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THE EFFECTS OF (±)-METHYLENEDIOXYMETHAMPHETAMINE AND (±)-METHYLENEDIOXYAMPHETAMINE IN MONKEYS TRAINED TO DISCRIMINATE (+)-AMPHETAMINE FROM SALINE

JONATHAN B. KAMIEN[a], CHRIS E. JOHANSON[b], CHARLES R. SCHUSTER[a,b,c] and WILLIAM L. WOOLVERTON[c,*]

Departments of [a] Behavioral Sciences, [b] Psychiatry, [c] Pharmacological and Physiological Sciences, Drug Abuse Research Center, Department of Psychiatry, Pritzker School of Medicine, The University of Chicago, Chicago, IL 60637 (U.S.A.)

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SUMMARY

Recently, attention has been focused on (±)-methylenedioxymethamphetamine (MDMA), a psychotomimetic agent chemically closely related to the psychomotor stimulant methamphetamine, and also to the hallucinogen mescaline. In the present experiment, the effects of MDMA and (±)-3,4-methylenedioxyamphetamine (MDA) were determined in rhesus monkeys that were trained to discriminate intravenously administered (+)-amphetamine (AMPH) from saline in a two-lever, food-maintained paradigm or to discriminate intragastrically administered AMPH from saline in a signalled electric shock avoidance paradigm. MDMA produced 100% drug-appropriate responding in all six monkeys, regardless of the procedure and route of administration while MDA substituted completely for AMPH in only two of three monkeys in each paradigm. The results suggest that MDMA has subjective effects that are similar to those of AMPH while MDA is somewhat less like AMPH.

Key words: (±)-Methylenedioxymethamphetamine — (±)-3,4-Methylenedioxyamphetamine — Amphetamine — Drug discrimination — Rhesus monkey

INTRODUCTION

Recently, attention has been focused on MDMA, a psychotomimetic agent chemically closely related to the psychomotor stimulant methamphetamine,

*To whom correspondence should be addressed at: Department of Pharmacological and Physiological Sciences, 947 E. 58th St., Chicago, IL 60637, U.S.A.

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and also to the hallucinogen mescaline. This compound has stirred interest due to its promotion as an adjunct to psychotherapy [1] and reports of increasing recreational use [2,3]. MDMA is a so-called 'designer drug' which has not yet undergone extensive scientific investigation. MDMA is also structurally similar to MDA which, like methamphetamine, has been shown to be neurotoxic [4–7]. These findings, together with the use of MDMA in humans and the lack of laboratory studies demonstrating the safety of MDMA, led the federal Drug Enforcement Agency, in June, 1985, to exercise emergency powers and place MDMA under Schedule I. Schedule I is reserved for drugs that have dependence potential but no accepted medical use. The DEA's stated intent is to review this emergency scheduling after a 1-year period, during which time laboratory testing of MDMA will be carried out. The present study, as well as two others [8,9] published in this issue, is part of a multi-laboratory effort to provide information about the behavioral effects of MDMA in animals. Another study that is part of this effort has reported that MDMA is toxic to serotonergic neurons in the central nervous system (CNS) of rats [10].

Subjective effects are an important component of the actions of a psychoactive drug. However, there have been no controlled studies designed to assess the subjective effects of MDMA in humans. Since the discriminative stimulus effects of drugs in animals are thought to predict their subjective effects in humans [11], drug discrimination studies with MDMA are of interest. Glennon and Young [12,13] studied the discriminative stimulus effects of MDMA, MDA, AMPH and the hallucinogen, 2,5-dimethoxy-4-methylamphetamine (DOM) using a drug discrimination paradigm. They reported that both MDMA and MDA substituted for AMPH in AMPH-trained rats. Further, MDA but not MDMA substituted for DOM in DOM-trained rats. Their findings suggest that MDMA is an AMPH-like discriminative stimulus while MDA has both psychomotor stimulant and hallucinogen-like discriminative stimulus effects. The purpose of the present study is to extend this work to another species, rhesus monkeys, utilizing two routes of administration, intravenous (i.v.) and intragastric (i.g.), and utilizing two drug discrimination procedures with behavior maintained by food-delivery or by shock-avoidance.

METHOD

Animals and apparatus

The subjects were 4 male (8002, 8.8 kg; 7039, 7.9 kg; 7037, 10.4 kg; 1024, 7.0 kg) and 2 female rhesus monkeys (8085, 4.2 kg; 8086, 5.0 kg). Monkeys 8002, 7039, and 7037 had participated in studies of drug self-administration and drug effects on schedule-controlled responding. Monkeys 7037, 8002, 8085 and 8086 had previously been trained to discriminate i.m. cocaine from saline [14]. All monkeys had been trained and tested with a wide range of compounds under the terminal conditions described below prior to the present study [15, and unpublished data]. All were individually housed in stainless steel cages in a room that was maintained at 23 C and on a 16 h/8 h light/dark cycle (light 0600–2200). Water was continuously available in the home cage and each

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animal was given a chewable multiple vitamin tablet 3 days/week. Prior to experimental sessions, the monkeys were seated in restraining chairs (Plas Labs, Lansing, MI) and placed in one of two wooden chambers (175 cm h × 85 cm w × 67 cm d) equipped with two response levers with associated white stimulus lights and a 34 watt white ceiling light. A seated monkey could press a lever to receive food pellets delivered by an automatic pellet dispenser (Ralph Gerbrands Co., Arlington, MA) or to avoid electric shocks (BRS/LVE, SG-903) delivered to their feet. Cables connected the cubicles to solid state programming and recording equipment located in an adjacent room.

Procedure

Three monkeys (1024, 8085, 8086; i.v. monkeys) were trained to discriminate i.v. AMPH and three monkeys (7037, 7039, 8002; i.g. monkeys) were trained to discriminate i.g. AMPH. For the i.v. monkeys, food intake was restricted to 1-g banana-flavored pellets (P. J. Noyes, Lancaster, NH) received in experimental sessions and post-session Purina monkey chow sufficient to maintain a weight that resulted in stable behavioral performance. The i.g. monkeys were fed 150–200 g Purina monkey chow every day after their sessions.

Training sessions. The three i.v. monkeys had been trained in a two lever, fixed-ratio 30 (FR30) food-reinforced operant schedule [14,15]. During training sessions, one lever was designated the drug lever and the other lever was designated the saline lever. Five minutes after an injection of AMPH (0.12 mg/kg for monkeys 8085 and 8086 or 0.25 mg/kg for monkey 1024) or an injection of saline, the house lights and the lever lights were illuminated. AMPH training injections were always i.v. while saline training injections were i.m., except for occasional i.v. administration of saline to rule out route of administration as a discriminative stimulus. Thirty consecutive responses on the lever appropriate to the injection resulted in the delivery of 7 banana-flavored pellets and turned off the lights. Responding on the lever that was inappropriate to the injection reset the response requirement on the other lever to 30. These sessions were terminated by food delivery, or 10 min, whichever came first. The monkey's lever choices were considered to be under the control of the injection when 80% or more of the responses occurred on the injection-appropriate lever for at least 7 of 8 consecutive sessions.

For the i.g. monkeys, the drug discrimination procedure has been described in detail previously [16]. Briefly, the three i.g. monkeys were trained in a two-lever, signalled trial procedure to avoid electric shock. One hour after an i.g. infusion of AMPH (0.56 mg/kg for monkeys 7037 and 8002 or 1.0 mg/kg for monkey 7039) or saline, the houselights and the lever lights were illuminated and responding on the lever appropriate to the infusion turned off the lights and prevented shock delivery. Responding on the lever that was inappropriate to the infusion started a 2-s change over delay during which responses that occurred on the appropriate lever had no programmed consequence. If an appropriate response was not made within 5 s of onset of the lights, shock (250 ms duration, 10 mA intensity) was delivered every 2 s until an appropriate

response was made. Following an appropriate response, there was a 55-s inter-trial interval. The session lasted for 30 trials or 40 min, whichever came first. The monkeys' lever choices were considered to be under the control of the infusion when more than 90% of the trials were completed on the appropriate lever for 6 consecutive sessions.

Testing. Test sessions for the i.v. monkeys were identical to training sessions with three exceptions: (1) saline or various doses of MDMA and MDA, were injected (i.v.), before the session, (2) food was available as a consequence of 30 consecutive responses on either lever, and (3) session length was unlimited and was terminated in all cases by food delivery. An AMPH and a saline training session were conducted between test sessions to maintain and affirm discriminative performance. For the i.v. monkeys, as long as the training criterion was maintained, every third session was a test session.

Test sessions in the i.g. monkeys were identical to training sessions with two exceptions: (1) saline or various doses of MDMA and MDA were infused intragastrically before the session, and (2) a response on either lever terminated the trial and avoided shocks. In these monkeys, AMPH or saline training sessions were conducted on Mondays, Tuesdays and Thursdays and test sessions on Wednesdays and Fridays. Test sessions were conducted as long as more than 90% of the trials were completed on the appropriate lever during the two previous training sessions.

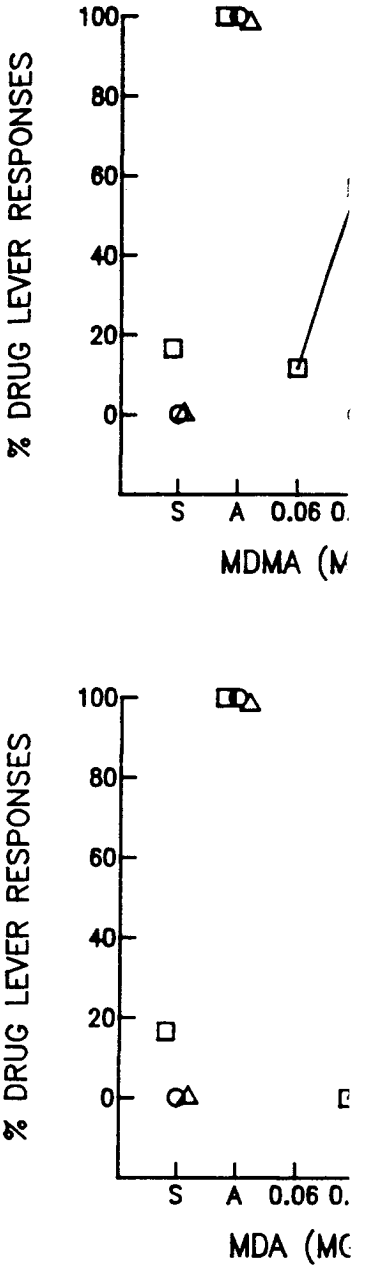
For both groups of monkeys, doses of MDMA and MDA were tested in a non-systematic order and ranged between 0.06 and 1.0 mg/kg in the i.v. monkeys and between 0.1 and 5.6 mg/kg in the i.g. monkeys. Each dose was tested twice in the i.v. monkeys, once with a saline training session and once with a drug training session preceding the test day. Tests in the i.g. monkeys were conducted once for each dose.

Data analysis. The percentage of the total responses that occurred on the drug lever during a test session was calculated for both groups of monkeys. For the i.v. monkeys, the results from each of the two tests conducted with each dose were averaged. If a test produced greater than 80% AMPH-appropriate responses in the i.v. monkeys (or AMPH-appropriate trials in the i.g. monkeys), a drug was considered to substitute for AMPH. Cumulative response rate for both levers was calculated for the i.v. monkeys and cumulative latency from the beginning to the termination of a trial was recorded for the i.g. monkeys.

Drugs. MDA hydrochloride, MDMA hydrochloride and AMPH sulfate were provided by the National Institute on Drug Abuse. Each drug was dissolved in 0.9% saline to a concentration that allowed administration of a constant volume of 0.1 ml/kg, regardless of the dose, which is expressed as the salt.

RESULTS

In training sessions, AMPH typically produced greater than 90% AMPH-appropriate responding while saline rarely occasioned drug-appropriate responding. In previous studies with the i.v. monkeys [15], 0.015–0.06 mg/kg



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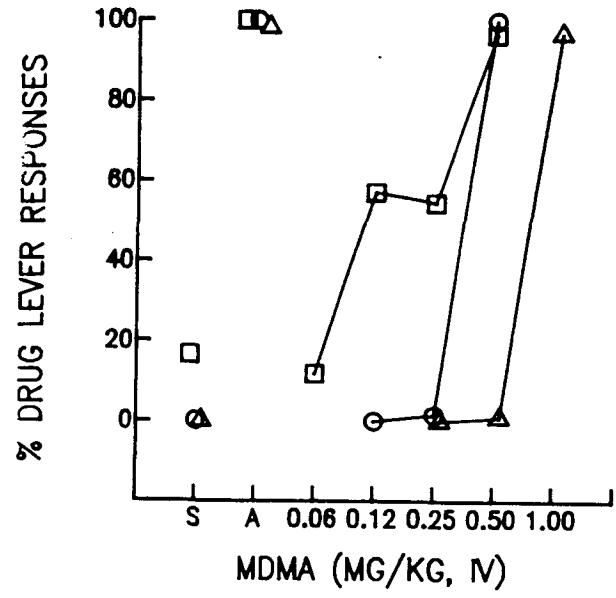


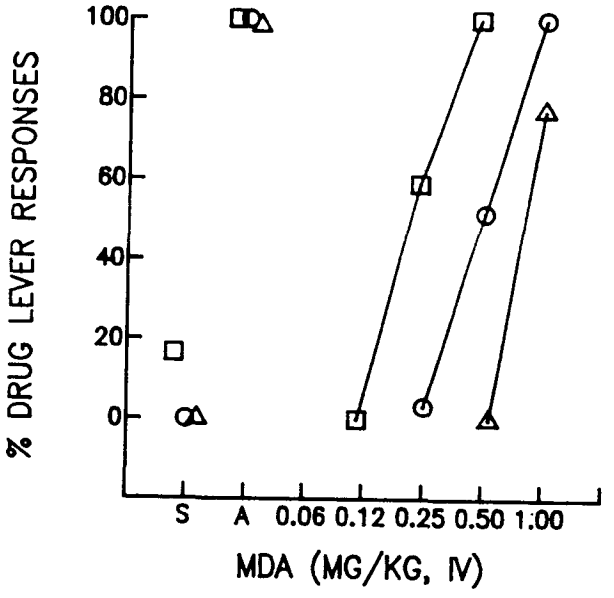
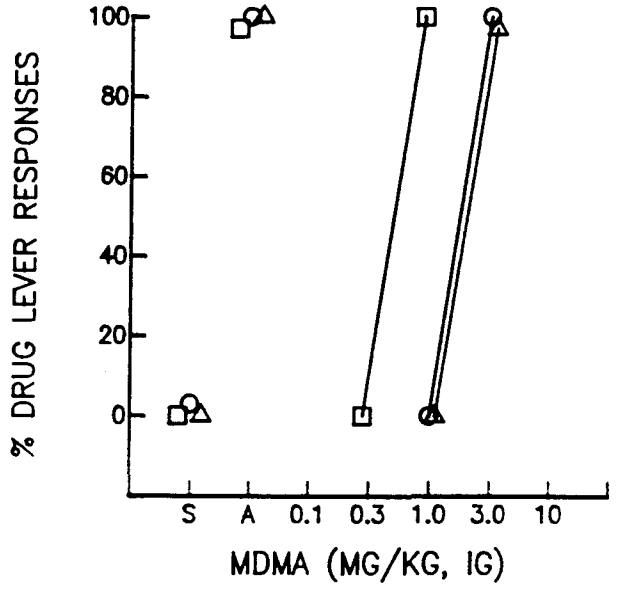


Fig. 1. Effects of MDMA (upper panel) and MDA (lower panel) in monkeys trained to discriminate intravenous AMPH from saline. Training doses of AMPH were 0.12 mg/kg, (○, 8085; □, 8086) or 0.25 mg/kg (△, 1024). Ordinate: the percent of responses during test sessions that occurred on the AMPH-appropriate lever. Each point is the mean of two determinations, one preceded by a saline training day and the other preceded by a drug training day. S = saline; A = training dose of AMPH.



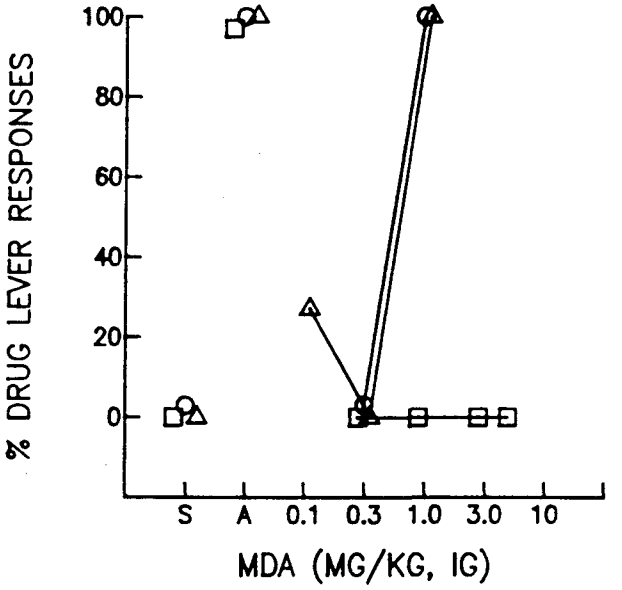


Fig. 2. Effects of MDMA (upper panel) and MDA (lower panel) in monkeys trained to discriminate intragastric AMPH from saline. Training doses of AMPH were 0.56 mg/kg, (△, 7037; □, 8002) or 1.0 mg/kg (○, 7039). Ordinate: the percent of trials during test sessions that were terminated by responses that occurred on the AMPH-appropriate lever. S = saline; A = training dose of AMPH.

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DISCUSSION

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AMPH produced a dose-related increase to above 80% AMPH-appropriate responding in test sessions while the rate of responding in this dose range was similar to saline rates. Pentobarbital, on the other hand, produced principally saline-appropriate responding at doses (4.0 or 8.0 mg/kg) that substantially reduced rate of responding. In previous studies with the i.g. monkeys [unpublished results], 0.1–0.3 mg/kg AMPH substituted for the training dose of AMPH, while pentobarbital did not substitute for AMPH in two (7037, 8002) of three monkeys. In test sessions, MDMA produced dose-related increases up to 100% in drug-appropriate responding in all monkeys, while saline always occasioned less than 20% drug-appropriate responding, whether the monkey was trained to discriminate AMPH via the i.v. or i.g. route. In the i.v. monkeys, 100% drug lever responding occurred following 0.5 mg/kg MDMA in 8085 and 8086 and 1.0 mg/kg MDMA in 1024 (Fig. 1, upper panel). The doses of MDMA that substituted for AMPH-reduced response rates to a mean of 0.2 ± 0.1 (S.E.M.) responses/s compared to 1.8 ± 0.4 responses/s following saline. In the i.g. monkeys, 100% AMPH-appropriate responding occurred following MDMA doses of 1.0 mg/kg in 8002 and 3.0 mg/kg in 7037 and 7039 (Fig. 2, upper panel). Cumulative latencies following the dose of MDMA that substituted for AMPH were essentially unchanged compared to cumulative latencies following saline.

MDA also produced dose-related increases in drug-appropriate responding up to 100% in two of three monkeys trained to discriminate i.v. AMPH and in two of three monkeys trained to discriminate i.g. AMPH. This occurred following 0.5 or 1.0 mg/kg i.v. and 1.0 mg/kg i.g. of MDA (Figs. 1 and 2, lower panels). As was the case with MDMA, substitution for AMPH by MDA in the i.v. monkeys was accompanied by large decreases in response rate (0.5 responses/s) by 8086 and 0.017 responses/s by 8085). Administration of 1.0 mg/kg of MDA produced 77% AMPH-appropriate responding in the third i.v. monkey (1024). Higher doses of MDA could not be tested in this subject due to a decrease of response rate to 0.03 responses/s following 1.0 mg/kg MDA. MDA did not produce AMPH-appropriate responding in the third i.g. monkey, even after a dose of 5.6 mg/kg. Higher doses were not attempted out of concern for the monkey's health.

DISCUSSION

MDMA produced AMPH-like discriminative stimulus effects in rhesus monkeys trained to discriminate AMPH from saline. These effects occurred regardless of route of administration or behavioral paradigm. Pentobarbital, on the other hand, did not substitute for AMPH in 5 of 6 monkeys thus emphasizing the pharmacological specificity of the AMPH discriminative stimulus. These results confirm and extend the findings of AMPH-like discriminative stimulus effects for MDMA in rats [12,13] and pigeons [8].

By the i.v. route, MDMA was from 8–16 times less potent than AMPH in producing AMPH-like discriminative stimulus effects. Unlike AMPH, however, the dose range of MDMA that engendered 100% AMPH-appropriate

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; A = training dose of AMPH.

responding caused large decreases in response rate. By the i.g. route, MDMA was from 3–10 times less potent that AMPH. It is not clear whether the differences in relative potencies observed in the two paradigms were due to route of administration and differences in bioavailability or due to other procedural differences. The i.g. doses of MDMA that substituted for AMPH were between two to three times higher than the i.v. doses of MDMA that substituted for AMPH.

MDA, on the other hand, substituted for AMPH completely in only four of the six monkeys tested. There was partial substitution (77%, 1024) in one of the i.v. monkeys but in the third i.g. monkey, MDA did not occasion drug-appropriate responding up to a dose of 5.6 mg/kg. MDA, when it substituted for AMPH, was about 16 times less potent than AMPH via the i.v. route and about three times less potent than AMPH by the i.g. route. Like MDMA, the dose range in which MDA substituted for AMPH was accompanied by a large decrease in rate of responding. The doses of i.g. MDA that substituted for AMPH were up to two times higher than the i.v. doses of MDA that substituted for AMPH. These results suggest that the MDA discriminative stimulus was less like AMPH than was the MDMA discriminative stimulus, and support the conclusion that MDMA and MDA differ in their stimulus properties [12,13].

Drug discrimination is a useful investigative technique for predicting possible subjective effects of a drug in humans [11], pharmacological classification of compounds [17], and providing in vivo evidence concerning the mechanism of action of drugs [e.g. 18]. Taken together with the results of others [8,12,13] the present study emphasizes the species generality of the AMPH-like discriminative stimulus properties of MDMA. Thus, MDMA would be expected to have AMPH-like subjective effects in humans. An important consideration in predicting the dependence potential of drugs is whether the compound is self-administered by animals. It has recently been found that MDMA is self-administered by rhesus monkeys [9]. Considered together, drug discrimination and self-administration results suggest that MDMA has dependence potential that is at least partially due to its similarity to AMPH.

ACKNOWLEDGMENT

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