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## Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine

J. Frank Nash and Bryan K. Yamamoto

*Departments of Psychiatry and Neuroscience, School of Medicine, Case Western Reserve University, Cleveland, OH 44106–5000 (USA)*

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The effect of repeated administration of either methamphetamine (MA), 3,4-methylenedioxymethamphetamine (MDMA) or vehicle on the extracellular concentrations of glutamate (GLU), aspartate, taurine, dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), was studied in awake, freely moving rats using in vivo microdialysis. MA (7.5 mg/kg, i.p.) administered every 2 h for a total of 3 injections, increased the extracellular concentration of GLU in the anteromedial striatum. By contrast, neither vehicle nor MDMA (9.2 and 13.8 mg/kg) increased GLU efflux following repeated administration. Both MA and MDMA increased the extracellular concentration of DA in the striatum. However, the cumulative increase in DA was significantly greater in the MDMA treated animals as compared to the MA group. The concentrations of DA, serotonin (5-HT) and their metabolites were determined in the striatum 7 days following the repeated administration of MA, MDMA and vehicle. MA, but not MDMA or vehicle, decreased the concentration of DA in the striatum. Conversely, MDMA (13.8 mg/kg) decreased the concentration of 5-HT, whereas MA, MDMA (9.2 mg/kg) and vehicle had no effect on striatal 5-HT content. These data are suggestive that the long-term (7 day) DA neurotoxicity produced by the repeated administration of MA is mediated, in part, by a delayed increase in extracellular concentrations of GLU. In contrast, repeated administration of MDMA, at a dose which produced a long-term (7 day) depletion of striatal 5-HT content, had no effect on GLU efflux in the striatum.

### INTRODUCTION

Numerous studies have established that high dose, repeated administration of methamphetamine (MA) is toxic to dopamine (DA) and serotonin (5-HT) axon terminals in the brain (for review see ref. 36). Similarly, structurally related phenethylamines have been found to produce varying degrees of serotonergic and/or dopaminergic neurotoxicity<sup>21,25</sup>. For example, single or repeated administration of the methylenedioxy derivative of MA, 3,4-methylenedioxymethamphetamine (MDMA), has been reported to produce serotonergic neurotoxicity in rats<sup>26,34</sup> as well as in non-human primates<sup>12,14,30</sup>. However, unlike MA, there is no evidence that MDMA administration produces long-term DA neurotoxicity<sup>2</sup>. The mechanism(s) by which MA and related compounds damage DA and 5-HT axon terminals remains to be established.

The formation of DA autoxidation products such as 6-hydroxydopamine (6-OHDA) following high dose administration of MA has been suggested to mediate the neurotoxic effects of MA<sup>1,17,18,37</sup>. It has been hypothesized that MA produces a massive release of DA which can be oxidized non-enzymatically to form 6-OHDA or

other reactive species (i.e. quinones) resulting in localized damage to DA and/or 5-HT axon terminals<sup>1,17,18,37</sup>. A number of pharmacological studies are supportive of the 'DA hypothesis' regarding the neurotoxic effects of MA. For example, depletion of brain DA content following treatment with the tyrosine hydroxylase inhibitor  $\alpha$ -methylparatyrosine prior to the administration of MA, blocks the formation of 6-OHDA<sup>1</sup> and the ability of MA to diminish DA as well as 5-HT concentrations<sup>10,35</sup>. Moreover, administration of L-DOPA and a peripheral decarboxylase inhibitor restores the neurotoxic effects of MA in these animals<sup>35</sup>. Although an analogous mechanism has been proposed to explain the 5-HT neurotoxic effect of MDMA<sup>24,41</sup>, this hypothesis does not address the difference between MDMA and MA with respect to the long-term depletion of DA produced exclusively by MA administration.

Excitatory amino acids such as glutamate (GLU) have been shown to damage neurons using a variety of experimental approaches (for review see refs. 27 and 32). Given the widespread distribution of GLU in the central nervous system<sup>40</sup>, it has been suggested that overactivity of glutamatergic neurotransmission may result in cell death. Even more intriguing is the possibility that

endogenous excitatory amino acids may mediate neuronal death observed in a number of neurodegenerative disorders.

Based on the evidence that GLU is neurotoxic, it is not surprising that the excitatory amino acids have been implicated in the neurotoxic effects of both MA and MDMA<sup>8,13,39,42</sup>. For example, Sonsalla et al.<sup>39</sup> found that the non-competitive *N*-methyl-D-aspartate (NMDA) antagonist, MK-801, blocked the DA neurotoxicity produced by repeated administration of MA in mice. Similarly, the NMDA antagonist, dextrorphan, was reported to produce a dose-dependent inhibition of MDMA-induced 5-HT depletion in the striatum of rats<sup>8</sup>. However, the ability of GLU antagonists to block the neurotoxic effects of MDMA has not been as consistent a finding compared to studies with MA<sup>13</sup>. Regardless, these data are suggestive that GLU may mediate some of the neurotoxic effects of these phenethylamines.

The present study examined the effect of repeated administration of MDMA and MA on the extracellular concentrations of GLU and DA using *in vivo* microdialysis. In addition, the concentration of DA, 5-HT and their metabolites were determined in the striatum of the animals used in the dialysis experiments, 7 days following drug administration.

## MATERIALS AND METHODS

### Animals

Male Sprague-Dawley rats weighing 225–300 g were purchased from Zivic Miller Laboratory (Allison Park, PA) and used in all experiments. Animals were housed 2 per cage in a temperature controlled room (23°C) with a 12/12 h lighting schedule (lights on at 06.00 h). Food and water were available *ad libitum*.

### Drugs

The racemic mixture of MDMA hydrochloride was generously provided by the National Institute on Drug Abuse (Rockville, MD). Chloral hydrate, MA hydrochloride and the HPLC standards were purchased from Sigma Chemical Co. (St. Louis, MO). MDMA and MA were dissolved in saline and administered *i.p.*, every 2 h for a total of 3 injections (see Experimental procedure).

### Experimental procedure

In the first experiment, rats were anesthetized using chloral hydrate (400 mg/kg, *i.v.*) and placed in a stereotaxic frame. A concentric dialysis probe was implanted into the anteromedial striatum (A: 1.2, L: 2.0, V: -6.5, from bregma) according to the atlas of Paxinos and Watson<sup>28</sup>. The probe was secured using a skull screw and dental cement and flushed with a modified Ringer's solution (in mM: NaCl 145, Na<sub>2</sub>PO<sub>4</sub> 6, KCl 1.7, KH<sub>2</sub>PO<sub>4</sub> 1.0, CaCl<sub>2</sub> 1.2 at pH 7.4). The animals were placed in clear plastic cages with food and water available *ad libitum*.

On the following day, the dialysis probe was connected to an infusion pump set to deliver modified Ringer's solution at a rate of 1.7  $\mu$ l/min. Each rat was perfused for 2 h prior to the initiation of each experiment. Following this initial perfusion, baseline samples were collected every 30 min over a 2 h time period. MDMA (9.2 or 13.8 mg/kg), MA (7.5 mg/kg) or vehicle was administered following the last baseline sample and at 2 h intervals thereafter for a total of 3 injections. Dialysate samples were collected every 30 min

for 6 h and the concentration of DA and its metabolites were determined.

In a separate experiment, the effect of MDMA, MA or vehicle on the extracellular concentration of GLU, aspartate and taurine in the anteromedial striatum was determined. Animals were anesthetized with chloral hydrate (150 mg/kg, *i.p.*) and ketamine (50 mg/kg, *i.p.*) and a guide cannula was implanted dorsal to the brain surface overlying the striatum (A: 1.2, L: 2.0). Three days following implantation of the guide cannula, a dialysis probe was inserted through the guide cannula and connected to an infusion pump set to deliver perfusate at a rate of 2.0  $\mu$ l/min. Following a 2 h baseline period, MDMA, MA and vehicle were administered at the doses and times stated previously and dialysis samples were collected every 30 min for 6 h.

Following termination of the dialysis studies, the animals were returned to their home cages. One week later, the animals were sacrificed and each brain was mounted on a dissecting pedestal and immediately frozen with dry ice. A 100–150  $\mu$ m slice was obtained at the level of the dialysis probe and the contralateral striata was removed. The concentrations of DA, 5-HT and their metabolites were determined in the tissue slices using previously reported procedures<sup>23</sup>.

### Dialysis probes

A concentric-shaped dialysis probe was constructed as previously described by Yamamoto and Pehek<sup>43</sup>. The dialysis membrane extended 4.0 mm beyond the tip of the 26 gauge stainless steel tubing. The percent recovery of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) using these dialysis probes was 8, 15 and 17%, respectively at a flow rate of 1.7  $\mu$ l/min at room temperature (23°C). The relative recoveries of GLU, aspartate and taurine were 15, 18 and 16%, respectively.

### Biochemical measurements

The concentrations of DA, DOPAC and HVA were determined in dialysate samples using previously reported HPLC procedures<sup>22,25</sup>. Briefly, each sample (50  $\mu$ l) was injected onto a 3  $\mu$ m C18 column (Phenomenex; Rancho Palos Verdes, CA) connected to a LC-4B amperometric detector (Bioanalytical Systems, W. Lafayette, IN) equipped with a glassy carbon electrode set at a potential of 0.65 V relative to the Ag/AgCl reference electrode. A Hewlett-Packard (HP 3396A) integrator was used to quantitate the concentrations of DA and its metabolites in the dialysate samples.

The concentrations of GLU, aspartate, taurine and other amino acids were measured using previously reported procedures<sup>6</sup>. Briefly, dialysate samples (25  $\mu$ l) were pre-column derivatized with *o*-phthalaldehyde and 3-mercaptoethanol for 2 min prior to injection onto the HPLC column. The HPLC system was identical to that described above.

### Statistical analysis

The effect of MA, MDMA and vehicle on the extracellular concentrations of DA, DOPAC, GLU, aspartate and taurine were statistically analyzed using a repeated measures analysis of variance (ANOVA). The effect of MA, MDMA and vehicle on tissue content of DA and 5-HT was analyzed using a one way ANOVA. Comparisons between individual means were done by Scheffe's post-hoc test. In all cases, treatment effects were considered statistically significant at  $P < 0.05$ .

## RESULTS

### Effect of MA and MDMA on extracellular concentrations of GLU, aspartate and taurine

The effect of MDMA, MA and vehicle on the extracellular concentrations of GLU and aspartate is illustrated in Fig. 1A and B. The first injection of MA (7.5

mg/kg) had no effect on the extracellular concentration of GLU (Fig. 1A). Following the second MA injection, GLU efflux began to increase, and was elevated significantly ( $P < 0.05$ ) 120 min later as compared to vehicle and MDMA treated rats. GLU concentrations continued to increase following the third injection of MA and were maximal at the termination of the experiment as compared to vehicle and MDMA treated rats (Fig. 1A). By contrast, neither vehicle nor MDMA (9.2 and 13.8 mg/kg) significantly increased the extracellular concentrations of GLU as compared to their respective baseline levels. In addition, MDMA and vehicle treated rats did not differ from each other with respect to GLU efflux throughout the course of the experiment.

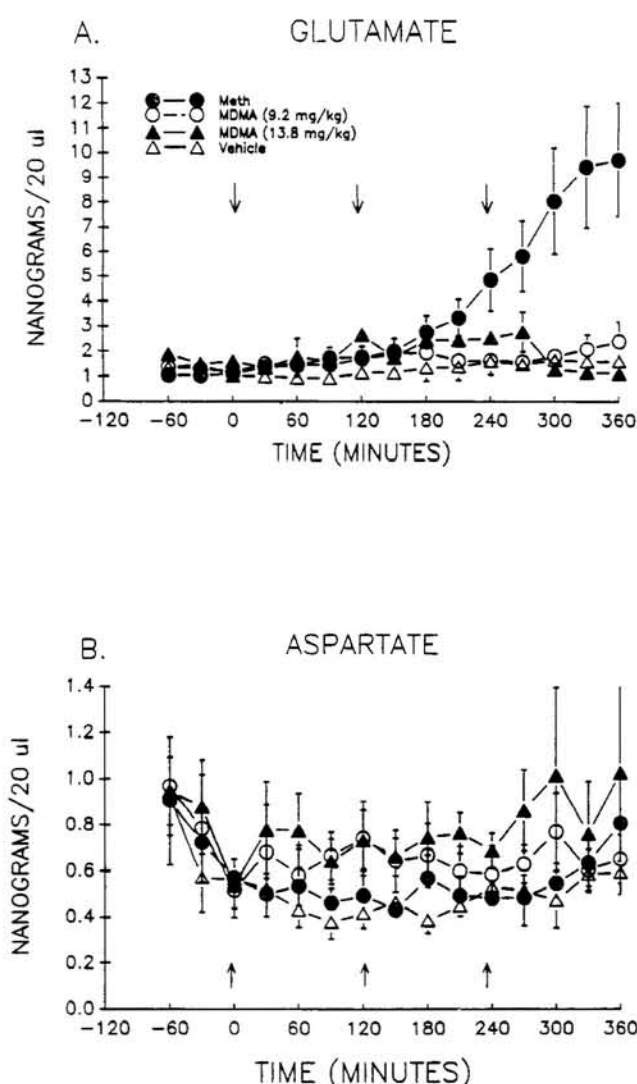


Fig. 1. Effect of repeated administration of methamphetamine (MA), 3,4-methylenedioxymethamphetamine (MDMA) and vehicle on the extracellular concentrations of glutamate (GLU) (A) and aspartate (B) in the striatum. Each value represents the mean  $\pm$  S.E.M. of 6 rats. MA (7.5 mg/kg), MDMA (9.2 or 13.8 mg/kg) or vehicle were administered every 2 h for a total of 3 injections as indicated by the arrow.

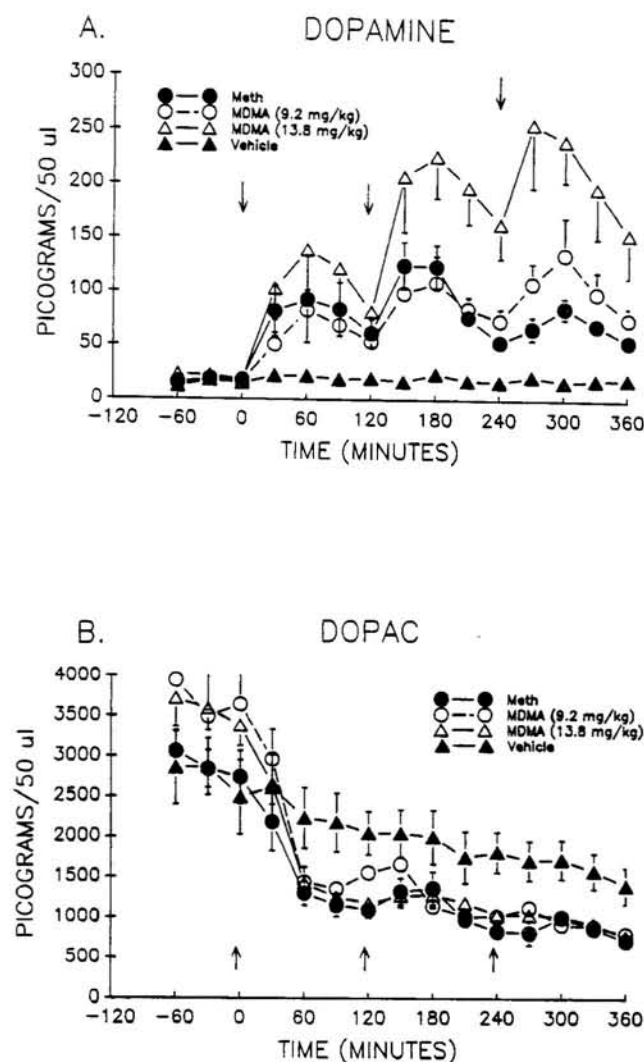


Fig. 2. Effect of repeated administration of MA, MDMA and vehicle on the extracellular concentrations of dopamine (DA) (A) and 3,4-dihydroxyphenylacetic (DOPAC) (B) in the striatum. Each value represents the mean  $\pm$  S.E.M. of 4-6 rats. MA (7.5 mg/kg,  $\bullet$ ), MDMA (9.2,  $\circ$ , or 13.8 mg/kg,  $\triangle$ ) or vehicle ( $\blacktriangle$ ) were administered every 2 h for a total of 3 injections as indicated by the arrows.

The extracellular concentration of aspartate was unaffected by the repeated administration of MA, MDMA and vehicle (Fig. 1B). There was no difference between the 4 treatment groups with respect to aspartate efflux. Similarly, neither vehicle nor the drugs used in these studies affected the extracellular concentration of taurine (data not shown).

#### Effect of MA and MDMA on the extracellular concentrations of DA and DOPAC

Consistent with a number of previous studies<sup>22,25,42,44</sup>, MA and MDMA administration increased the extracellular concentration of DA in the anteromedial striatum as illustrated in Fig. 2A. MA (7.5 mg/kg) significantly ( $P$

TABLE I

Effect of repeated administration of methamphetamine (MA), 3,4-methylenedioxymethamphetamine (MDMA) and vehicle on the striatal monoamine concentrations 7 days following administration

| Treatment | Dose | pg/ $\mu$ g protein |                   |                  |                |                |
|-----------|------|---------------------|-------------------|------------------|----------------|----------------|
|           |      | 5-HT                | 5-HIAA            | DA               | DOPAC          | HVA            |
| Vehicle   |      | 3.44 $\pm$ 0.42     | 4.47 $\pm$ 0.41   | 93.6 $\pm$ 3.9   | 22.3 $\pm$ 3.4 | 10.7 $\pm$ 1.4 |
| MA        | 7.5  | 3.33 $\pm$ 0.92     | 3.78 $\pm$ 0.78   | 67.7 $\pm$ 17.7* | 18.9 $\pm$ 4.1 | 8.1 $\pm$ 1.1  |
| MDMA      | 9.2  | 3.08 $\pm$ 0.68     | 3.95 $\pm$ 0.42   | 122.0 $\pm$ 15.5 | 28.8 $\pm$ 4.9 | 12.9 $\pm$ 2.2 |
| MDMA      | 13.8 | 1.88 $\pm$ 0.10*    | 3.38 $\pm$ 0.31** | 83.7 $\pm$ 4.3   | 18.9 $\pm$ 1.3 | 8.1 $\pm$ 0.5  |

Each value represents the mean  $\pm$  S.E.M. of 4–12 rats. The asterisks indicates a significant effect as compared to vehicle treated control.

\* $P < 0.05$  (two-tailed), \*\* $P < 0.05$  (one-tailed).

$< 0.05$ ) increased DA efflux following the first injection as compared to vehicle treated rats. The extracellular concentration of DA remained elevated throughout the entire experiment. MDMA (9.2 and 13.8 mg/kg) produced a dose-dependent increase in DA efflux (Fig. 2A). The increase in DA release following the first and second administration of MDMA (9.2 mg/kg) was identical to the response obtained in rats treated with an equimolar dose of MA. However, following the last injection of MDMA (9.2 mg/kg), the increase in DA was significantly ( $P < 0.05$ ) greater than that observed in the MA group (Fig. 2A). MDMA (13.8 mg/kg) produced a significantly ( $P < 0.05$ ) greater increase in DA efflux following the second and third injections as compared to MA, MDMA (9.2 mg/kg) and vehicle treated rats. As was the case with MA, extracellular concentrations of DA remained elevated following the administration of MDMA (9.2 and 13.8 mg/kg) throughout the experiment, as compared to baseline DA concentrations.

Both MDMA (9.2 and 13.8 mg/kg) and MA significantly ( $P < 0.05$ ) decreased the extracellular concentration of DOPAC as compared to vehicle treated rats (Fig. 2B). The concentration of DOPAC was maximally reduced 60 min following the first drug injection and did not return to baseline levels throughout the course of the experiment.

#### Striatal concentrations of DA, 5-HT and their metabolites 7 days following repeated administration of MA and MDMA

The post-mortem tissue content of DA, 5-HT and their metabolites was determined in the animals used in the dialysis studies, 7 days following drug administration. These values are presented in Table I. Repeated administration of MA (7.5 mg/kg) produced a significant ( $P < 0.05$ ) decrease in the concentration of DA in the striatum as compared to vehicle and MDMA treated rats. At the dose used in this study, MA (7.5 mg/kg) had no effect on the concentration of 5-HT and 5-HIAA in the

striatum. Repeated administration of MDMA (9.2 and 13.8 mg/kg) did not alter striatal DA content. However, the high dose of MDMA (13.8 mg/kg) significantly reduced the striatal concentrations of 5-HT and 5-HIAA as compared to vehicle, MA and MDMA (9.2 mg/kg) treated rats (Table I).

#### DISCUSSION

Repeated administration of MA increased the extracellular concentration of the endogenous excitatory amino acid, GLU, in awake, freely moving rats as measured by in vivo microdialysis. By contrast, repeated administration of an equimolar dose of MDMA had no effect on GLU efflux in the anteromedial striatum. Moreover, the administration of a higher dose of MDMA, which depleted striatal 5-HT content 7 days following administration, had no effect on GLU efflux. Although both MA and MDMA increased DA release, the cumulative effect of repeated administration of MDMA on the extracellular concentration of DA was significantly greater than that of MA. In the present study, MA significantly decreased the post-mortem tissue concentration of DA in the striatum, 7 days following repeated administration. Conversely, neither MDMA nor vehicle had an effect on DA content in the striatum. These data are suggestive that MA-induced GLU release may mediate the dopaminergic neurotoxic effects of this compound.

The ability of repeated MA administration to acutely increase the extracellular concentration of GLU in the striatum and decrease post-mortem tissue DA content, 7 days following administration, is consistent with the hypothesis that GLU plays a role in the neurotoxic effects of this compound. As stated previously, Sonsalla et al.<sup>39</sup> reported that MA-induced DA depletion in mice was blocked by the non-competitive NMDA antagonist, (+)MK-801. Similarly, MK-801 has been found to block MA-induced long-term decreases in tryptophan hydrox-



ylase activity in rats<sup>13</sup>. In contrast to MA, repeated administration of MDMA had no effect on extracellular GLU concentration or striatal DA content. Taken together, these data are suggestive that GLU release following repeated administration of MA may directly damage DA axon terminals.

There are at least 3 possible mechanisms by which MA administration increases GLU efflux in the present study. First, it is possible that MA directly stimulates the release of GLU in the striatum. However, to our knowledge there is no evidence to support a direct effect of MA on GLU efflux either *in vitro* or *in vivo*. Moreover, the increase in the extracellular concentration of GLU was greatest after the last injection of MA which is suggestive that MA does not directly stimulate GLU release. The second possibility is that GLU efflux increases as a result of DA disinhibition. That is, MA-induced DA efflux was attenuated after the third injection as compared to the first 2 DA responses (Fig. 2A). Since DA agonists have been reported to inhibit potassium stimulated GLU release *in vivo*<sup>45</sup> and from striatal slices<sup>33</sup> and synaptosomes<sup>9,19</sup>, it is possible that MA-induced GLU release is the result of a decrease in DA inhibition following the third injection of MA. Moreover, the ability of MDMA to maintain high extracellular concentrations of DA coupled with the lack of effect on GLU efflux is additional inferential evidence which supports this hypothesis. Finally, the increase in GLU may be a compensatory response to the decline in extracellular DA concentration produced by MA administration which is independent of any disinhibition. This hypothesis is based on the findings that GLU stimulates DA release from rat striatal slices<sup>3,5,31</sup>, *in vitro* as well as *in vivo*<sup>38</sup>. However, in the present study the increase in extracellular GLU was not accompanied by an increase in extracellular DA concentration which would be predicted based on this hypothesis. It should be noted that the studies described in this manuscript do not directly test any of these hypotheses. Therefore, the mechanism by which MA increases GLU efflux requires much more study.

In the MDMA treated rats, DA efflux was increased to the same extent by each subsequent drug injection. If DA serves to inhibit GLU release, as suggested in the preceding paragraph, then the ability of MDMA to maintain an elevated extracellular concentration of DA throughout the entire experiment may account for its lack of an effect on GLU efflux. Alternatively, MDMA-induced 5-HT release may result in an inhibition of GLU release. For example, 5-HT inhibits the release of endogenous GLU in potassium stimulated cerebellum synaptosomes<sup>29</sup> and brain slices<sup>20</sup>. Regardless, the lack of an effect of MDMA on GLU efflux and long-term (7 day) DA neurotoxicity clearly illustrates a difference be-

tween these structurally related compounds.

The tolerance or tachyphylaxis observed in the MA treated rats with respect to DA release did not occur in rats treated with MDMA. This difference is inferential evidence that MA and MDMA affect DA transmission via different mechanisms. It is hypothesized that MA releases DA primarily from cytosolic stores and that the slight activation of tyrosine hydroxylase produced by MA cannot restore this pool of DA following repeated administration. In contrast, MDMA stimulates tyrosine hydroxylase activity as evaluated by an increase in DOPA accumulation following decarboxylase inhibition<sup>24</sup>. This serves to replenish the supply of DA, and therefore may not affect subsequent DA efflux after repeated administration. In addition, studies in our laboratory are suggestive that MDMA affects not only cytosolic but also vesicular stores of DA (Nash, unpublished data).

If MA-induced increase in GLU is, in part, responsible for the DA neurotoxicity, the question remains why are DA terminals selectively damaged? GLU is reported to be an axon-sparing neurotoxin<sup>27,32</sup>. Yet high dose MA administration has selective effects on DA axon terminals without decreasing gamma-aminobutyric acid or cholinergic markers of neurotoxicity in the striatum<sup>11</sup>. One possibility is that MA-induced DA release increases the metabolic burden of these DA axon terminals making them more vulnerable to the effects of GLU. In fact, NMDA type GLU receptors have been reported to be localized on DA nerve terminals<sup>16</sup> and could presumably mediate the excitotoxic effect of GLU on the presynaptic element via an increase in  $Ca^{2+}$  influx. This is an attractive hypothesis since it would account for the well known finding that  $\alpha$ -methylparatyrosine blocks the long-term neurotoxic effect of MA on DA axon terminals<sup>1,10</sup>. Regardless, the GLU-mediated selectivity of MA-induced toxicity for terminals over cell bodies requires further study.

The repeated administration of the high dose of MDMA used in this study produced a significant decrease in the striatal concentration of 5-HT, 7 days following administration. In contrast, MA (7.5 mg/kg) had no effect on striatal 5-HT content which agrees with the results of Kovachich et al.<sup>15</sup>. MDMA produced a dose-dependent increase in DA efflux in the striatum similar to previous studies<sup>22,44</sup>. The cumulative increase in extracellular DA concentration produced by the 13.8 mg/kg dose of MDMA was significantly greater than that produced by MDMA (9.2 mg/kg) and MA (7.5 mg/kg). In addition, the DA response to the low dose of MDMA and MA was quite similar and neither drug had an effect on 5-HT levels. Thus, these data are consistent with the hypothesis that MDMA-induced 5-HT depletion is,

in part, mediated by an acute increase in the extracellular concentration of DA.

The results presented herein are preliminary with regard to the neurotoxic mechanism(s) of MA and as such should be interpreted cautiously. Nevertheless, these data are the first direct evidence that repeated administration of MA increases GLU efflux in the striatum. Given the preponderance of data implicating DA in the neurotoxic effects of MA<sup>1,10,35</sup>, the mechanistic interaction between DA and GLU in MA toxicity remains to be established. However, it has been reported that the neurotoxic effects of NMDA, kainic acid and ibotenic acid in the striatum are, in part, dependent on an intact nigrostriatal pathway since 6-OHDA lesions of this circuit greatly reduce the neuronal damage produced by these compounds<sup>4,7</sup>. In addition, the inability of MDMA to increase the extracellular concentration of GLU coupled with its lack of effect on striatal DA content, 7 days following administration, is inferential evidence that in-

creasing GLU results in DA neurotoxicity. In any event, these data raise a number of important issues which require further study.

In conclusion, both MA and MDMA are known psychostimulants with potent DA-releasing properties and neurotoxic effects on DA and/or 5-HT neurons. The present data provide evidence that the mechanisms of their neurotoxic effects are different. MA may exert an excitotoxic effect on DA and 5-HT neurons via a direct or indirect effect on GLU efflux whereas MDMA-induced toxicity to primarily 5-HT neurons is mediated by an increase in DA release.

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