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Effects of MDMA on Complex Brain Function in Laboratory Animals

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FREDERICK, D. L. AND M. G. PAULE. *Effects of MDMA on complex brain function in laboratory animals.* NEUROSCI BIOBEHAV REV **21**(1) 67–78, 1997.—This review surveys experiments that have examined the effects of acute and chronic MDMA exposure on schedule-controlled operant behaviors thought to engender responses that reflect the expression of complex brain functions. Such functions include time estimation, short-term memory, learning, motivation, and color and position discrimination. Recent experiments conducted in the Behavioral Toxicology Laboratory at the National Center for Toxicological Research concerning MDMA's acute and long-term effects on rhesus monkey performance in an operant test battery are compared to previous studies involving the effects of MDMA on operant behaviors. Results of these experiments suggest that when given acutely, MDMA disrupts complex brain functions associated with learning and time estimation more than those associated with short-term memory and visual discrimination, and that behavioral tasks requiring relatively high rates of responding are particularly sensitive to the disruptive effects of MDMA. Repeated exposure to doses of MDMA sufficient to produce long-lasting changes in brain neurotransmitter systems results in residual effects (e.g. tolerance, sensitivity) on behavioral task performance when subjects are subsequently challenged with acute MDMA, whereas baseline (non-challenged) performance of these tasks after such exposure generally remains unchanged. Although the experiments described herein were conducted on a relatively small number of non-human subjects, they raise the possibility that long-term effects on cognitive processes may also occur in humans exposed to repeated or acute high doses of MDMA. Published by Elsevier Science Ltd.

MDMA Brain function Neurotransmitter system Cognitive processes Short-term memory

INTRODUCTION

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA or "Ecstasy") is a phenylisopropylamine amphetamine analog possessing both stimulant-like (dopaminergic) and hallucinogen-like (serotonergic) properties (42,50,68), presumably as a result of its serotonin (5-HT) and dopamine (DA) releasing effects, and/or its ability to inhibit 5-HT and/or DA reuptake or monoamine oxidase (7,25,33,42). In laboratory animals, the acute behavioral effects of MDMA appear to be qualitatively more like stimulants than hallucinogens, but they remain distinguishable from those of both of these drug types. Drug discrimination studies have shown that MDMA substitutes for the psychomotor stimulant amphetamine, but not for the hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) (47), which suggests a dopaminergic mediation of the discriminative properties of MDMA. However, MDMA has also been shown to substitute for several potent 5-HT releasing compounds, such as fenfluramine, norfenfluramine, and the alpha-ethylhomologue of MDMA, *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) (28,47,58). The effects of MDMA on locomotor activity are distinct from those of amphetamine (19,20,66), and are believed to be mediated by the 5-HT system (11,48,51), whereas the effects of MDMA on response rates of laboratory animals performing under various operant schedules (e.g. 18,35,45) tend to be more stimulant-like than hallucinogen-like. Human users report that MDMA produces a variety of euphoric, mood-altering effects that are not accompanied by intense perceptual changes and feelings of detachment from the self that are associated with LSD and other hallucinogens (23,58). Although these observations suggest that MDMA's effects on brain functions, as evidenced by its behavioral effects, are likely due to its stimulant and hallucinogenic properties, the exact mechanism by which MDMA produces its unique psychotropic effects remains uncertain.

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Nichols (46) proposed the term "enactogenic" as a new pharmacological classification for MDMA and other substituted amphetamines because the effects of these drugs in animals and humans are distinct from hallucinogens and stimulants and their structure–activity relationships did not conform to those accepted for classical hallucinogens. Additionally, some in the mental health care profession began experimenting with MDMA as an adjunct to psychotherapy on the supposition that MDMA may facilitate client/therapist interaction (22), and these individuals believed MDMA to be a new type of compound (46). However, in 1985 MDMA was assigned to Schedule 1 under the Controlled Substance Act by the Drug Enforcement Agency (DEA) (32) in response to its increased recreational use (49), and concerns over its potential toxicity to serotonergic nerve terminals, a consequence associated with exposure to the related compound methylenedioxyamphetamine (52). In the United States, drugs assigned to Schedule 1 are considered to have a high potential for abuse and no accepted medical use, and can only be used for experimental purposes if approved by the DEA. MDMA has since been shown to cause short- and long-term decreases in brain 5-HT concentrations, tryptophan hydroxylase activity (rate-limiting in 5-HT synthesis), and 5-HT uptake site density. It has also caused the degeneration of fine serotonergic axon terminals in rodents and, to a greater extent in monkeys, when administered under a short course, high dose treatment regimen, typically twice daily for four consecutive days (1–3,12,14,27,53,54,63).

The MDMA-induced changes in the 5-HT system are frequently cited as evidence of serotonergic neurotoxicity, although relatively few functional (behavioral) changes have been noted in animals exposed to MDMA at doses sufficient to produce such neurochemical changes (39,40,55,62). Moreover, unlike other well-characterized neurotoxicants (such as MPTP, which reliably produces overt Parkinson-like motor symptoms in humans and laboratory animals), no such consistent, readily identifiable pathology has been described in human MDMA users (although various acute reactions, including death, have been described; see 49, 50).

Whether the neurotoxic effects noted in animals after MDMA exposure can be generalized to humans remains uncertain. The perceived absence of functional toxicity attributable to MDMA exposure, along with its putative psychotherapeutic utility has led some to suggest that MDMA-induced alterations in the 5-HT system may actually reflect a type of therapeutic neuroplasticity, rather than neurotoxicity (24). However, behavioral deficits after exposure to serotonergic neurotoxicants have historically been difficult to demonstrate, and relatively few controlled studies (animal or human) have focused on detecting functional deficits associated with repeated MDMA exposure (for additional information concerning behavioral effects of serotonergic neurotoxins see, 39, 40, 62 and 65). It is possible that the inability of these studies to demonstrate functional consequences after MDMA exposure reflects the use of behavioral endpoints that were not sensitive to MDMA-induced changes in the 5-HT system. Additionally, the neurochemical and neurohistological effects of MDMA noted in animals may not be sufficient to alter their behavior, but such changes may result in an increased sensitivity to other drugs and/or stressors, and could possibly lead to a more rapid decline in certain aspects of complex brain function than would be expected to occur as part of the normal aging process. Thus, in light of the demonstrated neurotoxic effects of MDMA in animals and the need for further examination of the functional consequences of such effects, the contention that it produces a therapeutic neuroplasticity, rather than neurotoxicity in humans, seems at best, premature.

The acute effects of MDMA on behavior have been assessed in several laboratory species using experimental procedures such as drug discrimination paradigms, tests of locomotor activity, conditioned taste aversion, and reflexive learning (see Table 1). Comparatively few studies, however, have examined MDMA's effects using schedule-controlled operant behavioral tasks in which correct performance is thought to depend primarily upon specific aspects of brain function (e.g.

TABLE 1
BEHAVIORAL STUDIES INVOLVING ACUTE MDMA ADMINISTRATION

Behavior/species	Reference
Acoustic and tactile startle response	
Rats	Kehne et al. (29); Mansbach et al. (41)
Associative and non-associative learning	
Rabbits	Romano and Harvey (57)
Aggression	
Mice	Miczek and Haney (44)
Conditioned place preference	
Rats	Bilsky et al. (4,5); Bilsky and Reid (6); Schechter (60)
Conditioned taste aversion	
Rats	Lin et al. (37,38)
Developmental behaviors	St. Omer et al. (67)
Drug discrimination	
Rats	Callahan and Appel (9); Bronson et al. (8); Glennon and Higgs (17); Nichols (46); Oberlender and Nichols (47); Schechter (58,59)
Electrical brain stimulation	
Rats	Hubner et al. (26)
Locomotor activity	
Rats	Gold et al. (19,20); Callaway and Geyer (10,11); Paulus and Geyer (48)
Mice	Miczek and Haney (44)
Milk drinking	Zacny et al. (70)
Sexual behavior	
Male rats	Bilsky et al. (4)

short-term memory, time estimation, learning, etc.). The present article will focus primarily on the acute effects of MDMA on laboratory animal behaviors thought to model specific complex brain functions and the functional consequences associated with repeated or chronic exposure to MDMA.

ACUTE EFFECTS OF MDMA ON COMPLEX BRAIN FUNCTION

In our laboratory at the National Center for Toxicological Research (NCTR), the acute effects of MDMA were assessed in three adult male rhesus monkeys using performance in the NCTR Operant Test Battery (OTB) (15). The specific tasks contained in the OTB have been described in detail elsewhere (61), and a diagram of the OTB behavioral panel is presented in Fig. 1. The OTB currently consists of five tasks thought to engender or elicit behaviors that are believed to model aspects of time estimation, short-term memory, motivation to work for food, learning, and color and position discrimination. During this experiment, behavioral test sessions were conducted daily (Monday–Friday) and lasted approximately 50 min. MDMA doses (0.1–1.0 mg/kg) were given intramuscularly, and behavioral assessments began approximately 30 min later. The remainder of this section will compare these results with those from other studies using operant tasks designed to model similar brain functions.

Time Estimation

For the time estimation task, subjects must hold a lever (see Fig. 1) in the depressed position for at least 10 s, but not longer than 14 s in order to receive a reinforcer (banana flavored food pellet). Correct performance of this task is thought to depend on the monkey's ability to accurately estimate elapsed time.

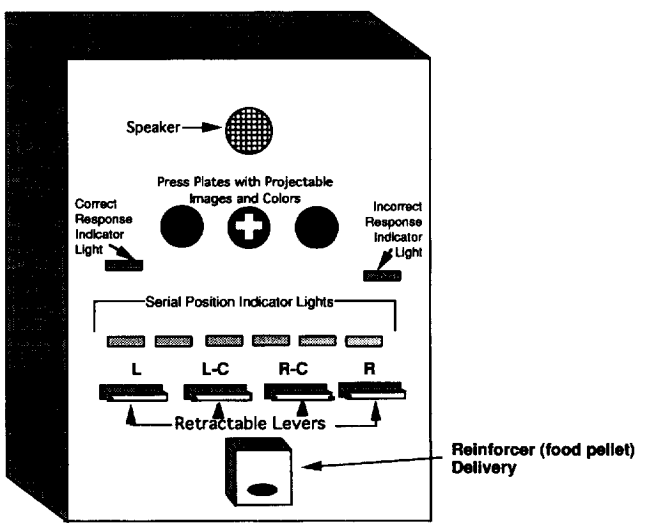

FIG. 1. Monkey operant test battery behavioral panel. Press plates are used for the STM and CPD tasks. Retractable levers were used for the TE, MOT, and LRN tasks.

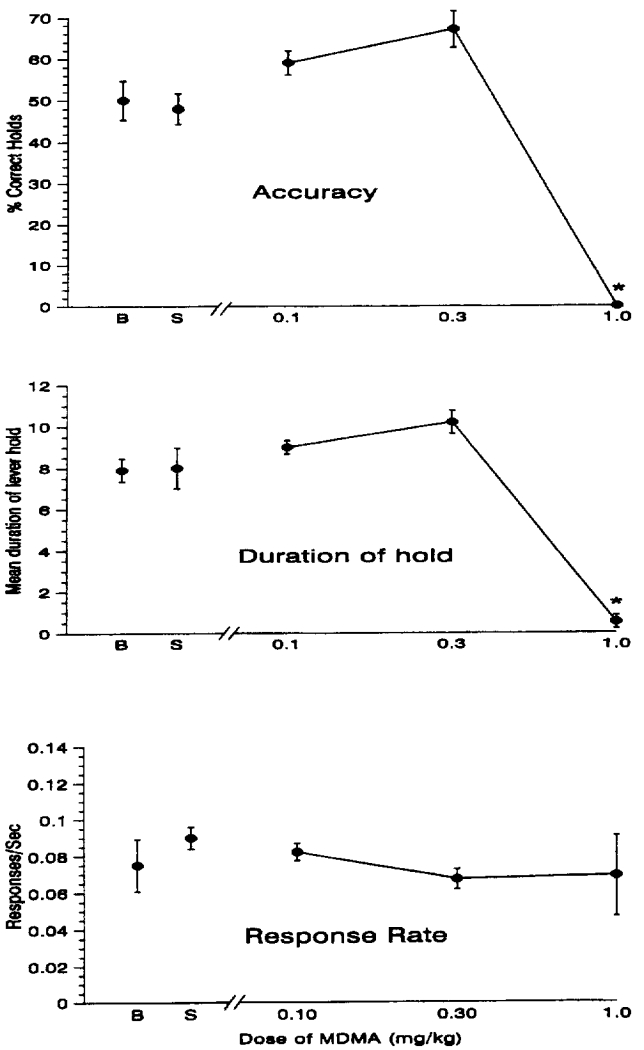

FIG. 2. Acute effects of MDMA on rhesus monkey (N=3) accuracy, mean duration of lever hold, and response rate (± SEMs) in a TE task. * Denotes significant difference ($p < 0.05$) from saline control performance. Adapted from (15).

At a dose of 1.0 mg/kg, MDMA abolished the monkeys' ability to correctly perform this task (hit the 4-s window of opportunity; Fig. 2). Monkeys generally emitted rapid response bursts (i.e. less than 1 s in duration), rather than holding the lever down for the required 10 s. In fact, no monkey ever hit the 4-s window of opportunity after receiving 10 mg/kg MDMA. Whether such results are related to the monoamine (i.e. 5-HT and dopamine) releasing effects of MDMA, or to its ability to inhibit reuptake or monoamine oxidase (7,25,33,42) is not known. These actions of MDMA should lead to increases in extracellular dopamine and may have produced slight tremors (although no gross motor effects were observed) in these animals, an effect which has been reported to occur in human MDMA users (23,36,49). Alternatively, the stimulant-like effects of MDMA may have produced perseverative behaviors that precluded appropriate performance of the time estimation task.

Li et al. (35) have also reported on the acute effects of MDMA (1.0–6.0 mg/kg; subcutaneously) on timing behavior in rats. Subjects performed under a differential-reinforcement-of-low-rates 72-s schedule, in which lever presses were reinforced only if a minimum of 72 s had elapsed since the last lever press. They found that acute exposure to MDMA increased response rates and decreased reinforcement rates in a dose-dependent manner. An increase in the frequency of rapid responses was also observed. As in our studies with monkeys, MDMA disrupted the rats' ability to correctly perform this task, but did not render them unable to respond.

The acute effects of MDMA have also been reported in pigeons performing under fixed-interval schedules of reinforcement. A fixed-interval schedule is one in which subjects are reinforced for the first response that occurs after a fixed amount of time has elapsed, typically from the onset of a cue (such as a light or a tone). In general, low rates of responding occur during the initial portion of a fixed interval, and high response rates are noted at the end of the interval (traditionally described as resembling a scallop). Miczek and Haney (44) reported a trend toward slightly higher response rates in mice performing under a fixed interval 10-min schedule at 1.0 and 3.0 mg/kg of MDMA, but decreased responding at 10 mg/kg. Consistent with the results of Frederick et al. (15) and Li et al. (35), Miczek and Haney also reported that an intermediate dose of MDMA increased responding early in the interval while decreasing response rates at the end of the interval. Nader et al. (45) reported that MDMA (0.1–10 mg/kg) decreased responding in pigeons performing under a fixed-interval 3-min schedule, and Glennon et al. (18) have reported similar effects on response rates of mice performing under a fixed-interval 30-s schedule.

Short-term Memory

For the short-term memory task, a delayed matching-to-sample procedure (the three horizontally aligned press plates) is used (see Fig. 1). A trial begins when one of seven geometric symbols (a sample) is projected onto the center press plate. Subjects must press this plate (an observing response) to acknowledge that the sample stimulus was observed. Following this observing response, the sample is extinguished and all plates remain dark for one of six randomly presented time delays (1–64 s), after which all three plates are illuminated, each with a different symbol, only one of which matches the original sample. A press to the "match" results in reinforcer delivery. Accuracy generally decreased in a delay-dependent fashion during both saline and drug sessions, but MDMA did not significantly affect any endpoint monitored in this task at any dose tested up to 1.0 mg/kg.

LeSage et al. (34) have assessed the acute effects of MDMA (0.32–5.6 mg/kg) in four pigeons performing a delayed matching-to-sample task. In this experiment, the center of three response keys was illuminated either red or green, and the pigeon pecked the center key to acknowledge that the sample stimulus had been observed. Immediately following this observing response, the center plate was extinguished and all three plates remained dark for one of three randomly presented time delays (0, 3, and 6s), after which the side plates were illuminated (one red and one green, presented randomly) and a response to the color that matched the sample resulted in reinforcer delivery. Under control conditions, response accuracy decreased in a delay-dependent manner (baseline accuracies at the 0-, 3-, and 6-s delays were about 97, 87, and 78%, respectively (Fig. 3)). MDMA produced dose-dependent decreases in response rate and accuracy, although the significance of these decreases was not assessed using traditional statistical analyses. Of particular interest is that the greatest MDMA-induced decrease in accuracy (percent change from control) was noted at the 0-s delay (accuracy was decreased to about 70% at 4.2 mg/kg of MDMA (Fig. 3)). Although control accuracy at the 3- and 6-s delays was less than that at the 0-s delay, the accuracy at both of these delays also decreased to roughly 70% at the 4.2 mg/kg dose. While response accuracy in these subjects was decreased by MDMA in a dose- and delay-dependent fashion, the effect was opposite to what would have been expected if MDMA had selectively affected short-term memory processes. That is, the greatest effects were seen under the 0-s delay, not the 6-s delay condition. These data suggest that processes associated with short-term memory are relatively insensitive to disruption by acute MDMA administration.

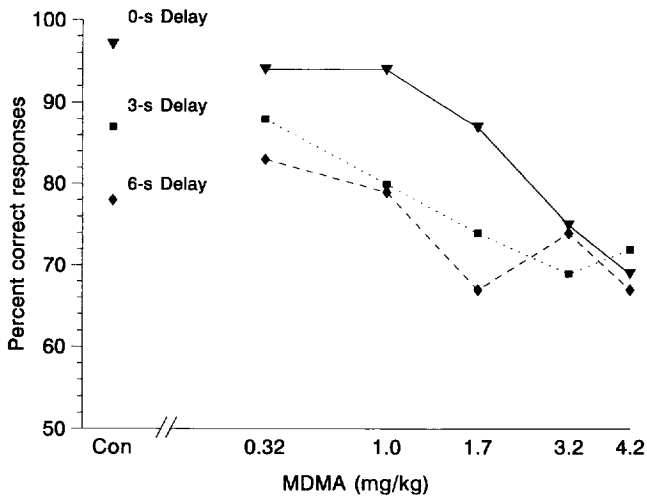

FIG. 3. Acute effects of MDMA on pigeon (N=4) accuracy in an STM task. Adapted from (34).

Learning

For the learning task, all four response levers are used, and subjects must acquire or learn a new sequence of lever presses each test session. The learning task begins with the presentation of a one-lever sequence. Each response on the correct one of four levers results in reinforcer delivery. After 20 correct, but not necessarily consecutive, response sequences (criterion performance), a 1-min time-out period is followed by the presentation of an "incremented" two-lever sequence in

which a response on a different lever is required before a response on the original lever results in reinforcer delivery. After 20 error-free two-lever sequences (i.e. no errors were made between the first and last correct lever presses of the required sequence), the task is incremented to a three-lever sequence and so on, up to a six-lever sequence or until the allotted task time expires. In addition to response rate and accuracy, within-sequence (retention) errors and between-sequence (acquisition) errors are also recorded. As noted for the time estimation task, MDMA significantly decreased response accuracy but did not affect the response rate at 1.0 mg/kg. Additionally, the number of acquisition errors were relatively higher at 1.0 mg/kg MDMA than were retention errors. Such effects suggest that processes associated with the retention of newly acquired information (i.e. short-term memory) are not as sensitive to disruption by MDMA as are processes associated with learning or acquiring new information. These results are consistent with the lack of any significant MDMA effects in the OTB short-term memory task, and the greater MDMA-induced decrease in accuracy at the 0-s delay (rather than the 3- and 6-s delays) in pigeons performing a similar short-term memory task (34).

The acute effects of MDMA on rhesus monkey performance of the OTB learning task are dissimilar to those reported by Thompson et al. (69), who utilized patas monkeys responding under a multiple repeated acquisition and performance schedule. In this schedule, subjects alternated between acquisition and performance components in each test session involving four response sequences using three levers. During the acquisition components, monkeys were to learn or acquire a new four-lever response sequence each session in order to receive a food reinforcer (e.g. left lever (L)–right lever (R)–center lever (C)–R). Once 10 reinforcers were earned or 15 min had elapsed, the acquisition component ended and the performance component began during which the required response sequence was fixed, i.e. presented every test session (e.g. LCLR). The performance component continued until 10 reinforcers were earned or 15 min elapsed. Sessions lasted for 2 h or until 100 reinforcers were earned. Acute MDMA (0.32–3.2 mg/kg, intramuscularly) decreased response rate in a dose-dependent fashion, but did not affect response accuracy in either the acquisition or performance components. Additionally, behavior in the performance and acquisition components was not differentially sensitive to disruption by MDMA, since both were affected at the same doses. Both the Thompson et al. (69) and the Frederick et al. (15) studies involved very small sample sizes (n=2 and 3, respectively) and different species of monkeys performing similar, but not identical, behavioral tasks. These factors may have contributed to the different findings on the effects of acute MDMA.

Motivation

To assess the motivation of subjects to work for food, a progressive ratio schedule of reinforcement is incorporated in the OTB. In this task, subjects are initially reinforced for making one or two presses to the response lever (see Fig. 1). Subsequent reinforcers require the subject to increase the number of lever presses by the number required for the first one. Performance in the motivation task was quite sensitive to disruption by acute MDMA administration: all endpoints monitored for this task were significantly decreased at the 1.0 mg/kg dose. The disruption noted in motivation task performance may be related to the anorectic properties of MDMA, a property for which it was originally patented in 1914 (31), and an effect reported by human users of the drug (23). MDMA has been reported to have similar rate decreasing effects in pigeons (45) and in mice (44) performing under fixed-ratio 30-response schedules of food reinforcement. In fixed-ratio schedules, reinforcers are delivered after a fixed number of responses (e.g. lever presses, key pecks) are made.

Color and Position Discrimination

In the color and position discrimination task (conditioned positioned responding), the three press plates are used (Fig. 1). Each trial begins with the illumination of the center press plate (either red, yellow, green, or blue). Subjects indicate that the color was observed by pressing the center plate, after which the side press plates are immediately illuminated white and the center plate becomes dark. If the center plate had been either red or yellow, a press to the left plate results in reinforcer delivery; if the center plate had been either blue or green, a press to the right plate results in reinforcer delivery. Performance of the color and position discrimination task was not significantly affected by any MDMA dose (0.1–1.0 mg/kg) tested, and these data are the only published on the effects of MDMA on performance of a simple color and position discrimination type task. The delayed matching-to-sample task used by LeSage et al. (34) did involve aspects of color discrimination (in that red and green samples were used), but they did not report any selective effects of MDMA on color choice accuracy.

Table 2 presents a summary of the acute effects of MDMA on rhesus monkey OTB performance. The relative sensitivity of each OTB task to disruption by acute MDMA was as follows: motivation = time estimation = learning > short-term memory or color and position discrimination. At the highest dose tested (1.0 mg/kg), response accuracy was significantly decreased in the time estimation and learning tasks, but this dose did not significantly affect response rates in these tasks. The acquisition and retention aspects of performance in the learning task were also differentially affected by acute MDMA (not represented in Table 2). MDMA's acute effects appear to be more disruptive to processes selective for learning and time estimation than to those processes selective for short-term memory or color and position discrimination. These effects may reflect the apparent MDMA-induced decrease in motivation to work for food, as evidenced by significant decreases in motivation task performance at the same doses that decreased time estimation and learning behaviors. The sensitivity of motivation behavior to the acute effects of MDMA likely reflects the anorectic properties of this drug.

TABLE 2

Task	Endpoint	Dose of MDMA (mg/kg) 0.0	0.1	0.3	1.0
Time estimation (TE)	PTC	—	—	—	*
	RR	—	—	—	—
	ACC	—	—	—	*
	Average hold	—	—	—	*
Short-term memory and attention (STM)	PTC	—	—	—	—
	Overall RR	—	—	—	—
	Observing RL	—	—	—	—
	Choice RL	—	—	—	—
	Overall ACC	—	—	—	—
Motivation (MOT)	PTC	—	—	—	*
	BP	—	—	—	*
	RR	—	—	—	*
Learning (LRN)	PTC	—	—	—	*
	Overall RR	—	—	—	—
	Overall ACC	—	—	—	*
Color and position discrimination (CPD)	PTC	—	—	—	—
	RR	—	—	—	—
	Observing RL	—	—	—	—
	Choice RL	—	—	—	—

*Denotes significant difference from vehicle (saline) performance.
PTC = percent task completed; RR = response rate;
ACC = accuracy; RL = response latency; BP = breakpoint.
Adapted from Frederick et al. (1995).

CHRONIC EFFECTS OF MDMA ON COMPLEX BRAIN FUNCTIONS

As mentioned previously, short course, high dose MDMA administration has been shown to cause long-lasting changes in 5-HT systems (i.e. decreased brain 5-HT and 5-HIAA concentrations, and suspected 5-HT axon terminal degeneration) in laboratory animals. However, from the relatively few studies that have compared post-treatment behavior to pre-exposure behavior or to the behavior of non-treated controls, few significant differences have been reported. The majority of these experiments have not used schedule-controlled operant behavioral procedures for their assessments (see Table 3). For example, Ricaurte et al. (55) demonstrated that T-maze performance of rats given MDMA (20 mg/kg, sc, twice daily for four days) was generally no different from that of controls even though the MDMA treatment resulted in substantial reductions in brain 5-HT. Very few attempts have been made to examine the functional consequences of repeated exposure to MDMA on schedule-controlled operant behaviors. In those that have, no significant changes in behavior have been noted after MDMA treatment, although long-term changes in sensitivity to acute MDMA challenge have been reported (16,34,35).

That so little evidence of functional alterations exists in animals treated with neurotoxic regimens of MDMA is somewhat surprising, considering that 5-HT systems have been implicated (either directly or through interactions with other neurotransmitter systems) as a significant neurochemical component in the expression of numerous central nervous system functions, including learning and memory. However, behavioral toxicity after exposure to monoaminergic neurotoxicants has often proved difficult to demonstrate (see 62, 65). Possible reasons for such observations include: the treatment regimens used did not sufficiently damage the 5-HT system enough to alter the observed behaviors; other brain areas functionally compensate for any damage that is induced; the behaviors that were monitored were not subserved by the 5-HT system; or, the behavioral tasks used were not sensitive to changes in the 5-HT system (29,55,62,65).

Recently, the effects of long-term MDMA administration were assessed in the same non-human primate subjects used in the acute MDMA experiment described earlier. Operant test battery (OTB) performance was monitored while gradually escalating doses of MDMA (0.1–20 mg/kg/day, intramuscularly) were administered twice daily for several months (16). Additionally, dose–response curves for the acute effects of MDMA on OTB performance were determined at several time points after chronic exposure. These acute MDMA challenges (effected at approximately 6-month intervals out to about 18 months after the end of chronic treatment) were designed to assess whether the chronic MDMA regimen produced residual changes (e.g. behavioral tolerance or sensitization) in OTB

TABLE 3
BEHAVIORS EXAMINED AFTER TREATMENT WITH NEUROTOXIC DOSES OF MDMA

Species/behavioral measure	Dosing paradigm	Reference
Rats		
Spatial navigation, skilled reaching, and foraging	10 mg/kg (ip), 2 × day, 4 consecutive days	Robinson et al. (56)
Emergence, hot plate response, auditory startle response, and complex maze navigation	5 and 10 mg/kg (po), 1 × day, 4 consecutive days	Slikker et al. (64)
Locomotor activity, open field behavior, one- and two-way avoidance, swimming ability, eight-arm radial maze	10, 20 and 40 mg/kg (sc) 2 × day, 4 consecutive days	Lorens et al. (39,40) Seiden et al. (62)
Sexual behaviors	40 mg/kg (sc), 2 × day, 4 consecutive days	Doran et al. (13)
Conditioned place preference/drug discrimination	20 mg/kg (sc), 2 × day, 4 consecutive days	Schechter (60)
Non-human primates		
Spontaneous home cage behavior	1.25, 2.5, and 20 mg/kg (po) 2 × day, 4 consecutive days	Ali et al. (2)
	5 and 10 mg/kg (po) 2 × day, 4 consecutive days	Slikker et al. (64)

TABLE 4

EFFECTS OF CHRONIC TREATMENT WITH ESCALATING DOSES OF MDMA ON OTB PERFORMANCE OF RHESUS MONKEYS. DATA AVERAGED OVER 2 WEEKS FOR EACH DOSE SHOWN

		Dose of MDMA (mg/kg)							
Task	Endpoint	Vehicle	0.1	0.3	1.0	1.75	5.6	10.0	20.0
Time estimation (TE)	PTC	—	—	—	—	—	—	—	*
	RR	—	—	—	—	—	—	—	—
	ACC	—	—	—	—	—	—	—	*
	Average hold	—	—	—	—	—	—	—	—
Short-term memory and attention (STM)	PTC	—	—	—	—	—	—	—	—
	Overall RR	—	—	—	—	—	—	—	—
	Observing RL	—	—	—	—	—	—	—	*
	Choice RL	—	—	—	—	—	—	—	—
	Overall ACC	—	—	—	—	—	—	—	—
Motivation (MOT)	PTC	—	—	—	—	*	*	*	*
	BP	—	—	—	—	—	—	—	*
	RR	—	—	—	—	*	*	*	*
Learning (LRN)	PTC	—	—	—	—	—	—	—	*
	Overall RR	—	—	—	—	—	—	—	—
	Overall ACC	—	—	—	—	—	—	—	*
Color and position discrimination (CPD)	PTC	—	—	—	—	—	—	—	*
	RR	—	—	—	—	—	—	—	—
	Observing RL	—	—	—	—	—	—	—	*
	Choice RL	—	—	—	—	—	—	—	—
	ACC	—	—	—	—	—	—	—	*

*Denotes significant difference from vehicle (saline) performance ($p < 0.05$).
PTC = percent task completed; RR = response rate; RL = response latency; ACC = accuracy; BP = breakpoint. Adapted from Frederick et al. (1995).

performance that might provide evidence of long-term functional alterations. It was thought that repeated exposure to such high doses of MDMA would produce marked effects in the 5-HT system. It was further speculated that one or more of the complex brain functions modeled in the OTB would likely be subserved, at least in part, by the 5-HT system and thus, some aspects of OTB performance would be sensitive to disruption of the 5-HT system.

The results of these studies have been reported in detail elsewhere (16). During the chronic treatment regimen, the daily doses of MDMA increased every 2 weeks. Behavioral tolerance was generally evident at each individual dose across each two-week treatment period. As shown in Table 4, performance in the motivation task was more sensitive to disruption than was behavior in the other OTB tasks. In fact, mean performance of the time estimation, short-term memory, learning, and color and position discrimination tasks was not significantly affected at MDMA doses of <20 mg/kg/day. Operant test battery performance after the chronic MDMA regimen generally returned to pretreatment baseline levels 2 or 3 weeks after the discontinuation of chronic treatment, and remained stable for the remainder of the experiment (approximately 20 months).

Residual tolerance to the acute effects of MDMA was evident in all OTB tasks at 6 and 12 months after chronic treatment, and even at 18 months in all but the motivation task. The relative order of task sensitivity to the disruptive effects of MDMA, however, changed during each acute assessment (see Table 5).

TABLE 5

CHRONOLOGY OF MDMA ADMINISTRATION

Experiment	Time between experiments	Duration of experiments	Relative order of task sensitivity to disruption by acute MDMA administration
Acute 1		≈ 2 months	MOT = TE = LRN > STM, CPD
	2 weeks		
Chronic		≈ 4 months	MOT > TE = LRN = STM = CPD
	≈ 5 months		
Acute 2		≈ 2 months	MOT > TE = LRN = STM > CPD
	≈ 5 months		
Acute 3		≈ 2 months	MOT = TE > LRN = STM = CPD
	≈ 5 months		
Acute 4		≈ 2 months	MOT > STM > TE, LRN, CPD

Approximately 1 month after the determination of the last acute MDMA dose–response curve, significant decreases in brain 5-HIAA concentrations and 5-HT uptake site densities were detected in the hippocampus of MDMA-treated monkeys (as compared to non-treated controls), whereas 5-HT and 5-HIAA concentrations in the other brain areas monitored were not significantly affected. A significant increase in striatal dopamine was also observed, but dopamine concentrations in other brain areas were not significantly different from those seen in controls. How or whether these neurochemical changes are related to the noted behavioral changes seen in these animals is not known. Following is a more detailed discussion of these findings and those of other studies that have examined the effects of repeated MDMA exposure on performance of similar behavioral tasks.

Color and Position Discrimination and Motivation

The effects of MDMA observed during the final acute dose–response assessment (approximately 18 months after the end of chronic treatment) are summarized in Table 6. Long-term MDMA administration did not fundamentally change the apparent relative sensitivities of either the color and position discrimination or the motivation task (with respect to the other OTB tasks) to the acute disruptive effects of MDMA. During the determination of all acute dose–response curves and during chronic treatment, the motivation task was either the most sensitive to MDMA or as sensitive as any other OTB task. On the other hand, the color and position discrimination task was either the least sensitive to MDMA or as insensitive as any other OTB task. Thus, repeated exposure to gradually escalating doses of MDMA did not appear to cause any permanent changes in the performance of these OTB tasks. Such results suggest that, in rhesus macaques, an intact hippocampal 5-HT system or an unaltered striatal dopamine system is not essential for the expression of behaviors thought to depend on color and position discrimination or motivation to work for food. Additionally, the acute dose of MDMA required to significantly disrupt motivation task performance was only 1.75 mg/kg after repeated MDMA treatment, whereas it was 1.0 mg/kg prior to such treatment. Thus, chronic MDMA treatment produced little "permanent" tolerance to the ability of MDMA to decrease the monkeys' motivation to work for food.

Time Estimation

During the first acute MDMA dose–response assessment, rhesus monkeys performing the time estimation task never held the lever in the depressed position for the necessary 10–14 s at 1.0 mg/kg MDMA (accuracy = 0, see Fig. 2). Subjects did continue to respond at rates where means were comparable to those seen in baseline or vehicle sessions, but many of these responses lasted less than 2 s in duration. Thus, the monkeys were able to respond, but they did not respond appropriately. Similar effects were also noted during chronic MDMA treatment, in that time estimation task accuracy was significantly decreased at the highest MDMA dose tested (20 mg/kg), yet response rates were not. During the final acute MDMA

TABLE 6

ACUTE EFFECTS OF MDMA ON OTB PERFORMANCE OF RHESUS MONKEYS AFTER CHRONIC EXPOSURE

		Dose of MDMA (mg/kg)					
Task	Endpoint	Vehicle	0.3	1.0	1.75	3.0	5.6
Time	PTC	—	—	—	—	—	—
estimation	RR	—	—	—	—	—	—
(TE)	ACC	—	—	—	—	— (1)	— (1)
	Average hold	—	—	—	—	—	—
Short-term	PTC	—	—	—	—	—	*
memory and	Overall RR	—	—	—	—	—	—
attention	Observing RL	—	—	—	—	—	*
(STM)	Choice RL	—	—	—	—	—	—
	Overall ACC	—	—	—	—	—	— (1)
Motivation	PTC	—	—	—	*	—	*
(MOT)	BP	—	—	—	*	—	*
	RR	—	—	*	*	—	*
Learning	PTC	—	—	—	—	—	—
(LRN)	Overall RR	—	—	—	—	—	—
	Overall ACC	—	—	—	—	—	—
Color and	PTC	—	—	—	—	—	—
position	RR	—	—	—	—	—	—
discrimination	Observing RL	—	—	—	—	—	—
(CPD)	Choice RL	—	—	—	—	—	—
	ACC	—	—	—	—	—	—

*Denotes significant difference from vehicle (saline) performance ($p < 0.05$).

PTC = percent task completed; RR = response rate; RL = response latency; ACC = accuracy; BP = breakpoint. Adapted from Frederick et al. (1995).

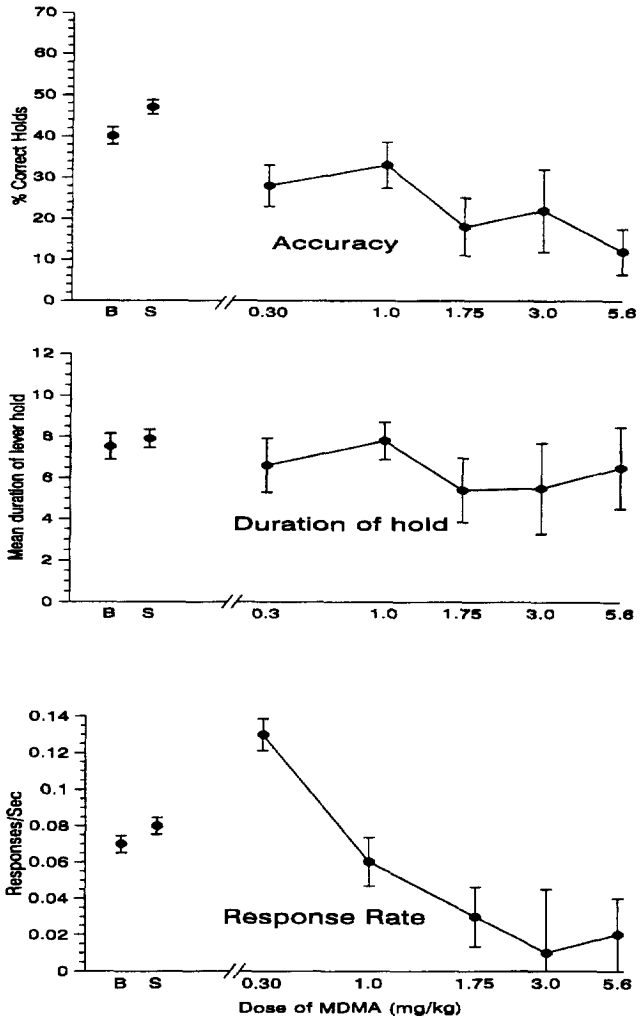

FIG. 4. Acute effects of MDMA on rhesus monkey (N=3) accuracy, mean duration of lever hold, and response rate (± SEMs) in a TE task approximately 18 months after chronic MDMA exposure. Adapted from (16).

dose–response assessment (see Table 6), no time estimation task endpoints were significantly affected at even the highest dose (5.6 mg/kg; recall that 1.0 mg/kg caused the accuracy to approach zero during the determination of the first acute dose–response curve). A comparison of response rates, accuracies, and mean duration of lever holds before (dose–response no. 1; Fig. 2) and after (dose–response no. 4; Fig. 4) chronic treatment shows that response rates were not significantly affected during the first acute dose–response curve, but a non-significant trend toward decreased rates was evident during dose–response no. 4. Also, mean durations of lever holds and accuracies were suppressed during the first acute dose–response curve at 1.0 mg/kg MDMA, whereas neither of these endpoints was significantly suppressed at ≤ 5.6 mg/kg MDMA 18 months after chronic MDMA treatment. These data suggest that long-term or permanent tolerance developed in response to the acute effects of MDMA on performance of this task. Such tolerance was accompanied by a decrease in the number of rapid response bursts caused by MDMA, and thus less of an MDMA-induced decrease in time estimation accuracy.

Possible reasons for the decreased sensitivity of the time estimation task to disruption by acute MDMA could include the following. First, repeated exposure to MDMA could have resulted in a decrease in the ability of MDMA to release monoamines (physiological tolerance). The decreased sensitivity of this and other OTB tasks to disruption by MDMA may be related to the noted long-term neurochemical changes in the 5-HT system, the dopamine system, or both. Second, it is quite possible that during the chronic treatment regimen, these monkeys simply "learned" how to perform the time estimation task better while under the influence of MDMA as their experience with the psychotropic effects of the drug increased. Such behavioral tolerance has been shown to occur during repeated exposure to several other psychoactive compounds (21,30). The development of metabolic tolerance (induction of metabolism) with amphetamine-like compounds is not likely to play a role in these observations (43).

Li et al. (35) compared dose–response curves for MDMA in rats before and 9 weeks after a short course, high dose regimen of MDMA (6 mg/kg twice daily for four consecutive days) using behavior in a differential reinforcement-of-low-rates 72-s task (described in the previous section) as the endpoint. As for the OTB time estimation task, correct performance under this schedule is thought to depend on the subject's ability to estimate elapsed time. Control rats were treated identically, only they were not given the high dose regimen of MDMA. Although significant decreases in brain 5-HT and 5-HIAA were observed in MDMA-treated rats (DA concentrations were not significantly affected), performance after such exposure was not significantly different from that seen prior to treatment. However, when MDMA-treated rats were challenged acutely with the same doses of MDMA used prior to the high dose regimen, response rates were higher and reinforcement rates were lower at each dose tested. No such differences were seen in control rats. Thus, as in the monkey (16), residual effects of high dose MDMA treatment (here in the form of increased sensitivity to MDMA) were observed when rats were acutely challenged with MDMA many weeks later. Baseline (non-drugged) behavior, however, was not significantly affected. Li et al. attributed the increase in response rate and decrease in reinforcement rate to a decrease in the normal inhibitory effects of the 5-HT system on the dopamine-mediated, psychomotor stimulant effects of MDMA.

Learning and Memory

The effects of repeated administration of escalating doses of MDMA on monkey performance of the learning task were similar to those observed for the time estimation task. Overall accuracy was significantly decreased at the highest MDMA dose tested (20 mg/kg/day), while the mean response rate was not affected at any dose tested. During the final acute

dose–response assessment (18 months after cessation of chronic treatment), accuracy and percent task completed in the learning task were not significantly affected at MDMA doses ≤ 5.6 mg/kg, whereas, prior to such treatment, 1.0 mg/kg MDMA significantly decreased these endpoints in this task. Thus, a clear residual or permanent tolerance to the disruptive effects of MDMA was evident in this task.

Before the chronic MDMA treatment regimen, doses ≤ 1.0 mg/kg did not significantly affect any endpoints in the OTB short-term memory task, suggesting that MDMA was not disrupting processes associated with the expression of short-term memory. During chronic treatment, there was a significant increase in the latency to make the observing response (i.e. initiate specific trials within the session) at the highest dose of MDMA tested (20 mg/kg/day), but no effects on accuracy or any other measures were seen. During the determination of the final acute MDMA dose–response curve, observing response latency was again significantly affected at the highest MDMA dose tested (5.6 mg/kg), and the percent task completed was also significantly decreased, but again accuracy was not affected (see Table 6). It should be noted that only one subject completed a sufficient number of trials (three) to be included in the accuracy analysis of the short-term memory task. The relative sensitivity of the short-term memory task to disruption versus the other OTB tasks by MDMA changed after chronic treatment (see Table 5), suggesting that long-lasting alterations in processes associated with performance of the short-term memory task occurred. Whether such changes reflect changes in processes associated with the expression of short-term memory or simply an alteration in the motivation of subjects to perform this task versus other OTB tasks remains to be determined.

LeSage et al. (34) have demonstrated that repeated daily exposure to fixed doses of MDMA results in a tolerance to the effects of acute, high dose MDMA exposure in pigeons (N=4) performing a short-term memory task (delayed matching-to-sample). Recall that LeSage et al. established dose–response curves for MDMA prior to short course, high dose MDMA exposure. Following the determination of an MDMA dose–response curve, pigeons were administered 3.2 mg/kg MDMA for 20 consecutive days, challenged with 4.2 mg/kg MDMA for one session, administered 3.2 mg/kg MDMA for five more sessions and then challenged with 5.6 mg/kg for one session. Subsequent acute MDMA challenges demonstrated that tolerance developed to MDMA's acute effects on both accuracy and response rate, suggesting that such a treatment regimen had affected processes associated with the expression of short-term memory. Since no neurochemical data were obtained from these birds, the observed behavioral effects cannot be related to changes in 5-HT or any other neurotransmitters.

SUMMARY

In MDMA-naïve animals, operant schedules in which correct performance is thought to depend upon the learning and time estimation capabilities of subjects appear to be more sensitive to the acute effects of MDMA than tasks thought to depend upon short-term memory and visual discriminations. Schedule-controlled operant behaviors thought to assess aspects of motivation to work for food also seem to be particularly sensitive to the acute effects of MDMA, possibly reflecting the anorectic properties of the drug. When repeatedly exposed to high and/or escalating doses of MDMA, residual effects (e.g. tolerance, sensitization) on task performance are apparent when subjects are challenged with acute MDMA, while baseline (non-drug) performance after such exposure generally remains unchanged. Although the experiments involving repeated exposure to presumably neurotoxic doses of MDMA were conducted on a relatively small number of subjects, they do suggest that repeated exposure to high doses of MDMA may produce persistent changes in central nervous system chemistry that are also accompanied by changes in some acute behavioral responses to MDMA. Behaviors thought to be associated with complex brain functions such as short-term memory, learning, and time estimation are somehow different after repeated exposure to high doses of MDMA. The recreational and psychotherapeutic use of MDMA should be considered with the knowledge that long-term effects on cognitive processes are possible.

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