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Some Behavioural and Neurochemical Aspects of Subacute (±)3,4-Methylenedioxymethamphetamine Administration in Rats

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McNAMARA, M. G., J. P. KELLY AND B. E. LEONARD. *Some behavioural and neurochemical aspects of subacute (±)3, 4-methylenedioxymethamphetamine administration in rats.* PHARMACOL BIOCHEM BEHAV 52(3) 479–484, 1995.—(±)3, 4-methylenedioxymethamphetamine (MDMA; "Ecstasy"), an increasingly popular recreational drug, is known to damage brain serotonin (5-hydroxytryptamine [5-HT]) neurons, whilst also having a less pronounced effect on the dopaminergic system. Treatment with MDMA results in an increased locomotor activity, elevated basal serum corticosterone concentrations, decreased exploratory activity, and changes in body temperature. The aim of this study was to examine the dose related effects of subacute administration of MDMA (5, 10, and 20 mg/kg IP twice daily for 4 days) on home cage locomotor activity, "open field" and "step-down passive avoidance" behaviours, changes due to an 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) challenge, and on plasma corticosterone and brain neurotransmitter concentrations. Total locomotor activity counts were significantly increased by both 10 and 20 mg/kg MDMA for the 4 days of drug administration. There were no significant differences seen in the "open field" or "step down passive avoidance" behaviour, in the 8-OH-DPAT induced hypothermia, or in basal serum corticosterone concentrations. MDMA caused a significant depletion of both 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in the frontal cortex and amygdala and a significant elevation of dopamine and noradrenaline in the hippocampus. Apart from the increase in locomotor activity following subacute administration, the observed behaviour of the MDMA treated rats would not appear to reflect the substantial changes in brain biogenic amine neurotransmitters.

(±)3, 4-methylenedioxymethamphetamine (MDMA) Locomotor activity "Open field" "Step-down passive avoidance" 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) Corticosterone Brain biogenic amines

MDMA [(±)3, 4-Methylenedioxymethamphetamine] is a 3, 4-methylenedioxy substituted phenylisopropylamine structurally related to amphetamine, and to hallucinogens such as mescaline (10). The unique behavioural effects of MDMA (popularly known as "Ecstasy" or "Adam") have led to its widespread abuse (28). The increased illicit use of MDMA has prompted an intensified effort to determine both the acute and subacute neurochemical effects of the drug.

In rats, a single injection of MDMA typically causes a biphasic reduction in brain 5-hydroxytryptamine (5-HT) and in its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) as well as a decrease in the activity of tryptophan hydroxylase, the rate limiting enzyme for 5-HT synthesis. MDMA (20 mg/kg) induces an acute depletion of 5-HT within 3–6 h of administration, after which point it returns to control levels within 24 h (30).

The neurotoxic effects of MDMA appear between 24 h and 1 week after drug administration. By 7 days, this second decrease in 5-HT concentrations is associated with a loss of functional 5-HT uptake sites indicating damage to serotoner-

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gic nerve terminals (30). MDMA produces marked degeneration of 5-HT nerve terminals in the cerebral cortex, hippocampus, and striatum at 2 weeks post-MDMA injection (16,20).

The effects of MDMA on the dopaminergic system are less pronounced (11,31). However, in vitro (11) and in vivo studies (32) have shown that MDMA stimulates the release and elevates the striatal content of dopamine, possibly by inhibiting intra neuronal monoamine oxidase activity (30,31).

Acutely administered MDMA elevates the serum corticosterone concentrations (18) in a manner similar to drugs that enhance serotonergic activity (5,6). This elevation in serum corticosterone concentration is probably due to activation of either 5-HT_2 or 5-HT_{1A} receptors (14).

Behaviourally, MDMA causes locomotor hyperactivity and suppresses investigatory behaviours (3). The administration of MDMA has been reported to produce hyperthermia (18), possibly due to stimulation of 5-HT_2 receptors (7,21).

As MDMA has little effects on sensory/motor function in man but has prominent effects on emotional state, a characteristic usually associated with limbic and cortical structures (15), the present study was designed to examine the dose response effects of subacute MDMA in rats on home cage locomotor activity. This method allows continuous measurements of locomotor activity without habituation and is useful in assessing if any drug tolerance develops and/or onset of long-term effects following drug withdrawal. The three doses of MDMA that were chosen for investigation were 5, 10, and 20mg/kg; representing a low, medium, and high dose range within which behavioural alterations could be observed. The typical daily dose ingested by MDMA users ranges from 50–200 mg, corresponding to a dose of 0.98 to 2.6 mg/kg. The highest daily dose of MDMA taken was 700 mg, corresponding to a dose of approximately 10 mg/kg (24). However, 2.5 mg/kg MDMA caused a significant depletion of 5-HT and 5-HIAA in several brain areas of rhesus monkeys (25), indicating that nonhuman primates are more sensitive to the 5-HT depleting effects of MDMA than are rodents, which suggests that the margin of safety in man may be narrow.

Previous studies have concentrated primarily on MDMA-induced neurotoxicity (16,28) and locomotor activity changes (3,26). In the present experiment, the effects of MDMA on "open field" and "step-down passive avoidance" behaviour, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) induced hypothermia, as a measure of the functional responsiveness of 5-HT_{1A} receptors (17), and plasma corticosterone concentrations were determined. A generalized behavioural assessment, as mentioned above, served as a preliminary study into MDMA-induced behavioural changes. Finally, the concentrations of brain biogenic amines were determined at the end of the study to assess whether there was a temporal relationship between the changes in the brain amine concentrations and the behavioural effects observed.

METHOD

Animals

Male Sprague–Dawley rats were obtained from Harlan Olac Ltd, Bicester, UK (initial weight on arrival 200–250 g). The animals were housed four per cage and maintained in a temperature controlled room (22°–24°C) with a 12L : 12D alternating cycle (lights on at 0800 h). Food and water were available ad lib. Rats were given a 1-week acclimatisation period prior to the start of the experiment.

Home-Cage Activity Measurements

On the day preceeding to the experiment, animals were singly housed to allow them to habituate to their new environment. Animals were placed into four groups of six animals by random selection. The cages were then placed in racks in the home cage activity monitor, to which infra-red sensors were attached thereby enabling locomotor activity to be measured over an 8-day period (19) (192 h in total, continuous activity). Home-cage locomotor activity was recorded 24 h prior to drug treatment (baseline activity), 96 h during which animals received drug and 72 h following ceasation of drug treatment.

"Open Field" Test

On the morning of day 7 (i.e., 7 days following commencement of MDMA administration), each rat was placed singly into the centre of the "open field" apparatus (8). The "open field" consisted of a circular base, 90 cm in diameter, which was divided into 10-cm squares by faint yellow lines. The wall surrounding the base was made of aluminium sheet (75 cm in height). Ambulation (number of squares crossed) scores were recorded for a 3-min observation period for each animal. The apparatus was illuminated by a 60 W bulb positioned 90 cm above the centre of the base.

Effect of 8-OH-DPAT on Rectal Temperature

The effect of 8-OH-DPAT on colonic temperature was determined on day 8 of the study (i.e., 8 days following first MDMA administration). Temperatures were recorded by means of a digital thermometer. The thermometer was inserted 5 cm into the colon of each rat. Temperatures were recorded prior to and 30, 60, and 120 min after injection with 8-OH-DPAT (0.15 mg/kg, SC).

"Step-Down Passive Avoidance" Test

On the morning of day 10 (i.e., 10 days following first MDMA administration), the animals were tested in the step-down passive avoidance apparatus. The apparatus consisted of a shuttlebox (40 cm × 30 cm) with a triangular platform mounted 4.5 cm above the grid floor. When the animal stepped off the platform, it received a 1.5 mA electric shock through the grid floor (12). The rat was then returned to its home cage and the procedure repeated. This procedure was continued until the animal remained on the platform for 2 min, or until a total of ten trials had been given.

Determination of Brain Biogenic Amine Concentrations

On day 11 of the study rats were killed by decapitation, the brains removed and the frontal cortex, left amygdala, left hippocampus, and striatum dissected (23). Concentrations of noradrenaline, dopamine, 5-HT, and 5-HIAA were measured by high performance liquid chromatography (HPLC) with electrochemical detection (27). The brain regions were homogenized by sonication in 1.0 ml elution buffer (pH 2.8), containing 0.1 M citric acid, 0.1 M sodium dihydrogen phosphate, 1.4 mM octane-1-sulphonic acid, 0.1 mM EDTA. This differed from the mobile phase in that it was "spiked" with 20 ng/50 μl *N*-methyl dopamine as an internal standard. Homogenates were centrifuged at 15,000 rpm in a Hettich Mikro/K refrigerated centrifuge for 15 min. A 50 μl sample of the supernatant was injected directly into a reverse phase column (RP18, 25 cm × 4 mm internal diameter, particle size 5 μm)

for separation of indoles and catecholamines (flow rate 1 ml/min). The neurotransmitters were quantified using a Merck-Hitachi D-2000 integrator

Serum Corticosterone Levels

Serum was prepared from trunk blood obtained immediately after decapitation. The blood was centrifuged at 2500 rpm in an MSE bench centrifuge for 10 min and the resultant supernatant was removed. Serum corticosterone was measured by a modification of the chloroform extraction, ethanol: sulphuric acid fluorescence technique (9). To a serum sample, 600 μl chloroform was added. Corticosterone was extracted by mixing for 15 s. The chloroform phase (500 μl) was removed to a tube containing 400 μl ethanol : sulphuric acid (35 : 65) and mixed again (15 s) to reextract corticosterone and develop fluorescence. The fluorescence of the acid phase was determined at excitation wavelength 474 nm, emission 518 nm.

Preparation of Drug

MDMA was dissolved in saline to give concentrations of 5, 10, or 20 mg/ml respectively. The appropriate dose was administered IP at 1 ml/kg and administered twice daily at doses of 5, 10, or 20 mg/kg (at 0800 and 2000 h) for 4 days. Controls received saline injections alone.

Statistical Analysis of Data

The data from the behavioural tests was examined using the Kruskal-Wallis test, followed by the Mann-Whitney *U*-test. The biochemical data was analyzed by a one-way analysis of variance, followed by Student's *t*-test. Probabilities < 0.05 were considered statistically significant.

RESULTS

There was no difference in the 24 h baseline activity between any of the groups prior to drug administration, and baseline activity for the vehicle treated group did not fluctuate significantly over the 8 day monitoring period. However, total activity counts were significantly increased in the 10 and 20 mg/kg MDMA treatment groups, compared to vehicle treated controls ($p < 0.05$ and $p < 0.01$, respectively) on days 1, 2, and 4 of drug administration, and also in the 20 mg/kg MDMA treatment group on day 3 of drug administration ($p < 0.05$). The total activity counts recorded for the 20 mg/kg MDMA dose group on days 2, 3, and 4 were lower than the counts recorded on day 1 of drug treatment (Fig. 1). However, this did not reach statistical significance. Activity had returned to baseline values within 24 h following the last administration of MDMA (Fig. 1).

Changes in the behaviour of the MDMA treated rats was further assessed following the ceasation of drug treatment. In the "open field," there was no significant difference in median (95% CI) ambulation between any of the treatment groups relative to the controls [65 (52-75)]. Neither were there any changes in median (95% CI) between any of the treatment groups relative to controls [3 (3-4)] in the "step-down passive avoidance" paradigm. Prior to 8-OH-DPAT challenge, there was no significant difference in rectal temperatures between any of the groups. A reduction in rectal temperature was observed 30 min after 8-OH-DPAT in all groups, with temperature having returned to baseline levels within 120 min of challenge. There were no significant differences in the magnitude

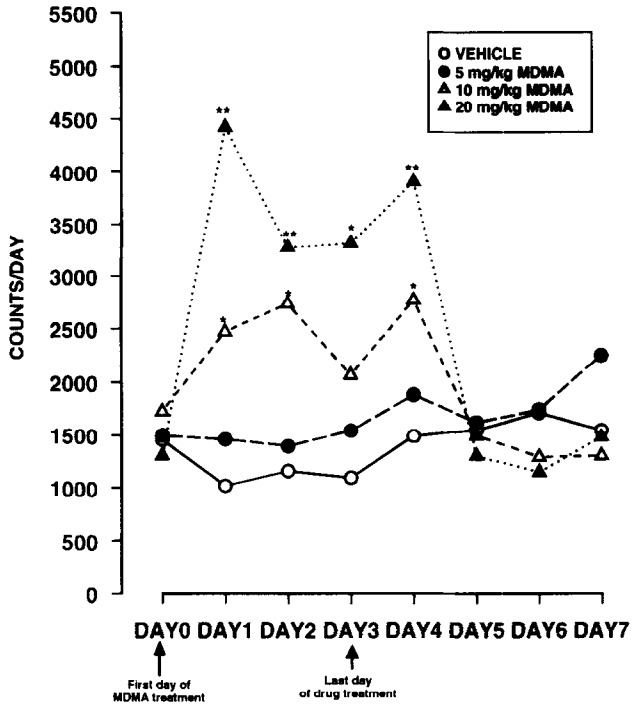

FIG. 1. Effect of IP subacute (±)3, 4-methylenedioxymethamphetamine (MDMA) administration on total locomotor activity in the rat. Data are represented as group median for $N = 6$. As compared with control, $*p < 0.05$, $**p < 0.01$ using a Mann-Whitney *U*-test.

of this response in any of the experimental groups relative to the controls (Table 1).

With regard to indoleamine concentrations, 5-HT and 5-HIAA were significantly decreased in both the amygdala and frontal cortex when compared to vehicle treated animals ($p < 0.001$ and $p < 0.01$, respectively) in the 20 mg/kg MDMA treated group. NA and DA levels were significantly increased in the hippocampus (NA in the 10 and 20 mg/kg MDMA dose group ($p < 0.05$) and DA in the 20 mg/kg MDMA dose group ($p < 0.01$)) when compared to vehicle treated animals (Table 2).

No significant differences in mean (± SEM) basal serum corticosterone concentrations were found between any of the groups (control value: 7.5 ± 1.4 μg/dl).

DISCUSSION

The present experiment examined the relationship between dose and behavioural and the neurochemical consequences following subacute treatment with MDMA. The low dose of MDMA (5 mg/kg) had no significant effect on home cage locomotor activity. Total locomotor activity counts were significantly increased in the 20 mg/kg drug treated group for the 4 days of MDMA administration and in the 10 mg/kg MDMA treated group on days 1, 2, and 4 of drug treatment. The MDMA induced hyperactive response was equally apparent after both the morning and evening administrations.

It would appear that the locomotor hyperactivity produced by MDMA is not due primarily to DA release, but is attributable to the release of presynaptic serotonin (26). It has been postulated that the MDMA induced hyperactivity is mediated via activation of 5-HT_1 receptors (4).

TABLE 1

EFFECT OF SUBCACUTE 3, 4-METHYLENEDIOXYMETHAMPHETAMINE TREATMENT ON BEHAVIOUR, 8-OH-DPAT INDUCED HYPOTHERMIA AND BASAL SERUM CORTICOSTERONE*

	Open Field (Ambulation)	Passive Avoidance (Number of Trials)	8-OH-DPAT [changes (°C) after 30 min]	Corticosterone (μg/dl)
Control	65 (52-75)	3 (3-4)	−3.0 (0.3)	7.5 (1.4)
5 mg/kg	77 (63-80)	2 (2-6)	−2.9 (0.1)	9.4 (1.4)
10 mg/kg	61 (58-94)	3 (2-3)	−3.4 (0.4)	11.0 (2.2)
20 mg/kg	94 (60-124)	2 (2-4)	−2.5 (0.4)	10.5 (3.1)

*"Open field" and "step-down passive avoidance" behaviours, 8-OH-DPAT induced temperature changes and corticosterone concentrations were determined 7, 8, 10, and 11 days after first 3, 4-methylenedioxymethamphetamine (MDMA) administration. Values are represented as median or mean. Numbers in parentheses are either the interquartile range (behavioural experiments) or the SEM (corticosterone and temperature change) respectively. In all groups $N = 6$. There was no significant differences from controls in any of the parameters.

Following the withdrawal of MDMA no marked changes in "open field" or "step-down passive avoidance" behaviour were observed. It has been reported that MDMA decreased investigatory rearings in the behavioural pattern monitor (BPM) (26). However, this behaviour was examined within 120 min of MDMA administration. It has also been reported that injection of 5, 6-dihydroxytryptamine into the mid-brain raphe nuclei, which depletes brain 5-HT concentrations, facilitated active avoidance (2). In the present experiment, it is conceivable that the "open field" and passive avoidance behaviours were examined too long after last MDMA administration to see consequences of acute 5-HT depletion, but too soon before the behavioural effects of serotonergic neurotoxicity were established. It is also possible that the behaviours that were assessed were not sensitive enough to detect the more subtle effects of MDMA treatment.

No significant differences in basal serum corticosterone concentrations were found between any of the groups, 7 days

TABLE 2

EFFECT OF SUBACUTE 3, 4-METHYLENEDIOXYMETHAMPHETAMINE ON NEUROTRANSMITTER CONCENTRATION IN REGIONS OF THE RAT BRAIN (ng/g WET TISSUE)*

	NA	DA	5-HIAA	5-HT
Amygdala				
Control	2272 ± 133	1801 ± 754	1062 ± 85	2863 ± 117
5 mg/kg	2555 ± 219	2405 ± 494	1146 ± 127	3019 ± 199
10 mg/kg	2239 ± 265	1277 ± 380	845 ± 119	2409 ± 335
20 mg/kg	2254 ± 100	1470 ± 196	566 ± 78‡	1381 ± 23§
Frontal cortex				
Control	1434 ± 65	214 ± 10	739 ± 72	1871 ± 154
5 mg/kg	1619 ± 132	239 ± 24	755 ± 72	1734 ± 195
10 mg/kg	1647 ± 120	463 ± 242	624 ± 48	1568 ± 119
20 mg/kg	1472 ± 138	273 ± 89	413 ± 37‡	954 ± 120§
Hippocampus				
Control	2609 ± 303	1322 ± 324	82 ± 3	3365 ± 624
5 mg/kg	2716 ± 288	1399 ± 262	85 ± 8	2842 ± 494
10 mg/kg	4320 ± 628†	2331 ± 583	115 ± 22	4208 ± 559
20 mg/kg	7346 ± 1569†	4183 ± 803‡	147 ± 25	4253 ± 521
Striatum				
Control	354 ± 44	38630 ± 4515	823 ± 80	1896 ± 120
5 mg/kg	620 ± 291	43720 ± 2140	883 ± 24	2088 ± 142
10 mg/kg	468 ± 95	43979 ± 4034	1005 ± 24	2348 ± 277
20 mg/kg	431 ± 98	43311 ± 2175	766 ± 179	1766 ± 335

*Neurotransmitter concentrations were determined 11 days after injection with 3, 4-methylenedioxymethamphetamine (MDMA). Each value represents group mean ± SEM. In all groups $N = 6$. †Indicates significantly different from saline control ($p < 0.05$, Student's one-tailed t-test). ‡Indicates significantly different from saline control ($p < 0.01$, Student's one-tailed t-test). §Indicates significantly from saline control ($p < 0.001$, Student's one-tailed t-test).

following last MDMA administration. It has been reported that MDMA (10 mg/kg, IP) elevated serum corticosterone concentrations 30 min after the administration and that the corticosterone concentration was still elevated 4 h later, possibly due to activation of 5-HT_2 or 5-HT_{1A} receptors (18). It has previously been found that the functional integrity of 5-HT_{1A} receptor coupled neuroendocrine responses are altered 2 weeks after a single dose of MDMA (2.0 or 20 mg/kg SC) (22). In the present study therefore, it would have been expected that some change in the corticosterone concentration would have occurred 7 days after the subacute administration of MDMA. However, no change could be detected.

MDMA (20 mg/kg) caused a significant depletion in 5-HT and 5-HIAA in the amygdala and frontal cortex, 7 days following the ceasation of drug tratment, a finding that is in agreement with others (30). 5-HT and 5-HIAA were also decreased in the striatum, but these changes did not reach significance. One possible explanation is that damage to serotonergic terminals in the striatum was not complete 7 days following MDMA, whereas 5-HT neurons in the frontal cortex or amygdala were more sensitive to the neurotoxic effects of the drug. In the present study, the levels of DA in the striatum are higher than reported levels for group-housed animals. Control values are 3.86 ± 0.45 μg/g wet tissue for DA in comparison to a control value of 0.98 ± 0.04 μg/g wet tissue for DA in the striatum of group-housed animals (29). It has previously been reported that singly housed rats exhibit greater elevations in extracellular DA in both dorsal and ventral striatum (13).

In the present study, the hippocampus seems to be resistent to MDMA-induced depletion of 5-HT and 5-HIAA levels 7 days following ceasation of drug treatment. Immunocytochemical investigations have revealed that the population of large beaded fibres emanating from the median raphe nuclei, which predominate in the molecular layer of the hippocampal CA_1 field, are relatively spared following exposure to MDMA (20). The increase in the DA concentrations in the hippocampus following 20 mg/kg MDMA could reflect a compensatory increase in DA synthesis following an initial depletion of DA, or a decrease in DA catabolism, or a combination of both (31).

The 10 and 20 mg/kg MDMA-induced increase in noradrenaline (NA) in the hippocampus may reflect an overall increase in sympathetic function. In man, MDMA has been reported to produce large increases in both systolic and diastolic blood pressure, an effect possibly mediated through antagonistlike effects at central α_2-adrenoceptors (1).

In summary, the present results indicate that the MDMA-induced increase in locomotor activity is dose and time dependent, and returns to normal following discontinuation of drug treatment. Behavioural effects of MDMA disappear on conclusion of administration of drug, while serotonergic neurotoxicity is apparent 7 days after last MDMA administration.

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