Pharmacology Biochemistry and Behavior, Vol. 61, No. 4, pp. 361–366, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00103-8

Effect of 3,4-Methylenedioxymethamphetamine (MDMA) on Hippocampal Dopamine and Serotonin

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Received 17 October 1997; Revised 24 March 1998; Accepted 8 April 1998.

SHANKARAN, M. AND G. A. GUDELSKY. *Effect of 3,4- methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin.* PHARMACOL BIOCHEM BEHAV **61**(4) 361–366, 1998—The 3,4-methylenedioxymethamphetamine (MDMA)-induced increase in the extracellular concentration of dopamine and the long-term depletion of 5-HT were studied in the hippocampus of the rat brain. MDMA produced a dose-dependent increase in the extracellular concentration of dopamine in the hippocampus, as well as in the striatum. The MDMA-induced increase in the extracellular concentration of dopamine in the hippocampus, but not in the striatum, was suppressed in rats treated with the norepinephrine uptake inhibitor, desipramine, and in rats in which noradrenergic neurons in the hippocampus were lesioned with DSP_4 (*N*-(2- chloroethyl)-*N*-ethyl-2-bromo benzylamine). However, the long-term depletion of 5-HT in the hippocampus produced by MDMA was unaltered in desipramine-treated rats. These results are supportive of the view that the MDMA-induced increase in the extracellular concentration of dopamine in the hippocampus is the result of an enhanced release of dopamine from noradrenergic neurons. In addition, the MDMA-induced depletion of 5-HT in the hippocampus appears not to involve dopamine-initiated processes, because suppression of MDMA-induced dopamine release did not attenuate the long-term depletion of 5-HT in the hippocampus. © 1998 Elsevier Science Inc.

MDMA Dopamine Serotonin Hippocampus

THE amphetamine analogue, 3,4-methylenedioxymethamphetamine (MDMA) produces a selective and long-term depletion of 5-HT in the brains of rodents and nonhuman primates (9). MDMA-induced toxicity of 5-HT axon terminals is evidenced by biochemical and immunocytochemical findings such as a decrease in tryptophan hydroxylase activity (30,35), reduction in [^{3}H]paroxetine-labeled serotonin uptake sites (1), and reduced immunostaining of 5-HT terminals (25,27). Although the exact mechanism of MDMA-induced toxicity of 5-HT terminals is unknown, evidence is supportive of the involvement of dopamine-dependent processes. It is well documented that MDMA releases dopamine both in vitro and in vivo from brain regions such as the striatum (15,23,38). The MDMA-induced release of dopamine has been shown to be attenuated by dopamine uptake blockers (23), as well as by tetrodotoxin (11); this is supportive of the involvement of both carrier-medicated and impulse-mediated processes in the mechanisms of MDMA-induced dopamine release.

It has been proposed that excess dopamine release contributes to the MDMA-induced depletion of 5-HT. The contention that excess dopamine release contributes to the MDMA-induced depletion of 5-HT is based, to a large extent, on the findings that drugs (e.g., GBR 12909, α-methyl tyrosine) that suppress the MDMA-induced release of dopamine diminish the magnitude of 5-HT depletion produced by MDMA (4,34), whereas L-DOPA potentiates MDMA-induced 5-HT depletion (31).

However, a role for dopamine in MDMA-induced 5-HT depletion has been difficult to reconcile in brain regions, such as the hippocampus, that are sparsely innervated by dopamine fibers. However, the hippocampus does contain dopaminergic innervations from the ventral tegmental area and the substantia nigra (28,36). Moreover, Bischoff et al. (2) have proposed that dopamine exerts a neurotransmitter role in the hippocampus. Thus, initial experiments in this study were undertaken to ascertain the extent to which MDMA increases

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the extracellular concentration of dopamine in this brain region. In addition, the potential contribution of noradrenergic neurons in the MDMA-induced efflux of dopamine in the hippocampus was assessed by examining the effects of MDMA in rats treated with desipramine, a selective norepinephrine uptake inhibitor, or DSP_4, a noradrenergic neurotoxin.

Finally, to evaluate the potential role of excessive dopamine release elicited by MDMA in the hippocampus in the long-term depletion of 5-HT in this brain region, the effect of MDMA on hippocampal concentrations of 5-HT was determined in rats treated with desipramine, inasmuch as this drug, as shown in the present study, selectively diminishes the MDMA-induced increase in the extracellular concentration of dopamine in the hippocampus.

METHOD

Animal Procedures

Male rats of the Sprague–Dawly strain (200–275 g, Zivic Miller Labs, Allison Park, PA) were used in the studies. The animals were housed three per cage in a temperature- and light-controlled room until the day of surgery.

In Vivo Microdialysis and Biochemical Procedures

Rats were anesthetized with ketamine/xylazine (70/7 mg/kg, IM), and a stainless steel guide cannula (21 gauge) was placed on the surface of the cortex above the anterolateral striatum (AP, +1.2 mm; L, 3.1 mm) or the ventral hippocampus (AP − 5.5 mm; L, 4.7 mm) according to the stereotaxic atlas of Paxinos and Watson (26). The hole surrounding the guide cannula was plugged with cyanoacrylic glue, and the cannula was secured to the skull with screws and cranioplastic cement. Following surgery, the rats were housed individually for 2–3 days before the dialysis experiment.

The dialysis probes were constructed of stainless steel tubing (26 gauge) and membrane (Spectra Pro, 6000 MW cutoff, 210 μm outside diameter) using a concentric flow design (40). The length of the dialysis membrane for probes for the striatum and hippocampus was 4.5 mm. The in vitro recoveries of the probes were 10–15% for dopamine, and no correction was made for recoveries.

On the day of the experiment, a dialysis probe was inserted through the guide cannula into the brain such that the tip of the dialysis membrane was either 7.0 mm below the surface of the brain into the striatum or 7.0 mm below the surface of the brain into the ventral hippocampus. The probes were connected to an infusion pump set to deliver Dulbecos phosphate-buffered saline containing 1.2 mM $CaCl_2$ at a rate of 1.8 μl/min. After a 2-h equilibration period, dialysis samples were collected every 30 min. At least four baseline samples were obtained prior to drug treatment. The placement of the probes in the striatum and ventral hippocampus was verified by visual examination of brain slices of a representative group of animals.

Biochemical Measurements

Extracellular concentrations of dopamine and tissue concentrations of norepinephrine were quantified with high-performance liquid chromatography (HPLC) with electrochemical detection using methods similar to those described elsewhere (10). Briefly, samples were injected onto a 3-mm C18 column (ESA Inc) connected to a ESA coulochem detector (ESA, Chelmsford, MA). The mobile phase consisted of 35 mM citric acid, 54 mM sodium acetate, 50 mg/l of disodium ethylenediamine tetraacetate, 70 mg/l of octanesulfonic acid sodium salt, 100 μl/l of triethylamine, 6% acetonitrile, 3% methanol, pH 4.2 pumped at a flow rate of 0.4 ml/min. Peak heights following injection of 20 μl samples were recorded with an integrator, and the quantity of norepinephrine and dopamine were calculated based on known standards. For the analysis of norepinephrine content in tissue, rats were killed after the completion of the dialysis experiment.

For postmortem analysis of brain 5-HT, the rats were killed by decapitation 7 days after MDMA administration. The tissues were kept frozen (−80° C) until analyzed for 5-HT levels. The tissue samples were homogenized with 0.2 N perchloric acid containing 0.1% cysteine and centrifuged for 10 min at 10,000 × *g*. An aliquot of the resulting supernatent fluid was analyzed for 5-HT by HPLC using a C18 column (Phenomemex, Torrance, CA) connected to a LC- 4B amperometric detector (Bioanalytical Systems, West Laffayette, IN). The mobile phase was the same as that utilized for the analysis of dopamine and norepinephrine. The retention times for norepinephrine, dopamine, and 5-HT were approximately 5, 8, and 18 min.

Drugs and Drug Treatments

The racemic mixture of MDMA hydrochloride was provided by the National Institute on Drug Abuse. DSP_4 was purchased from RBI (Natick, MA), and desipramine hydrochloride was purchased from Sigma Chemical Co (St. Louis, MO). Drugs were administered IP and were accomplished in a volume of 1 ml/kg.

Chemical lesion with DSP_4. Chemical lesions of the noradrenergic neurons were produced with the use of DSP_4 10–14 days prior to the dialysis experiment. Rats received fluoxetine (5 mg/kg, IP) 60 min prior to the administration of DSP_4 (60 mg/kg, IP) to prevent depletion of brain 5-HT (14,16). In 10 out of 12 rats treated with DSP_4, the mean depletion of norepinephrine in the hippocampus was 85% compared to control animals. The concentrations of dopamine in the hippocampus and the striatum were not significantly altered by DSP_4 treatment. Only those animals that exhibited a NE depletion greater than 70% were considered in the analysis of the data of the dialysis experiments.

Desipramine treatment. Inhibition of the norepinephrine transporter was accomplished by treatment of rats with desipramine (10 mg/kg, IP) 60 min prior to the administration of MDMA. This dose of desipramine appears to selectively inhibit the uptake of norepinephrine (5,18).

Statistical Analysis

Analysis of the tissue concentrations was performed using a two-way analysis of variance. Differences between treatment groups were determined with the use of the Student–Newman– Keuls test. Data from dialysis experiments was analyzed using a two-way repeated measures analysis of variance (Sigmastat, Jandel Scientific). Multiple pair-wise comparisons were performed using the Student–Newman–Keuls test. Treatment differences were considered statistically significant at $p < 0.05$.

RESULTS

The administration of MDMA (5 and 20 mg/kg, IP) resulted in a dose-dependent and significant ($p < 0.05$) increase in the extracellular concentration of dopamine in the hippocampus. The dopamine concentration of the hippocampal di-

alysate increased from approximately 0.4 pg/sample to more than 10 pg/sample following administration of 20 mg/kg of MDMA (Fig. 1).

The effect of MDMA on the extracellular concentration of dopamine in the hippocampus was also determined in rats treated with desipramine (10 mg/kg, IP) and in rats in which noradrenergic neurons were lesioned by treatment with DSP_4 (60 mg/kg, IP) 10 days earlier. The MDMA- induced increase in the extracellular concentration of dopamine in the hippocampus of rats treated acutely with desipramine or 10 days earlier with DSP_4 was significantly ($p < 0.05$) less than that in MDMA-treated controls (Fig. 2A). Treatment of rats with desipramine (10 mg/kg, IP) or DSP_4 (60 mg/kg, IP) alone did not alter the extracellular concentration of dopamine in the hippocampus (data not shown). In contrast to the suppressive effects of desipramine and DSP_4 on the MDMA-induced increase in the extracellular concentration of dopamine in the hippocampus, neither desipramine nor DSP_4 altered the MDMA-induced increase in the extracellular concentration of dopamine in the striatum (Fig. 2B).

The effect of desipramine also was evaluated on the MDMA-induced depletion of 5-HT in the hippocampus. The concentration of 5-HT in the hippocampus was reduced by approximately 50%, 7 days after the administration of MDMA (20 mg/kg, IP) (Fig. 3). In rats treated with desipramine, there was no significant alteration in the magnitude of the MDMA-induced depletion of 5-HT in the hippocampus. In addition, 5-HT concentrations in the hippocampus were not altered by treatment with desipramine alone (Fig. 3).

DISCUSSION

The ability of MDMA to increase the extracellular concentration of dopamine in the striatum is well documented (15,38). Evidence is supportive of the view that the release of dopamine in the striatum after administration of MDMA involves both carrier- and impulse-mediated mechanisms (11,23,39). In the present study, the extracellular concentration of dopamine in the hippocampus also was increased following the administration of MDMA. In addition, the magnitude of the increase relative to baseline values of the extracellular concentration of dopamine in the hippocampus is at least as great as that demonstrated previously in the striatum (11,39). In view of evidence of dopaminergic innervation in the hippocampus (28,37), as well as the localization of dopamine receptors in this brain region (3,21), there is a neuroanatomical basis for the suggestion that MDMA enhances the release of dopamine from dopaminergic terminals in the hippocampus.

However, the effect of MDMA on the release of dopamine in the hippocampus was almost completely suppressed in rats treated with DSP_4 or desipramine. The inhibitory effect of desipramine and DSP_4 was specific for the hippocampus and was

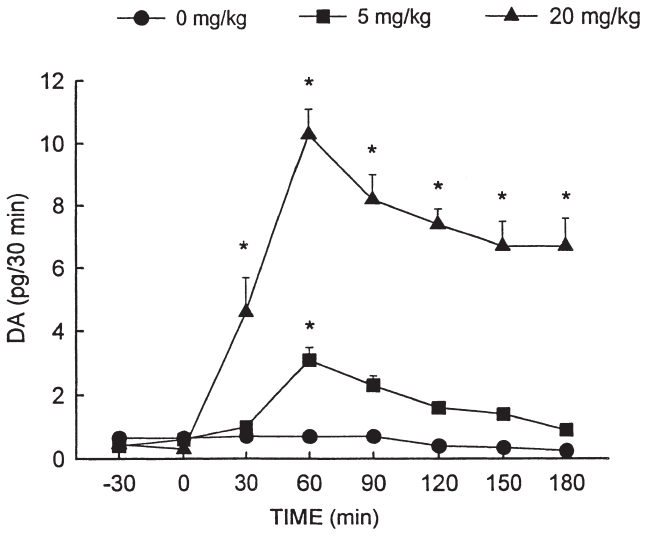

FIG. 1. Effect of MDMA on the extracellular concentration of dopamine in the hippocampus. MDMA at the indicated doses was injected IP at time 0. the values represent the mean ± standard error of four to six rats. *Indicates values that differ significantly ($p < 0.05$) from those of the control (0 mg/kg) animals.

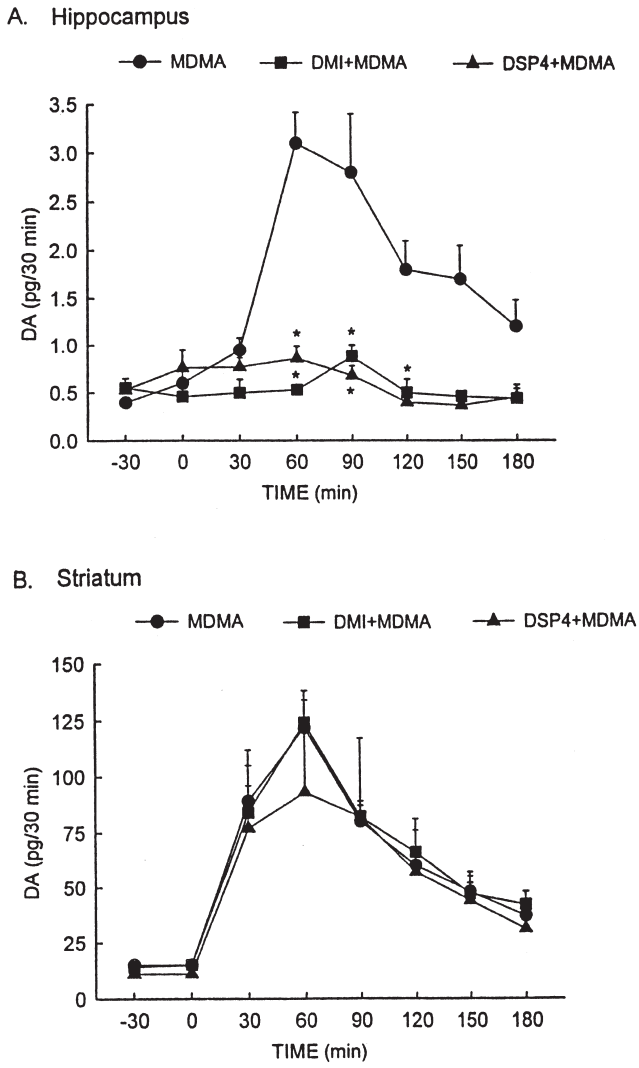

FIG. 2. Effect of MDMA on the extracellular concentration of dopamine in the striatum and hippocampus of rats treated with desipramine (DMI) or DSP_4. MDMA (5 mg/kg, IP) was administered at time 30 min, which was 1 h after an IP injection of desipramine (10 mg/kg) or 10 days after treatment with DSP_4 (60 mg/kg, IP). Values represent the mean ± standard error of six to eight rats. *Indicates values that differ significantly ($p < 0.05$) from those for the MDMA-treated rats.

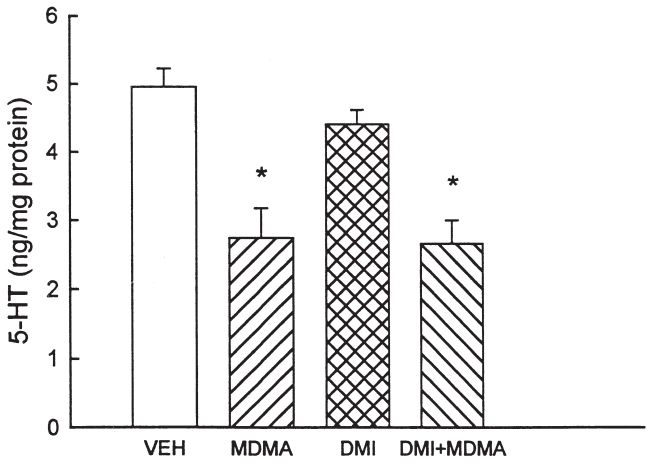

FIG. 3 Effect of MDMA and desipramine (DMI) on the concentration of 5-HT in the hippocampus. Desipramine (10 mg/kg, IP) was injected 1 h prior to the administration of MDMA (20 mg/kg, SC). The rats were killed by decapitation 7 days following treatment with MDMA. Each value represents the mean ± SE of four to six rats. *Indicates values that differ significantly ($p < 0.05$) from that for the vehicle (VEH)-treated animals.

not observed in the striatum. DSP_4 is thought to produce a selective depletion of brain norepinephrine (16,19), and desipramine is a selective norepinephrine uptake inhibitor (29). The current data are suggestive that the MDMA-induced increase in hippocampal extracellular dopamine is a result of the release of dopamine from terminals of noradrenergic neurons. These data are consistent with the view that MDMA, after being taken up into nonadrenergic nerve terminals, may increase the efflux of cytosolic dopamine from noradrenergic neurons via the norepinephrine transporter. It is suggested that desipramine either prevents the entry of MDMA into the nonadrenergic terminal or prevents the efflux of dopamine out of the terminal.

The excessive release of dopamine elicited by MDMA has been proposed to contribute to the mechanism whereby MDMA produces the long-term depletion of 5-HT. This contention is based primarily on reports in which drugs, such as GBR 12909 or α-methyl tyrosine, that suppress the MDMA-induced release of dopamine in the striatum, also attenuate the MDMA-induced depletion of 5-HT in this brain region (23,34). Moreover, Nash and Nichols (22) have demonstrated that in the striatum there is a strong correlation for MDMA analogues between the magnitude to increase striatal dopamine release and the magnitude to deplete striatal 5-HT. There is considerable evidence in support of the view that the excessive dopamine release produced by MDMA may promote oxidative damage that contributes to the long-term depletion of brain 5-HT (6,12,33).

However, it is difficult to envision a role of dopamine in the MDMA-induced depletion of 5-HT in brain regions such as the hippocampus that are sparsely innervated with dopamine. Nevertheless, as illustrated in the present study, MDMA elicits a prolonged increase in the extracellular concentration of dopamine in the hippocampus that appears to be dependent on noradrenergic terminals. It is conceivable that dopamine-initiated mechanisms could contribute to MDMA-induced 5-HT toxicity in brain regions devoid of dopaminergic, but not both dopaminergic and noradrenergic, terminals.

In the present study, suppression of the MDMA-induced increase in hippocampal extracellular dopamine was not associated with an attenuation of MDMA-induced 5-HT depletion. Treatment of rats with desipramine suppressed the MDMA-induced increase in the extracellular concentration of dopamine in the hippocampus but did not alter the extent of 5-HT depletion produced by MDMA in this brain region. Thus, in the hippocampus, as opposed to the striatum, the MDMA-induced depletion of 5-HT may involve mechanisms that are largely independent of dopamine. However, the report that bilateral lesions of the substantia nigra with 6-hydroxydopamine attenuated the MDMA- induced depletion of 5-HT in the hippocampus (32) is not consistent with this view.

Although the long-term depletion of hippocampal 5-HT by MDMA is well documented, there are few studies that have focused on the mechanisms of toxicity in this brain region. Schmidt et al. (31) have demonstrated that MDL 11,939, a 5-HT_2 antagonist, prevented the MDMA-induced depletion of 5-HT in the hippocampus. The neuroprotective effect of MDL 11,939 was ascribed to the modulation of the MDMA-induced activation of dopamine function. However, the determinants of dopaminergic function were assessed only in the striatum. The role of 5-HT_2 receptors in MDMA-induced 5-HT neurotoxicity is complicated further by the ability of these drugs to attenuate MDMA-induced hyperthermia (20,24).

Although it has been proposed that reactive oxygen species (i.e., hydroxyl radicals) and accompanying oxidative damage may be derived from the enzymatic and/or auto-oxidation of dopamine that is released by MDMA in brain regions such as the striatum (33), the mechanism by which MDMA produces depletion of serotonin in the hippocampus may involve oxidative damage due to quinones that are independent of dopamine. Hiramatsu et al. (13) have shown that quinones are formed during the metabolism of MDMA, and the quinones rapidly form glutathione adducts. Thus, reactive oxygen species (i.e., quinones) may also be formed from the metabolism of MDMA itself. Regardless of the origin of potential reactive oxygen species, neuroprotection against MDMA toxicity offered by spin trap agents, such as phenylbutyl nitrone (6) and antioxidants and sulfhydryl promoting agents (12) and the increased formation of stable adducts of hydroxyl radicals, viz., 2,3- dihydroxybenzoic acid, following MDMA treatment (7), further support the hypothesis that free radicals may contribute to MDMA-induced neurodegeneration of 5-HT terminals.

Other metabolites of MDMA also have been implicated as contributors to the mechanism of MDMA-induced neurotoxicity. Johnson et al. (17) and Elayan et al. (8) have demonstrated that 2,4,5-trihydroxymethamphetamine, a metabolite of MDMA, decreases the activity of hippocampal tryptophan hydroxylase, and this is accompanied by a decline in the concentration of 5-HT in the hippocampus. The hippocampal serotonergic system appears to be the most sensitive to the effect of this metabolite, and its selective localization in the serotonergic nerve terminal could explain the 5-HT depleting effects of MDMA.

In summary, MDMA produces an increase in the extracellular concentration of dopamine in the hippocampus, and this increased release of dopamine appears to originate from noradrenergic terminals. Although MDMA increases the extracellular concentration of dopamine in the hippocampus, the long-term depletion of 5-HT in this brain region produced by MDMA appears to involve dopamine independent mechanisms.

ACKNOWLEDGEMENTS

The technical assistance of Wenjun Zhu is gratefully acknowledged. This work was supported by USPHS DA07427.

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