Pharmacology Biochemistry & Behavior, Vol. 33, pp. 741–747. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effects of (±)3,4-Methylenedioxymethamphetamine (MDMA) on Brain Dopaminergic Activity in Rats

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Received 1 September 1988

MATTHEWS, R. T., T. H. CHAMPNEY AND G. D. FRYE. *Effects of (±)3,4-methylenedioxymethamphetamine (MDMA) on brain dopaminergic activity in rats.* PHARMACOL BIOCHEM BEHAV **33**(4) 741–747, 1989.—Acute treatment with (±)3,4-methylenedioxymethamphetamine (MDMA) at high doses (10 and 30 mg/kg, IP), but not lower doses increased locomotor activity in male rats. MDMA did not consistently produce any other stereotyped behaviors at any dose. Dopamine (DA) turnover rate as estimated by the ratio of brain tissue levels of 3,4-dihydroxyphenylacetic acid (DOPAC) over DA was decreased in the striatum for up to two hours after acute treatment with 10 mg/kg of MDMA. DA turnover rate was inconsistently decreased in the olfactory tubercle and medial basal hypothalamus, and was unchanged in the medial prefrontal cortex and the substantia nigra/ventral tegmental area. Two hours after a 30 mg/kg injection of MDMA, DA turnover rate was decreased in all brain areas tested. MDMA and d-amphetamine partially reversed a haloperidol-induced elevation of striatal DOPAC levels. In contrast, the nonamphetamine stimulant, amfonelic acid, enhanced haloperidol's effect. In chloral hydrate-anesthesized rats, MDMA injected IV partially inhibited spontaneous firing rate of DA neurons in the substantia nigra (34% decrease at 4 mg/kg of MDMA). Seventeen days after subchronic MDMA treatment (10 or 20 mg/kg, IP, twice per day for four days), DA and DOPAC levels were unchanged in all brain areas tested as compared to levels in control rats. It is concluded that acute treatment with high but not low doses of MDMA has a weak amphetamine-like effect on nigrostriatal as well as mesolimbic/mesocortical and tuberoinfundibular DA neurons in rats. Repeated treatment with MDMA does not appear to be toxic to mesotelencephalic or tuberoinfundibular DA neurons.

MDMA Dopamine DOPAC DOPAC/DA ratio Locomotor activity DA neuron activity Haloperidol Amfonelic acid D-Amphetamine Nigrostriatal Mesocortical/mesolimbic Tuberoinfundibular

(±)3,4-Methylenedioxymethamphetamine (MDMA) is a frequently abused amphetamine analog that produces mild stimulation and a sense of well-being in humans (3). Pharmacological and behavioral studies in experimental animals suggest that acute intoxication with MDMA has characteristics of both indirect dopaminergic (DA) agonists, such as amphetamine, and indirect serotonergic (5HT) agonists, such as fenfluramine (13, 17, 19, 28, 31, 37). However, the relative roles of these two neurotransmitters in the central pharmacology of MDMA remain to be determined.

To date, acute pharmacological studies on the interaction of MDMA with DA neurons have been primarily limited to striatal tissue (17, 31, 32, 35). The striatum receives DA innervation primarily from the substantia nigra or A-9 subdivision of the brainstem (11). Functionally, the striatum is primarily involved in sensory/motor integration (29). However, MDMA has little effect on sensory/motor function in humans but has prominent effects on emotional state, a characteristic usually associated with limbic and cortical structures. Most DA neurons which innervate limbic and cortical areas belong to the mesolimbic/mesocortical (A-10) subdivision of the brainstem and these pathways have been shown to subserve motor as well as cognitive and limbic (emotional) functions (14,18). A-10 DA neurons also appear to play an important role in the self-administration of several different types of drugs of abuse in humans and animals (14,36). Therefore, it is important to study the effects of MDMA on A-10 DA neuron systems as well as on the A-9 system. A third subdivision of DA neurons is the tuberoinfundibular (A-12) system which is involved in regulation of pituitary hormone release (26). Recent evidence has shown that MDMA affects serum hormone levels (27) suggesting possible effects of MDMA on A12 DA neurons also.

The present study was designed to measure several behavioral and biochemical indices of DA neurotransmission in rats after acute or chronic MDMA treatment with emphasis placed on A-9, A-10 and A-12 DA terminal regions. In addition, the acute effects of MDMA on neuronal impulse flow of midbrain DA neurons was tested.

METHOD

Animals

Drug-naive male albino Sprague-Dawley rats (175–225 g, Harlan Sprague-Dawley, Inc., Houston, TX) were used in all experiments. Rats were housed in pairs with continuous access to standard lab chow and water under a 12 hour/12 hour light/dark cycle with lights out at 6:00 p.m. All acute biochemical experi-

ments were begun at 9:00 a.m. and chronic experiments were completed between 3:00 and 5:00 p.m. on the last day of the experiment.

Measurement of Behavior

Locomotor activity was evaluated as previously described (2). Immediately following IP drug injection each animal was placed in a clear plastic observation cage (46 × 24 × 20 cm high). The animal's behavior was observed for 1 minute at 10- to 30-minute intervals as described below. Each 1-minute observation period was divided into four equal parts and a score of 1 was recorded for each 15-second interval in which locomotion occurred. Stereotyped behavior was assessed in a similar fashion and was defined as the rapid, repetitive occurrence of any motor activity that is not normally repetitive (for example, head bobbing, circling or incessant licking/sniffing of the same object). A behavioral response was not considered stereotyped unless it occurred in all four intervals of the 1-minute observation period.

Acute or Subchronic Drug Treatment

For acute drug treatment experiments, groups of 5 or 6 rats were injected with various doses of (±)MDMA or with saline, IP, and returned to their home cages. Rats were killed in a separate room at various times after injection. Some experiments were repeated and data were combined for statistical analysis.

For subchronic drug treatment experiments, groups of 4 rats were injected with saline (SC) or MDMA (10 or 20 mg/kg, SC) once every 12 hours for four days followed by a 17-day recovery period. An additional group of four rats was injected once with p-chloroamphetamine (10 mg/kg, IP) followed by a 17-day recovery period. This experiment was repeated four times for the saline and 10 mg/kg MDMA groups and the last three repetitions of the experiment included 20 mg/kg MDMA and p-chloroamphetamine groups. Therefore, a total of sixteen rats served as saline controls with sixteen 10 mg/kg MDMA-injected rats, twelve 20 mg/kg MDMA-injected rats and twelve p-chloroamphetamine-injected rats.

Biochemical Assays

Rats were decapitated and brains were placed in ice-cold saline within 30 seconds. Brain areas were dissected free of surrounding tissue on an ice-chilled glass plate, weighed, and frozen on dry ice. Medial prefrontal cortex (mPFC) samples were taken as a wedge of cortex on either side of the midline anterior to the rostrum of the corpus callosum (4). Olfactory tubercles (OT) were pinched from the ventral brain surface with forceps. Tissue samples were removed bilaterally from the rostral dorsal poles of the striatum taking care to avoid the nucleus accumbens. Medial basal hypothalamus (MBH) samples consisted of a bilateral wedge of tissue cut from the ventral brain surface which included the mammillary bodies, infundibular region and ventral periventricular nuclei. Brainstem samples included all structures from a cut between the posterior edge of the mammillary bodies and the rostral superior colliculus caudally to a cross section through the caudal medulla. Only one-half (cut on the midline) of the brainstem sample was assayed. DA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels were assayed as described elsewhere (8). In brief, each brain sample was sonicated in 0.16 N perchloric acid containing epinine (100 ng/ml) as an internal standard. After centrifugation, supernatant aliquots were injected onto a high performance liquid chromatography column (reverse phase C-18 column) and solutes were detected by electrochemistry. DA and DOPAC levels were quantified by measuring chromatogram peak heights as compared to extracted and internal standards and expressed as ng/g wet weight of tissue sample.

Unit Recordings

Extracellular action potentials of midbrain DA neurons were recorded from rats as described previously (23). In brief, rats were anesthetized with chloral hydrate (400 mg/kg IP initially, supplemental doses given IV as needed) and incisions and pressure points were injected with mepivacaine HCl, (2% solution). Rats were mounted in a stereotaxic frame and holes were drilled in the skull over the substantia nigra (3.0 mm anterior to lambda, 2.0 mm lateral to midline) or the ventral tegmental area (3.0 mm anterior, 0.5 mm lateral) according to the atlas of König and Klippel (20). Body temperature was maintained at 37 ± 1°C with a heating pad. Action potentials were recorded with insulated tungsten microelectrodes, and the signals were amplified and counted by computer. Drugs were injected through a tail vein catheter. Recording locations were verified by histological examination of electrode tracks after electrode tip placements were marked by electolytic lesions (+10 μA for 15 seconds).

Drugs

Haloperidol and d-amphetamine were gifts from McNeil Pharmaceuticals and S.K. and F. Labs (Philadelphia, PA), respectively. (±)MDMA was obtained from the National Institute of Drug Abuse (Bethesada, MD). Amfonelic acid was purchased from Research Biochemicals Inc. (Natick, MA) and apomorphine from Sigma Chemical Co. (St. Louis, MO). All doses of drugs are free base weights except MDMA which is expressed as the weight of the HCl salt form.

Statistics

Data were analyzed by one- or two-way analysis of variance with significant differences between groups determined by the Student Newman-Keuls test with a homogenous "N" (16).

RESULTS

Behavior Studies

Locomotor activity and stereotyped behaviors were measured after acute IP injections of saline or 0.3, 1.0, 3.0, 10 or 30 mg/kg of (±)MDMA. Neither saline nor MDMA caused stereotyped behaviors (licking, sniffing, circling, head bobbing or weaving) for up to 6 hours after injection. Only the two highest doses of MDMA caused a significant change in locomotor activity ($p<0.05$ vs. saline; Fig. 1). MDMA at 10 and 30 mg/kg increased locomotor activity for up to 75 minutes after injection.

In order to determine whether repeated MDMA treatment caused tolerance, MDMA (10 mg/kg, IP) or saline was injected once per day for 5 days (n = 6 per group). Four days after the last injection, all chronically-treated rats were challenged with MDMA (10 mg/kg, IP) and locomotor behavior was quantified as in acute experiments. Out of a maximum possible activity score of 28 per rat obtained during the first 2 hours postdrug (4 points per observation time × 7 observation times), chronic saline-injected rats had a mean activity score of 12.7 ± 3.2 following acute MDMA treatment while chronic MDMA-treated rats had a mean score of 11.5 ± 2.5 following acute treatment (not significant vs. chronic saline). Locomotor activity of acute saline-injected ani-

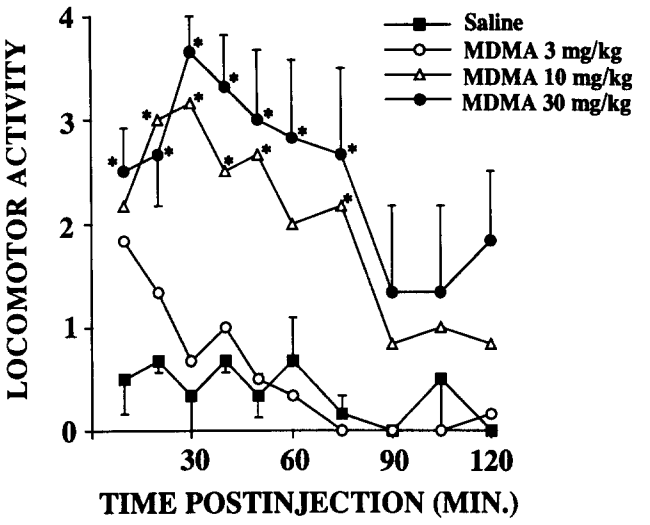

FIG. 1. Effects of acute MDMA (3, 10 or 30 mg/kg) or saline treatment on spontaneous locomotor activity in rats. Rats were injected IP with drug or saline at time 0 and the number of intervals in which locomotor activity occurred was recorded for each of the indicated time points. Points represent the mean ± S.E.M. for n = 6. *$p<0.05$ vs. saline-injected rats. The S.E.M.'s are omitted from the 3 and 10 mg/kg doses for clarity.

mals was 0.17 ± 0.17 ($p<0.01$ vs. either MDMA group).

Biochemical Studies

The acute time-related effects of MDMA (10 mg/kg, IP) on levels of DA and a major DA metabolite, DOPAC were measured in tissue samples of A-9 (striatum) and A-10 (olfactory tubercles, OT; medial prefrontal cortex, mPFC) DA nerve terminal areas as well as the A-12 DA neuron region (hypothalamus, MBH) and the A-9/A-10 DA neuron soma region (brainstem). MDMA significantly increased DA levels only in the striatum and MBH for up to two hours after drug injection ($p<0.05$ vs. saline; Fig. 2). DOPAC levels were decreased in the striatum but were unchanged in all other areas. Significant changes in DA and DOPAC were apparent at the first time point (15 min) and changes in DA levels were maximal at two hours while changes in DOPAC were maximal within 30 min. The ratio of DOPAC to DA, a measure of DA turnover, had the largest decrease in the striatum (45% at 30 min) and turnover remained depressed for at least two hours (Fig. 2). Other brain areas showed a nonsignificant tendency toward decreased DA turnover except for a significant decrease in the olfactory tubercle at two hours after MDMA treatment (Fig. 2).

Dose-related effects of MDMA (1, 3, 10 or 30 mg/kg, IP) were assessed two hours after drug treatment in tissue samples from all five brain areas previously examined. MDMA caused a dose-dependent increase in DA levels only in the striatum (Fig. 3). DOPAC levels were decreased in all brain areas at the highest MDMA dose, but a clear dose-dependent decrease was seen only in the MBH (Fig. 3). MDMA decreased the DOPAC/DA ratio in most brain areas after 10 mg/kg and in all brain areas after 30 mg/kg. Note, however, that the effects of 10 mg/kg MDMA two hours postinjection as shown in Fig. 2 differ from similar data in Fig. 3 with respect to areas of the brain with significant changes in DA metabolism.

MDMA was also tested for its ability to modify haloperidol-induced stimulation of striatal DOPAC formation (Table 1).

TABLE 1

DA AND DOPAC LEVELS IN RAT STRIATUM AFTER ACUTE DRUG TREATMENT[a]

Treatment (mg/kg)	DA (μg/g/tissue)	DOPAC (μg/g/tissue)
Saline	10.54 ± 1.17	1.69 ± 0.11
HALO (0.3)	9.8 ± 0.49	4.35 ± 0.17*
HALO (0.3) + MDMA (30)	8.71 ± 0.83	2.39 ± 0.14†
HALO (0.3) + D-AMPH (5.0)	10.54 ± 0.77	2.41 ± 0.23†
HALO (0.3) + AFA (2.5)	3.88 ± 0.17*	8.25 ± 0.53‡

[a]Drugs were given SC 90 minutes before decapitation; all values are the mean ± S.E.M. from 4 to 6 animals. HALO = haloperidol, D-AMPH = d-amphetamine, AFA = amfonelic acid.

*$p<0.01$ vs. saline; †$p<0.05$ vs. saline; ‡$p<0.001$ vs. HALO only.

Haloperidol alone (0.3 mg/kg) caused a 2.6-fold increase in striatal DOPAC levels. When injected along with haloperidol, both MDMA (30 mg/kg) and d-amphetamine (5.0 mg/kg) partially reversed the increase in DOPAC, whereas the nonamphetamine psychomotor stimulant, amfonelic acid (2.5 mg/kg), further increased DOPAC levels to 4.9-fold above control levels. Striatal DA levels were significantly reduced only by combined treatment with haloperidol and amfonelic acid ($p<0.001$ vs. saline; Table 1).

MDMA was tested for possible long-term effects on DA metabolism of A-9, A-10 and A-12 DA neurons. Repeated injections with MDMA (10 or 20 mg/kg, twice daily for four days) or a single injection of the serotonergic neurotoxin, p-chloroamphetamine (10 mg/kg) caused no changes in brain DA or DOPAC levels 17 days after the last drug injection. MDMA given repeatedly at 20 mg/kg caused 8 deaths (66% mortality), while no deaths occurred in saline, 10 mg/kg MDMA of p-chloroamphetamine treatment groups.

Unit Recording Studies

MDMA was tested for its effects on spontaneous activity of A-9 DA neurons in anesthetized rats as measured by extracellular single unit recording techniques. MDMA given IV dose-dependently inhibited spontaneous activity of DA neurons with a 34 ± 12% inhibition at 4 mg/kg. Higher doses of MDMA (8 or 16 mg/kg cumulative dose) caused no more than a 60% decrease in firing rate (n = 6; Fig. 4). Apomorphine (10 μg/kg, IV) further slowed the firing rate when given after MDMA, and haloperidol (0.1 mg/kg, IV) increased the firing rate above baseline (Fig. 4). MDMA at 16 mg/kg and higher doses caused a toxic interaction with the general anesthetic in several animals.

DISCUSSION

The present behavioral, biochemical and electrophysiological results are generally consistent with and extend the findings of previous reports suggesting that acute and chronic MDMA treatment have relatively weak effects on brain DA neurotransmission, as compared to more robust effects on serotonin neurotransmission (17, 31, 32, 34, 35). However, the present studies do refocus attention on an amphetamine-like indirect action of MDMA on DA neuron pathways at behaviorally active doses. First, the decrease in DA turnover as measured by a decrease in the DOPAC to DA ratio after acute MDMA treatment is consistent with the hypothesis that MDMA enhances DA-receptor stimulation and conse-

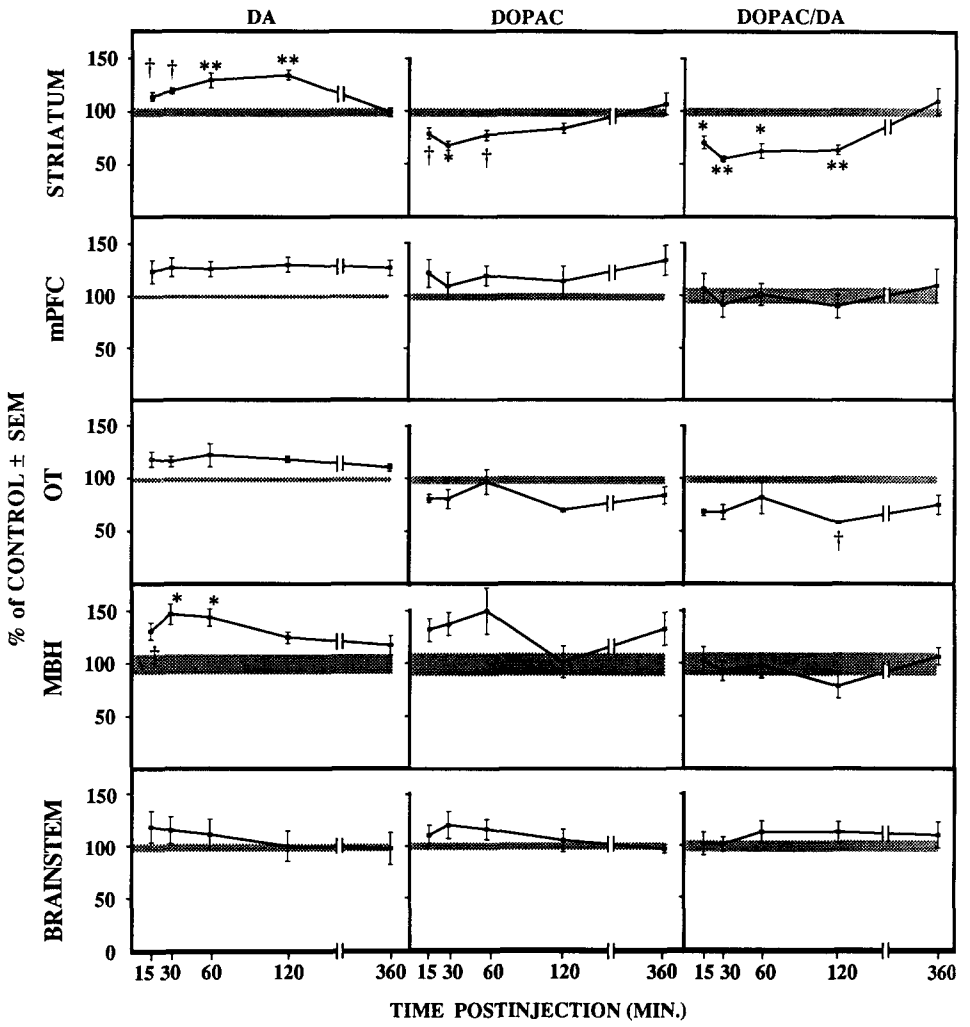

FIG. 2. Time-related effects of MDMA on DA and DOPAC levels and on the DOPAC/DA ratio in: striatum, medial prefrontal cortex (mPFC), olfactory tubercle (OT), medial basal hypothalamus (MBH) and brainstem. MDMA (10 mg/kg, IP) or saline (IP) was injected at time 0 and rats were killed at various times thereafter. Each point represents the combined data from two separate experiments with 5 animals per point in each experiment, except for OT in which 5 animals per point were done in one experiment. Data are expressed as a percent of saline-injected controls (n = 5 for OT, n = 10 all others) with the standard error of saline values indicated by the hatched areas on either side of 100%. Control values for DA (ng/g tissue ± S.E.M.), DOPAC (ng/g tissue ± S.E.M.) and DOPAC/DA were, respectively: *striatum*, 9051 ± 409, 4242 ± 756, 0.47 ± 0.08; *mPFC*, 78.7 ± 7.9, 35.1 ± 2.8, 0.45 ± 0.04; *OT*, 5477 ± 206, 1587 ± 124, 0.29 ± 0.02; *MBH*, 297 ± 24.8, 179 ± 27.6, 0.64 ± 0.13; *brainstem*, 109 ± 6.8, 58.1 ± 5.9, 0.53 ± 0.06. †$p<0.05$, *$p<0.01$, **$p<0.001$ vs. saline-injected rats.

quently increases negative feedback regulation of DA turnover. Others have reported a similar decrease in DA turnover after acute MDMA treatment (31, 32, 35). Others have also shown that MDMA has little affinity for DA receptors but does release ^{3}H-DA from the striatum and endogenous DA from the striatum and nucleus accumbens suggesting that MDMA is an indirect DA agonist (17, 22, 31, 37). An alternative mechanism by which MDMA may decrease DOPAC/DA ratios is by inhibiting intraneuronal monoamine oxidase activity, an action which would not necessarily increase DA receptor stimulation but would decrease intraneuronal catabolism of DA to DOPAC and shunt more DA to extraneuronal metabolism. This might result in increased striatal homovanillic acid (HVA) levels after acute MDMA treatment. Two studies have reported an increase in striatal HVA after acute treatment (32, 35), while a third study reported no change in HVA (31). However, no direct data are presently available, suggesting that MDMA is an effective inhibitor of brain monoamine oxidase activity.

Second, drug interaction experiments reported here show that both MDMA and d-amphetamine partially reversed the increase in striatal DOPAC accumulation caused by a DA receptor antagonist, haloperidol. In contrast, the nonamphetamine indirect agonist, amfonelic acid, enhanced the haloperidol-induced DOPAC accumulation. Others have shown that nonamphetamine stimulants, but not amphetamines, may mobilize intracellular DA stores and accentuate increased DA turnover caused by haloperidol

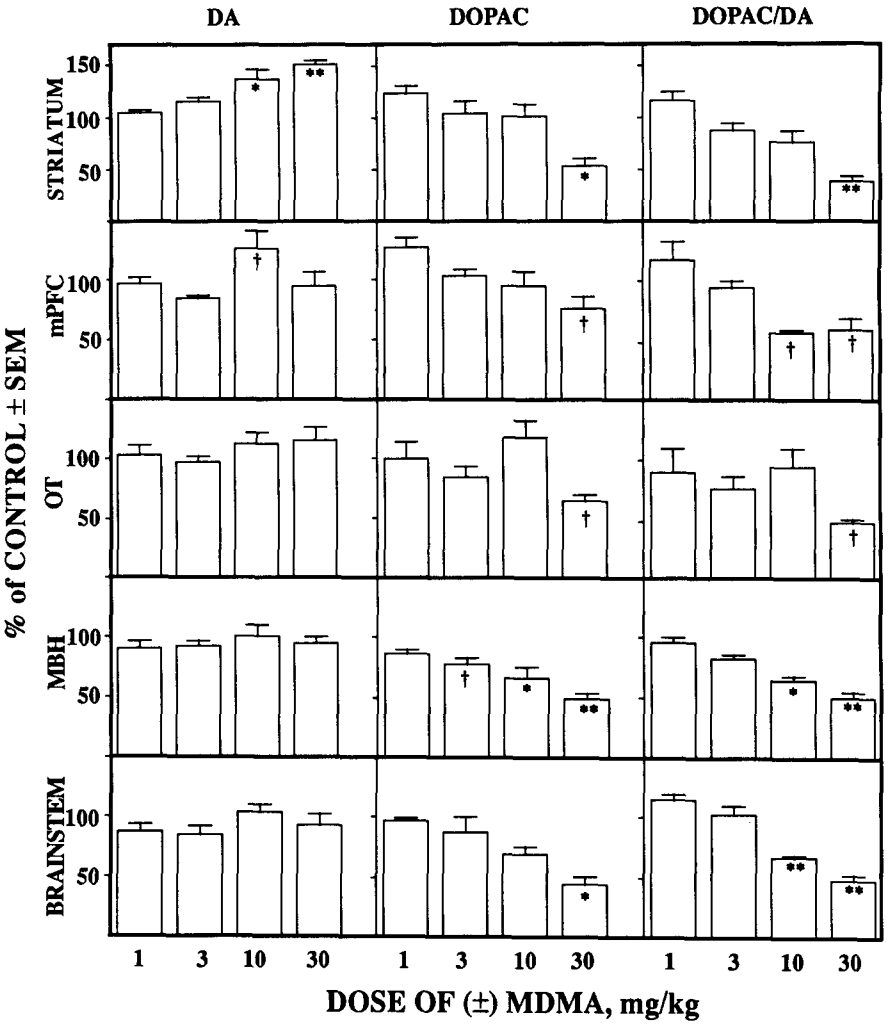

FIG. 3. Dose-related effects of MDMA on DA and DOPAC levels and on the DOPAC/DA ratio in various brain regions. Values are expressed as the mean ± S.E.M. of saline-injected animals. All animals were killed 2 hr after injection (IP). Control values for DA (ng/g tissue ± S.E.M.), DOPAC (ng/g tissue ± S.E.M.) and DOPAC/DA were, respectively: *striatum*, 12,670 ± 960, 4530 ± 310, 0.37 ± 0.04; *mPFC*, 135 ± 11, 52.1 ± 5.3, 0.40 ± 0.06; *OT*, 7617 ± 1027, 3971 ± 713, 0.60 ± 0.17; *MBH*, 547 ± 63, 117 ± 12, 0.22 ± 0.02; *brainstem*, 205 ± 9.9, 87.1 ± 9.0, 0.42 ± 0.03. †$p<0.05$, *$p<0.01$, **$p<0.001$ vs. saline-injected controls. n = 6 for both controls and drug-injected groups. See Fig. 2 legend for key to abbreviations.

(12,33). Therefore, our data suggest that MDMA does not mobilize DA stores and is an amphetamine-type DA indirect agonist.

Third, electrophysiological and behavioral data suggest that MDMA is at most a weak DA agonist even at high doses. Electrophysiological data show that even high doses of MDMA produce at most a 60% decrease in firing rates of A-9 DA neurons. In contrast, both amphetamine and nonamphetamine stimulants have been shown to potently decrease spontaneous activity of DA neurons through feedback inhibition, autoreceptor stimulation or both (6, 7, 12, 24). For example, the ED_{50} for firing rate inhibition of A-9 DA neurons by d-amphetamine was reported as 1.6 mg/kg (6).

In behavioral experiments, amphetamine and nonamphetamine stimulants increase locomotor activity in rats in a dose-dependent manner. At higher doses of these drugs, the increase in activity is masked by the appearance of stereotype behaviors (15,29). These effects have been shown to be primarily due to the DA agonist properties of these drugs since locomotor and stereotype behaviors can be blocked by haloperidol and, in the case of indirect agonists, can also be blocked by depletion of DA from nerve terminals. In the present data, high doses of MDMA (10 and 30 mg/kg) increased locomotor activity, but failed to produce stereotype behaviors. In addition, our data show no evidence of tolerance or sensitization to repeated MDMA treatments over 1 week, in contrast to significant sensitization to d-amphetamine-induced locomotor activity demonstrated by others after repeated d-amphetamine injections (21). Finally, in operant behavior experiments reported from several laboratories, MDMA has been shown to substitute for d-amphetamine in discriminative stimulus para-

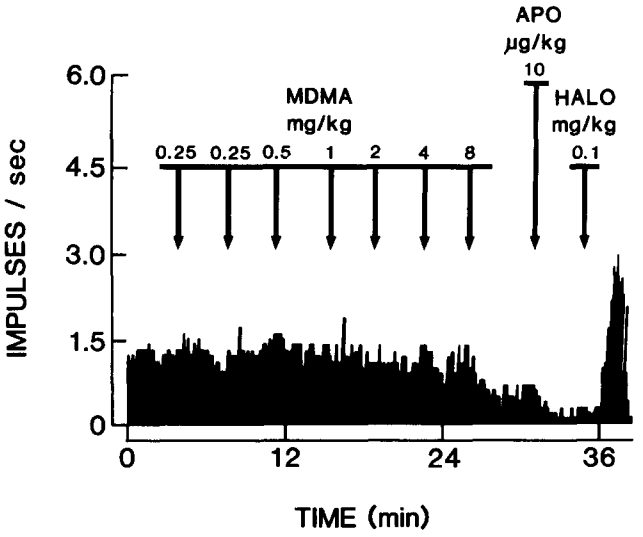

FIG. 4. Effects of MDMA, apomorphine (APO) and haloperidol (HALO) on the spontaneous firing rate of an A-9 DA neuron. Arrows indicate time and noncumulative dose of each drug injection (IV). Each bar of the histogram represents the average spikes/second in consecutive 10-second periods.

digms in rats, pigeons, and monkeys but was less potent than amphetamine in maintaining operant behavior (10, 13, 19). Taken together, the accumulated results to date would suggest that MDMA is a weak, indirect, DA agonist.

Acute treatment with MDMA appears to have little preferential effect on DA metabolism in A-10 vs. A-9, or A-12 DA systems. Thus, 10 mg/kg of MDMA had inconsistent effects on DA turnover in A-9, A-10 and A-12 DA neuron terminal areas while 30 mg/kg decreased turnover in all areas tested. In addition, preliminary electrophysiological experiments on A-10 DA neurons suggest that MDMA is equipotent in inhibiting spontaneous activity of A-10 and A-9 DA neurons (Matthews, unpublished observations). These data do not support the hypothesis that MDMA has prominent or selective effects on mesolimbic/mesocortical DA neurons, whose activities are thought to be involved in the rewarding effects of many other drugs of abuse (5,36).

Chronic treatment with MDMA caused no change in DA or DOPAC levels or in the DOPAC/DA ratio in any brain region tested. These data agree with previous reports that MDMA at similar doses was not toxic to DA nerve terminals in the cortex or striatum or to DA neurons in the hypothalamus and brainstem (1, 9, 25, 30). Our data extend the areas tested to include mesolimbic DA nerve terminals in the olfactory tubercle.

In summary, acute administration of MDMA at high doses induces some effects that are characteristic of DA agonists, i.e., increased locomotor activity, decreased DA turnover, and inhibition of DA neuronal impulse flow. However, MDMA does not resemble psychomotor stimulants of the nonamphetamine type, such as cocaine and amfonelic acid in their ability to mobilize vesicular DA stores. In spite of MDMA's preferential effects on mood and emotion as compared to sensory/motor stimulation in man, MDMA appears to have no preferential effects on mesocortical/mesolimbic DA neurons as compared to nigro-striatal DA neurons in rats. Finally, chronic administration of MDMA at up to 40 mg/kg/day does not appear to be toxic to A-9, A-10 or A-12 DA systems.

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