundle (MFB-LH coordinates: 4.0 mm posterior to bregma, 1.4 mm lateral from the midline suture, and 8.5 mm ventral to the skull surface). The electrodes were placed through small burr holes in the skull and attached permanently to the surface with an acrylic platform. After surgery, animals received 60000 units of penicillin (Bicillin[®]) IM and were given at least 1 week for post-operative recovery before behavioral testing was begun. Animals were maintained on a 12 h light/dark cycle (lights on at 0600 hours), housed individually

* Current address: Research Institute Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA 92037, USA

Offprint requests to: C. Kornetsky

in stainless steel cages, and had ad lib access to food and water.

Training and testing procedure. Animals were trained and tested on a rate-independent procedure similar to that described previously (Esposito and Kornetsky 1977) in an acrylic chamber (20 × 20 × 35 cm) with a cylindrical manipulandum mounted on one wall. Reward thresholds are determined using a discrete trial task in which the presentation of a noncontingent stimulus (S1) signals the availability of an identical contingent pulse of the same intensity (S2). The intensities of both the noncontingent S1 and contingent S2 (both with pulse frequencies of 100 Hz) are covaried in descending and ascending columns using a modification of the psychophysical method of limits. Each trial begins on the average of one every 15 s. A response, i.e., one-quarter turn of the wheel manipulandum within 7.5 s after the onset of the S1, results in the immediate delivery of the S2. Additional microswitch closures that occur within 3.5 s after a correct response are recorded and analyzed but have no schedule consequences. Responses made during an intertrial interval institute a 30-s delay or time-out period before the onset of the next trial to punish unsolicited responding. Thus, in this procedure it is to the subjects advantage to make discrete wheel turns only in response to stimuli that are sufficiently rewarding.

Animals required approximately four 1-h training sessions to learn the task and approximately four additional sessions for the establishment of a stable threshold level, whereupon subcutaneous vehicle (saline) injections were begun. Animals were tested with vehicle injections for at least 5 days before drug administration was initiated.

Racemic MDMA was dissolved in isotonic saline and administered subcutaneously. All injections were made in volumes of 1 ml/kg body weight and the sequence of doses was counterbalanced between animals. Vehicle days were interspersed between each day of drug treatment so that animals received drug only twice weekly.

Statistical analysis. In this study reward thresholds were computed after each treatment for each animal using a variation of the Litchfield-Fertig probit analyses method (Goldstein 1964). Per cent response at each intensity level was converted to the corresponding probit value which was treated as the dependent variable. "Least squares" regression analysis was used to determine the line of "best fit", with the $\log_{10}$ of the stimulus intensity (μ A) being the independent variable. The threshold is by definition the interpolated intensity resulting in a 50% response (probit = 5). Each post-drug power function was logarithmically adjusted to compensate for any difference between the drug pre-injection session and the mean of all saline pre-injection sessions. This procedure involved the addition or subtraction of the $\log_{10}$ of the difference between the threshold of the drug pre-injection session and the mean threshold of all saline pre-injection sessions. Post-injection data were excluded from further analysis if the pre-injection threshold exceeded 2 standard deviations of the mean of all pre-injection thresholds.

The adjusted post-drug thresholds were transformed to standard scores (z-scores) based on the mean and standard deviation of the individual subject's post-saline thresholds. A z-score that exceeded ± 2.0 (greater than the 95% confidence interval) was preselected as the level of significance.

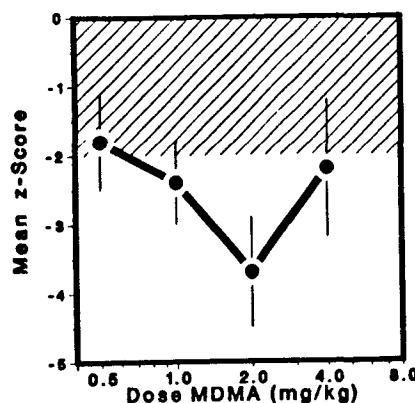


Fig. 1. The mean dose response curve of MDMA on the reward threshold of four rats. POST threshold data has been converted to standard z-scores based on the mean and standard deviation of the saline control days of each animal. A z-score of ± 2 , greater, demonstrates a significant change in threshold and denotes the 95% confidence limits

Dose-effect curves, based on z-scores, were generated for each of the four animals.

Histology. After completion of behavioral testing the animals were killed with an overdose of Cloropent[®] and perfused intracardially with saline and then 10% buffered formalin. The brains were then removed from the skull, embedded and sectioned frozen at 40 μ . Sections were stained with cresyl violet and luxol fast blue, and examined under a light microscope to determine the site of electrode placement.

Results

The mean dose-response curve for the effect of MDMA on the reward threshold of the four animals is shown in Fig. 1. The threshold intensities were transformed into z-scores and the error bars indicate the standard error of the mean z-score at each dose. As is evident from the graph the mean maximally effective dose of MDMA was 2.0 mg/kg. MDMA produced a dose-dependent lowering of the reward threshold, with the minimally effective dose varying only slightly from animal to animal. In one of the four animals 0.5 mg/kg was sufficient to produce a significant ($P \leq 0.05$) lowering in threshold current, while doses 1.0–2.0 mg/kg were required for lowerings in the remaining three animals. In all animals at least two of the tested doses of MDMA produced significant lowerings; effects were observed between 0.5 and 4.0 mg/kg.

Histological analysis revealed that the electrode tips of the four animals were within the MFB-LH area.

Discussion

These results demonstrate that racemic MDMA significantly lowers the threshold for intracranial stimulation to the medial forebrain bundle-lateral hypothalamic area, clearly indicating that this compound has effects on this reinforcement system which are similar to those of opioid and stimulant substances of abuse (Kornetsky 1985).

Recent evidence suggests that racemic MDMA may act as both an indirect dopamine agonist and a serotonin re-

tor agonist. Drug discrimination studies have indicated that MDMA possesses discriminative stimulus properties similar to the indirect dopamine agonists *d*-amphetamine (Glennon and Young 1984) and 1-cathinone (Schechter 1986). Other studies, however, have demonstrated that MDMA has affinity for 5-HT₁ and 5-HT₂ receptors (Lyon et al. 1986) and can generalize for various serotonergic agonists (Schechter 1986).

While structurally related to both amphetamine and mescaline, results obtained from drug discrimination experiments (Glennon et al. 1982; Glennon and Young 1984) and clinical reports (Anderson et al. 1978; Shulgin and Nichols 1978; Greer and Strassman 1985) indicate that MDMA has a stimulant component to its activity but produces little, if any, hallucinogenic effect. These findings, in conjunction with previous observations (unpublished) in which we failed to find significant threshold lowering effects of LSD on brain-stimulation reward, indicate that MDMA's reinforcing effects are most likely mediated by the same substrates which subserve amphetamine reward.

We are currently completing studies which more conclusively address the relative importance of dopamine and serotonin in MDMA's euphoriant effects.

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