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DISCRIMINATIVE STIMULUS PROPERTIES OF (±)-3,4-METHYLENEDIOXYMETHAMPHETAMINE AND (±)-3,4-METHYLENEDIOXYAMPHETAMINE IN PIGEONS

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SUMMARY

Pigeons trained to discriminate (+)-amphetamine (AMPH) from saline in a two-key food-maintained drug discrimination paradigm, were used to investigate the discriminative stimulus (DS) effects of two structural analogues of amphetamine, namely (±)-3,4-methylenedioxymethamphetamine (MDMA) and (±)-3,4-methylenedioxyamphetamine (MDA). After discrimination performance was stable (90% injection-appropriate responding), test sessions with various doses of AMPH were conducted and a dose-dependent relationship for AMPH-appropriate responding was obtained. Both MDMA (3.0 mg/kg) and MDA (3.0 or 5.6 mg/kg) substituted for AMPH; however, at these doses MDA produced a greater decrease in response rate compared to AMPH and MDMA. Furthermore, while MDMA and MDA were similar in potency in producing drug-appropriate responding, both were less potent than AMPH. These results indicate that MDMA and MDA have DS effects similar to AMPH in pigeons.

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

INTRODUCTION

At this time there is a paucity of data regarding the behavioral effects of MDMA and a related compound MDA. They are both close structural analogs of the psychomotor stimulant amphetamine [1] and the hallucinogen

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mescaline [2] suggesting that they may have effects similar to stimulants, hallucinogens or both. One approach for determining the pharmacological classification of these compounds is to assess their DS properties in animals [3,4] which may correspond to subjective effects in humans [5,6]. Glennon and Young [1,7] found that MDA produced both stimulant-like and hallucinogen-like effects [8]. In contrast, MDMA failed to share DS properties with the hallucinogenic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) [8] but did produce AMPH-appropriate responding in rats [1]. The purpose of the present study was to evaluate the DS properties of MDMA and MDA in pigeons trained in a two-key food-maintained drug discrimination paradigm to discriminate AMPH from saline.

METHOD

Animals

Subjects were three white Carneaux pigeons maintained at 80% of their free-feeding weights and housed individually with water and grit freely available. To supplement food obtained during the experimental session, Purina Pigeon Checkers were provided after the session to maintain reduced weights. The pigeons had previously been trained to discriminate 2.0 mg/kg AMPH from saline in a two-key food-maintained drug discrimination procedure and had been tested with a variety of drugs [9].

Apparatus

The experiment was conducted in two ventilated custom-made operant chambers (inside dimensions 32 × 28 × 32 cm). The front and back panels were aluminum and the side walls were plastic. Each chamber was equipped with two translucent response keys (2.5 cm diameter; G6315, Ralph Gerbrands Co., Arlington, MA) which were transilluminated during the experimental session by white 7-W lamps (IEE Van Nuys, CA) located behind the keys. The keys were 12.5 cm apart and located approx. 24 cm above the floor of the chamber. Purina Pigeon Checkers were made available from a food magazine (G5610A, Ralph Gerbrands Co., Arlington, MA) centered between and below the response keys, 7.6 cm above the floor. The food magazine was illuminated during food delivery. A 6-W white houselight, located behind the back panel, provided indirect illumination during experimental sessions. Programming and data collection were accomplished by a Rockwell AIM 65 microcomputer and cumulative recorders (Ralph Gerbrands Co., Arlington, MA) which were located in an adjacent room.

Training

The three pigeons used in this experiment had previously been trained to discriminate 2.0 mg/kg of AMPH from saline [9] under the terminal training conditions. Under these conditions, each pigeon was injected with AMPH (2.0 mg/kg) or saline in a 1.0 ml/kg volume 10 min before the session. Following this pre-treatment period, the experimental session began, signalled by the

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illumination of both keys and the houselight. Thirty consecutive responses on the injection-appropriate key under a fixed-ratio 30 schedule (FR 30) resulted in 3-s access to food. Responses on the incorrect key reset the fixed-ratio requirement on the correct key. For pigeons No. 408 and No. 3380 the left key was correct after AMPH administration and for pigeon No. 428 the right key was correct after AMPH. The opposite key was designated correct following saline injections. The drug-key-reinforcer relationship was maintained throughout the experiment. Each session lasted until 50 reinforcers were delivered or until 30 min had elapsed, whichever occurred first.

Training sessions continued until the percent of total responses on the correct key was above 90% and the number of responses emitted on the incorrect key before the first reinforcer was delivered was less than 30 for seven consecutive sessions. The injection preceding each session was selected from a pseudorandom sequence, with the restriction that no condition would occur for three consecutive sessions.

Testing

In order to evaluate the stimulus properties of MDMA and MDA and other doses of AMPH, test sessions were conducted. Throughout a test session, 30 consecutive responses on either the AMPH-appropriate or saline-appropriate key resulted in food delivery. In all other respects test sessions were identical to training sessions. Between test sessions, training sessions continued to be conducted. AMPH and saline were administered in a double alternation sequence with test sessions every third session, i.e., saline, AMPH, test, AMPH, saline, test, etc. If during a training session an animal failed to meet the training criteria, further testing was postponed until the animal met these criteria for at least two consecutive sessions.

Initially a dose-response function for AMPH was established during testing sessions. Subsequently, doses of MDMA and MDA were tested once with three or four doses of each compound tested in a mixed order. For each pigeon, the dose-response function for each drug was completed before another compound was tested. After the completion of each dose-response function, pigeons were given test sessions with either 2.0 mg/kg AMPH or saline.

Data analysis

A drug was considered to produce DS effects similar to those of the training dose of AMPH if at least 80% of the total responses during the test session were emitted on the AMPH-appropriate key. If no reinforcers were obtained during the test session, the data were not included in the analysis of drug-appropriate responding. In addition to recording the distribution of responses, the overall response rate (responses/sec) on the two keys was determined for each session. Doses of test compounds were tested until at least 80% of the responses occurred on the AMPH-appropriate key or until a dose was reached which substantially reduced response rate.

Drugs

AMPH, MDMA, and MDA were gifts from the National Institute on Drug Abuse. These drugs were dissolved in 0.9% saline and the doses are expressed in terms of the salt.

RESULTS

All three pigeons emitted greater than 90% of the responses on the injection-appropriate key throughout most of the experiment. Rates of responding during training sessions were similar following administration of either the training dose of AMPH or saline. During test sessions the rate of responding of the three pigeons ranged from 1.80 to 2.86 responses/s following saline and from 1.64 to 2.35 responses/s following AMPH (2.0 mg/kg). AMPH produced a dose-related increase in the percentage of responses emitted on the AMPH-appropriate key. At the lowest dose tested (0.3 mg/kg), less than 4% of responding occurred on the AMPH-appropriate key in all three pigeons, whereas at 1.0 and 3.0 mg/kg more than 90% of responding occurred on the AMPH-appropriate key. AMPH also produced a dose-related decrease in the rate of responding. The dose of 3.0 mg/kg reduced response rate to the same extent as the training dose (2.0 mg/kg) in two pigeons; however, in No. 3380 this dose completely suppressed responding.

MDMA produced a dose-related increase in the percentage of responses emitted on the AMPH-appropriate key (Fig. 1). The doses of MDMA that produced predominantly drug-key responding reduced response rate to no less than 1.25 responses/s. Pigeon No. 408 was more sensitive to the AMPH-like properties of MDMA in that doses of 0.3 and 1.0 mg/kg produced 78% and 74% AMPH-appropriate responding. In addition, 3.0 mg/kg reduced rate to 0.03 responses/s, whereas in the other two pigeons this dose did not substantially reduce response rate.

Administration of MDA resulted in AMPH-appropriate responding greater than 90% in the three pigeons tested (Fig. 1). In contrast to MDMA, the doses of MDA that substituted for AMPH (3.0 and 5.6 mg/kg in No. 3380 and 5.6 mg/kg in No. 408 and No. 428) decreased response rate to less than 0.15 responses/s in every pigeon.

DISCUSSION

The findings that MDMA and MDA both have DS properties similar to AMPH in the present experiment are consistent with drug discrimination results in rats [1,7,8] and rhesus monkeys [10]. Moreover, drugs from disparate pharmacological classes such as morphine and diazepam did not substitute for AMPH in pigeons [9] confirming the pharmacological specificity of these results.

Furthermore, in each of these species MDMA and MDA were similar to each other in potency but less potent than AMPH. For instance, in rats trained to discriminate 1.0 mg/kg AMPH, the ED_{50}s for substitution of MDMA (1.7 mg/

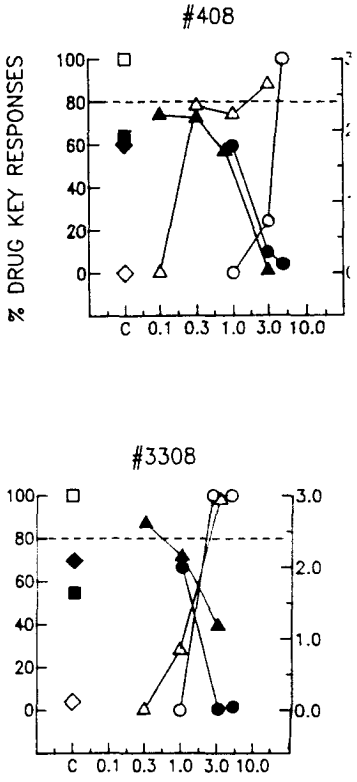

Fig. 1. Effects of MDMA and MDA
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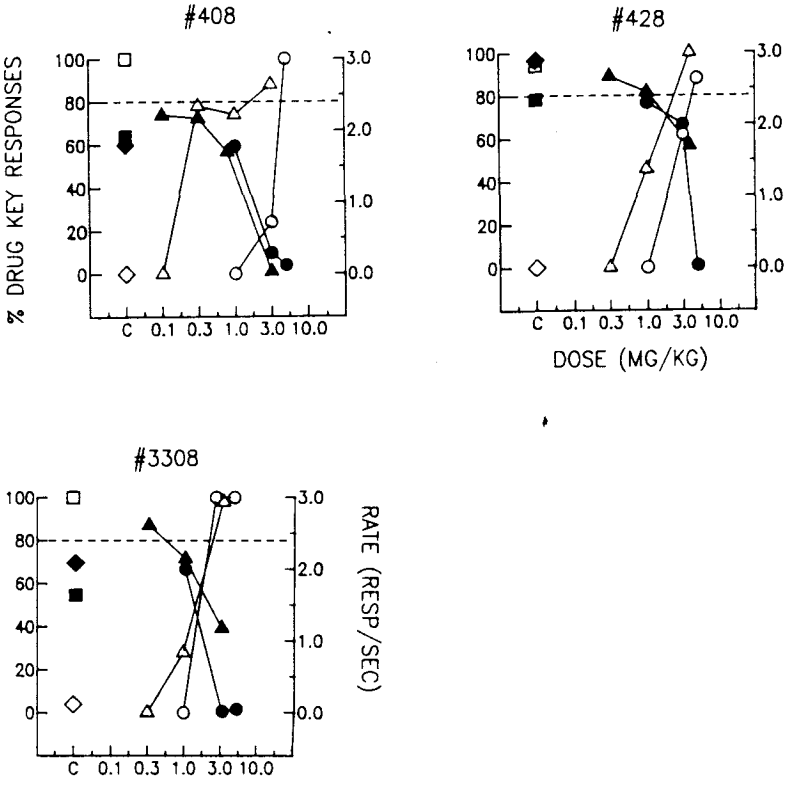

Fig. 1. Effects of MDMA and MDA in pigeons trained to discriminate AMPH from saline. Open symbols indicate the percent of AMPH-appropriate responding as a function of dose during substitution test sessions with MDMA (—) and MDA ( ). The open symbols above control (c) are the percent of drug-key responding following test sessions of 2.0 mg/kg AMPH ( ) and saline ( ). The dashed line represents the 80% criterion used to determine if a given drug dose substituted for AMPH. Closed symbols indicate response rate (resp./s), which was calculated by dividing the total number of responses emitted on both keys by the session time.

kg) and MDA (2.3 mg/kg) were not significantly different [1,7]. In rhesus monkeys trained to discriminate 0.125 or 0.250 mg/kg AMPH, both MDMA and MDA substituted for AMPH at 0.5–1.0 mg/kg when given intravenously [10]. When administered intragastrically, substitution for 0.56 or 1.0 mg/kg AMPH occurred at 1.0 to 3.0 mg/kg for MDMA and 1.0 mg/kg for MDA [10]. In pigeons, MDMA substituted for AMPH at 3.0 mg/kg and MDA substituted for AMPH at 3.0 or 5.6 mg/kg.

In summary, this study provides additional behavioral evidence that MDMA and MDA have DS effects similar to AMPH regardless of route of administration, training dose, or species. Even though both test compounds produced AMPH- appropriate responding in the present study, relative to MDMA and AMPH, MDA produced a greater decrease in response rate at doses that substituted for AMPH. This suggests that MDA produces more non-specific

disruptive effects on behavior than MDMA at doses that substitute for AMPH in the pigeon.

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CHOICE OF BLIND ME
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SUMMARY

In the present study, a ch
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Key words: Methadone —

INTRODUCTION

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