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The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat

Bryan K. Yamamoto * and Linda J. Spanos

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272-9623, U.S.A.

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The effects of the recently classified Schedule I amphetamine analog, 3,4-methylenedioxymethamphetamine ((±)-MDMA) on caudate and nucleus accumbens dopamine release and metabolism were studied by in vivo voltammetry and HPLC with electrochemical detection. Monitored over a 3 h period, the magnitude of increase in dopamine release and the onset of effect were dose-dependent and similar for both brain areas following the 2.5 and 5 mg/kg dose of the drug. However, responses were different for these brain regions using 10 mg/kg of MDMA; the magnitude of increase was greater and the onset of effect more immediate in caudate. Analysis of dopamine and DOPAC tissue content in both caudate and nucleus accumbens verified the voltammetry results. This study provides the first evidence that MDMA induces dopamine release in vivo and that this effect is region, time- and dose-dependent.

3,4-Methylenedioxymethamphetamine (MDMA); Voltammetry; Dopamine release; Caudate nucleus; Nucleus accumbens; Dopamine metabolism

1. Introduction

The popular recreational and street use of methylenedioxymethamphetamine ((±)-MDMA) and its recent classification by the United States Federal Drug Enforcement Agency as a Schedule I drug has prompted investigations into its mechanism of action, potential for abuse, and possible neurotoxic effects. While Schedule I has usually been reserved for the psychedelic drugs and hallucinogens, previous studies have shown that MDMA has a much lower potential for sensory disruption than the classical hallucinogens (Shulgin and Nichols, 1978). Rather MDMA (nicknamed 'Ecstasy') has been reported to enhance communication, sense of awareness, intimacy, and self-esteem without disrupting thought processes (Shulgin and Nichols, 1978). These properties have thus prompted its use as an adjunct to psychotherapy (Baum, 1985).

In vitro studies have suggested that MDMA acts primarily on the serotonergic system. These effects resemble those of parachloroamphetamine (PCA). When administered acutely or chronically in high doses, MDMA has been shown to release [^{3}H]5-HT (Johnson et al., 1986; Schmidt et al., 1987), decrease tryptophan hydroxylase activity (Stone et al., 1986), decrease 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) tissue content in striatum, hippocampus and cortex (Stone et al., 1986; Schmidt, 1987), and block 5-HT uptake (Schmidt, 1987). In contrast, the effects on the dopaminergic system are less remarkable. Although MDMA appears to stimulate the in vitro basal release of dopamine from striatal slices (Johnson et al., 1986) and elevate striatal dopamine tissue content (Schmidt, 1987; Stone et al.,

* To whom all correspondence should be addressed: Department of Pharmacology, Northeastern Ohio Universities College of Medicine, 4209 State Route 44, Rootstown, OH 44272-9623, U.S.A.

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1986), the magnitude of these effects is less than related compounds such as MDA, amphetamine and methamphetamine (Johnson et al., 1986; Stone et al., 1986).

Most initial studies have focussed on the 5-HT system using in vitro assays of 5-HT function. Although they have helped to elucidate the possible mechanism of action and neurotoxicity of MDMA (Schmidt et al., 1986; Stone et al., 1986; Schmidt, 1987), doses approximately 4-10 times the human dose have been used. Therefore, in order to obtain a more relevant and dynamic measure of MDMA action on specific brain dopaminergic systems, this study uses low doses of the drug to investigate the acute effects on in vivo dopamine release in awake behaving animals. Activation of the striatal dopaminergic system has been implicated as the cause of the stereotypic response seen after amphetamine administration (Scheel-Krüger, 1971), while the mesolimbic dopamine area may be involved in the reinforcing properties and euphoria inducing effects of MDMA (Beardsley et al., 1986). Therefore, in this study, dopamine release was monitored simultaneously in caudate and nucleus accumbens following MDMA administration.

This study presents the first dynamic measure of low doses of MDMA on in vivo dopamine release in the awake-behaving rat. Dopamine release was differentially increased in caudate and nucleus accumbens in a manner that was time- and dose-dependent and suggestive of both an extrapyramidal and mesolimbic dopaminergic influence of the drug.

2. Materials and methods

2.1. Electrochemical methods

Male Sprague-Dawley rats weighing between 280 and 350 g were anesthetized with chloral hydrate (150 mg/kg) and ketamine (50 mg/kg) i.p. and placed in a stereotaxic frame. Dopamine release was monitored by in vivo voltammetry using stearate-modified carbon paste electrodes placed into the anterodorsal caudate (AP + 1.9, lat. + 2.5, vert. − 4.2) and nucleus accumbens (AP + 1.9, lat. + 1.5, vert. − 6.5) according to the coordinates of Paxinos and Watson (1982). Carbon paste working electrodes with stearic acid incorporated into the paste were constructed as previously described (Blaha and Lane, 1983) to provide selectivity for dopamine over DOPAC and ascorbate. Stearic acid (100 mg) was dissolved in 1.0 ml of mineral oil heated to 37 °C and then mixed with 1.5 g of carbon powder (Ultra Carbon). Voltammetric recordings were made using a CV37 voltammograph (Bioanalytical Systems Inc.) and linear sweep voltage scans from −0.20 to +0.40 V (scan rate 5 mV/s) with semidifferential signal processing. The Ag/AgCl reference and stainless steel set screw auxillary electrodes were placed directly onto the cortex. The working electrode was automatically scanned at 5 min intervals. Using the stearate-modified electrode, the oxidation peak current at 0.12 V is proportional to the extracellular concentration of dopamine in the caudate and thus monitors any changes in dopamine release (Blaha and Lane, 1983). The 3 electrode array was cemented into place using a 6 channel connector (Plastic Products, Roanoke, VA) and dental acrylic. All animals were allowed to recover for at least 1 week to minimize any effects of surgical trauma on the specificity and discriminability of dopamine release.

Voltammetric recordings from the awake-behaving rat were made via a 5 channel electrical swivel. Current measurements for each rat were allowed to stabilize for at least 1 h until 6 successive recordings (30 min) differed by no more than 1%. Following this stable baseline measurement, 2.5, 5.0 or 10 mg/kg MDMA was injected i.p. and current recordings were followed for 3 h. Rats were then killed by decapitation and electrode placements histologically verified.

A separate group of animals was similarly implanted with electrodes into the nucleus accumbens and was injected i.p. with the dopamine-β-hydroxylase inhibitor, FLA-63 (30 mg/kg) to examine the possible contribution of norepinephrine to the dopamine release measurements.

2.2. Biochemical measurements

As an extension of the electrochemical results and to provide an additional measure of

dopaminergic function and metabolism, separate experiments were conducted to determine the effect of MDMA on tissue content of dopamine and its metabolite dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens and caudate.

Rats were injected i.p. with 2.5, 5.0, or 10.0 mg/kg of MDMA. Controls were injected with saline vehicle. They were then killed after 60 or 120 min following MDMA. The brains were rapidly removed, frozen on dry ice, and sliced into 400 μm thick coronal sections. Anterodorsal caudate and nucleus accumbens were punch-dissected using an 18 gauge needle and stored frozen at $-80\,^{\circ}$C for not more than 7 days until assayed. Samples were homogenized in 0.1 M perchloric acid and centrifuged at $13\,000 \times g$ for 4 min. The resulting supernatant was then assayed for dopamine and DOPAC by high performance liquid chromatography with electrochemical detection. The compounds were separated on a C_{18}, 5 μm column using a mobile phase consisting of 0.15 M monochloroacetic acid, 0.68 mM sodium octyl sulfate, 0.1 mM Na_2EDTA, 3.5% acetonitrile and 1.8% tetrahydrofuran, pH 3.2. Flow rate was 1.5 ml/min. Detection was with a glassy carbon electrode maintained at a potential of +0.7 V vs. a Ag/AgCl reference electrode by a model LC4B amperometric controller (Bioanalytical Systems Inc.). Protein content of each sample was determined by the method of Bradford (1976).

2.3. Chemicals and drugs

All chemicals were of reagent grade quality. MDMA was generously provided by Dr. Richard Hawks, National Institute on Drug Abuse, and was dissolved in 0.9% saline. FLA-63 (Aldrich Chemical Company, Inc. Milwaukee, WI) was suspended and sonicated in 0.9% saline. All drug dosages were administered i.p. in a volume of 1 ml/kg.

2.4. Statistics

All voltammetry data expressed as a percent of baseline, were analyzed by a 3-way analysis of variance with repeated measures followed by post-hoc Tukey tests for multiple comparisons. The chromatography data were analyzed by a 1-way analysis of variance for independent groups followed by post-hoc Tukey tests. Significance for all tests was set at $P < 0.05$.

3. Results

3.1. Effect of MDMA on dopamine release

Electrochemical recordings were allowed to stabilize for at least 1 h. MDMA was administered at doses of 2.5, 5.0 and 10.0 mg/kg only after the recordings differed by no more than 1% for the last 30 min of the baseline period. Data from these experiments are shown in fig. 1. Figure 1A illustrates that MDMA produced a dose-dependent increase in dopamine release in caudate. Furthermore, differences in the time course of release depended on the dose of MDMA ($P < 0.05$, time $\times$ dose interaction). The smallest dose (2.5 mg/kg) produced a 21% increase ($P < 0.05$) in dopamine release after 50 min whereas the 5 mg/kg dose produced a maximum increase of 28% above baseline after 115 min ($P < 0.05$). The 2.5 mg/kg dose returned to control levels by this time while the 5.0 mg/kg dose of MDMA did not return to baseline until 150-180 min after injection. The highest dose (10 mg/kg) produced a gradual increase in dopamine release for the initial 75-90 min following administration. After this time, there was a sharp and marked increase. Because of this and for illustrative purposes, the y-axis and the line representing the 10 mg/kg dose is broken so as to include the peak effect of this dose. This reached a maximum of 372% of control 115 min after injection ($P < 0.01$). Although the increase was followed by a rapid decline towards baseline, dopamine release remained significantly elevated at 180 min ($P < 0.05$).

Dopamine release in nucleus accumbens is shown in fig. 1B. Similar to striatum, there was a dose-dependent effect by MDMA on both the magnitude and time course of dopamine release ($P < 0.01$). The maximum effects produced by the 2.5 and 5.0 mg/kg doses were 119 and 123%, respectively ($P < 0.05$). However, the time courses of these effects were different. Dopamine release

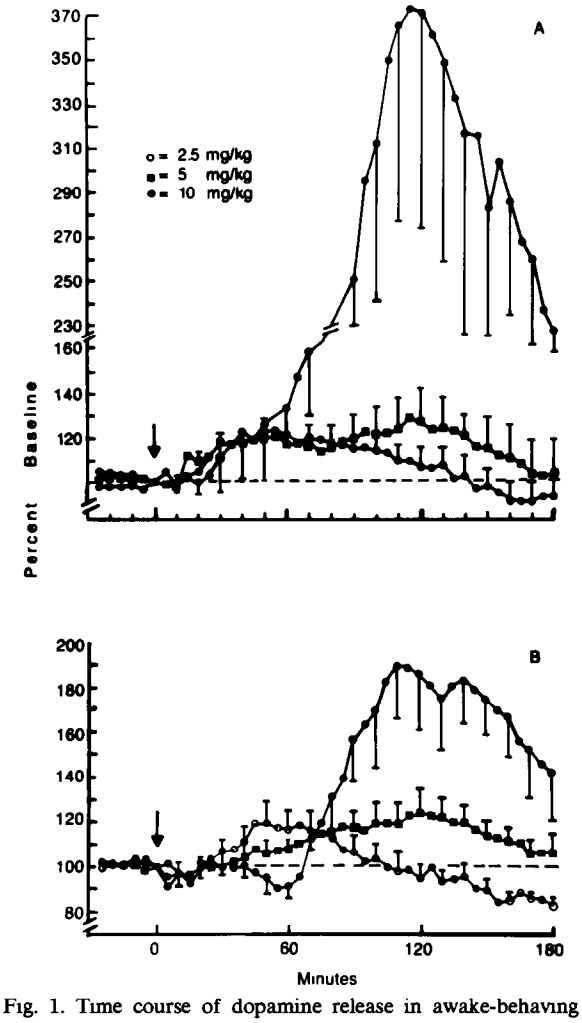

Fig. 1. Time course of dopamine release in awake-behaving rats following three different doses (2.5, 5 and 10 mg/kg) of MDMA Semiderivative voltammograms were recorded once every 5 min. (A) Anterodorsal caudate and (B) nucleus accumbens. The data are presented as a percentage of the 100% preinjection baseline value, calculated by averaging the last six values of the baseline current just prior to drug injection (indicated by the arrow). Each point represents the mean ± S.E.M. from 10 animals

after the 2.5 mg/kg dose peaked 40-50 min following injection and returned to control values after 85-90 min. Release then declined to below baseline after 150 min. The time course of MDMA after the 5.0 mg/kg dose was more prolonged and produced a maximum effect after 120 min. This effect returned to baseline by 170 min. The time course and magnitude of effect were further increased following the highest dose of MDMA (10 mg/kg). Unlike the lower doses, the increase in release was not observed until 70 min following injection. However, the maximum effect (189% of baseline, $P < 0.05$) appeared within the same time range of 110-120 min as that seen for the 5.0 mg/kg dose but did not return to baseline levels during the time course examined.

MDMA-induced dopamine release also differed between caudate and accumbens (area vs. MDMA interaction, $P < 0.01$). The most dramatic difference between the two areas was the magnitude of effect at the highest dose. Dopamine release in caudate was increased to 372% of baseline whereas accumbens increased to 189% of control. The onset of action was also faster in the caudate. A significant increase ($P < 0.05$) in caudate was seen as early as 40 min after MDMA compared to 70 min for nucleus accumbens. The time courses for the different regions at the 2.5 mg/kg dose also differed. Caudate dopamine release at these doses was more prolonged compared to nucleus accumbens. Release in caudate returned to basal levels 110 min following 2.5 mg/kg whereas release in accumbens was not different from control by 85 min. No differences in the time course of MDMA action were observed between areas at the 5.0 mg/kg dose.

To test for the possible contribution by norepinephrine to the electrochemical measures of dopamine release from nucleus accumbens, the dopamine-β-hydroxylase inhibitor, FLA-63 (30 mg/kg) was injected into separate groups of animals. These results indicated that FLA-63 had no significant effect on the electrochemical measures from nucleus accumbens during the 3 h following injection.

3.2. Effects of MDMA on dopamine and DOPAC tissue content

The results from the biochemical measures of dopamine and DOPAC tissue content in caudate and nucleus accumbens are shown in figs. 2 and 3, respectively. The lowest dose of MDMA (2.5 mg/kg) produced no significant changes in dopamine or DOPAC in either area compared to vehicle-injected animals (0 min). Significant in-

creases in caudate dopamine were found 60 and 120 min after 5.0 mg/kg ($P < 0.05$). Nucleus accumbens dopamine was elevated only at the 120 min time point ($P < 0.05$). No effects were noted on caudate or nucleus accumbens DOPAC content. The highest dose of MDMA (10 mg/kg) increased dopamine content after 60 and 120 min in both areas ($P < 0.05$). In contrast, DOPAC

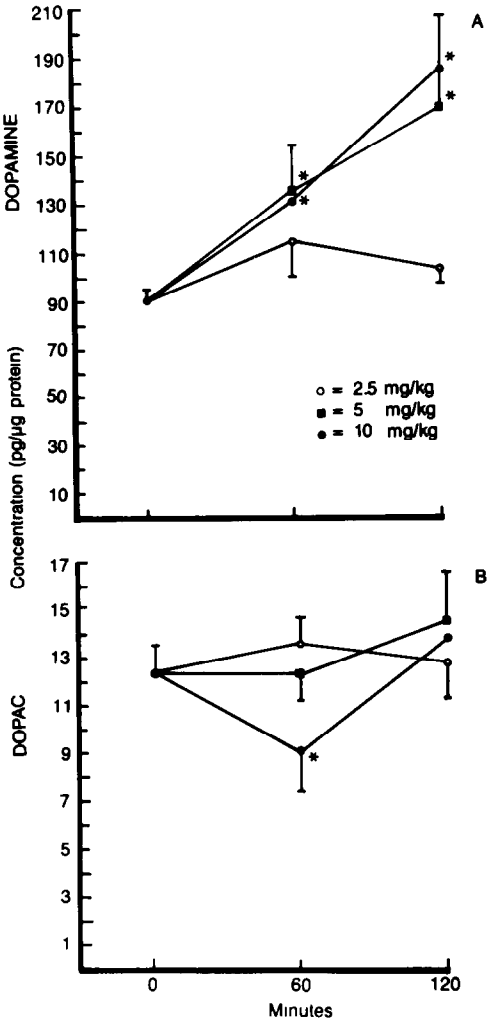

Fig. 2. The effect of three different doses of MDMA on anterodorsal caudate. (A) Dopamine and (B) dihydroxyphenylacetic acid (DOPAC) tissue content 60 or 120 min after drug administration. The 0 min time point represents saline-injected control animals. Tissue concentrations are expressed in pg/μg protein. Each point represents the mean ± S.E.M. obtained from six animals. * $P < 0.05$ compared to 0 min.

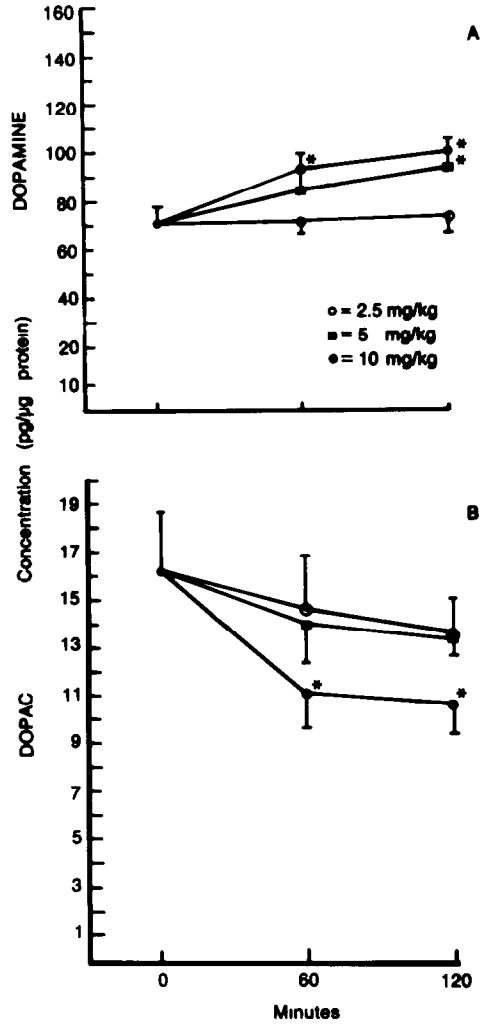

Fig. 3. The effect of three different doses of MDMA on nucleus accumbens. (A) Dopamine and (B) dihydroxyphenylacetic acid (DOPAC) tissue content 60 or 120 min after drug administration. The 0 min time point represents saline-injected control animals. Tissue concentrations are expressed in pg/μg protein. Each point represents the mean ± S.E.M. obtained from six animals. * $P < 0.05$ compared to 0 min.

levels in caudate and nucleus accumbens were decreased after 60 and 120 min following injection ($P < 0.05$).

4. Discussion

The results of this study provide the first evidence that MDMA increases dopamine release in

both caudate and nucleus accumbens of the awake-behaving rat. Using in vivo voltammetry, the effects of MDMA on dopamine release were shown to be both dose- and time-dependent. Furthermore, MDMA appears to differentially affect the nigrostriatal and mesolimbic dopaminergic systems. Greater increases in dopamine release were seen in the caudate compared to the nucleus accumbens at the highest dose of MDMA. In contrast, the lower doses produced similar increases in both areas. The time course of effect was also dose- and region-dependent. The 10 mg/kg dose produced an immediate increase in dopamine release in caudate in contrast to a delayed effect (70 min) in nucleus accumbens. The duration of action at the lower doses was more abbreviated but compared to the 5.0 mg/kg dose, the 2.5 mg/kg dose exhibited the shortest time course. These effects however, were similar in each area. The voltammetry results were verified and extended by tissue measures of dopamine content. Dopamine increased in both caudate and nucleus accumbens and persisted throughout the 120 min time course. Similar to the release experiments, dopamine content was increased to a greater extent in caudate.

There have been a few reports that in vivo electrochemical measurements of catecholamine release may be accompanied by changes in the extracellular concentration of ascorbate following acute amphetamine injections (Dayton et al., 1981; Gonon et al., 1981). The experiments reported here have used the stearate-modified graphite paste electrodes similar to those originally reported by Blaha and Lane (1983). This modification has been shown to enhance selectivity for dopamine release in striatum over ascorbate and DOPAC. With unmodified electrodes, ascorbate injections increased the electrochemical signal, while the monoamine oxidase (MAO) inhibitor, pargyline decreased the baseline measurement indicating that the majority of the signal (80-90%) represented ascorbate and DOPAC. In contrast, ascorbate had no effect on the signal measured by stearate-modified electrodes, while pargyline increased it, presumably due to the accumulation of dopamine as a result of decreased metabolism by MAO. Further in vitro evidence has shown that stearate-modified electrodes are selective for dopamine over ascorbate. Only dopamine produced a peak between 0.15 and 0.20 V (Yamamoto et al., 1982; Freed, 1986). Stearate modification does not, however, discriminate between dopamine and norepinephrine. Although this is not a concern in the caudate, since norepinephrine is virtually undetectable compared to dopamine, a previous study by Versteeg et al. (1976) has shown that norepinephrine concentrations in nucleus accumbens are about 10% of dopamine and thus could confound the voltammetric detection of dopamine release. In the present study, we verified that the contribution of norepinephrine to the dopamine signal in this brain region was negligible. There was no change in the peak height compared to baseline for 3 h after administration of the dopamine-β-hydroxylase and norepinephrine synthesis inhibitor, FLA-63. Therefore, these modified electrodes most likely measure dopamine and not ascorbate, norepinephrine or DOPAC in response to MDMA.

Administration of 10 mg/kg of MDMA produced a greater increase in dopamine release in the caudate compared to nucleus accumbens. This may be partially explained by the difference in the degree of dopaminergic innervation to these brain areas; the tissue content of dopamine in caudate is approximately 15-20% greater than that of nucleus accumbens (figs. 2 and 3). However, this content difference cannot explain the 95% difference in dopamine release in response to the drug. Studies have shown that dopamine release in nucleus accumbens corresponds to hyperlocomotion while in the striatum, dopamine release results in stereotypy and postural changes (Kelly et al., 1975; Freed and Yamamoto, 1985). Additionally, it was shown that d-amphetamine at low doses resulted in pref-erential activation of locomotor activity while higher doses produced stereotypy. In agreement with these findings, the lowest dose of MDMA in the present study simply produced increased locomotion with slight, equivalent increases in dopamine release from both areas. However, the highest dose of MDMA produced a relatively greater increase in dopamine release from caudate compared to nucleus accumbens. Therefore, similar to d-amphetamine, MDMA at low

doses may act on both caudate and nucleus accumbens while at stereotypic doses, MDMA preferentially influences caudate.

MDMA effects on dopamine release could also be secondary to its primary effect on the serotonergic system and may be reflective of a regional differential effect on this neurotransmitter. MDMA has been suggested by others to act primarily on the serotonergic system by acutely increasing in vivo release and chronically acting as a neurotoxin to 5-HT neurons. Previous studies have shown it to be an MAO and tryptophan hydroxylase inhibitor and to inhibit 5-HT reuptake (Schmidt, 1987; Stone et al., 1986; Fellows and Bernheim, 1950). Although not quantified in the present study, casual observation revealed that rats injected with MDMA exhibited behaviors characteristic of the serotonin syndrome similar to that seen with parachloroamphetamine (Kutscher and Yamamoto, 1979). These behaviors typically occurred within 30 min following the 10 mg/kg dose. The above neurochemical effects and the observation of the 5-HT syndrome early in the time course of MDMA action may reflect an initial 5-HT release prior to the rise in dopamine efflux. This may explain the regional differences in onset of dopamine release at the higher doses.

Johnson et al. (1986) showed that MDMA is a potent releaser of 5-HT. It has also been shown that 5-HT release is inhibitory on both striatal and mesolimbic dopaminergic activity (Lloyd, 1978; Nicolau et al., 1979). Of the two brain regions examined, the nucleus accumbens is more densely innervated by 5-HT terminals, particularly in the rostral-caudal plane investigated in the present study. Therefore, due to the greater density of 5-HT innervation, the delayed onset of dopamine release at higher MDMA doses may simply reflect increased inhibition in the nucleus accumbens compared to caudate during the earlier time points.

Tissue content analysis of dopamine corresponded with the voltammetry results and provided additional evidence that dopamine metabolism as well as release was also affected by MDMA. Both areas showed increases in dopamine content following MDMA (figs. 2 and 3). However, analysis of DOPAC content resulted in definite and persistent decreases in nucleus accumbens but small, transient decreases in caudate. These overall decreases in DOPAC levels are consistent with the proposed MAO-inhibiting action of MDMA (Fellows and Bernheim, 1950). However, DOPAC levels are determined by numerous other factors such as the rate of dopamine synthesis and release, COMT activity, and energy transport mechanisms. These differential effects on limbic vs. striatal DOPAC levels are very similar to previous results reported for the antidepressant, amineptine. Similar to our present findings with MDMA, amineptine has been reported to produce a slight and transient decrease in DOPAC levels in caudate but a persistent, clear-cut decrease in nucleus accumbens (DeSimoni et al., 1986). This drug is believed to be an indirect dopamine agonist and like MDMA, its differential action may be due to inherent functional differences between these two areas. The clearance rate of DOPAC has been reported to be higher in mesolimbic compared to striatal tissue (Westerink and Korf, 1976). This may account for the greater effect seen in the nucleus accumbens where DOPAC is rapidly transported out of the region. An alternative explanation is that autoreceptors on dopamine neurons in nucleus accumbens are more sensitive to dopamine agonists than those on nigrostriatal terminals (Bannon and Roth, 1983). Therefore, the larger decrease in DOPAC content in nucleus accumbens may reflect an enhanced auto-regulated feedback inhibition and subsequently, a diminished stimulation of dopamine release. While it may be that MDMA possesses indirect dopamine agonist effects, these same mechanisms probably act in concert with the previously reported serotonergic effects of this drug.

Although dopamine content paralleled dopamine release at 5 and 10 mg/kg, no changes were seen in dopamine content at the 2.5 mg/kg dose where small but significant increases in release were observed. This could be explained by at least two different mechanisms. Dopamine content may not be altered at this lowest dose due to the release-enhancing effect of MDMA without an increase in synthesis or decrease in catabolism. This, in fact, is supported by results indicating an enhanced in vitro release of dopamine from tissue slices (Johnson et al., 1986; Schmidt et al., 1987),

the lack of an acute effect of MDMA on tyrosine hydroxylase activity (Stone et al., 1986), and the absence of changes in DOPAC content following the 2.5 mg/kg dose (figs. 2 and 3). Therefore, the finding that tissue contents of dopamine and DOPAC do not change does not exclude the possibility that dopamine release increases. Thus, changes in extracellular dopamine detected by voltammetry may be a more sensitive measure of release than measures of dopamine and DOPAC tissue content. The alternate explanation for the discrepancy at the lowest dose of MDMA on content and release is an ascorbate amplification effect on the in vivo electrochemical response to dopamine release (Echizen and Freed, 1986). Although ascorbate is not measured directly by stearate-modified carbon paste electrodes (Yamamoto et al., 1982; Blaha and Lane, 1983; Freed, 1986), the electrochemical measure of dopamine release in response to MDMA could be amplified by ascorbate via an electrocatalytic reaction (Dayton et al., 1980) to yield a greater increase in apparent release at the 2.5 mg/kg dose. This amplification effect does not, however, negate our present in vivo findings and the in vitro results of others (Johnson et al., 1986; Schmidt et al., 1987) that dopamine release is qualitatively increased in response to MDMA.

In conclusion, the presently described dopaminergic properties of MDMA are complemented by other studies which show that the reinforcing effect of MDMA (Beardsley et al., 1986) may be due, in part, to the reward properties of dopamine itself (Wise, 1984). Furthermore, the serotonergic neurotoxicity seen with MDMA could be due to increased dopamine release similar to that reported for methamphetamine (Schmidt et al., 1985). Future research is therefore needed to investigate the dopaminergic component of MDMA action on its potential abuse liability and neurotoxicity.

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