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MDMA and Learning: Effects of Acute and Neurotoxic Exposure in the Rat

TOM BYRNE, LISA E. BAKER AND ALAN POLING

Western Michigan University, Department of Psychology, Kalamazoo, MI 49008

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BYRNE, T., L. E. BAKER AND A. POLING. *MDMA and learning: Effects of acute and neurotoxic exposure in the rat.* PHARMACOL BIOCHEM BEHAV **66**(3) 501–508, 2000.—In two experiments, the effects of MDMA on the acquisition of lever-press responding of rats were examined under procedures in which water delivery was delayed by 0, 10, or 20 s relative to the response that produced it. In the first study, experimentally naive, water-deprived rats received an intraperitoneal injection of MDMA (0, 1.0, 3.2, or 5.6 mg/kg) prior to one 8-h experimental session. Response acquisition was observed under all conditions at all drug doses. MDMA increased the total number of responses emitted and the total number of water deliveries earned in dose-dependent fashion, but only when reinforcement was immediate. Under conditions of delay, MDMA had no effect on either measure. Under all reinforcement conditions, higher doses of MDMA typically produced an initial reduction in lever pressing, and in that sense interfered with learning. In the second study, rats received an MDMA injection regimen previously shown to be neurotoxic. Control rats received saline solution according to the same injection schedule. Two weeks after completing the regimen, rats were water deprived and exposed to behavioral procedures as described for the first experiment. Although MDMA significantly reduced 5-HT and 5-HIAA levels in the striatum and prefrontal cortex, mean performance of rats exposed to MDMA did not differ from that of rats exposed to vehicle. Twenty-five percent of the rats exposed to MDMA and delayed reinforcement did fail to acquire responding, which suggests that further study of the effects of neurotoxic doses of MDMA on initial response acquisition is warranted. © 2000 Elsevier Science Inc.

Response acquisition Delayed reinforcement MDMA Rats

THE effects of (±) 3,4-methylenedioxymethamphetamine (MDMA) on complex operant behavior have been evaluated in several studies, which are reviewed elsewhere (9,11). Most of those studies examined the effects of acute administrations of relatively low doses. Although results vary somewhat across studies, the authors of one recent review indicate that, under those conditions, "MDMA disrupts complex brain functions associated with learning and time estimation more than those associated with short-term memory and visual discrimination, and behavioral tasks requiring relatively high rates of responding are particularly sensitive to the disruptive effects of MDMA" [(9), p. 67]. Repeated exposure to high doses of MDMA enduringly depletes serotonin (5-hydroxytryptamine, 5-HT) and disrupts operant behavior under some procedures, but not others [e.g., (1,3,12,28,30)].

The purpose of the present study was to examine the effects of single and repeated doses of MDMA in rats exposed to another learning assay, specifically, one that involves the initial acquisition of lever-press responding. Recent studies suggest that that MDMA may induce cognitive (or behavioral) impairment in humans (1,16,19), as do extrapolations from animal studies (8,11). No one has previously examined whether the drug interferes with the initial acquisition of operant behavior, but such an effect would be significant in human users, many of whom are young and in the process of acquiring new behaviors. If preclinical results suggest that MDMA disrupts initial response acquisition, it may well be worthwhile to look for such adverse effects in humans who use the drug recreationally.

The first studies examining drug effects on the initial acquisition of lever pressing appeared in 1971 (26,27). In those studies, rats not trained to lever press were placed in a test chamber containing a single lever. Each press on that lever immediately produced food. Prior to testing, each subject received an injection of chlorpromazine, chlordiazepoxide, or vehicle. In general, subjects that received either drug acquired responding more slowly than subjects that received vehicle. Moreover, both drugs reduced the total number of re-

Requests for reprints should be addressed to Alan Poling, Department of Psychology, Western Michigan University, Kalamazoo, MI 49008.

sponses and food deliveries relative to saline-control levels. Therefore, chlordiazepoxide and chlorpromazine interfered with learning.

Early in the 1990s, researchers demonstrated that rats would acquire lever pressing in the absence of hand shaping or autoshaping when reinforcement (food or water delivery) was delayed by up to approximately 30 s, although learning was impaired at longer delays (4,5,13,29,31). Recently, the effects of *d*-amphetamine and chlorpromazine on initial response acquisition with both immediate and delayed reinforcement were assessed (2,15). Given the characteristic observation that poorly learned behaviors are more easily disrupted by drugs than are better-learned behaviors (20,21), it was of interest to determine whether drugs interfered with the initial acquisition of operant behavior to a greater extent when reinforcement was delayed than when it was immediate.

That outcome was evident when the effects of chlorpromazine (2, 6, and 10 mg/kg) were examined under immediate-reinforcement and 8-s resetting delay procedures (2). Under both procedures, responses on a lever that produced water and responses on a lever that had no consequences were compared. Regardless of whether reinforcement was immediate or delayed, the 10-mg/kg dose greatly reduced responding on both the reinforcement and the no consequences lever. For rats exposed to delayed reinforcement, chlorpromazine at 2 and 6 mg/kg produced a dose-dependent decrease in the percentage of total lever presses allocated to the lever that produced reinforcers (water deliveries). This did not occur under conditions of immediate reinforcement. These results support the possibility that delaying reinforcement may allow for the detection of drug effects not apparent when reinforcement is immediate.

With *d*-amphetamine (1.0, 5.6, and 10.0 mg/kg), in contrast, results did not differ when reinforcement was immediate or delayed by 8 or 16 s (15). In a single 8-h sessions, rats learned to press the lever that produced water at all drug doses and under all delay conditions.

d-Amphetamine did not alter the distribution of responses on the two levers, but doses of 5.6 and 10 mg/kg substantially slowed response acquisition relative to vehicle-control levels, and in that sense interfered with learning. Those doses produced a general disruption of lever pressing under all procedures, probably by inducing stereotypies that were incompatible with lever pressing. In general, these findings are consistent with those obtained in studies that examined the effects of *d*-amphetamine on learning under other procedures (e.g., repeated acquisition, mazes). As Evans and Wenger pointed out in a review of the effects of amphetamine and other stimulants, the results of those studies suggest that: "There is no detrimental effect of these psychomotor stimulants on 'learning' until doses that produce a general behavioral disruption are achieved" [(6), p. 636].

Although some exceptions have been reported, MDMA and amphetamine often produce similar effects on operant behavior [for a review, see (14)]. Given this similarity, we hypothesized that MDMA would slow the acquisition of lever pressing under initial response-acquisition procedures similar to those used to study *d*-amphetamine, but would not alter the distribution of responding on the two levers or produce different effects when reinforcement was immediate or delayed. This hypothesis was tested in the present study. In both experiments, responding on two levers was compared. Responses on one (the reinforcement) lever produced water, whereas responses on the other (cancellation) lever prevented any scheduled water delivery. Recent research (29) suggests that this procedure is superior to the procedure used in prior drug studies (2,15), in which responding on a reinforcement and no consequences lever was compared. The latter procedure allows for the adventitious reinforcement of lever presses, and provided only equivocal evidence of response acquisition at delays (16 and 32 s) where acquisition was clearly evident under the reinforcement/cancellation procedure (29).

EXPERIMENT 1

Method

Subjects. Ninety-six experimentally naive male Sprague–Dawley rats, approximately 60 to 70 days of age, served as subjects. The rats were water deprived as described below, and were housed individually with unlimited access to food in a colony area with a 12-h light/dark cycle that provided ambient illumination from 0800 until 2000 h. In both experiments, rats were housed and handled in accordance with the ethical standards promulgated by the American Psychological Association.

Apparatus. Eight MED Associates (St. Albans, VT) operant test chambers were used. The chambers were 28 cm long by 21 cm wide by 21 cm high. During response-acquisition sessions, two response levers separated by 8.5 cm were mounted on the front panel 7 cm above the chamber floor. The levers were removed during dipper-training sessions. A minimum force of 0.14 N was required to operate the levers. A receptacle, located in the center of the front panel 3 cm above the chamber floor, allowed access to a dipper filled with 0.1 ml of tap water when the dipper was raised. Chambers were illuminated by a 7-W bulb mounted on the ceiling. An exhaust fan in each chamber masked extraneous noise and provided ventilation. Programming of experimental events and data recording were controlled by an IBM-compatible microcomputer equipped with MED-PC software.

Behavioral procedures. All subjects were water deprived for 24 h prior to one dipper-training session. Dipper-training sessions were 90 min in length, and entailed delivering water under a variable-time 60-s schedule. Under this schedule, 4-s dipper presentations occurred randomly on average once every 60 s, regardless of the subject's behavior. All rats were observed to drink from the dipper by the end of the session. At the end of dipper-training sessions rats were returned to their home cages and given 20-min access to water.

Twenty-four hours after dipper training subjects were exposed to one response-acquisition session. Response-acquisition sessions began at approximately 2200 h and lasted for 8 h. Rats were randomly assigned to 12 acquisition conditions (groups), with eight rats in each group. Subjects in all groups were exposed to a tandem fixed-ratio 1 not-responding-greater-than-*t* schedule on the reinforcement lever. Here, the first response initiated a delay of *t* s, after which water was delivered for 4 s. Any response that occurred during the delay reset the *t* interval. Values of *t* were 0, 10, and 20 s for different groups. Four groups were exposed to each delay value. The left lever was designated as the reinforcement lever for four randomly selected rats in each group, and the right lever was designated as the reinforcement lever for the remaining rats. If a response occurred on the other (cancellation) lever during a delay (*t*) interval, the scheduled water delivery did not occur. Responses on this lever at other times had no scheduled consequences, but were recorded. For subjects that received immediate 4-s water deliveries, the value of *t* was 0 s; therefore, responses on the cancellation lever had no pro-

grammed consequences, although they were recorded. Because previous studies have demonstrated that no-water and yoked-control subjects emit far fewer lever presses than rats exposed to delay values equal to or greater than those utilized in this study (5,15,29), no such controls were used in the present investigation. Under all conditions, responses on the two levers were recorded in 5-min bins across the course of the session. Total water deliveries during each session were also recorded.

Pharmacological procedures. Each delay value (0, 10, and 20 s) and drug dose (0, 1.0, 3.2, or 5.6 mg/kg MDMA) was examined in a single group of eight rats. All injections were given intraperitoneally 15 min prior to the start of the response-acquisition sessions, and rats were placed in the operant chambers 5 min prior to session commencement. MDMA (National Institute on Drug Abuse, Rockville, MD) was dissolved in isotonic saline solution and prepared at an injection volume of 1 ml/kg. Doses and presession injection intervals were based on pilot data from our laboratory, and are similar to those characteristically used in behavioral studies with rats (11).

Results

Data from one rat in the 3.2 mg/kg, 10-s group were lost due to equipment failure. With that exception, data from all subjects were included in the analysis. All subjects, except for one rat in the 5.6-mg/kg, 20-s delay group, exhibited accelerated rates of reinforcement-lever responding across time, and thus showed clear evidence of response acquisition. Figure 1 shows mean cumulative reinforcement-lever responses (acquisition curves) for each group. In general, through much of the session, increasing delay of reinforcement decreased responding on the reinforcement lever. Nonetheless, for groups injected with vehicle, the total number of responses emitted in the session was similar regardless of delay value. This is not the case for rats exposed to MDMA, which emitted the most responses when reinforcement was immediate. This effect is most evident in rats that received 5.6 mg/kg.

As shown in Fig. 1, rats injected with vehicle or 1.0 mg/kg MDMA started responding soon after the session began. Rats began responding later in the session when exposed to MDMA at doses of 3.2 and 5.6 mg/kg, although they responded at rates comparable to or higher than those of vehicle-control rats once responding began. Most subjects injected with 5.6 mg/kg did not start responding until about 100 min into the session.

Figure 2 depicts mean total reinforcement lever responses and mean total reinforcers obtained by subjects in each group. For rats exposed to immediate reinforcement, MDMA increased the total number of reinforcement lever responses and resulting water deliveries in a dose-dependent fashion. For groups exposed to delays of 10 or 20 s, however, MDMA did not affect the total number of reinforcement lever responses or reinforcers earned. Analysis by two-way ANOVA showed a significant interaction of the effects of drug and delay on total reinforcement lever responses ($F = 3.22$, $p < 0.01$), which indicates that reinforcement delay modulated the effects of MDMA. For data collected under the immediate reinforcement condition, multiple comparisons with a Tukey HSD revealed significant differences in reinforcement lever responding between vehicle and 3.2 mg/kg ($q = 5.65$, $p < 0.01$) groups, as well as between vehicle and 5.6 mg/kg ($q = 5.63$, $p < 0.01$) groups. Differences among all other groups ex-

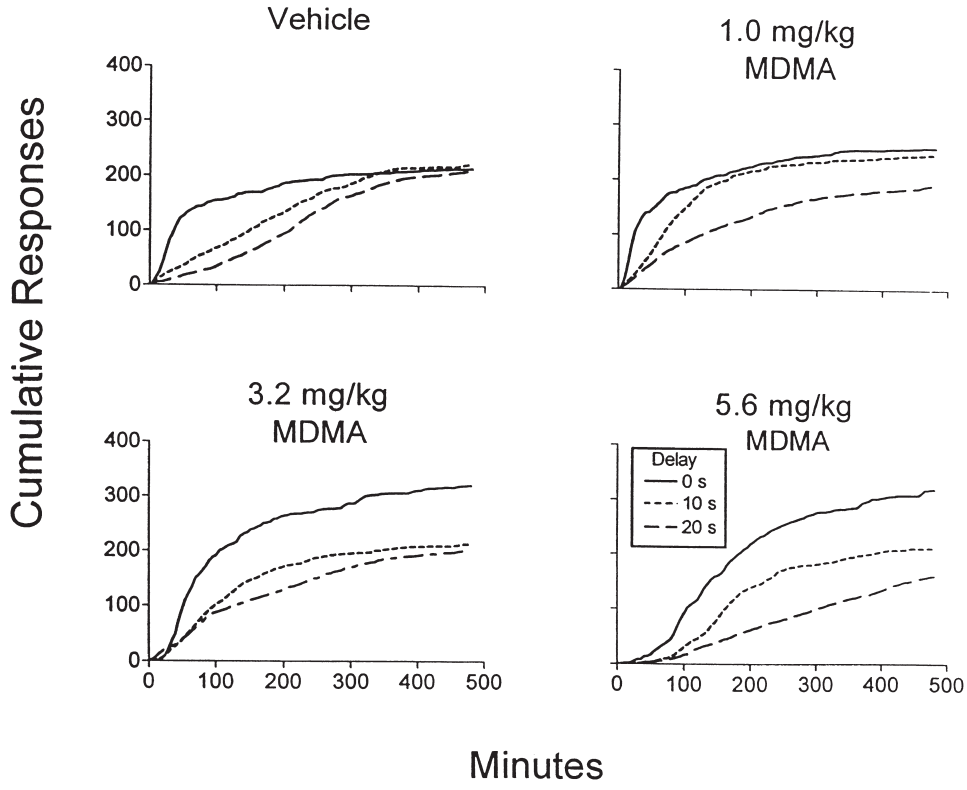

FIG. 1. Mean cumulative reinforcement lever responses under each experimental condition.

posed to immediate reinforcement, and among all groups exposed to delayed reinforcement, were not significant at the 0.05 level.

A second measure of learning, differential responding on the reinforcement and cancellation levers, is shown in Fig. 3, which depicts the mean ratio of reinforcement lever to cancellation lever responses for each group. For all groups, the majority of responses were emitted on the reinforcement lever. ANOVA revealed that MDMA ($F = 0.50$, $p > 0.05$) and delay length ($F = 2.82$, $p > 0.05$) did not significantly affect the proportion of responses that occurred on the reinforcement lever.

Discussion

Although MDMA increased the latency for responding to begin, and in that sense interfered with learning, the drug did not decrease the total number of reinforcement lever responses emitted or affect the development of differential responding on the reinforcement and cancellation levers regardless of whether reinforcement was delayed or immediate. If, however, these measures were compared early in the session, statistically significant differences would be apparent. That this is so underscores a potential problem with the use of 8-h experimental sessions: Acquisition curves are influenced by the onset and offset of drug action. Given this, and the fact that in the absence of drug lever-press acquisition is evident in nearly all rats within 1 to 2 h (15,29,31), we recommend that session length be no longer than 2 h in future studies using initial response acquisition procedures.

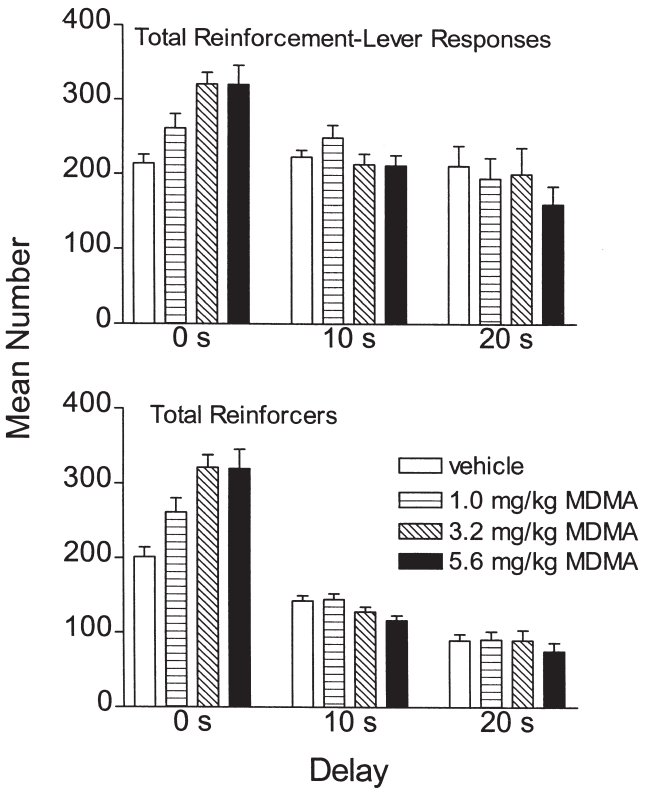

FIG. 2. Mean total reinforcement lever presses emitted and mean total reinforcers earned under each experimental condition. Bars indicate 1 SE.

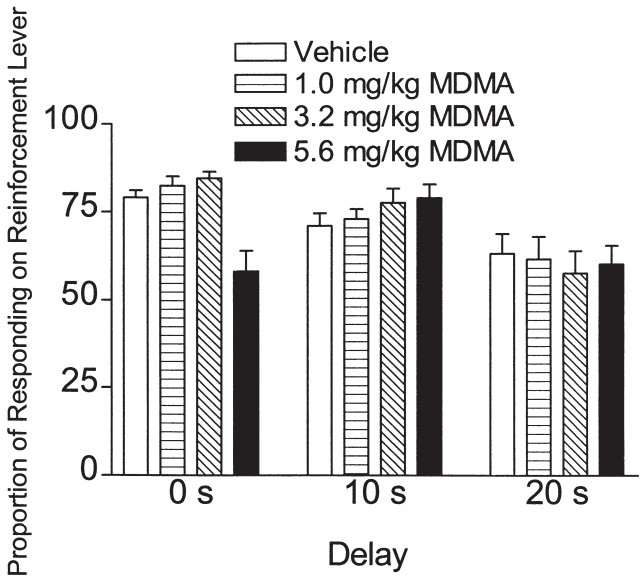

FIG. 3. Mean proportion of total responses emitted on the reinforcement lever under each experimental condition. Bars indicate 1 SE.

Despite the fact that shorter sessions would appear to increase the sensitivity of the initial response-acquisition assay, two interesting outcomes were evident with 8-h sessions. One, noted above, is that MDMA slowed response acquisition. A second is that the drug increased the total number of responses emitted on the reinforcement lever under conditions of immediate reinforcement but not under conditions of delayed reinforcement. This effect may be due to MDMA acting as an establish operation (EO), which is a variable that alters the reinforcing (or punishing) effectiveness of other events (17). Under the conditions of the present study, the primary EO was water deprivation. MDMA produces hyperthermia (25), however, and it is plausible that increasing body temperature increases the reinforcing effectiveness of water. If so, rats exposed to MDMA were under the influence of two EOs—water deprivation and MDMA-induced hyperthermia. The effects of hyperthermia became evident only when the effects of water deprivation weakened substantially. This occurred only after a relatively large number of water deliveries, and this occurred only in rats exposed to immediate reinforcement. This mechanism accounts nicely for the difference in the effects of MDMA under conditions of delayed and immediate reinforcement, but it is presently hypothetical. Direct support for the proposition that MDMA increases the reinforcing effectiveness of water under some conditions could be obtained easily by, for example, utilizing a progressive-ratio schedule.

In general, MDMA produced effects comparable to those observed previously with *d*-amphetamine under initial response acquisition procedures (15). MDMA and amphetamine often produce similar effects on operant behavior under other procedures [for a review, see (14)], therefore, it is not surprising that the drugs had similar effects on response acquisition. In contrast to *d*-amphetamine, however, MDMA slowed response acquisition at doses that did not produce gross behavioral incapacitation.

TABLE 1

MEAN LEVELS (ng/g) OF 5-HT AND 5-HIAA IN THE PREFRONTAL CORTEX AND STRIATUM OF CONTROL AND MDMA-TREATED RATS

	Prefrontal Cortex		Striatum	
	5-HT	5-HIAA	5-HT	5-HIAA
Control rats	145.0 (8.1)	30.6 (1.7)	186.0 (25.8)	86.3 (6.2)
MDMA-treated rats	49.4 (4.6)*	10.6 (1.1)*	107 (22.3)*	37.1 (3.8)*

The number in parentheses is 1 SE. Asterisks indicate that values obtained in control rats were significantly higher than those obtained in MDMD-treated rats ($p < 0.01$ except for 5-HT in the striatum, where $p < 0.05$).

EXPERIMENT 2

Experiment 1 demonstrated that acute exposure to relatively low doses of MDMA interfered with one measure of initial response acquisition, but not with others. Experiment 2 examined how repeatedly exposing rats to a relatively high MDMA dose, one shown in previous studies to be neurotoxic in the sense of producing lasting serotonin depletion (18,22,23), would affect the initial acquisition of lever-press responding.

Method

Subjects and apparatus. Forty-eight experimentally naive male Sprague–Dawley rats, approximately 60 to 70 days of age at the start of the experiment, served as subjects. The rats

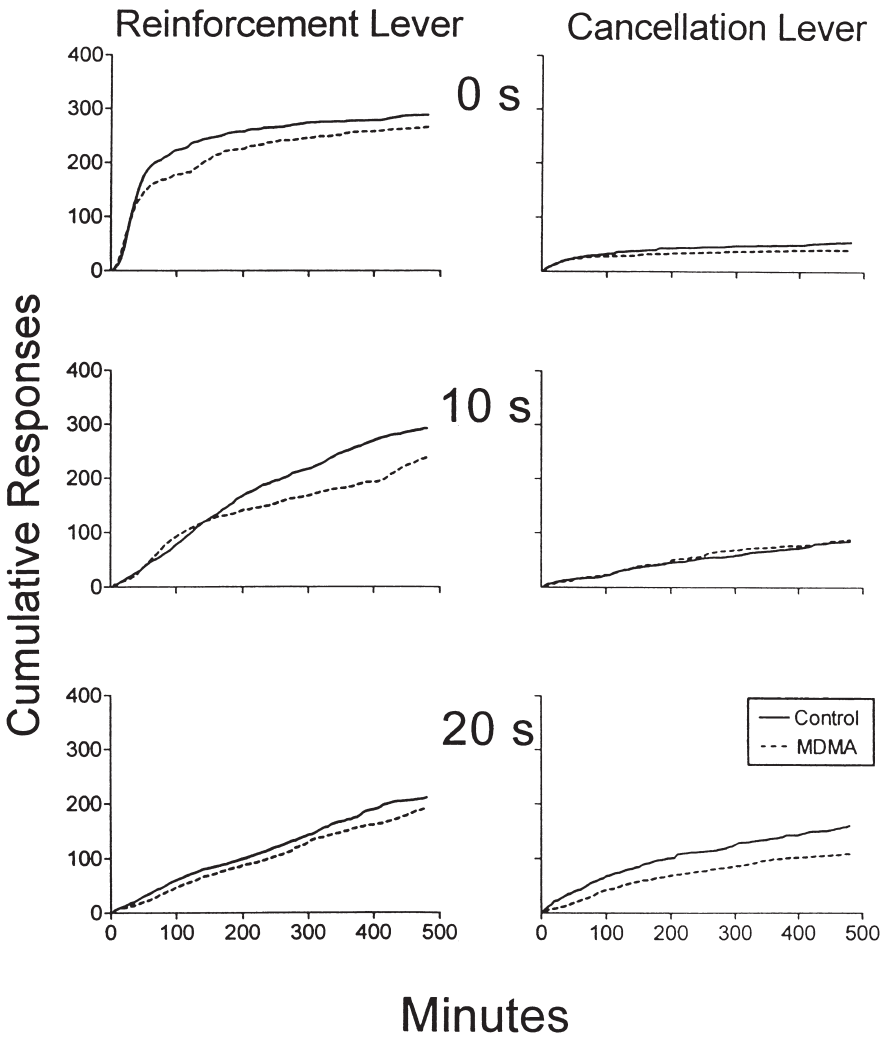

FIG. 4. Mean cumulative reinforcement lever and cancellation lever responses under each experimental condition.

were housed and water deprived as described in Experiment 1, and tested in the equipment used in that experiment.

Pharmacological procedures. Rats were randomly assigned to MDMA or vehicle dosing regimens. Twenty-four rats received subcutaneous (SC) injections of 20 mg/kg MDMA (National Institute on Drug Abuse, Rockville, MD) twice a day (0800 and 2000 h) for 4 days. The remaining 24 rats received SC injections of isotonic saline solution according to the same schedule. Fourteen days after the regimen was completed, behavioral procedures commenced. Previous findings suggest that by this time there would be no remaining behavioral effects of MDMA itself, but there would be significant decreases in 5-HT concentrations (22,23).

Behavioral procedures. Rats were exposed to dipper-training and experimental sessions as described in Experiment 1. Three delay values (0, 10, and 20 s) were examined. MDMA-treated subjects were randomly assigned to three groups of eight, and each group was exposed to one of the delay values. Control subjects were treated in comparable fashion. Data were collected as in Experiment 1.

Neurochemical analyses. Twenty-four to 48 h after behavioral testing was completed, eight randomly selected MDMA-treated rats and eight randomly selected control rats were decapitated. Their brains were rapidly removed and placed in an ice-chilled aluminum brain slicing matrix (ASI instruments, Warren, MI). The prefrontal cortex and corpus striatum were dissected from brain slices in a manner similar to that described elsewhere (10). Using the brain matrix as a guide, five 2-mm sections were sliced from the anterior end of the forebrain. The prefrontal cortex was dissected from the fourth slice and the corpus striatum was dissected from the fifth slice. Tissue samples were placed in microcentrifuge tubes and frozen on dry ice, then stored at −80°C until analyzed.

Just prior to analysis, tissue samples were sonicated in 500 ml buffer (0.1 N perchloracetic, 10% ethylenediaminetetraacetic acid, 5% glutathione), then centrifuged under refrigeration for 14 min at 1400 rpm, with a G force of approximately 125 g. A 400-ml aliquot of the supernatant was pipetted into 1.5-ml clear glass vials, to which 10 ml of an internal standard (0.1 concentration) was added. The vials were covered with stoppers and placed into a refrigerated autosampler tray for immediate chromatographic analysis.

Analysis of tissue samples was performed on a reverse-phase high-performance liquid chromatography (HPLC) system using electrochemical detection. The mobile phase consisted of 8% acetonitrile, 48 mM citric acid, 1 mM potassium phosphate dibasic, and sodium octylsulfonate (35 mg/l) vacuum filtered (4 mM), adjusted to a pH of 2.3 and stored at room temperature. The HPLC system consisted of a quaternary pump (Perkin Elmer, Norwalk, CT) operating at a rate of 1.5 ml/min. Samples and standards were injected by an autosampler (Perkin Elmer ISS200) at a volume of 50 ml/injection, which passed through a Zorbax Rx-C8 column (Rockland Technologies, Chadds Ford, PA) equipped with a compatible guard column. Solutions were analyzed by an electrochemical detector (MF-9000 Amperomatic, Bioanalytical Systems, West Lafaytte, IN) equipped with a glassy carbon electrode set to operate at 20 nA with an applied potential of 800 mV. Signals were filtered at 0.10 Hz before they were recorded and stored using Millennium Software (Waters Chromatography, Milford, MA). Within 20 min, peaks were detected for 5-HT and for 5-hydroxyindole acetic acid (5-HIAA), which is a metabolite of 5-HT. Results were calculated and are reported as ng/g tissue.

Results

Mean levels of 5-HT and 5-HIAA in the prefrontal cortex and striatum are shown in Table 1. In both areas, levels of these neurochemicals were lower in the rats that received MDMA. Statistical analysis via *t*-tests revealed that levels of both 5-HT, $t(14) = 10.28$, $p < 0.01$, and 5-HIAA, $t(14) = 9.52$, $p < 0.01$, were significantly lower in the prefrontal cortex of the MDMA-treated rats than in the saline-control group. The differences in striatal 5-HT, $t(14) = 2.32$, $p < 0.05$, and 5-HIAA, $t(14) = 6.74$, $p < 0.01$, levels between groups also were statistically significant.

Data for one MDMA-treated rat exposed to 10-s delay of reinforcement were lost due to equipment failure. With this exception, data for all subjects were included in the analysis of behavioral results. All subjects, except for two MDMA-treated rats exposed to 20-s delays, showed evidence of response acquisition. Figure 4 shows mean cumulative reinforcement lever and cancellation lever responses for all groups. Acquisition as evidenced by cumulative responding on the reinforcement lever did not appear to be affected by the MDMA regimen under any of the conditions. Similarly, there was no effect of MDMA treatment on cancellation lever responding. Both control and MDMA-exposed rats responded faster early in the session when reinforcement was immediate than when it was delayed. Increasing delay de-

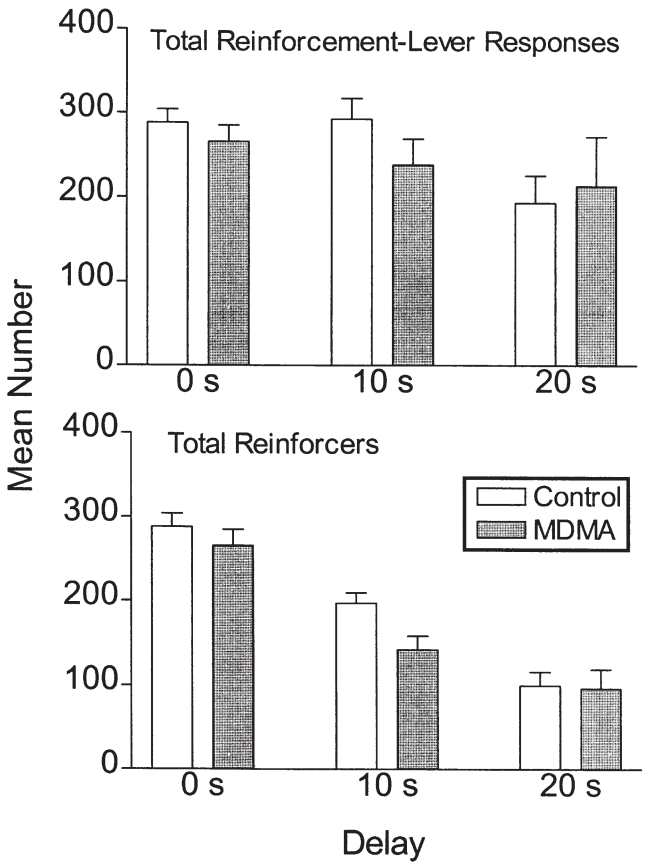

FIG. 5. Mean total reinforcement lever presses emitted and mean total reinforcers earned under each experimental condition. Bars indicate 1 SE.

creased lever pressing for all subjects regardless of MDMA exposure.

Mean total reinforcement lever responses and mean total reinforcers earned are shown in Fig. 5. There was no statistically significant effect of drug treatment on total reinforcement lever responses ($F = 0.48, p > 0.05$) or on total reinforcers earned ($F = 3.6, p > 0.05$). Delay length also did not affect total reinforcement lever responses at the 0.05 significance level ($F = 2.83, p > 0.05$), but this variable did significantly affect the total number of reinforcers earned ($F = 53.85, p < 0.01$). There was no significant interaction between drug exposure and delay length with respect to either total responses emitted or reinforcers earned.

Discussion

As in prior investigations [e.g., (3,12,18,24)], repeated exposure to high doses of MDMA produced substantial 5-HT depletion in the present study. Such exposure did not, however, consistently disrupt response acquisition regardless of whether reinforcement was immediate or delayed. The finding that MDMA-induced depletion of 5-HT did not interfere with learning is consistent with earlier observations indicating an absence of learning impairment in monkeys exposed to repeated acquisition (and other) procedures (7). There are three main reasons why MDMA-induced 5-HT depletion may not affect behavior (7). First, 5-HT may not play an important role in mediating performance in a given learning task, or other brain systems may compensate for 5-HT deficits. Second, the specific assay used may not be sensitive enough to detect the effects of neurotoxicity. Third, the neurotoxic effects may not be large enough to cause any detectable behavioral deficits.

No one has investigated the neurotransmitter systems that are responsible for learning under procedures like those used in the present study. Experiment 1 revealed, however, that acute doses of MDMA, which primarily affect serotonergic activity, slow the acquisition of responding under such procedures. This outcome suggests that initial response acquisition procedures are sensitive to the learning impairment induced by drugs that affect 5-HT systems. With respect to the possibility that the degree of serotonin depletion is insufficient to produce learning impairment, it is noteworthy that two of eight MDMA-treated rats exposed to 20-s reinforcement delays failed to acquire lever pressing over the course of the 8-h session. In prior studies from our laboratory in which similar procedures were used, response acquisition was observed in nearly all rats (2,15,29,31), regardless of whether they received chlorpromazine, *d*-amphetamine, or no drug. Therefore, the fact that 25% of the rats that received 20 mg/kg twice a day for 4 days failed to acquire responding with a 20-s reinforcement delay suggests that the drug treatment disrupted learning, although this effect was not evident when group data were considered.

Possibly, the two rats that failed to acquire responding under these conditions experienced substantially greater neurotoxicity than the six rats that exhibited acquisition. Unfortunately, neurochemical analyses were only conducted with 8 of the 24 MDMA-treated animals, selected at random, and neither of the two rats that failed to acquire responding was selected. For those animals that were selected for neurochemical analysis, there was no indication that behavior differed as a function of 5-HT or 5-HIAA levels. It is, however, possible that exceptionally strong depletion occurred in the two animals that failed to acquire lever press responding with a 20-s reinforcement delay, and was responsible for the behavioral impairment. In general, the degree of neurotoxicity produced by MDMA is directly related to dosage (18). A worthwhile follow-up to Experiment 2 would involve examining whether doses higher than 20 mg/kg, the dose used in that experiment, consistently interferes with initial response acquisition, especially when reinforcement is delayed. The results of Experiment 1 and of prior studies (2,15,20) indicate that such procedures are sensitive to acute drug effects, but it remains to be determined whether they also are sensitive to the effects of enduring drug-induced changes in neurotransmitter systems.

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