

# Effect of MDMA Neurotoxicity Upon Its Conditioned Place Preference and Discrimination

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SCHECHTER, M. D. *Effect of MDMA neurotoxicity upon its conditioned place preference and discrimination.* PHARMACOL BIOCHEM BEHAV 38(3) 539-544, 1991.—Experiments were conducted to investigate the functional consequences of a neurotoxic regimen of MDMA administration upon two behaviors, conditioned place preference and drug discrimination. Rats were trained to discriminate 1.5 mg/kg MDMA from its vehicle and their discriminative performance was shown to be dose-responsive. Subsequently, MDMA was observed to produce a conditioned place preference as three conditioning sessions with 1.5 mg/kg MDMA paired with the nonpreferred chamber increased the time the rats spent in the chamber paired with MDMA. Administration of a purportedly neurotoxic dose (20 mg/kg subcutaneous) of MDMA, twice-a-day for four days, did not affect this conditioned place preference when it was redetermined at a time of maximal neurochemical compromise. In contrast, sensitivity to 1.0 mg/kg MDMA in the drug discrimination task was shown to be significantly decreased after the neurotoxic regimen. Results are discussed in light of MDMA effects upon both central serotonergic and dopaminergic neurons.

MDMA	Neurotoxicity	Stimulus properties of drugs	Drug discrimination	Behavior
Conditioned place preference		Dopamine Rats	Serotonin	

THE illegal "designer drug" 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is being used by an ever increasing abuser population, especially amongst college students (16). The observation that the desmethyl analogue of MDMA, viz., methylenedioxyamphetamine or MDA, produces neurotoxicity to specific serotonergic (5HT) neurons in the rat brain (18), stimulated numerous researchers to investigate the possibility of similar 5HT structural damage produced by MDMA. Indeed, studies in rodents demonstrated that acute and/or repeated administration of MDMA produces long-term reductions in the concentrations of 5HT and its metabolite 5-HIAA (1, 3, 22, 24, 25, 28), as well as destruction of 5HT nerve terminals (2,14). The functional consequences of serotonergic compromise after MDMA, as well as its neurotoxic potential in humans, is, at present, unclear.

Many laboratories (4, 13, 19, 20) have reported experiments that indicate that MDMA can function as a drug capable of controlling differential responding in a drug discrimination paradigm. In contrast, MDMA has not been employed in the conditioned place preference (CPP)-test as have many dopaminergically mediated amphetamine-like drugs of abuse [review (6)]. It was, therefore, the purpose of this study to investigate if the reinforcing properties of MDMA would allow the establishment of a conditioned place preference, and to see if using a regimen of MDMA administration that has been reported to produce neurotoxicity to 5HT neurons would affect this conditioned place preference. In addition, the effect of repeated (neurotoxic) administrations of MDMA upon rats' ability to discriminate its interoceptive cue properties would also be determined.

## METHOD

### Subjects

The group of animals trained to discriminate MDMA, and tested after conditioning in the CPP paradigm, were 12 experimentally naive male Sprague-Dawley rats purchased from the Zivic-Miller Laboratories (Allison Park, PA). They weighed 125–150 g at the beginning of the experiment and were individually housed in a room maintained on a 12-h light (0600–1800)/12-h dark cycle and kept at temperatures between 20–22°C. They were offered water ad lib, as well as daily rationing of commercial rat chow. This feeding regimen was adjusted to maintain their body weights at approximately 85–90% of expected free-feeding weight values.

### Discrimination Training

Twelve commercially available rodent operant chambers (Lafayette Instrument Corp., Lafayette, IN) were used as the experimental space. Each chamber contained two levers situated 7 cm apart and 7 cm above a grid floor. A food receptacle was mounted 2 cm above the grid floor, midway between the two levers. Each operant chamber was enclosed in a sound-attenuated cubicle with an exhaust fan used for ventilation. Solid-state programming equipment (Med Assoc., E. Fairfield, VT), located in an adjacent room, was used to control and record the discrimination sessions.

A detailed protocol of the training procedure can be found in a previous publication (19). Briefly, the rats were trained to dis-

criminate MDMA (1.5 mg/kg) from vehicle (V; distilled water) in a two-lever, food-motivated operant task. Prior to the initiation of training, one lever was designated as the "vehicle lever" and the other lever as the "MDMA lever." Twenty min prior to each training session, the food-deprived rats received an intraperitoneal (IP) injection (1 ml/kg volume) of either MDMA (1.5 mg/ml) or V. After MDMA administration, responses on the MDMA lever resulted in food reinforcement (45 mg Noyes food pellet), whereas responses on the vehicle lever had no programmed consequence. Likewise, responses on the vehicle lever following V administration produced reinforcement. The reinforcement schedule was set at a fixed ratio of 10 (FR 10), i.e., 10 state (either MDMA or vehicle)-appropriate lever responses yielded one reinforcement; this reinforcement schedule was attained by beginning on an FR 1 schedule and gradually increasing the reinforcement requirement over 6 days until an FR 10 schedule was reached. Once this occurred, daily sessions were conducted until animals had made 400 responses upon the state-appropriate lever. Training sessions were conducted once per day according to the two-week repeating schedule: MDMA, V, V, MDMA, MDMA; V, MDMA, MDMA, V, V, where V = vehicle and MDMA = training dose of 1.5 mg/kg. The training schedule was continued until the first lever pressed ten times was state-appropriate in eight of ten consecutive daily sessions. When this criterion was attained, the number of the first session of the ten consecutive sessions was the measurement referred to as the sessions-to-criterion (STC 1). The animals were required to choose the state-appropriate lever on one additional set of 8 of 10 consecutive sessions; this measurement constituted the sessions-to-criterion 2 (STC 2).

#### *Dose-Response Effect of MDMA*

After all the rats attained the training criterion and were thus judged able to discriminate between 1.5 mg/kg MDMA and its vehicle, the rats received various doses of MDMA (dose-response; DR) different from the training dose according to the following biweekly schedule: MDMA-DR<sub>1</sub>-V-DR<sub>2</sub>-MDMA, DR<sub>2</sub>-V-DR<sub>1</sub>-MDMA-DR<sub>3</sub>, etc., where MDMA = the MDMA training dose; V = vehicle; DR<sub>1</sub> = one other dose of MDMA; DR<sub>2</sub> = second other dose of MDMA, etc. Doses were administered IP at 20 min prior to testing and, on these test days, the animals were allowed to lever press until 10 responses were made on either of the two levers. At that time, the rat was immediately removed from the operant test chamber without receiving reinforcement and placed into its home cage in order to preclude any reinforcement (training) after a dose different than the 1.5 mg/kg MDMA training dose. MDMA, in doses of 0.5, 0.75, and 1.0, was administered on two occasions with one test session following a maintenance session with 1.5 mg/kg MDMA and the other following a maintenance session with vehicle. During these maintenance sessions, the lever first pressed ten times by the animal was considered as the "selected" lever, the animal was then allowed to make 400 responses upon the state-appropriate lever and, thereby (on the FR 10 schedule), received 40 reinforcements. This dose-response procedure allowed calculation of the dose of MDMA that produced 50% discriminative performance, i.e., the ED<sub>50</sub> value.

The lever pressed ten times was designated the "selected" lever. The percentage of rats selecting the lever appropriate for MDMA was the quantal measurement of discrimination. In addition, the number of lever-presses made upon the MDMA lever divided by the total number of presses on the MDMA and vehicle levers at the time that the tenth response was made on either lever,  $\times 100$ , constitutes the quantitative measurement. The quantal data were analyzed by application of the method of Litchfield and Wilcoxon (10) which employs probits vs. log-dose effects and

generates ED<sub>50</sub> values. The quantitative data were calculated and analyzed with a Student's paired *t*-test with  $p < 0.05$  chosen as the criterion for significance.

#### *Conditioned Place Preference Procedure*

The apparatus used in this paradigm consisted of two modular testing chambers (Model No. 85000, Lafayette Instrument Co., Lafayette, IN) each measuring 30  $\times$  20.5  $\times$  18 cm and connected by a central corridor measuring 30  $\times$  19.5  $\times$  20 cm. These test modules were covered by a translucent Plexiglas top which allowed light from either a white or red light bulb into the chamber. The top of each of the three units could be opened to permit entry or removal of the rat. One of the modules consisted of a black smooth Plexiglas floor and was illuminated by a red light. The other module was lighted with a white bulb and had a grid floor with wood shavings placed under this floor. These physical differences allowed for distinction by three senses, viz., tactile (floors), visual (lighting) and olfactory (presence vs. absence of "wood" smell). The central corridor, the choice area, was gray and nondistinctive. All testing was carried out between 1100–1600 h in a darkened laboratory with a source of "white noise."

The conditioning sequence consisted of three phases. The first phase, the preconditioning phase, was three days in duration. On these days the animal was placed into the gray choice area and allowed free access to both test modules for a 15-min period. The apparatus was thoroughly washed between rats to eliminate olfactory cues. The last day of preconditioning, i.e., day 3, constituted the baseline preference day. The cumulative time that the rat had at least two front paws in either the "black" (red-lighted) or "white" (-lighted) compartment was measured by observation through a one-way glass window on the side of each module.

The next phase was eight days of conditioning trials. After the baseline day (day 3), the side referred to as the nonpreferred (NP) was determined and it was this side that was paired with MDMA. On every other day the rat was administered 1.5 mg/kg MDMA IP and returned to its home cage for 10 min to allow for maximal central efficacy of the drug. After this time, it was placed into the nonpreferred side for a 30-min period. The rat was confined to that side by the insertion of panels that prevented its egress. On alternate days, the animal was administered (IP) an equal volume (1 ml/kg) of V and was placed into the opposite (preferred; P) side at the same postadministration time and for the same 30 min duration of confinement.

After the eight pairings, four with 1.5 mg/kg MDMA and four with its vehicle, the last phase, the preference test, was conducted. The same parameters were used as on day 3, i.e., the rat (without being injected) was placed into the choice area and allowed free access to the entire test apparatus for a 15-min period during which the total time spent in each modular environment was recorded.

The actual measurements were the number of *s* in which the animals had at least two paws in either chamber during the 15-min test periods on days 3 and 12. These number of *s* did not generally add up to 900 *s* (60 *s*  $\times$  15 min) as the time that the animal spent in the choice area was not included. After the conditioning trials, the amount of time spent on a nonpreferred side was determined and was compared to baseline. The second measurement used was the difference (scores) between the time spent in the nonpreferred side and the amount of time spent in the preferred side ("NP-P"). This second measurement allows for consideration of data on the amount of time spent in the side originally preferred at baseline and, therefore, the side paired (during four conditioning sessions) with V. These two measurements were subjected to analysis of variance (ANOVA) with two repeated

TABLE 1

SCHEDULE OF SUBCUTANEOUS ADMINISTRATION OF SALINE OR A HIGH, NEUROTOXIC DOSE (20 mg/kg) OF MDMA (MDMATx) AND TESTING OF CONDITIONED PLACE PREFERENCE AND DISCRIMINATION TO LOWER DOSES OF MDMA

Day	a.m.		p.m.	
	Series I/Series II		Series I/Series II	
1	Saline/MDMATx		Saline/MDMATx	
2	Saline/MDMATx		Saline/MDMATx	
3	Saline/MDMATx		Saline/MDMATx	
4	Saline/MDMATx		Saline/MDMATx	
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13	—		1.0 MDMA	
14	vehicle		1.5 MDMA	
15	—		0.5 MDMA	
16	vehicle—P side			
17	MDMA—NP side			
18	vehicle—P side			
19	MDMA—NP side			
20	Preference Test			

measures, i.e., baseline and preference tests in *s*. The *F* ratio comparisons were calculated for both the NP and the NP-P measurements and were followed by individual comparisons with the Newman-Keul's post hoc test to determine which measurements differed. Subsequently, a Student's *t*-test, using paired data, was conducted to compare baseline and preference test measurements.

#### Saline and MDMA Neurotoxic Regimen

After the first discriminative dose-response relationship was determined and followed by the first CPP-test, a regimen of morning and afternoon subcutaneous (SC) administrations of saline was given over a four-day period; this regimen ended ten days prior to redetermining the dose-response relationship and 13 days prior to redetermining the conditioned place preference. This regimen was intended to investigate if saline administrations twice-a-day for 4 days, as well as the absence of training for 10 days, would affect discrimination of MDMA. As the first dose-response relationship for MDMA (above) indicated that 0.75 and 1.0 mg/kg produced relatively similar quantal measurements (59.1 and 63.6%, respectively), the doses to be used in the dose-response relationship after repeated saline administration were chosen to be 0.5, 1.0 and 1.5 mg/kg.

Once the stability of the dose-response relationship after multiple subcutaneous saline injection was determined, the next phase of the experiment was to administer a neurotoxic dose (20 mg/kg) of MDMA SC twice-a-day for 4 days; a regimen reported to produce 5HT neurotoxicity in animals sacrificed 14 days after its initiation (2,3). The regimen used after saline and MDMA, as well as the sequence of dose-response discrimination and conditioned place preference experiments is detailed in Table 1. Series I refers to the saline regimen and Series II denotes the 20 mg/kg MDMA administrations over a 4-day period. In each case, the rats went without any training/testing until the 13th day when, in the afternoon, 1.0 mg/kg MDMA was tested in extinction. This

TABLE 2

SESSIONS-TO-CRITERION AND DOSE-RESPONSE RELATIONSHIP IN RATS ( $n=11$ ) TRAINED TO DISCRIMINATE 1.5 mg/kg ( $\pm$ ) MDMA FROM ITS VEHICLE

Dose MDMA (mg/kg)	Dose-Response	
	Quantal	Quantitative (S.D.)
1.5	86.4	74.7 (6.2)
1.0	63.6	61.6 (10.2)
0.75	59.1	57.6 (3.3)
0.5	27.3	31.5 (2.6)
0.0 (vehicle)	18.2	21.4 (0.4)
ED <sub>50</sub> (95 C.L.)	0.72 mg/kg (0.57–0.91)	

was followed on day 14 with a nonreinforced vehicle test in the morning and a trial with 1.5 mg/kg MDMA (training dose) in the afternoon. Lastly, the afternoon session of the 15th day was conducted 20 min after administration of 0.5 mg/kg MDMA. In all of these four tests, the rat was immediately removed upon making 10 responses on either of the two levers. On the next day (day 16) the vehicle was administered IP and the animals were placed 10 min later for a 30-min period of confinement in their preferred side (P). On the next day, 1.5 mg/kg MDMA was injected and the rat was confined to its nonpreferred (NP) side for the same duration. This was repeated again on the next two (the 18th and 19th) days. The 20th day was used as a preference test in which the rat received no injection and was allowed to freely enter either one of the two modules for a 15-min period. Between Series I and II, i.e., after saline administration and prior to repeated MDMA treatment, the rats were retrained with two vehicle and two MDMA discrimination sessions, on alternate days, to ensure that they were capable of discriminating between MDMA and its vehicle.

#### RESULTS

As previously reported (4, 13, 19, 20), MDMA is a psychoactive drug that is capable of controlling differential responding in a drug discrimination paradigm. Accordingly, rats were readily trained to discriminate 1.5 mg/kg racemic MDMA from its distilled water vehicle, with the first of ten consecutive sessions in which the state-appropriate lever was chosen on at least 8 occasions starting on a mean of 9.2 sessions (STC 1: Table 2). The training criterion of 8 out of 10 consecutive correct sessions was met for the second time at a mean of 21.8 sessions and all rats were judged able to discriminate between MDMA and its vehicle after 45 training sessions. Once all rats reached criterion performance, doses of MDMA lower than the training dose were administered during test sessions. During these dose-response experiments, one of the 12 rats died of causes unrelated to the experiment and the results reflect this fact ( $n=11$ ). The training dose (1.5 mg/kg) of MDMA produced 86.4% of first lever selections (pressed 10 times first) upon the MDMA-appropriate lever (Table 2). When 1.0 mg/kg MDMA was administered, 63.6% of first selected lever choices were on the MDMA lever and lowering the dose to 0.75 and 0.5 mg/kg reduced the percentage of first choice lever selection upon the MDMA lever to 59.1 and 27.3%, respectively. Administration of vehicle during interspersed main-

TABLE 3

DISCRIMINATIVE PERFORMANCE AFTER VARIOUS DOSES OF MDMA 13-15 DAYS AFTER 20 mg/kg MDMA OR SALINE TWICE-A-DAY FOR FOUR DAYS

Dose (mg/kg)	After Saline		After MDMA	
	Quantal	Quantitative (SEM)	Quantal	Quantitative (SEM)
1.5	90.9	80.6 (6.3)	72.7	61.6 (7.9)
1.0	81.8	80.1 (7.9)	45.5	43.6 (11.8)*
0.5	18.2	25.4 (7.1)	9.1	18.2 (8.2)
ED <sub>50</sub> (95% C.L.)	0.71 mg/kg (0.52-0.98)		1.07 (0.76-1.49)	

\*Significantly lower than quantitative measurement for 1.0 mg/kg MDMA after multiple saline administrations,  $p < 0.01$  (paired  $t$ -test).

tenance trials produced 18.2% of selected lever choices on the MDMA lever or (to look at it a different way) 81.8% upon the vehicle-appropriate lever. These results allowed for an ED<sub>50</sub> value of 0.72 mg/kg (95% confidence limits: 0.57-0.91).

The results of testing 0.5-1.5 mg/kg MDMA after repeated (eight) treatments with saline are presented on the left side of Table 3. When 1.0 mg/kg MDMA was tested on the afternoon of the 13th day, nine of the rats selected the MDMA lever. This yields a quantal measurement of 81.8% and a quantitative measurement of 80.1% was determined. In the morning session of the next day one rat chose the MDMA lever after vehicle (data not shown) and, in the afternoon session, following the training dose of 1.5 mg/kg MDMA, ten of the eleven animals chose the MDMA lever. On the last day of postsaline testing, i.e., day 15, administration of 0.5 mg/kg MDMA resulted in two of the animals choosing the MDMA-appropriate lever.

Following a (second) determination of conditioned place preference (below) and a period of 4 days of retraining, consisting of two maintenance (reinforced) sessions with saline alternated with two 1.5 mg/kg MDMA maintenance sessions, the animals received 20.0 mg/kg MDMA SC twice-a-day for four days. The results of testing the same doses of MDMA 13, 14 and 15 days after initiation of this regimen appear on the right side of Table 3. Eight of the animals (72.7%) selected the MDMA lever after 1.5 mg/kg and following 1.0 mg/kg, tested on the 13th day, the number of animals selecting the MDMA lever dropped to five of eleven (45.5%). After vehicle administration, none of the rats selected the MDMA lever. On the last day of post-MDMA testing, 0.5 mg/kg MDMA administration resulted in only one rat choosing the MDMA-correct lever. When the quantitative measurements are compared following the MDMA neurotoxic regimen to those measurements following the repeated administrations of saline, there is a significant decrease in discriminative performance after 1.0 mg/kg MDMA ( $p < 0.01$ ; paired  $t$ -test) indicating that the generalization of this dose for the training dose was affected.

The results of conditioned place preference experiments appear in Table 4. The first exposure of rats trained in the drug discrimination paradigm to the novel situation in the modules used for the conditioned place preference test resulted in a mean of 221.5 s spent by the 11 animals in the least (non-)preferred side ("Baseline"; Table 4A). In addition, the animals spent a mean of 455.5 s in the preferred side and this is evident in the difference score (NP-P data in Table 1B) where 221.5 (s spent in NP side) minus 455.5 (s spent in P side) appears as -234.0 s. After 4 pairings with each of 1.5 mg/kg MDMA and its vehicle, this group of rats spent an average of 469.3 s in the nonpreferred

TABLE 4

EFFECT OF REPEATED SALINE OR MDMA (20 mg/kg) ADMINISTRATIONS UPON CONDITIONED PLACE PREFERENCE TO 1.5 mg/kg MDMA

Baseline	MDMA	20th day Saline	20th day MDMA
A. Mean Time (s ± SD) Spent in Nonpreferred (NP) Side			
221.5 (82.1)	469.3 (144.5)	487.0 (114.3)	492.8 (223.2)
B. Difference Scores: Mean Time (s ± SD) in NP Side Minus P Side			
-234.0 (232.7)	228.2 (254.2)	251.5 (204.3)	235.9 (3739)

side; a significant ( $F = 11.52$ , ANOVA,  $p < 0.01$ ) increase in time spent.

When a second CPP test was conducted following the repeated saline administration (represented by Series I in Table 1), the preference test on day 20 ["20th day (post-) saline" in Table 4] indicated a nonsignificant increase in time spent in the nonpreferred side, i.e., 487.0 s on the average. Likewise, a third CPP-test conducted on the 20th day following the initiation of repeated neurotoxic MDMA dosing (Series II in Table 1) resulted in a mean of 492.8 s spent in the nonpreferred side; nonsignificantly different from that seen with the first or the postsaline MDMA preference determination.

#### DISCUSSION

Like other drugs of abuse, such as amphetamine and cocaine, MDMA has been shown to produce conditioned place preference. The former drugs, as well as others that include bupropion, methylphenidate, nomifensine and apomorphine, have in common the ability to facilitate dopamine transmission either by stimulating release, preventing its reuptake or directly stimulating dopamine receptors (6). This relationship has led to the suggestion that the rewarding properties of the drugs, as they are measured by the conditioned place preference test, may be mediated by central dopamine. This hypothesis is evidenced by the ability of specific dopamine receptor antagonists, or specific neurotoxin lesions of dopaminergic neurons, to block the drug-induced conditioned place preference (6). The present study is the first in the literature to show that the Schedule I drug MDMA can produce conditioned place preference in the CPP-task and suggests the possibility that this behavioral effect of MDMA is mediated by dopaminergic neurons. This hypothesis has been suggested by research in this (20), as well as many other laboratories (5, 7, 8, 11, 23, 27, 29).

The methodology used in the present study infers that multiple CPP-tests, as they are employed to indicate animals' preference (or aversion) to a particular drug, do not change simply as a consequence of the time between CPP-tests. This inference has been addressed in a study investigating the capacity of morphine to establish a conditioned place preference in which the animals' preferences were established and the CPP-test was then repeated three more times for a total of 4 tests over a one-month period. The results indicate that as long as the subjects are placed during continued conditioning on each side of the chamber an equal number of times, they show no particular preference for the side of conditioning across multiple tests in the apparatus (17). This stability in preference after multiple CPP tests has also been shown to occur with intraperitoneal cocaine in which tests were run 4, 7 and 30 days after the initial CPP-test (12). In the present study, the initial preference for MDMA, measured prior to repeated administrations of either saline or a neurotoxic dose of MDMA, was maintained after these two manipulations; thus the neurotoxic

regimen of MDMA did not appear to affect animals' preference for the drug.

In contrast, there was a decrease in the animals' ability to discriminate the interoceptive cues produced by MDMA. In fact, discrimination of the intermediate dose of (1.0 mg/kg) MDMA was shown to be significantly decreased after the MDMA chronic regimen when compared to results postsaline. Initially, the rats learned to discriminate 1.5 mg/kg MDMA and administration/testing of lower doses indicated a response gradient that was dose-responsive. The  $ED_{50}$  value was 0.72 mg/kg; remarkably similar to that reported previously in this laboratory, i.e., 0.73 mg/kg (19), and to the  $ED_{50}$  value of 0.79 mg/kg reported in another laboratory using a similar paradigm (13).

Using a dose and regimen of MDMA administration previously shown to produce significant 5HT neuronal degeneration 14 days after its initiation (3), a decrease in the rats' ability to discriminate MDMA and a negligible change in their preference was observed. A recent report (9) indicated that a similar repeated regimen of MDMA, to deplete 5HT levels in the brain, produced an increase in the psychomotor stimulant-like effects of MDMA. These authors suggest that the depletion of 5HT by the repeated administrations of MDMA acts to reduce the inhibitory influence of 5HT and, thus allows MDMA, when tested 14 days later, to exert a stronger psychomotor effect; an action thought to be mediated by dopaminergic systems. The same reciprocity between 5HT and dopamine in the discriminative properties of MDMA has previously been suggested (20) and this neurotransmitter balance may explain the results of the present experiments using drug discrimination and conditioned place preference. Thus the

preference observed in the conditioned place preference paradigm may be mediated by the dopaminergic effects of MDMA which, after serotonin neuronal degeneration, may increase. In the case of MDMA discrimination, the 5HT degeneration may, in fact, have compromised the animals' ability to discriminate the interoceptive cue which more than likely is mediated by serotonergic mechanisms in the brain (20).

Repeated, orally administered MDMA, at 10 mg/kg for 4 consecutive days, was recently shown to have no significant effect upon rat behaviors, such as emergence, hot plate response, auditory startle and complex maze behavior, when tested 2–4 weeks after administration (26). These authors suggest that the tests used in their study may not have been adequately sensitive enough to detect the functional consequences of 5HT degeneration produced by MDMA. It appears that drug discrimination as employed herein is sensitive enough to detect the neurotoxic effects of MDMA on a distinctly trained behavior in the rat. Most recently (21) a regimen of administration of fenfluramine, a drug with potential for serotonin neurotoxicity, was shown to have the opposite effect on fenfluramine discrimination, i.e., the animals were shown to have increased sensitivity to various doses of this agent.

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