Pharmacology Biochemistry & Behavior, Vol. 39, pp. 569–574. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

3,4-Methylenedioxyamphetamine (MDA) Self-Administration and Neurotoxicity

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Received 19 December 1990

MARKERT, L. E. AND D. C. S. ROBERTS. *3,4-Methylenedioxyamphetamine (MDA) self-administration and neurotoxicity.* PHARMACOL BIOCHEM BEHAV **39**(3) 569–574, 1991.—3,4-Methylendioxyamphetamine (MDA), a drug with both stimulant- and hallucinogen-like properties, has been used for both medical and recreational purposes. The present study examined the reinforcing effects of MDA in rats and evaluated the resulting neurotoxicity. Self-administration of various doses (0.10, 0.05 and 0.025 mg/injection) was examined on a Fixed Ratio 1 (FR1) and a Progressive Ratio (PR) schedule. MDA supported self-administration at all doses on the FR1 schedule, but overdoses and deaths occurred at the 0.10 mg/injection dose. The breakpoints established on the PR schedule were relatively low. High performance liquid chromatography analyses of the cortex, hippocampus, striatum and nucleus accumbens subsequent to MDA self-administration revealed significant depletion of 5-HT in the hippocampus. The results suggest that MDA is moderately reinforcing and that self-administration of low doses of MDA over several days is selectively neurotoxic.

MDA Self-administration Neurotoxicity

3,4-METHYLENEDIOXYAMPHETAMINE (MDA) is a synthetic amphetamine derivative which produces stimulant- and hallucinogen-like sensations (6). Concern about the recreational use of MDA has increased since the demonstration that it may cause damage to specific neurotransmitter systems (18).

Neurotoxicity studies on rats revealed that a single injection of 5 mg/kg IP produced a significant depletion of serotonin (5-HT) in the hippocampus; chronic treatment caused degeneration of serotonergic fields in the hippocampus, striatum and neocortex (1, 16, 18, 23). Whether these dosages fall within the reinforcing range is not known. There have been no studies that have examined MDA self-administration in rats; therefore, it is not known whether MDA-induced neurotoxicity is evident at reinforcing dosages.

The present experiments were performed to determine at what doses (if any) rats would self-administer MDA and whether MDA self-administration could result in damage to forebrain 5-HT systems. In addition, we sought to estimate the motivation to self-administer MDA through the use of a progressive ratio (PR) schedule.

Drugs

Cocaine hydrochloride was purchased from BDH Chemicals Ltd., Toronto, Canada. (±)3,4-Methylenedioxyamphetamine hydrochloride was obtained from the Bureau of Dangerous Drugs, Health and Welfare, Canada.

METHOD

Male Wistar rats (Woodlyn Farms, Guelph, Ontario) weighing 300–350 g were initially food deprived and trained to press a lever for food reward. Thereafter, food and water was available ad lib. Rats were subsequently implanted under pentobarbital (50 mg/kg) anaesthetic with an indwelling jugular cannula (21) and housed individually in Plexiglas chambers.

Self-administration behavior was examined during daily 5 hour sessions. Pilot data showed that drug-naive rats (N=6) would self-administer MDA 0.10 mg/0.120 ml saline/injection at a variable operant rate (data not shown). In an attempt to limit the variability, animals were first screened for stable cocaine self-administration (0.60 mg/0.120 ml saline/injection) prior to being offered MDA. Such pretraining has been used frequently in many laboratories (8, 9, 17, 20). One group (N=6) was tested on MDA 0.10 mg/0.120 ml saline injection (expressed as the salt) for 7 days and a different group (N=6) of rats was tested on MDA 0.05 and 0.025 mg/0.120 ml saline/injection for 5 days at each dose.

An additional group of rats, which demonstrated a regular response pattern for cocaine on an FR1 schedule, was examined on a PR schedule of cocaine reinforcement. This consisted of a 5-hour daily session during which the response requirements escalated after each injection according to the following series: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, 999. The last ratio completed during the session was defined as the "breaking point." After at least one week of baseline PR training reinforced with cocaine, rats (N=6) were switched to MDA (0.10 mg/injection) on the same PR schedule for 7 days and breaking points recorded.

After completion of the self-administration part of the experiment, rats which had self-administered MDA 0.10, 0.05 and 0.025 mg/injection on the FR schedule (N=17) were housed

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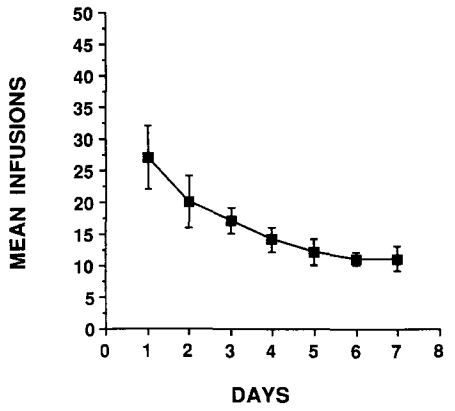

FIG. 1. Intake of MDA 0.10 mg/injection over the initial 7 day period of self-administration. Data points represent the mean (±SEM) infusions of 12 rats.

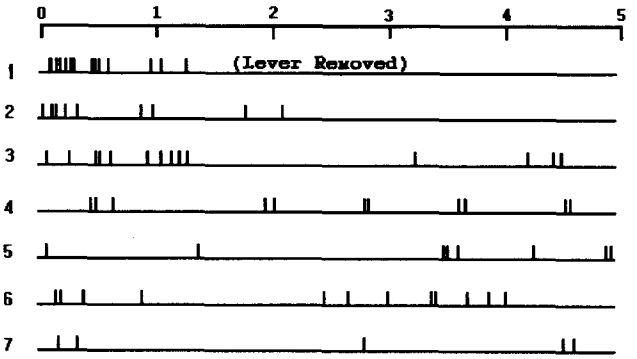

FIG. 2. An example of the pattern of MDA self-administration behavior reinforced by MDA 0.10 mg/injection. Each line represents an event record for one daily five-hour session. Vertical lines represent drug infusions. Some variation was evident across days. The lever was removed after 1½ hours on day 1 to prevent overdose.

singly in shoebox cages for at least two weeks with food and water ad lib. These rats, along with drug-naive rats to be used for comparison (N=9), were decapitated, using a guillotine, and the brain quickly removed. A consistent 2-mm slab of tissue was taken on a brain cutting block over crushed ice, and the frontal cortex, hippocampus, striatum and nucleus accumbens dissected out on ice and stored in 27×5 mm micro polypropylene capsules at −70°C. High performance liquid chromatography with coulometric detection (24) was used to determine levels of amines and metabolites.

RESULTS

Acquisition

Twelve out of the 16 rats tested on the 0.10 mg/injection dose completed the protocol. On their first day of exposure to MDA, two rats died as a result of drug overdose, and two other rats showed initially high rates of infusions resulting in hyperthermia, piloerection and lethargy. To prevent further overdoses and lethality, the experimental procedure for further subjects was altered so that a daily maximum of 3 ml of the MDA solution was available, and the levers were removed if excessive responding was observed within the first hour of the five-hour session. On subsequent days, a reliable pattern of MDA self-administration usually developed. However, two overdose deaths did occur after 5–6 days of MDA exposure.

Figure 1 shows the mean level of intake over a 7 day period for rats on MDA (0.10 mg/inj) on the FR1 schedule. The elevated intake on days 1–3 was associated with stereotypic head and body movements. After this initially high and variable period, the mean intake became more stable on days 4–7. The mean intake was 16.0 infusions/day over the 7 test days. Although drug intake stabilized somewhat, most subjects showed daily fluctuations with high levels of infusions on one day and low levels the next. Figure 2 shows the daily event records over 7 days for one subject on the FR1 schedule reinforced by a 0.10 mg/injection MDA. This rat began to demonstrate an overdose response pattern on day 1, and the lever was removed.

Dose Manipulation

A different group of rats (N=6) tested on MDA at a dose of 0.05 mg/injection showed the same basic rate of infusion and pattern of intake as the group on 0.10 mg/inj. Some subjects showed fluctuations in intake with daily highs and lows, while others showed generally low rates of intake. The mean daily intake over the 5 days was 12.8 infusions/day. No overdose deaths occurred at any time at this dose. Subsequent to this, four of these rats were tested on MDA 0.025 mg/injection for 5 days. Rats on this dose had a mean daily intake of 19.0 infusions/day over 5 days and showed a significant increase in rate of infusions, $t(3) = -7.14$, $p<0.01$, over the rate at 0.05 mg/injection. There was no significant difference in total mg of drug intake, $t(3) = 0.80$, $p>0.01$, over the rate at 0.05 mg/injection. There was no significant difference in total mg of drug intake, $t(3) = 0.80$, $p>0.05$, between the 0.025 and 0.05 doses. Figure 3 demonstrates the difference in mean number of infusions over 5 days between the 0.025 and 0.05 mg/injection doses for four individual subjects revealing a compensatory increase in rate of infusion when the dose is decreased.

Progressive Ratio

The break points on the PR schedule reinforced by MDA (0.10 mg/injection) are presented in Table 1. Although rats would self-administer MDA (0.10 mg/injection) on an FR1, the present experiment suggested that rats will not respond to higher

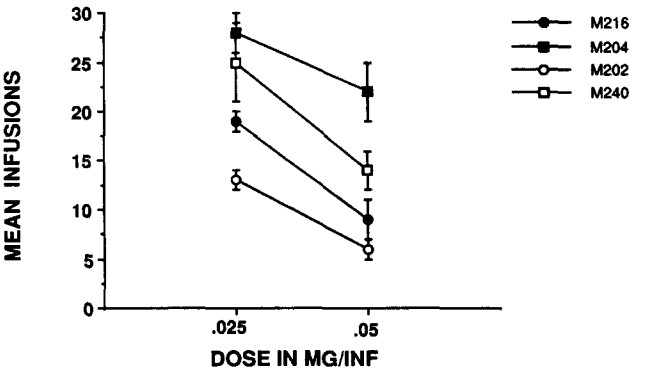

FIG. 3. Effect of dose manipulation on MDA self-administration. Each point represents the mean (±SEM) daily intake for 4 individual rats over 5 days.

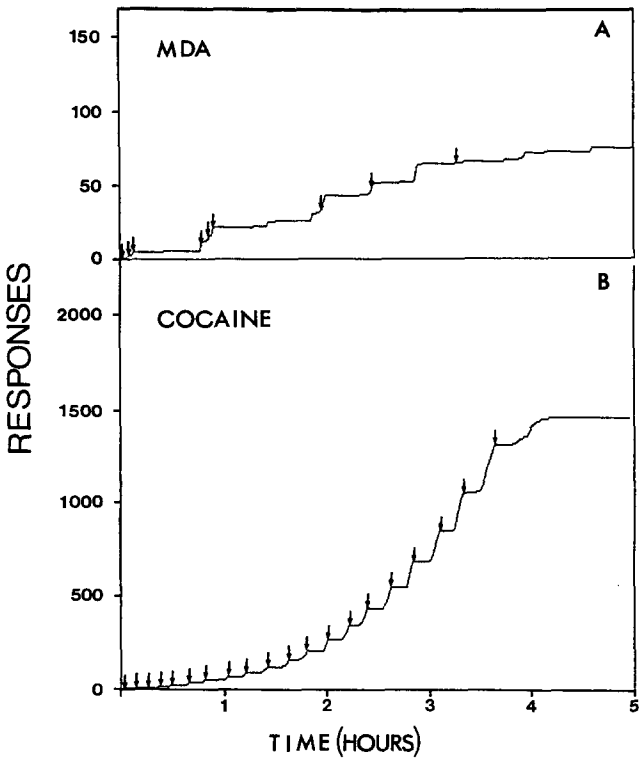

FIG. 4. Comparison of pattern of MDA self-administration with cocaine self-administration on a progressive ratio schedule. Panel A is a cumulative record showing pattern of responses and infusions (indicated by arrows) for one subject which responded well on MDA 0.10 mg/injection on the progressive ratio schedule during one daily five hour session. Panel B shows a cumulative record for a different subject on cocaine 0.60 mg/injection on the progressive ratio schedule during one daily five-hour session. Note the change in scale between Panel A and Panel B.

ratios to receive an injection of the drug. On the PR schedule, rats failed to earn more than 9 infusions in 5 hours and maintained a low level of MDA self-administration over a period of 7 days. The highest ratio completed was never more than 25. Figure 4 represents a cumulative record of an animal self-administering MDA to this level. Because of the self-limiting nature of the PR schedule, no overdose deaths occurred. Preliminary data at other doses (0.05 and 0.025) again demonstrated that MDA did not support high breaking points on the PR schedule.

Neurotoxicity

The levels of monoamines and metabolites (expressed as ng/mg protein) taken from controls or from animals that had self-administered MDA are shown in Table 2. For purposes of statistical analysis, data from rats which self-administered MDA (0.10, 0.50, 0.025 mg/injection) were collapsed into one group, as total mg of drug intake was the most important factor under consideration. Also, as mentioned previously, rats titrated their daily number of infusions depending on the drug dose, leading to overall similar amounts of drug intake regardless of dose. Compared to the control group, the MDA group was found to have significantly less 5-HT in the hippocampus, $t(23) = 2.81$, $p < 0.01$. No other comparisons reached statistical significance.

TABLE 1

	Day						
	1	2	3	4	5	6	7
M36	25	9	9	12	15	12	NR
M31	9	15	NR	6	9	15	12
M32	15	6	9	NR	12	12	12
M69	25	20	12	25	20	15	4
M77	9	6	4	6	4	4	9
M78	20	9	2	4	1	6	4

Numbers indicate the final ratio (breaking point) completed by rats (N = 6) during daily 5-hour sessions on a progressive ratio schedule for MDA reinforcement (0.10 mg/injection). NR indicates one day when no data were collected due to a power failure.

Average daily drug intake ranged from 0.38 to 2.45 mg, and total overall drug intake ranged from 6 to 18 mg. Total intake and 5-HT level were negatively correlated ($r = -.52$, $p < 0.05$), suggesting that, as cumulative drug intake increased, 5-HT levels decreased.

DISCUSSION

Ricaurte et al. (18) and others (1, 16, 23, 26) have reported that IP injections of MDA cause degeneration of forebrain 5-HT systems in rats. The present results demonstrate that this neurotoxicity is evident within the dose range that is self-administered.

Previous evidence suggests that the hippocampus is most sensitive to the neurotoxic effects of MDA. Ricaurte et al. (18) showed that the hippocampus was the first region to experience a decrease in 5-HT levels after exposure to a single injection of 0.5 mg/kg MDA. Battaglia et al. (1) presented immunocytochemical evidence that MDA ablated a population of fine axons throughout CA1 while many of the thicker axons in all regions were spared. In order to deplete 5-HT in other regions, and to cause a concomitant decrease in 5-HIAA, MDA must be administered chronically at high doses, e.g., 20 mg/kg (1, 16, 18). Silver staining after this treatment also revealed degeneration of nerve terminals in the hippocampus and striatum which appeared to be serotonergic (18). In the present study, MDA toxicity was observed following small IV doses self-administered over many days. With this pattern of drug intake, MDA toxicity was limited to the serotonergic innervation of the hippocampus, consistent with the idea that this area is the most sensitive.

The present investigation was undertaken to establish the dose range of MDA that would be self-administered by rats. The only previous report that we are aware of used baboons as subjects. Griffiths et al. (9) showed that baboons would respond on an FR 160 schedule to obtain injections of MDA 1.0, 2.0 and 5.0 mg/kg.

The present data demonstrated that, after a 2–3-day acquisition period, rats developed a relatively stable level of MDA self-administration at the 0.10 mg/injection (approximately 0.30 mg/kg) dose with daily fluctuations being evident in some subjects. Fluctuations were also evident in the daily intake of some rats on the 0.05 mg/injection and 0.025 mg/injection doses. The general pattern of intake (e.g., rapid successions of infusions) was similar at all doses examined (see Fig. 2). As well, when rats were exposed to the 0.05 and 0.025 mg/injection doses, alterations in dose produced a compensatory increase or decrease in self-administration. When compared to cocaine (22), MDA infusion is not as consistent and seems somewhat erratic at all

doses examined. Specifically, there were relative highs and lows over days, a cyclic pattern which has been demonstrated in MDA, 3,4-methylenedioxymethamphetamine (MDMA) (9,11) and d-amphetamine self-administration (9).

The highest dose of MDA tested sometimes caused two types of overdose to occur. Overdose deaths occurring at the initial exposure to MDA were similar to that from d-amphetamine self-administration studies (29). It is likely that a delayed drug onset led to a toxic overdose before the animal learned the response/reinforcement relationship (12,28).

A second overdose phenomenon occurred on MDA about one week after initial exposure. This phenomenon has been observed in animals with unlimited access to a drug, but is not common during limited access (10). It is possible that overdoses at this time resulted from a cumulative effect of MDA causing neurotoxic effects. Increased self-administration of amphetamine and/or overdose deaths have been reported after intracerebroventricular destruction of 5-HT-containing neurons with 5,7-dihydroxytryptamine (5,7-DHT) (13) or after injections of methysergide or cyproheptadine to rats with 5,7-DHT lesions of the medial forebrain bundle (12). Such lesions also lead to increased stereotyped behavior, suggesting the possibility that the bursts of stereotyped lever responding may have contributed to the drug overdose phenomenon (12,13).

Progressive Ratio Schedule

Rats tested under a progressive ratio schedule for MDA reinforcement responded to moderately low break points. The highest break point was 25. By comparison, we have shown that rats will respond to break points of several hundred for IV cocaine reinforcement (see Fig. 4, panel B) (22). These data suggest that MDA is modestly reinforcing compared to cocaine, and rats are not highly motivated to receive this drug.

Alternatively, it may be that MDA is a powerful reinforcing stimulus, but the PR schedule for some reason underestimates that animal's motivation to self-administer the drug. For example, it has been shown that MDA (1.0–3.0 mg/kg) can disrupt the performance of monkeys or pigeons required to respond on multiple schedules (14,27). The performance of the rats on the PR schedule may have been disrupted since they received between 2 and 5 mg daily. Considering also the important role of the hippocampus in learning and memory processes (7), it is possible that toxicity in this region may adversely affect performance on schedules such as the one used in progressive ratio studies.

Another possibility is that the way the PR schedule was implemented in this study may have been inappropriate for the evaluation of MDA reinforcement. Bennett and Roberts (2) have

TABLE 2

MONOAMINE AND METABOLITE LEVELS TWO WEEKS AFTER MDA SELF-ADMINISTRATION

	NE	MHPG	5-HT	5-HIAA	
			Hippocampus		
Control	5.72	1.53	0.95	5.26	
	± 0.80	± 0.50	± 0.26	± 0.30	
MDA	6.50	0.99	0.36*	6.09	
	± 0.49	± 0.27	± 0.06	± 0.31	
% of Control	113%	65%	38%*	115%	
			Cortex		
Control	5.08	0.61	0.89	3.32	
	± 0.50	± 0.13	± 0.20	± 0.44	
MDA	4.51	0.55	0.99	4.47	
	± 0.28	± 0.05	± 0.19	± 0.50	
% of Control	89%	90%	112%	135%	
	DOPAC	Dopamine	HVA	5-HT	5-HIAA
			Nucleus Accumbens		
Control	42.98	89.22	8.43	10.26	16.69
	± 2.45	± 8.08	± 0.95	± 1.13	± 1.57
MDA	37.38	91.52	7.75	11.89	20.66
	± 2.94	± 5.52	± 0.72	± 0.76	± 3.75
% of Control	87%	103%	92 %	116%	124%
			Striatum		
Control	42.53	113.20	12.45	8.21	14.63
	± 2.60	± 9.13	± 1.85	± 1.92	± 2.29
MDA	53.16	142.41	17.00	6.60	16.86
	± 3.21	± 6.83	± 1.74	± 0.68	± 1.28
% of Control	125%	107%	137%	80%	115%

Values in ng/mg of protein represent the mean ± SEM. Control N = 9. MDA N = 17.
*$p<0.01$ determined by two-tailed Student's t-test.

shown that different PR schedules can profoundly influence the breaking points obtained. For example, the same PR schedule employed here drastically underestimated the motivation to self-administer heroin. It appears that rats are most motivated to receive the first heroin injection of the session and are less motivated to respond with each succeeding injection. Conversely, the motivation to obtain cocaine is increased after the first few injections, and the highest break points are obtained well into the test session. Since the first few injections under the PR schedule used in the present study can be earned with relatively little effort, animals would respond initially, but would not respond to high break points further into the session; i.e., motivation to begin a session may be high, but this was not measured.

The present experiment does reveal that, while rats may take a high number of infusions on FR1, when forced to pay a high behavioral price, the self-administration behavior extinguishes. These data emphasize the idea that the demonstration of self-administration for a drug on an FR1 schedule is only a qualitative demonstration that a drug can serve as a reinforcer (21). However, a definitive statement as to the quantitative nature of the reinforcing effects of MDA must await further testing, possibly with other PR schedules.

Tentatively, then, experimental evidence seems to reflect the drug statistics in that, while MDA is an abused substance, it is not one which is self-administered to a large extent (3). The present data and those of Griffiths et al. suggest that MDA was less reinforcing than cocaine (8,22), for which the experimental evidence of extremely high levels of self-administration reflect population trends.

Conclusion

To conclude, this series of experiments provided evidence that MDA is self-administered by rats and is toxic at self-administered doses. Evidence of toxicity at self-administered doses is of concern because self-administration more closely resembles human drug-taking behavior than does systemic injection (4). The possibility exists that human drug abusers also are vulnerable to selective neurotoxicity.

The present investigation also provided information on how to approach a relatively unknown substance and test it for lethality, toxicity and abuse potential at self-administered doses, providing groundwork for development of a model on which to base studies of unknown compounds which are becoming increasingly available (15).

ACKNOWLEDGEMENTS

This work was supported by the Medical Research Council (of Canada). L.E.M. is supported by a Natural Sciences and Engineering Research Council of Canada Postgraduate Scholarship.

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