3,4-Methylenedioxymethamphetamine Produces Glycogenolysis and Increases the Extracellular Concentration of Glucose in the Rat Brain

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ABSTRACT

Oxidative and/or bioenergetic stress is thought to contribute to the mechanism of neurotoxicity of amphetamine derivatives, e.g., 3,4-methylenedioxymethamphetamine (MDMA). In the present study, the effect of MDMA on brain energy regulation was investigated by examining the effect of MDMA on brain glycogen and glucose. A single injection of MDMA (10–40 mg/kg, s.c.) produced a dose-dependent decrease (40%) in brain glycogen, which persisted for at least 1 h. MDMA (10 and 40 mg/kg, s.c.) also produced a significant and sustained increase in the extracellular concentration of glucose in the striatum. Subjecting rats to a cool ambient temperature of 17°C significantly attenuated MDMA-induced hyperthermia and glycogenolysis. MDMA-induced glycogenolysis also was prevented by treatment of rats with the 5-hydroxytryptamine_2 (5-HT_2) antagonists 6-methyl-1-(1-methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1 methylpropyl ester maleate (LY-53,857; 3 mg/kg i.p.), desipramine (10 mg/kg i.p.), and iprindole (10 mg/kg i.p.). LY-53,857 also attenuated the MDMA-induced increase in the extracellular concentration of glucose as well as MDMA-induced hyperthermia. Amphetamine analogs (e.g., methamphetamine and parachloroamphetamine) that produce hyperthermia also produced glycogenolysis, whereas fenfluramine, which does not produce hyperthermia, did not alter brain glycogen content. These results support the conclusion that MDMA induces glycogenolysis and that the process involves 5-HT_2 receptor activation. These results are supportive of the view that MDMA promotes energy dysregulation and that hyperthermia may play an important role in MDMA-induced alterations in cellular energetics.

3,4-Methylenedioxymethamphetamine (MDMA), a ring-substituted amphetamine analog, is widely abused as a recreational drug, and there is concern that the drug may damage serotonergic nerve terminals (Green et al., 1995). MDMA-induced neurotoxicity of serotonergic nerve terminals in rodents and nonhuman primates is evidenced by several biochemical and immunocytochemical findings such as depletion of tissue concentration of 5-HT and its major metabolite, 5-hydroxyindoleacetic acid (Stone et al., 1986; Schmidt, 1987), decrease in the activity of the enzyme tryptophan hydroxylase (Schmidt and Taylor, 1987), reduction in the [³H]paroxetine-labeled 5-HT reuptake sites (Battaglia et al., 1987), and reduced immunostaining of 5-HT terminals (O'Hearn et al., 1988).

Although the exact mechanism involved in MDMA-induced 5-HT neurotoxicity remains to be elucidated, oxidative stress has been reported to play an important role in this process (Gudelsky, 1996; Colado et al., 1997; Shankaran et al., 1999a,b). MDMA increases the formation of hydroxy radicals (Colado et al., 1997; Shankaran et al., 1999a,b) and reduces the concentration of the endogenous antioxidants vitamin E and ascorbic acid (Shankaran et al., 2001). Furthermore, the administration of antioxidants prevents the MDMA-induced depletion of brain 5-HT (Colado and Green, 1995; Gudelsky, 1996; Shankaran et al., 2001).

In addition to the potential role of oxidative stress in MDMA neurotoxicity, there is evidence for a role of bioenergetic stress in the toxicity produced by amphetamine analogs. The concomitant administration of MDMA and the mitochondrial inhibitor malonate into the striatum has been shown to cause a significant reduction in 5-HT tissue concentration, whereas the local administration of either drug alone was ineffective (Nixdorf et al., 2001). Moreover, the administration of antioxidants prevents the MDMA-induced depletion of brain 5-HT (Colado and Green, 1995; Gudelsky, 1996; Shankaran et al., 2001).

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ABBREVIATIONS: MDMA, 3,4-methylenedioxymethamphetamine; PCA, parachloroamphetamine; ANOVA, analysis of variance; 5-HT, 5-hydroxytryptamine; LY-53,857, 6-methyl-1-(1-methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1 methylpropyl ester maleate.
ulate the neurotoxic effects of methamphetamine (Stephens et al., 1998).

There are also several reports that amphetamine analogs deplete brain glycogen, which is the single largest energy reserve of the brain and is localized primarily in astrocytes (Tsacopoulos and Magistretti, 1996). The systemic administration of amphetamine and parachloroamphetamine (PCA) has been shown to deplete brain glycogen in mice (Hutchins and Rogers, 1970) and rats (Heuther et al., 1997), respectively. In addition, Poblete and Azmitia (1995) have reported that MDMA activates glycogen phosphorylase, an enzyme responsible for the breakdown of glycogen, in astroglial-rich primary cultures.

In the present study, the effect of MDMA to promote glycogenolysis in brain tissue and increase the extracellular concentration of glucose in the striatum in vivo is documented. In addition, the roles of 5-HT 

Materials and Methods

Animal Procedures

Adult male rats (200–275 g) of the Sprague-Dawley strain (Charles River Breeding Laboratories, Portage, Canada) were used in the studies. The animals were housed three per cage in a temperature- and humidity-controlled room with a 12-h light/dark cycle and allowed food and water ad libitum. Animals undergoing surgery were housed one per cage postoperatively. All procedures were in strict adherence to the National Institutes of Health guidelines and approved by the Institutional Animal Care and Use Committee.

Chemicals, Drugs, and Drug Treatment

(±)-MDMA hydrochloride and (+)-fenfluramine hydrochloride were provided by the National Institute on Drug Abuse. LY-53,857, desipramine hydrochloride, (±)-PCA hydrochloride, and (+)-methamphetamine hydrochloride were obtained from Sigma-Aldrich (St. Louis, MO). Iprindole hydrochloride was obtained from Wyeth-Ayerst Pharmaceuticals (St. Davids, PA). All the drugs were dissolved in 0.15 M NaCl. NADP disodium salt, hexokinase, glucose-6-phosphate dehydrogenase, and amyloglycosidase were purchased from Roche Diagnostics Corp. (Indianapolis, IN). All reagents were prepared as described previously (Nahorski and Rogers, 1972).

Brain glycogen was determined 1 h following the administration of MDMA, methamphetamine, PCA, or fenfluramine, except in the experiment in which the time-dependent relationship of the effect of MDMA was determined. LY-53,857 (3 mg/kg, i.p.) was administered 30 min prior to the administration of MDMA, whereas desipramine (10 mg/kg, i.p.) and iprindole (10 mg/kg, i.p.) were administered 1 h prior to administration of MDMA. For the experiment in which rats were maintained at a cool ambient temperature, the animals were kept at 17°C for 2 h prior to and following the administration of MDMA.

Biochemical Measurements

Assay of Tissue Glycogen. Rats were killed by decapitation, and the brains were removed from the skull and immersed in liquid nitrogen within 10 s. The cerebellum was removed, and the brains were stored at −80°C until analysis. Procedures for the analysis of glycogen were similar to those described by Nahorski and Rogers (1972). Approximately 250 mg of brain tissue were weighed and homogenized in 3 ml of 0.03 N HCl at 0°C. The homogenate was placed in boiling water for 5 min. Assay tubes contained 300 μl of acetate buffer (pH = 4.6), 100 μl of the homogenate or glycogen standard, and 10 μl of amyloglycosidase or water. The tubes were vortexed and incubated at room temperature for 30 min. After incubation, 1.33 ml of Tris buffer (pH = 7.8), 0.66 ml of MgCl₂ (10 mM), 100 μl of ATP (2 mg/ml), and 10 μl of NADP (10 mg/ml) were added to each tube. The tubes were vortexed and subjected to centrifugation at 10,000g for 5 min. The supernatants were transferred to other tubes, and the fluorescence (excitation 350 nm/emission 460 nm) was measured in a fluorescence spectrophotometer (Model F-2000; Hitachi Instruments, Inc., Naperville, IL). Ten μl of hexokinase (1 mg/ml) and 10 μl of glucose-6-phosphate dehydrogenase (0.2 mg/ml) were then added, and the tubes were vortexed and incubated at room temperature for 30 min. The fluorescence was again measured. The difference in the fluorescence values was corrected for sample, reagent, and enzyme blank. Glycogen values are reported as glucose equivalents (micromoles per gram of tissue).

Glucose Assay. Glucose in the dialysis samples was assayed by using a modified method of the glycogen assay (Nahorski and Rogers, 1972). Assay tubes contained 1.33 ml of Tris buffer (pH = 7.8), 0.66 ml of MgCl₂(10 mM), 100 μl of ATP (2 mg/ml), 10 μl of NADP (10 mg/ml), and 20 μl of dialysate sample or glucose standard. The tubes were vortexed, and fluorescence of the sample was measured as described above. Ten μl of hexokinase (1 mg/ml) and 10 μl of glucose-6-phosphate dehydrogenase (0.2 mg/ml) were added, and the tubes were vortexed and incubated at room temperature for 30 min prior to fluorescence determination. Glucose values were reported as millimolar concentration.

In Vivo Microdialysis Procedures. Rats were implanted with a stainless steel guide cannula under ketamine/xylazine (70:6 mg/kg, i.m.)-induced anesthesia 48 to 72 h prior to the insertion of the dialysis probe. On the day of the dialysis experiment, a concentric style dialysis probe was inserted through the guide cannula into the striatum. The coordinates for the tip of the probe were A, 1.2 mm; L, 3.1 mm; and V, −7 mm from bregma, according to the stereotaxic atlas of Paxinos and Watson (1986). The microdialysis probes were constructed as described previously (Yamamoto and Pekhe, 1990). The dialysis surface of the membrane (SpectraPor; 6000 molecular weight cutoff and 210-μm outside diameter) for the striatum was 4.5 mm in length. On the day of the dialysis experiment, the probe was connected to an infusion pump set to deliver glucose-free Dulbecco’s phosphate-buffered saline containing 1.2 mM CaCl₂ at a rate of 1.8 μl/min. After a 2-h equilibration period, dialysis samples were collected every 30 min. At least three baseline samples were obtained prior to drug treatment.

Body Temperature Measurements. On the day of the experiment, the rats were allowed to acclimate at 24 or 17°C for 2 h before body temperatures were measured. Measurements of rectal temperature were made using a thermocouple and a thermister probe. The probe was lubricated with a small amount of petroleum jelly and inserted 5 cm into the rectum of each rat for at least 30 s until a stable temperature was obtained. LY-53,857 (3 mg/kg, i.p.) was administered 30 min prior to administration of MDMA (10 mg/kg, s.c.). Measurements were taken every 30 min for a 1-h period prior to administration of MDMA and for a 1.5-h period following the injection of the drug. The change in body temperature was determined by subtracting the body temperature at time 0 from the maximal body temperature recorded after MDMA administration.

Statistical Analysis

The effect of MDMA, methamphetamine, PCA, and fenfluramine on brain glycogen was analyzed with one-way ANOVA. The effects of cool ambient temperature and 5-HT₃ antagonists on MDMA-induced glycogenolysis were analyzed with two-way ANOVA. Glucose data from dialysis experiments were analyzed with two-way repeated-measures ANOVA. Multiple pairwise comparisons were performed using the Student-Newman-Keuls test. Treatment differences for all the data were considered statistically significant at p < 0.05.
Results

A time-dependent reduction in brain glycogen was evident following the systemic administration of MDMA (Fig. 1). Brain glycogen concentrations were reduced by 45% following the administration of MDMA (40 mg/kg, s.c.). Significant ($p < 0.05$) reductions in the brain concentration of glycogen were observed 30 min and 1 h after an injection of MDMA. Values for brain glycogen in rats 2 and 4 h after drug treatment did not differ significantly from those of vehicle-treated animals.

The dose dependence of MDMA-induced glycogenolysis is depicted in Fig. 2. Although brain glycogen concentrations were reduced significantly ($p < 0.05$) following the administration of each of the doses (10, 20, and 40 mg/kg, s.c.) of MDMA, the magnitude of the effect was greatest at 40 mg/kg (Fig. 2).

The extent to which MDMA induced glycogenolysis was dependent upon the ambient temperature at which the drug was administered. Maintenance of rats at 17°C for 2 h prior to the administration of MDMA markedly attenuated MDMA-induced glycogenolysis. Whereas the administration of MDMA (20 mg/kg, s.c.) resulted in a 25 to 30% reduction ($p < 0.05$) in the brain concentration of glycogen in rats maintained at 24°C, MDMA had no significant effect on brain glycogen in rats maintained at 17°C (Fig. 3). The alteration of ambient temperature alone did not significantly affect brain glycogen content.

The effects of 5-HT antagonists with high affinity for 5-HT$_2$ receptors on the reduction of brain glycogen by MDMA are shown in Fig. 4. Treatment of rats with LY-53,857 (3 mg/kg, i.p.), desipramine (10 mg/kg, i.p.), or iprindole (10 mg/kg, i.p.) resulted in a significant ($p < 0.05$) attenuation of the MDMA-induced reduction in the brain concentration of glycogen.

Although MDMA produced a significant ($p < 0.05$) reduction in the brain concentration of glycogen in LY-53,857- and iprindole-treated rats, the magnitude of the reduction was significantly ($p < 0.05$) less than that produced in the vehicle-treated controls. MDMA-induced glycogenolysis was com-
pletely abolished in desipramine-treated rats. Treatment with LY-53,857, iprindole, or desipramine alone did not significantly alter brain glycogen content.

Attenuation of MDMA-induced glycogenolysis by either a cool ambient temperature (17°C) or the 5-HT2 antagonist LY-53,857 was associated with a suppression of MDMA-induced hyperthermia. At an ambient temperature of 24°C, the administration of 10 or 20 mg/kg of MDMA increased the body temperature of rats by 1.1 and 1.4°C, respectively. (Table 1). Maintenance of rats at 17°C or treatment of rats with LY-53,857 (3 mg/kg, i.p.) completely prevented MDMA-induced hyperthermia.

The brain concentration of glycogen also was quantified following the administration of other amphetamine analogs. Methamphetamine (10 mg/kg, i.p.) and PCA (10 mg/kg, i.p.) produced significant ($p < 0.05$) reductions of 42 and 45%, respectively, in the brain concentration of glycogen. However, the administration of fenfluramine (10 mg/kg, i.p.) did not significantly alter brain glycogen content (Fig. 5).

In addition to the evaluation of the effects of MDMA on the brain concentration of glycogen, the effect of MDMA on the extracellular concentration of glucose in the striatum was investigated using in vivo microdialysis. The systemic administration of MDMA (10 or 40 mg/kg, s.c.) resulted in an immediate and sustained increase ($p < 0.05$) of 30 to 45% in the extracellular concentration of glucose in the striatum. (Fig. 6).

### TABLE 1
MDMA-induced hyperthermia in rats maintained at different ambient temperatures or treated with the 5-HT2 antagonist LY-53,857

<table>
<thead>
<tr>
<th>Treatment/Condition</th>
<th>Dose of MDMA (mg/kg)</th>
<th>Δ Body Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24°C</td>
<td>20</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>17°C</td>
<td>20</td>
<td>0.0 ± 0.4*</td>
</tr>
<tr>
<td>Exp. 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle + MDMA</td>
<td>10</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>LY-53,857 + MDMA</td>
<td>10</td>
<td>−0.3 ± 0.1*</td>
</tr>
</tbody>
</table>

* $p < 0.05$ for the comparison in Experiment 1 to rats treated with MDMA at 24°C or in Experiment 2 to rats treated with vehicle + MDMA.

![Fig. 4. Effect of 5-HT2 antagonists on MDMA-induced glycogen depletion.](image)

![Fig. 5. Effect of amphetamine analogs on the concentration of glycogen in brain.](image)

![Fig. 6. Effect of MDMA on the extracellular concentration of glucose in the striatum of rats.](image)
The extracellular concentration of glucose in the striatum remained elevated for at least 5 h following the administration of MDMA. In contrast, the perfusion of MDMA (100 μM) by reverse dialysis through the dialysis probe for 5 h did not significantly alter the extracellular concentration of glucose (Fig. 7).

Treatment of rats with LY-53,857 was used to assess the role of 5-HT2 receptors in the stimulatory effect of MDMA on extracellular glucose. Administration of LY-53,857 (3 mg/kg, i.p.) markedly attenuated (p < 0.05) the MDMA-induced increase in the extracellular concentration of glucose in the striatum (Fig. 8). The response of extracellular glucose in rats treated with LY-53,857 and MDMA did not differ from that in rats treated with LY-53,857 and vehicle. Administration of LY-53,857 alone did not significantly alter the extracellular concentration of glucose.

**Discussion**

In the present study, treatment with MDMA resulted in a dose- and time-dependent enhancement of glycogenolysis in the forebrain of the rat. The induction of glycogen breakdown elicited by MDMA is consistent with the effects of other amphetamine analogs on brain glycogen content. Both PCA and d-amphetamine have been reported to reduce brain glycogen content (Nahorski and Rogers, 1975; Nowak, 1988; Heuther et al., 1997). Poblete and Azmitia (1995) have reported that under in vitro conditions MDMA increases the activity of glycogen phosphorylase, the enzyme responsible for the breakdown of glycogen. Inasmuch as glycogen represents the primary energy source of the brain (Tsacopoulos and Magistretti, 1996), these results are consistent with the view that MDMA produces an acute decrease in the energy stores in the brain. Although much of the glycogen in the brain is stored in glia, it is not possible to conclude on the basis of the present results whether MDMA-induced glycogenolysis occurs in glia or neurons.

The systemic administration of MDMA also increased the extracellular concentration of glucose in the striatum. Although the effect of MDMA on brain glycogen was transient (i.e., less than 2 h) in nature, it is noteworthy that the MDMA-induced increase in the extracellular concentration of glucose was much longer in duration (i.e., greater than 5 h). Thus, it appears that a single injection of MDMA produces a prolonged effect on energy substrates in the brain.

It seems likely that the increase in extracellular glucose may be the result of the breakdown of brain glycogen. Alternatively, increased brain glucose could reflect an acute action of MDMA in the periphery to increase circulating blood glucose. However, MDMA did not increase peripheral blood glucose (data not shown).

Although MDMA produced a prolonged increase in the extracellular concentration of glucose, it is not possible to determine on the basis of the present data whether this response is reflective of an increased neuronal energy demand or simply a consequence of glycogen breakdown in glia. Amphetamine analogs have been reported to affect various indices of energy utilization. Stephens et al. (1998) reported that methamphetamine increases the extracellular concentration of lactate in the striatum. In addition, amphetamine analogs have been shown to affect ATP content, lactate, and concentrations of energy substrates (Nahorski and Rogers, 1973; LaManna et al., 1976; Sylvia et al., 1977; Chan et al., 1994; Huang et al., 1997). The ability of MDMA to promote glycogenolysis and increase the extracellular concentration of glucose could be viewed as one means of facilitating increased neuronal energy utilization. However, Wilkerson and London (1989), using 2-deoxy-[14C]glucose autoradiography, reported that MDMA had little effect on cerebral glucose utilization in the caudate putamen, although increases were noted in other brain regions. Inasmuch as the extent of 2-deoxy-[14C]-glucose uptake is thought to reflect neuronal activity, these data do not support the view that the MDMA-
induced increase in the extracellular concentration of glucose is indicative of increased glucose utilization.

In the present study, MDMA-induced glycogenolysis was attenuated in rats treated with the 5-HT₂ antagonist LY-53,857. Furthermore, two other drugs, viz., desipramine and iprindole, that exhibit affinity for 5-HT₂ receptors in the 100 to 200 nM range (Palvimaki et al., 1996) also antagonized the MDMA-induced decrease in brain glycogen content. Desipramine and iprindole were used in the present study in view of the findings of Quach et al. (1982), who reported that 5-HT itself induced glycogenolysis in cortical slices in vitro and that 5-HT-induced glycogenolysis was attenuated by desipramine and iprindole. It is not possible to exclude the possibility that the actions of desipramine involve the noradrenaline transporter in the present study. However, a commonality of LY-53,857, iprindole, and desipramine is relatively high affinity for the 5-HT₂ receptor. Although MDMA itself exhibits weak 5-HT₂ agonist activity (Nash et al., 1994), it seems reasonable to speculate that excessive 5-HT released by MDMA is the ligand responsible for the 5-HT₂ receptor-mediated induction of brain glycogenolysis.

It is well recognized that MDMA produces hyperthermia in the rat (Nash et al., 1988; Schmidt et al., 1990; Dafters, 1994), and that activation of 5-HT₂ receptors is thought to mediate the increase in body temperature produced by MDMA (Nash et al., 1988; Schmidt et al., 1990). Consistent with these aforementioned studies, the administration of the selective 5-HT₂ antagonist LY-53,857 attenuated MDMA-induced hyperthermia. Notably, LY-53,857 also attenuated the MDMA-induced decrease in brain glycogen and the increase in the extracellular concentration of glucose in the striatum. Thus, the possibility exists that 5-HT₂ receptors are involved indirectly in the mechanism of MDMA-induced glycogenolysis; 5-HT₂ receptors may not directly regulate glycogen formation/breakdown but rather modulate energy regulation through alterations in body temperature. In further support of this view is the present finding that maintenance of rats at a modestly cool ambient temperature (i.e., 17°C) prevented not only MDMA-induced glycogenolysis but also MDMA-induced hyperthermia. This finding is in agreement with the work of Nowak (1988), who reported that amphetamine-induced hyperthermia and glycogenolysis were less at 17 than at 27°C. Also consistent with a role of hyperthermia in the MDMA-induced alteration in energy regulation is the finding that the administration of MDMA via reverse dialysis into the striatum did not alter the extracellular concentration of glucose, whereas a significant increase was observed following the systemic administration of MDMA. Although the concentration of MDMA (100 μM) perfused into the striatum is sufficient to evoke dopamine and 5-HT release comparable with that produced by the systemic administration of the drug, the local perfusion of MDMA does not produce hyperthermia (Nixdorf et al., 2001). Thus, there appears to be an association between the propensity of MDMA to evoke hyperthermia and induce glycogenolysis. The association between the elicitation of hyperthermia and the induction of glycogenolysis is strengthened further by the finding that glycogenolysis also was enhanced by methamphetamine and PCA but not by fenfluramine. This is noteworthy inasmuch as methamphetamine and PCA, but not fenfluramine, elicit hyperthermia (Colado et al., 1997; Wallace et al., 2001). Thus, glycogenolysis is enhanced by amphetamine analogs (e.g., MDMA, methamphetamine, and PCA) that elicit hyperthermia but is unaltered by an analog (e.g., fenfluramine) that does not alter body temperature. Although the present data demonstrate an association between stimulant-induced hyperthermia and glycogenolysis, the nature of the neuron-glial interactions that underlie this interaction are not known.

The contribution of psychostimulant-induced hyperthermia to the long-term neurotoxic effects of these drugs is well recognized. Maintenance of rats at cold ambient temperature prevents not only MDMA-induced hyperthermia but also the long-term neurotoxic effects of MDMA on 5-HT axon terminals (Broening et al., 1995). In addition, many pharmacological agents that prevent MDMA-induced 5-HT neurotoxicity also attenuate the hyperthermic response to MDMA, and the blunting of the hyperthermic response may contribute to the mechanism of neuroprotection. However, the mechanism whereby hyperthermia exerts a permissive role in MDMA-induced neurotoxicity has not been elucidated. On the basis of the present results, it is tempting to speculate that MDMA-induced hyperthermia results in a reduction in brain energy stores that imparts a vulnerability to 5-HT neurons to further toxicological mechanisms. Heuther et al. (1997) have made a similar proposal.

Depletion of cellular energy stores that accompany MDMA-induced hyperthermia could exacerbate an already compromised cellular energetic state resulting from the continued activation of the 5-HT transporter and, subsequently, Na⁺/K⁺-ATPase. Ultimately, MDMA-induced energy impairment may result in ionic dysregulation, the accumulation of intracellular Ca²⁺, and, ultimately, Ca²⁺-mediated proteolytic damage to 5-HT terminals. Altered Ca²⁺-homeostasis also may contribute to the generation of free radicals and/or mitochondrial dysfunction. Thus, MDMA-induced hyperthermia and the accompanying disruption of cellular energetics may contribute to the processes of oxidative and bioenergetic stress that appear to mediate MDMA-induced 5-HT neurotoxicity.

References


serotonergic presynapses elicited by the consumption of 3,4-methylenedioxymethylamphetamine (MDMA, "ecstasy") and its congeners. J Neural Transm 104:771–794.
Shankaran M, Yamamoto BK, and Gudelsky GA (2001) Ascorbic acid prevents 3,4-methylenedioxymethamphetamine (MDMA)-induced hydroxyl radical formation and the behavioral and neurochemical consequences of the depletion of brain 5-HT. Synapse 40:65–64.

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