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Acute Effects of Methylenedioxymethamphetamine (MDMA) on Several Complex Brain Functions in Monkeys

DAVID L. FREDERICK,*[1] MICHAEL P. GILLAM,*
RICHARD R. ALLEN† AND MERLE G. PAULE*‡

*Division of Neurotoxicology and †Computer Based Systems, Inc.,
National Center for Toxicological Research/FDA, Jefferson, AR 72079-9502
‡Departments of Pharmacology and Toxicology, and Pediatrics,
University of Arkansas for Medical Sciences, Little Rock, AR 72205

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FREDERICK, D. L., M. P. GILLAM, R. R. ALLEN AND M. G. PAULE. *Acute effects of methylenedioxymethamphetamine (MDMA) on several complex brain functions in monkeys.* PHARMACOL BIOCHEM BEHAV 51(2/3) 301-307, 1995.—The effects of MDMA were assessed in rhesus macaques using behavior in an operant test battery (OTB) consisting of five food-reinforced tasks designed to model aspects of time estimation, short-term memory, and attention, motivation, learning, and color and position discrimination. Testing occurred 30 min after intramuscular. injections of MDMA (0.0, 0.1, 0.3, and 1.0 mg/kg). The behavioral endpoints monitored included percent task completed, response rate or latency, and response accuracy. Percent task completed was significantly decreased in the time estimation, learning, and motivation tasks at 1.0 mg/kg as compared to saline controls. Response accuracies in the time estimation and learning tasks were also decreased at 1.0 mg/kg. Response rate was decreased at 1.0 mg/kg in the motivation task but was not significantly affected in any other tasks. No behavioral endpoints were significantly affected in the short-term memory and attention and color and position discrimination tasks at any dose tested. Results indicate that time estimation, motivation, and learning are more sensitive to the acute effects of MDMA than are short-term memory and attention and color and position discrimination.

MDMA Ecstasy Monkey Operant behavior Learning Short-term memory Time perception Motivation Color and position discrimination Food reinforcement Serotonin Amphetamine Hallucinogen

THE PHENYLISOPROPYLAMINE 3,4-methylenedioxymethamphetamine (MDMA), a ring-substituted amphetamine analog also known as Ecstasy, has been proposed by some as a useful adjunct for psychotherapy based on subjective reports that it increases the user's capacity for intimacy, trust, and introspection (13). In 1985 MDMA was assigned to Schedule 1 under the Controlled Substance Act by the Drug Enforcement Agency (18) in response to increased recreational use and concerns over potential toxicity to serotonergic nerve terminals. Such toxicity had been shown to occur in rats administered high subcutaneous (SC) doses of the structurally similar compound 3,4-methylenedioxyamphetamine (MDA) every 12 h for 4 consecutive days (27). The neurotransmitter serotonin (5-HT) has been implicated, either directly or through interactions with other neurotransmitter systems, as a significant component involved with MDMA's actions in a number of CNS functions. Two of these functions, learning and memory, have received considerable experimental attention [see (14) for brief review]. Subsequent research has shown that MDMA induces short- and long-term depletion of brain 5-HT levels in rodents when administered SC (2,5) or orally (8,37,38). MDMA toxicity to serotonergic neurons has also been shown in monkeys when administered SC (28) or orally (1,28,37,38). Whether MDMA is neurotoxic to humans is at present uncer-

[1] Requests for reprints should be addressed to David L. Frederick, Division of Neurotoxicology, HFT-132, National Center for Toxicological Research, 3900 NCTR Road, Jefferson, AR 72079-9502.

tain. The serotonergic depletion induced in rodents and primates generally results from the administration of doses of MDMA greater than those typically used by humans (12) and has been shown to occur only after multiple daily administrations.

Although evidence of MDMA neurotoxicity noted in rodents and primates after relatively high doses is abundant, MDMA's acute effects on schedule-controlled behaviors have not been studied in great detail in either species and attempts have generally focused on single operant behaviors. MDMA has been shown to produce dose-dependent decreases in schedule-controlled responding in pigeons (19,22), to increase response rates and decrease reinforcement rates of rats performing a differential-reinforcement-of-low-rates task (20), and to decrease accuracy of monkeys performing a repeated acquisition task at doses that had little effect on learning or performance of response chains (39).

To generate a more comprehensive neurobehavioral profile on the acute effects of MDMA, the present experiment used performance by monkeys in an operant test battery (OTB). The OTB was devised to permit the simultaneous assessment of multiple behaviors, each believed to model different brain functions. The tasks and the brain functions they were designed to model include: temporal response differentiation (time estimation), delayed matching-to-sample (short-term memory and attention), progressive ratio (motivation to work for food), incremental repeated acquisition (learning), and conditioned position responding (color and position discrimination). These tasks have been shown to be differentially sensitive to the effects of a variety of psychotropic agents (23). It has also been demonstrated that performance of well-trained rhesus monkeys is generally no different from children (24). The doses of MDMA used in the present study (0.1–1.0 mg/kg) were chosen based on unpublished data from this laboratory and the criteria that the highest dose severely affected most OTB endpoints measured and the lowest dose was without significant effects.

We hypothesized that the 5-HT system is involved in one or more of the brain functions modelled by the behaviors in the OTB and that disruption of any of those systems subserving those functions by acute MDMA administration would be detectable by monitoring OTB task performance. The similarity in OTB performance between monkeys and children is of particular importance with regard to extrapolating to humans the impact of behavioral (and possibly neurotoxic) effects of acute MDMA exposure in primates.

METHOD

Subjects

Three adult male rhesus monkeys (*Macaca mulatta*) between 10 and 11 years of age and weighing from 9–10 kg served as subjects. All had previously been trained under the schedules of behavior used in the OTB for several years and had been used as subjects in previous studies on the acute effects of several psychoactive compounds (9,10,32–35). Animal housing, feeding, and so forth were as previously described (32). Briefly, each monkey was individually housed and fed its daily allotment of food immediately after each test session. Water was available ad lib. Animal care and procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines and approved by the NCTR Institutional Animal Care and Use Committee.

Apparatus

The apparatus have been previously described in detail (32) and consisted of portable primate restraint chairs, sound-attenuated behavioral chambers, operant panels, and computer consoles. The operant panels were equipped with three rear-projection press-plates, four retractable levers, six serial position indicator lights, and correct and incorrect response indicator lights. The press-plates, levers, and indicator lights were aligned horizontally, with the press-plates and serial position indicator lights located above the levers. Symbols and colors were projected onto the press-plates from the rear. When operated, both levers and press-plates effected a switch closure. Serial position and correct and incorrect indicator lights were illuminated from behind the panel with various colors. A trough for reinforcer (190-mg banana-flavored food pellet) delivery was centered below the levers.

Operant Schedules

The use and description of the tasks contained in the OTB have also been reported in detail elsewhere (23,32), and a diagram of the behavioral test panel is shown in Paule et al. (26). A brief description of each task follows.

Time estimation task (temporal response differentiation). Only the left lever was extended and active. Subjects were required to hold the lever in the depressed position for a minimum of 10 s but not longer than 14 s. Releasing the lever within the 4-s window resulted in reinforcer delivery. Releasing the lever too early or too late ended the current trial, after which the monkey could immediately start another trial.

Short-term memory and attention task (delayed matching-to-sample). Only the three press-plate manipulanda were used (levers were retracted). At the start of each trial, one of seven geometric symbols (the sample) was projected onto the center plate in a random fashion (side press-plates were dark). To continue the trial, each monkey was required to make an observing response (a press) to the center plate. After the observing response was made, the center plate was extinguished for one of six time delays (i.e., 2, 4, 8, 16, 32, and 48 s, presented pseudorandomly) during which all three press-plates were dark. After the time delay, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the match resulted in reinforcer delivery and initiation of a new trial with another sample stimulus (presented randomly). A nonmatching response was followed by a 10-s time-out period (all plates darkened) and then initiation of a new trial.

Motivation task (progressive ratio). Only the far-right retractable lever was extended and active. Each monkey was required to increase the number of lever presses required for each subsequent reinforcer. Initially, one or two lever presses (depending on the individual monkey but the same for each subject every test session) resulted in reinforcer delivery. The number of responses required for the next reinforcer was increased by the initial number of lever presses required for the first reinforcer. Thus, if two lever presses were required for the initial reinforcer, four lever presses were required for the next, then six, eight, and so forth. The ratio increments were chosen so that marked periods of pausing or cessation of responding generally occurred during each baseline (noninjection) or vehicle control session.

Learning task (incremental repeated acquisition). All four retractable levers were extended and the serial position and correct and incorrect response indicator lights were used. Subjects were required to acquire or learn a new sequence of lever

presses each test session. The learning task began with the presentation of a one-lever sequence (IRA1). Each response on the correct one of the four levers resulted in reinforcer delivery. After 20 correct, but not necessarily consecutive, response sequences (criterion performance), a 1-min time-out period was followed by the presentation of an incremented two-lever sequence (IRA2) in which a response on a different lever was required before a response on the original (IRA1) lever produced a reinforcer. After 20 errorless (i.e., no errors were made between the first and last correct lever presses of the required sequence) two-lever sequences, the task was incremented to a three-lever sequence, and so on, up to a six-lever sequence or until the allotted task time had elapsed. The serial position indicator lights signalled position in the response sequence, indicating the remaining number of correct responses necessary for reinforcer delivery. Incorrect responses were followed by a 2-s time-out (illumination of the incorrect response indicator light) but did not reset the response requirement; thus, error correction was permitted. Correct responses were followed by illumination of the appropriate serial position indicator light and a 1-s time-out with illumination of the correct response indicator light.

Color and position discrimination task (conditioned position responding). Only the three press-plates were used (levers were retracted). At the start of each trial, the center plate was illuminated with either solid red, yellow, blue, or green (side press-plates were dark). Subjects continued the trial by making an observing response (a press) to the center plate, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate color had been either blue or green, a response to the right press-plate (white) resulted in reinforcer delivery and initiation of a new trial. If the center press-plate had been either red or yellow, a response to the left press-plate (white) resulted in reinforcer delivery and initiation of a new trial. Responding to the incorrect position initiated a 10-s time-out period followed by the initiation of a new trial. The sequence of color presentation was random.

Behavioral Testing Procedure

Behavioral test sessions were conducted daily (Monday–Friday) and lasted approximately 50 min. Monkeys were rotated through nine identical behavioral test chambers so that in general, no monkey was placed in the same chamber on 2 consecutive test days. Behavioral schedules alternated daily. For example, if the motivation (10 min), learning (35 min), and color and position discrimination (5 min) tasks were presented on 1 test day, the time estimation (20 min) and short-term memory and attention (30 min) tasks were presented the next test day.

Drug and Dosing Procedure

MDMA was provided by the National Institute on Drug Abuse (Rockville, MD). The purity was determined to be >99% by high-performance liquid chromatographic analysis at NCTR. MDMA was dissolved in saline (vehicle) so that the final injection volume was 0.1 ml/kg and doses (0.0, 0.1, 0.3, and 1.0 mg/kg) were administered intramuscularly (IM) in a randomized order. A dose of 1.75 mg/kg was given to one of the three subjects and produced a complete suppression of responding. The 1.75-mg/kg dose was not administered to the remaining two subjects, and the data obtained from the subject receiving this dose were not included in the analyses. MDMA injections were given on Tuesdays and/or Fridays, whereas vehicle injections were given on Tuesdays, Thursdays, and/or Fridays. Testing without prior injection was conducted on Mondays and Wednesdays. Because of the daily alternation of behavioral tasks, all MDMA doses were given twice to provide dose-response data for each operant task. Approximately 30 min after injection, each monkey was placed into an operant chamber and the behavioral session began 1 min later. Inspection of cumulative response records under vehicle and drug conditions indicated that at effective doses MDMA affected responding in each task throughout the 50-min test sessions.

Behavioral Endpoints

The endpoints measured in each task have been described in detail elsewhere (37). Three fundamental measures were monitored for most tasks: percent task completed (PTC), response rate or latency, and response accuracy.

PTC. The PTC data are measures of predetermined performance criteria and are functions of both response rate and response accuracy. The PTC measure is calculated by dividing the total number of reinforcers earned in a given session by the total number of reinforcers possible × 100. The total number of reinforcers possible for a given task was chosen arbitrarily based on the length and difficulty of the task. The PTC endpoint is a convenient and comprehensive measure showing intra-animal stability, and has proven useful for comparing drug effects on performance across tasks.

Response rate and response latency. The response rate for each of the time estimation and learning tasks was calculated by dividing the total number of lever presses by the total session time (in seconds). The response rate for the short-term memory and attention, learning, and color and position discrimination tasks was calculated by dividing the total number of responses by the total session time − time-out and delay periods (in seconds). For the short-term memory and attention and color and position discrimination tasks, mean response latencies were also calculated for both observing and choice responses. If a monkey did not make an observing and/or choice response for 300 s, a maximum response latency of 300 s was used in the analyses. In addition to overall response rate for the learning task (collapsed across sequences of different lengths), response rates were measured for individual response sequence lengths or levels within the learning task.

Response accuracy. Response accuracy for the short-term memory and attention and color and position discrimination tasks was calculated by dividing the number of correct responses by the total number of trials in a given session × 100. For the time estimation and learning tasks, response accuracy was calculated by dividing the total number of correct lever presses by the total number of lever presses in a given session × 100. Response accuracy is not applicable for the motivation task.

Other measures. For the time estimation task, mean duration of lever hold and for the motivation task, the break points (the number of lever presses made to obtain the last reinforcer of the task) was also calculated. Interresponse times (from press initiation to press initiation) were recorded for the motivation and color and position discrimination tasks. For the learning task, within-sequence (recall) errors and between-sequence (acquisition) errors were also recorded. Recall errors occur after the subject has entered into a response sequence (the first correct lever press for that sequence), but before the last correct lever press for that sequence (an exit from that sequence). For example, once the first correct lever of a three

response chain sequence was pressed, a recall error occurred every time an incorrect lever was pressed before reinforcer delivery (i.e., completion of the response chain). A recall error could not occur during the one-lever sequence. Acquisition errors occurred before the first correct lever press (entry) of a particular response sequence.

Statistical Analysis

For each behavioral endpoint in each task, the overall effect of drug treatment on performance was determined using a one-way repeated-measures analysis of variance (ANOVA). If overall significance was evident ($p < 0.05$), then performance at each dose was compared to saline control performance using a Bonferroni correction (21). For a subject's data to be included in the time estimation and color and position discrimination task's accuracy analyses, a minimum of three trials had to be completed. For inclusion in the short-term memory and attention and learning task's accuracy analyses, a minimum of 10 trials had to be completed.

RESULTS

Table 1 shows the results from the five OTB tasks. Baseline (noninjection) data were not significantly different from those for saline vehicle injections for any of the behavioral end points monitored. In Table 1 and for all subsequent references, "overall" refers to data combined across all lever-hold durations in the time estimation task, all time delays in the short-term memory and attention task, and across all response-sequence lengths in the learning task.

Time Estimation Task

MDMA significantly decreased accuracy, PTC, and mean duration of lever hold in the time estimation task at 1.0 mg/kg. The frequency of lever holds that were longer than 2 s in duration are shown in Fig. 1. Response bursts (lever holds > 2 s), common in this task, are shown in Fig. 2.

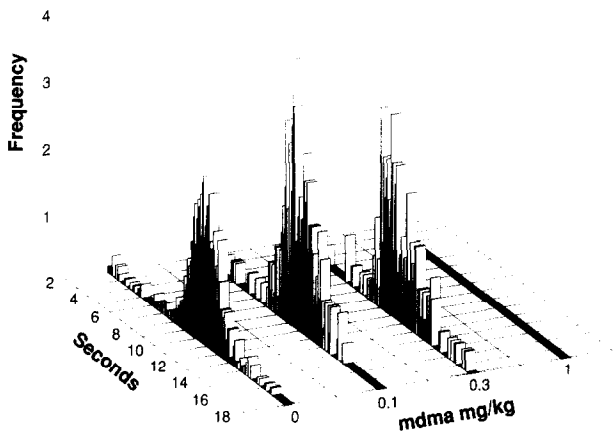

FIG. 1. Effect of MDMA on duration of lever hold in the time estimation task for holds > 2 s in duration. Data are means for all three subjects unless otherwise indicated. Responding was completely suppressed at 1.00 mg/kg MDMA.

Short-Term Memory and Attention Task

MDMA produced no significant change in any short-term memory and attention task end point (data not shown).

Motivation Task

MDMA significantly decreased response rate, PTC, and break point in the motivation task at 1.0 mg/kg. Fig. 3 shows average interresponse time distributions obtained across moti-

TABLE 1

OPERANT TEST BATTERY RESULTS

Task	Endpoint	Baseline	Saline	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg
Time	PTC	38 ± 4.8	37.2 ± 11.5	44.7 ± 5.8	42.2 ± 5.6	0*
Estimation	RR	0.1	0.1 ± 0.01	0.1	0.1	0.1 ± 0.01
	ACC	48.4 ± 8.5	49.8 ± 13	58.1 ± 5	67.4 ± 9.6	0*
	Avg. Hold	7.9 ± 0.6	8 ± 1	9 ± 0.2	10.2 ± 0.6	0.5*
Short-term memory	PTC	35.1 ± 6.3	35.6 ± 7.3	26.7 ± 10.8	24.2 ± 8.7	16.1 ± 9.6
and attention	Overall RR	0.2 ± 0.1	0.2 ± 0.1	0.1	0.1 ± 0.1	0.04 ± 0.03
	Overall ACC	76.8 ± 7.5	76.4 ± 9	73.1 ± 7.8	64.5 ± 17	75.2 ± 3.2
	Observing RL	5 ± 1	4.2 ± 1.3	10 ± 5.4	8.6 ± 3.1	109.7 ± 95.2
	Choice RL	1.9 ± 0.6	2.6 ± 0.3	11.3 ± 4.8	5.5 ± 2.8	9.6 ± 5.2
Motivation	PTC	20.2 ± 0.2	20.6 ± 1.7	20.6 ± 1.7	18.6 ± 0.6	1.9 ± 0.9*
	RR	3 ± 0.4	2.8 ± 0.4	3.1 ± 0.2	2.5 ± 0.3	0.1*
	BP	129.2 ± 16.1	125.4 ± 17.1	129.3 ± 11.1	118.7 ± 13.8	14 ± 1.4*
Learning	PTC	82.1 ± 7.9	83.2 ± 4	81.9 ± 13.4	95.3 ± 2.4	25.6 ± 13.1*
	Overall RR	2 ± 0.5	1.5 ± 0.5	1.4 ± 0.8	2.1 ± 0.4	0.13 ± 0.1
	Overall ACC	71.3 ± 5.8	72.7 ± 3.8	71.3 ± 6.4	78 ± 1.1	51.4 ± 8.1*
Color and position	PTC	96.8 ± 2.7	99.1 ± 0.9	72.2 ± 27.8	100	40.6 ± 30.4
discrimination	RR	1.1 ± 0.1	1.1 ± 0.2	0.7 ± 0.4	1.2 ± 0.2	0.4 ± 0.3
	ACC	96.3 ± 1.9	98.7 ± 0.4	92.3 ± 7.7	99.5 ± 0.5	77.1 ± 22.9
	Observing RL	1.8 ± 0.3	1.8 ± 0.3	7.1 ± 5	1.6 ± 0.32	101.9 ± 99
	Choice RL	0.2	0.3	0.6 ± 0.4	0.2	1.7 ± 1.5

PTC, percent task completed; RR, response rate (s); ACC, accuracy; RL, response latency; BP, break point.
*Significant difference from vehicle (saline) performance ($p < 0.05$).

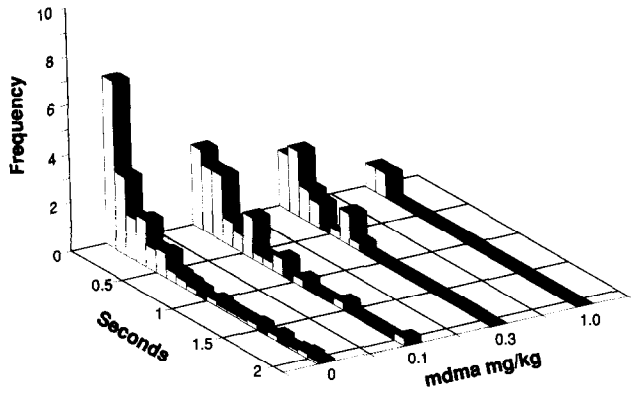

FIG. 2. Effect of MDMA on duration of lever hold in the time estimation task for holds < 2 s in duration. Data are means for all three subjects unless otherwise indicated.

vation task sessions and illustrates the marked decrease in response frequency at the 1.0-mg/kg dose.

Learning Task

MDMA significantly decreased overall response accuracy and PTC in the learning task at 1.0 mg/kg, but the overall response rate was not significantly affected at any dose tested. At doses of ≤ 0.3 mg/kg all subjects were able to complete IRA1–IRA4 sequences. At the 1.0-mg/kg dose, no subject was able to complete 20 errorless three-lever sequences (IRA3) necessary to advance to IRA4. The effects of MDMA on between-sequence (acquisition) acquisition and within-sequence (recall) errors for the learning task at the two-lever sequence (IRA2) are shown in Figs. 4 and 5, respectively.

Color and Position Discrimination Task

MDMA produced no significant change in any color and position discrimination task endpoint measured. Figure 6 shows average interresponse time distributions obtained across color and position discrimination task sessions.

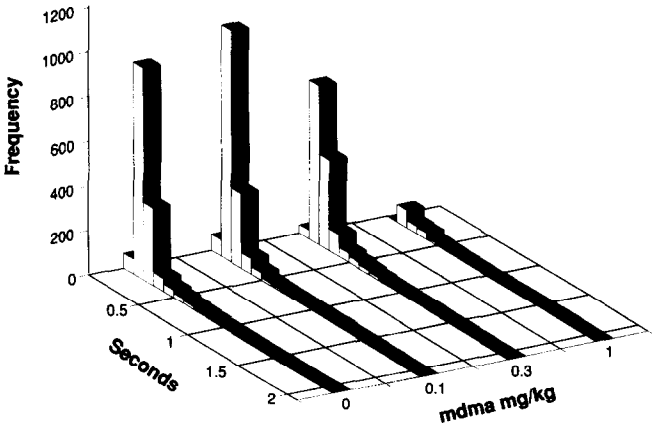

FIG. 3. Interresponse time distributions for the motivation task. Data are means for all three subjects unless otherwise indicated. MDMA produced a significant dose-dependent decrease in all other motivation task end points measured (data not shown). Responding was nearly completely suppressed at 1.00 mg/kg MDMA.

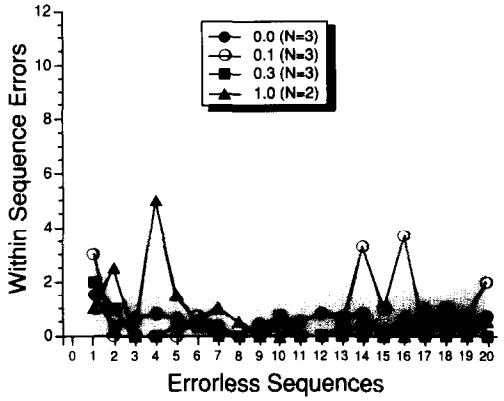

FIG. 5. Effect of MDMA on acquisition errors in the learning task at the two-lever sequence (IRA2). Data are means for all three subjects unless otherwise indicated. The shaded area represents the 95% confidence interval constructed from vehicle control sessions.

DISCUSSION

In the present experiment, MDMA significantly disrupted performance of the time estimation, learning, and motivation tasks, but did not significantly affect the short-term memory and attention or color and position discrimination tasks at any dose tested. In the time estimation and learning tasks, response rate and response accuracy were differentially affected by acute MDMA administration, whereas all endpoints monitored for the motivation task were equally sensitive to disruption by MDMA. The acute effects of MDMA on OTB performance are distinguishable from all other drugs tested in this lab using similar procedures. These include: atropine (31), caffeine (3), chlorpromazine (6), cocaine (25), *d*-amphetamine (34), Δ-9-tetrahydrocannabinol (32), diazepam (36), marijuana smoke (33), MK-801 (4), morphine (35), nicotine (unpublished results), pentobarbital (7), phencyclidine (9), and physostigmine (10).

It is difficult to compare the current results with other studies of the behavioral effects of MDMA, for two primary reasons. First, few acute studies have examined the effects of MDMA exposure using behavioral tasks similar to those

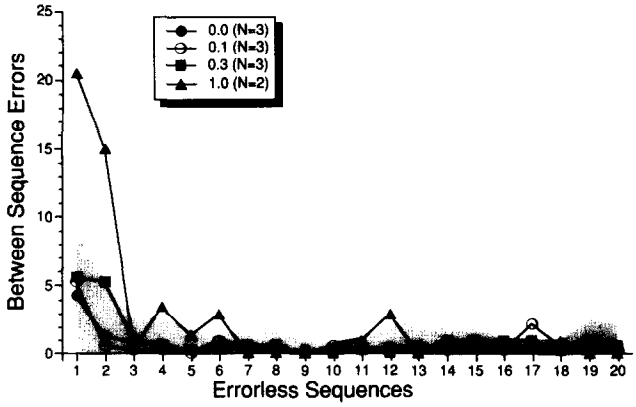

FIG. 4. Effect of MDMA on recall errors in the learning task at the two-lever sequence (IRA2). Data are means for all three subjects unless otherwise indicated. The shaded area represents the 95% confidence interval constructed from vehicle control sessions.

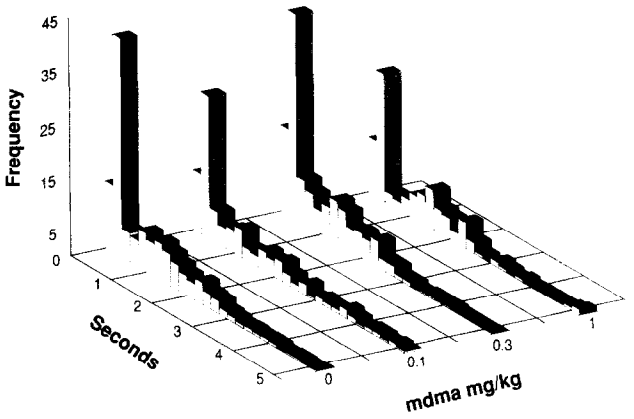

FIG. 6. Interresponse time distributions for the color and position discrimination task. Data are means for all three subjects unless otherwise indicated. MDMA produced no significant changes in any color and position discrimination task end points measured (data not shown).

affected by MDMA in the present experiment. Second, a great deal of emphasis has been placed on assessing behavioral deficits due to MDMA toxicity resulting from repeated exposure to relatively high doses (16,29,30,38). For example, a typical paradigm designed to produce long-term depletion of brain 5-HT levels in rhesus macaques involves twice-daily administration of 5–10 mg/kg of MDMA for 4 consecutive days (15,38). In the current study the dose range was 0.1–1.0 mg/kg and MDMA was administered no more than twice a week and never on consecutive days. To our knowledge, no study has shown MDMA to be neurotoxic when administered in low, intermittent doses for a short period of time. Thus, the disruption in performance of the time estimation, learning, and motivation tasks seen in the present experiment is not likely due to toxic depletions in 5-HT. Furthermore, MDMA (at the doses used in the present experiment) produced no significant disruption in performance of either the color and position discrimination or short-term memory and attention tasks, and performance during baseline and vehicle (saline) sessions demonstrated that MDMA was not producing residual behavioral effects.

In the time estimation task, a high dose of MDMA significantly disrupted the monkeys' ability to hold the lever in the depressed position for durations > 2 s. However, monkeys continued to emit response bursts (holds < 2 s in duration) at the same dose. Thus, correct performance of this task (i.e., accuracy) was completely disrupted, although overall response rate was not significantly affected. The acute effects of MDMA on the time estimation task are consistent with those of Li et al. (20), who reported that MDMA decreased reinforcement rate and response accuracy of rats trained to respond under a differential-reinforcement-of-low-rate 72-s schedule by increasing the frequency of short interresponse times in a dose-dependent fashion.

MDMA also decreased response accuracy in the learning task at a dose that did not significantly affect response rate. This decrease in accuracy was accompanied by a dose-dependent increase in between-sequence (acquisition) errors, whereas within-sequence (retention) errors were not similarly affected. A high number of between-sequence errors indicates that subjects are having difficulty learning or acquiring the correct new, or incremented, sequence of lever presses, or that response perseveration is a prominent drug effect. Within-sequence errors occur when subjects exhibit difficulty in recalling or performing the previously learned sequence and are thought to reflect a relatively short-term memory impairment. MDMA produced few within-sequence errors at any dose tested, indicating that the monkeys' ability to remember a recently learned sequence was not impaired by MDMA, and suggests that short-term memory processes were not disrupted. This interpretation is further supported by the lack of any significant MDMA-induced disruption of performance in the short-term memory (delayed matching-to-sample) task. These data are, however, dissimilar to those reported by Thompson et al. (39), in which MDMA decreased response rate in a dose-dependent fashion, but had no affect on the response accuracy of two patas monkeys responding under a multiple schedule (acquisition-performance) four-response sequence.

The acute effects of MDMA on motivation task (progressive ratio) performance (decreased response rate, break point, and percent task completed) may have been due to MDMA's anorectic properties, for which it was originally patented in 1914 (18). MDMA has been shown to have similar dose-dependent effects on response rate in mice (11) and pigeons (22) responding under fixed-ratio schedules. That response rates in the time estimation and learning tasks were not significantly lowered at the dose that decreased response rate in the motivation task suggests that responding under these schedules may be itself reinforcing enough to sustain responding, even when motivation to work for food is deceased.

MDMA did not significantly affect performance of either the color and position discrimination or short-term memory and attention tasks at any dose tested in the current studies. Because no effects were detected in these tasks, it is difficult to speculate what effects higher doses of MDMA might have on their performance. LeSage et al. (19), however, reported that acute MDMA decreased accuracy and response rates of four pigeons responding under a delayed matching-to-sample procedure. To our knowledge, no comparative data exist with respect to MDMA's effects on tasks involving color and position discrimination.

Although it is well documented that MDMA is toxic to serotonergic nerve terminals when administered to rodents and primates at high doses over several consecutive days, acute MDMA administration in the present experiment did not result in any permanent behavioral changes and was almost certainly not neurotoxic as defined by lasting decreases in 5-HT concentrations. Performance of the tasks believed to model time estimation, learning, and motivation was significantly disrupted by MDMA, but these disruptions did not persist when the exposure was discontinued. MDMA decreased response accuracy in the time estimation and learning tasks at a dose that did not significantly affect response rate. MDMA's acute effects on learning task performance appeared to be more selective for processes thought to depend on acquisition of new information than on retention of previously acquired information. The tasks designed to model short-term memory and attention and color and position discrimination were not significantly affected at any dose tested.

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