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Acute Effects of 3,4-Methylenedioxymethamphetamine (MDMA) on Monoamines in Rat Caudate

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GOUGH, B., S. F. ALI, W. SLIKKER, JR. AND R. R. HOLSON. *Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on monoamines in rat caudate.* PHARMACOL BIOCHEM BEHAV **39**(3) 619–623, 1991.—Extracellular levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and serotonin (5-HT) were assayed in the caudate of freely moving rats using microdialysis and high performance liquid chromatography with electrochemical detection (HPLC-EC) to detect changes in their release. Dialysates were assayed at 20-minute intervals for four hours after an intraperitoneal (IP) injection of MDMA (10 mg/kg). In a separate study to determine MDMA effects on total caudate levels of the above neurochemicals, animals were injected IP with MDMA (10 mg/kg) and then sacrificed at 20, 60, 120 and 180 minutes after treatment. Brains were quickly removed, and caudate nuclei were dissected for neurochemical analysis using HPLC-EC. MDMA elicited an amphetamine-like increase in DA release, followed by an increase in DA content. DOPAC and HVA were both reduced in homogenate. 5-HT release was also increased, followed by a drop in caudate homogenate levels by three hours. DA extracellular content was 686% of control at 80 minutes; caudate homogenate levels were 122% at 120 minutes. 5-HT extracellular release was 123% at 20 minutes, then decreased thereafter. It is concluded that the acute effect of MDMA on caudate is at least as great on the DA as it is on the 5-HT system.

MDMA Cerebral microdialysis Dopamine Serotonin Caudate nucleus

THE amphetamines and their analogs constitute a large and growing family of substances with high potential for human abuse. It is thus of particular concern that most of these substances, including amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and parachloroamphetamine (PCA) possess varying degrees of toxicity towards the serotonin system in the brain, at least in experimental animals at high doses. Since MDMA is currently among the most commonly abused of the above compounds, it is especially important to determine the mechanism of the widely reported serotonergic toxicity of this popular recreational drug.

An understanding of the mechanisms of MDMA neurotoxicity depends upon our knowledge of the acute effects of this compound on the brain. There have already been several reports of acute MDMA effects on striatal content of monoamines and their metabolites (6, 8, 9, 14, 15, 19–23). Most reports agree that, in rats, a single dose of not less than 10 mg/kg of racemic MDMA will lower caudate serotonin (5-HT) content within three hours of administration (6, 13, 15, 19, 22, 23). These reports disagree as to whether this 5-HT depletion is preceded by a brief rise in caudate content of serotonin (19,22), but there is unanimity concerning a concomitant monotonic drop in caudate content of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin (14, 15, 19, 22, 23).

Neostriatal levels of dopamine (DA) and its metabolites (DOPAC and HVA) are also affected acutely by MDMA. Within a few hours of a single MDMA injection, DA levels are elevated (8, 9, 15, 22, 23, 25) or unchanged (14), while DOPAC levels are reduced (8, 9, 14, 15, 22, 23, 25). Paradoxically, while DOPAC is decreased, HVA levels are enhanced (14, 15, 22, 23).

Release studies in synaptosomes (10) and in striatal slices (7, 13, 14) agreed that MDMA triggers an efflux of 5-HT, accompanied by a less substantial release of dopamine. These in vitro findings have recently been supported by reports of MDMA-stimulated release of caudate dopamine, as measured either by voltametry (25) or microdialysis (5). This last study also measured extraneuronal levels of DOPAC, 5-HIAA and HVA in caudate dialysate. Consonant with findings in homogenates, dialysate levels of DOPAC and 5-HIAA were reduced by MDMA. However, MDMA also decreased HVA levels (25), contrary to reported effects of MDMA on caudate tissue levels of HVA (see above). Due to problems with detection sensitivity, neither of these recent in vivo studies was able to measure MDMA effects on 5-HT release.

This study was conducted to further assess MDMA effects on caudate release and metabolism of monoamines and their

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major metabolites. In vivo cerebral microdialysis was used to quantify the effects of a single 10-mg/kg injection of racemic MDMA in conscious female rats. Sensitivity of this system was adequate for measurement of serotonin content of dialysate. Study objectives included replication of the single literature report of MDMA effects using microdialysis, determination of in vivo MDMA effects on caudate release of serotonin and of MDMA effects on HVA levels in dialysate, and comparison of drug effects on microdialysate to those in tissue homogenates.

METHOD

Brain Dialysis and HPLC Assay

Female Sprague-Dawley rats (NCTR breeding colony, 250–300 g) were housed two per cage and maintained in a temperature (22–24°C)- and humidity (40–60%)-controlled room with a 12-hour alternating light/dark cycle. They were allowed free access to standard laboratory food and water. To implant the microdialysis guide cannula, animals were anesthetized with sodium pentobarbital (50 mg/kg IP) and placed into a stereotaxic frame (Köpf, Topanga, CA). The level dorsal skull surface was exposed, and a small hole was drilled to allow implantation of the intracerebral guide cannula (Carnegie Medicine, Stockholm, Sweden) in the caudate. Coordinates were AP 0.2 mm; Lat 3 mm; DV 6.5 mm relative to bregma (11). The guide cannula was fixed to the skull of the rat with dental acrylic and two anchor screws. Body temperature during surgery and recovery from anesthesia was maintained at 37°C with a small heating pad (Deltaphase Isothermal Pad, Braintree Scientific, Braintree, MA) under the animal. To avoid effects of anesthesia and to allow recovery from surgical trauma, the dialysis experiments were started no sooner than three days after surgery. On the morning of the test, the animal was hand-held, and the dialysis probe was inserted through the guide cannula and into the underlying caudate. Microdialysis probes used in this study were CMA/10 (Bioanalytical Systems, West Lafayette, IN) and measured 14 mm in length and 0.65 mm in diameter. The membrane tip was 2.0 mm by 0.5 mm. The probes had an in vitro recovery efficiency of between 13 and 18% at a flow rate of 1.0 μl/min. Ringers solution [147 mM Na^+; 2.3 mM Ca^+; 4 mM K^+; 155.6 mM Cl (12); pH 6.2] was perfused at a flow rate of 1.0 μl/min using a CMA/100 microinjection pump (Carnegie Medicine, Stockholm, Sweden). Animals undergoing testing were housed in an awake animal system (20 in. diameter, 12 in. deep glass bowl with balancing arm) with wire tether and single channel swivel. Dialysates were collected at 20-minute intervals into 250-μl conical tubes. After stable baseline values for catecholamines were established (usually two hours), animals were injected with MDMA (10 mg/kg, IP). Controls for injection effect were not included, since pilot studies could detect no effect of saline injection on dialysate levels of monoamines or their metabolites at 20-min collection intervals.

The dialysates were assayed for DA, DOPAC, 5-HIAA, 5-HT and HVA by HPLC-EC (BAS 460 system; Bioanalytical Systems, West Lafayette, IN) using a Phase-II cartridge column (BAS, 100 × 3.2 mm, 3 micron). The mobile phase consisted of 0.15 M monochloric acetic acid, 0.86 mM sodium octyl sulfate, 0.67 mM EDTA, and 2.5% acetonitrile, pH 3.0. Flow on the column was 1.0 ml per minute at 40°C with an electrode operating at an applied voltage of 0.8 V. Retention time for elution of all compounds under investigation was less than 10 minutes; each sample was assayed immediately after collection to prevent decomposition. Pilot studies in rat and monkey showed that, in our system, 3MT formed a separate peak and did not coelute with serotonin.

Levels of neurotransmitters in the caudate were monitored for at least five hours after MDMA treatment. Animals were then sacrificed by overdose of anesthesia, and brains were removed and fixed in formal saline. Each fixed brain was sectioned from the anterior tip to the probe position and examined to confirm probe position.

Caudate Homogenate and HPLC Assay

Female Sprague-Dawley rats (NCTR breeding colony, 250–300 g) were housed as previously described. Twelve animals were treated with vehicle (physiological saline), and 28 were dosed with MDMA (10 mg/kg, IP). At 20, 60, 120 and 180 minutes after treatment, 3 controls and 7 MDMA-treated animals were killed by decapitation. Brains were quickly removed, and the caudate nucleus was dissected, frozen over dry ice and stored at 70°C. Each caudate was later assayed for neurotransmitter levels by the method outlined by Ali et al. (1). Briefly, tissues were weighed and diluted with a measured volume (1:5, w/v) of 0.1 N perchloric acid. The cells were then disrupted by ultrasonication for 15 seconds in a conical tube which was immersed in a small ice bath. Cell debris was removed by centrifugation of the sonicate at 10,000 × g, for 10 minutes at 4°C. The supernatant was then filtered in the cold (4°C) through a 0.45-micron microfilter (MF-1 microcentrifuge filter, BAS, West Lafayette, IN). Aliquots of the filtrate were injected directly onto an HPLC-EC system for separation of monoamines and their metabolites.

The mobile phase consisted of 0.15 M monochloric acetic acid, 0.5 mM octyl sodium sulfate, 4.5% acetonitrile and 1.2% tetrahydrofuran, pH 3.0. Separation of the compounds was accomplished on a BAS 460 liquid chromatograph using a Biophase ODS column, 250 × 4.6 mm, 5 micron. The mobile phase flow rate was 0.7 ml/min with an applied electrode voltage of 0.8 V.

Statistics

All microdialysis data were converted to percent of individual baseline (e.g., for microdialysis, the levels obtained after two consecutive 20-minute periods of stable values), then analyzed with a repeated-measures ANOVA. If the overall effect of time was significant at $\alpha = 0.05$, then post hoc comparisons between baseline and subsequent time points were conducted using paired *t*-tests. (Paired *t*-tests are required due to the repeated-measures nature of this analysis.)

For the caudate homogenate experiment, three vehicle control animals were killed at each of the four time points. One-way ANOVA across time points for these controls gave no significant effect of time for DA, 5-HT, or any metabolites. Consequently, these 12 caudates were pooled as a "time zero" control. Changes over time (0, 20, 60, 120 and 180 minutes after MDMA) were then assessed with a standard one-way ANOVA, followed by Duncan's Multiple Range tests for post hoc comparisons when the overall ANOVA was significant at $p < 0.05$.

RESULTS

Administration of MDMA at 10 mg/kg produced significant alterations in catecholamines in the caudates of female rats. These changes, seen in both extracellular dialysate and tissue homogenate samples, were more pronounced in the extracellular fluid than in the whole-tissue homogenate samples.

MDMA triggered a pronounced increase in dopamine content of dialysate, $F(9,55) = 2.75$, $p < 0.02$. DA values increased sharply to 148% of control values within 20 minutes after treatment and reached a maximum increase nearly seven-fold above control

values 80 minutes after treatment; DA then decreased to near control levels at 180 minutes after treatment (Fig. 1A).

Microdialysate concentrations of DOPAC and HVA, the major metabolites of dopamine, decreased significantly after MDMA exposure [DOPAC, $F(9,56) = 15.91$, $p<0.0001$; HVA, $F(9,56) = 3.72$, $p<0.0017$]. DOPAC and HVA decreased to 63% and 64% of control values at 80 and 120 minutes, respectively, after treatment, then showed only partial recovery at 180 minutes after treatment (Fig. 1B,C).

Serotonin levels increased, $F(9,52) = 4.02$, $p<0.01$, to levels 4.5 times control 80 minutes after treatment, then decreased rapidly to less than half of control 180 minutes after exposure (Fig. 2A). The overall MDMA-stimulated increase in 5-HT never quite reached significance, since some animals peaked 20 min earlier than others. Maximal rise above baseline (irrespective of timing of that rise) was 232%, and this rise was significant by a paired t-test, $t(5) = 2.6$, $p<0.05$. A small decrease was also noted for 5-HIAA (Fig. 2B); however, this did not attain statistical significance, $F(9,56) = 2.01$, $p<0.0618$.

In caudate nucleus homogenates, DA increased to 122% of control at 120 minutes after treatment (Fig. 1A), but this change again did not reach statistical significance, $F(4,35) = 2.50$, $p<0.06$ (Fig. 1A). DOPAC and HVA both decreased in caudate homogenates after MDMA treatment (Fig. 1B,C). The decrease in DOPAC was significant, $F(4,35) = 11.72$, $p<0.0001$, whereas the decrease in HVA did not reach statistical significance, $F(4,35) = 1.70$, $p<0.173$. DOPAC decreased to 59% of control and HVA decreased to 76% of control 60 minutes after treatment. DOPAC and HVA levels showed a partial recovery by 180 minutes after exposure (Fig. 1A,B).

Serotonin showed distinct changes in caudate homogenate samples. Serotonin increased to 123% of control 20 minutes after MDMA exposure, then decreased to 72% of control at 180 minutes after treatment (Fig. 2A). These changes in 5-HT were significant over time, $F(4,35) = 3.35$, $p<0.0201$. The metabolite 5-HIAA increased sharply to 160% of control 20 minutes after treatment, then steadily decreased to 69% of control 180 minutes after treatment (Fig. 1B). The changes in 5-HIAA did not prove to be significant over time, $F(4,35) = 1.16$, $p<0.3436$.

Analysis of metabolite-to-neurotransmitter ratios in caudate homogenates are shown in Table 1. The DOPAC/DA ratio decreased significantly at the earliest time point (20 minutes), remaining at that value thereafter. The HVA/DA ratio showed a similar but less pronounced trend. This ratio was significantly lower than control at 60, 120 and 180 minutes after injection.

The ratio of 5-HIAA/5-HT was 3.03 ± 0.58 at zero time and 2.71 ± 0.48 at 180 minutes after treatment. The ratio changes seen in 5-HIAA/5-HT were not significant at any time after treatment.

DISCUSSION

Extracellular neurotransmitter levels are believed to directly reflect release; such released neurotransmitters are subject to rapid degradation, accounting for the very low levels of neurotransmitter and the high level of their metabolites in dialysates. [Parenthetically, the low levels of DA and 5-HT in caudate dialysates also account for the high standard errors seen in this and other experiments (5); these levels are near current HPLC resolution limits.] Conversely, tissue levels of neurotransmitter are much less labile, and increased content generally reflects increased synthesis. Consequently, the relative magnitude of such changes is substantially lower than for dialysates, while actual concentrations are much higher. Given these differences between the two techniques, those experiments showed relatively good agreement between effects of MDMA on dialysates and on tis-

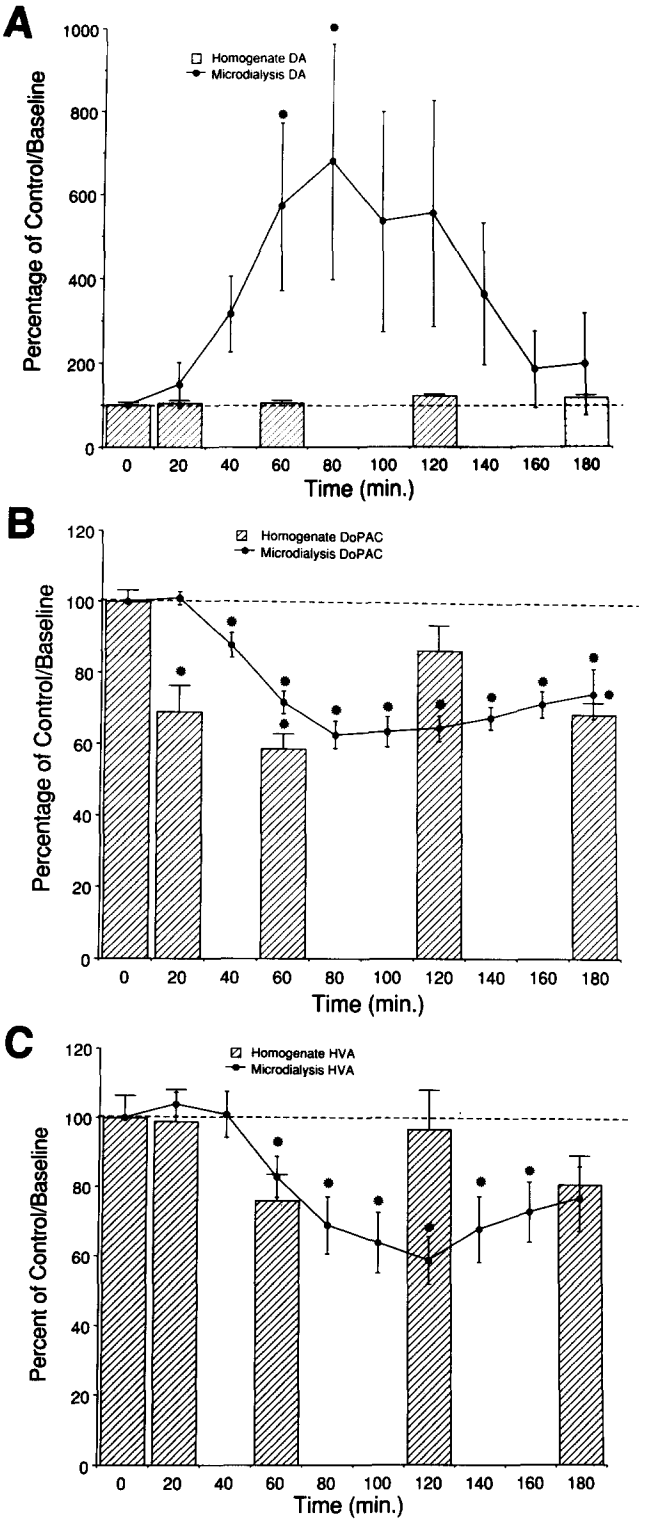

FIG. 1. MDMA-induced changes in dopamine and metabolites. Lines represent results for dialysate; bars represent content of caudate homogenate. Both are shown as percentage of respective baseline or control, ±SEM. *Indicates that points are significantly different from control/baseline. (A) Dopamine. Control values for homogenate were 22.7 ng/mg; for dialysate, baseline content was 14.6 pgm/10 μl. (B) DOPAC. Control values for homogenate were 2.01 ng/mg; for dialysate, baseline content was 776 pgm/10 μl. (C) HVA. Control values for homogenate were 1.12 ng/mg, for dialysate, baseline content was 936 pgm/10 μl.

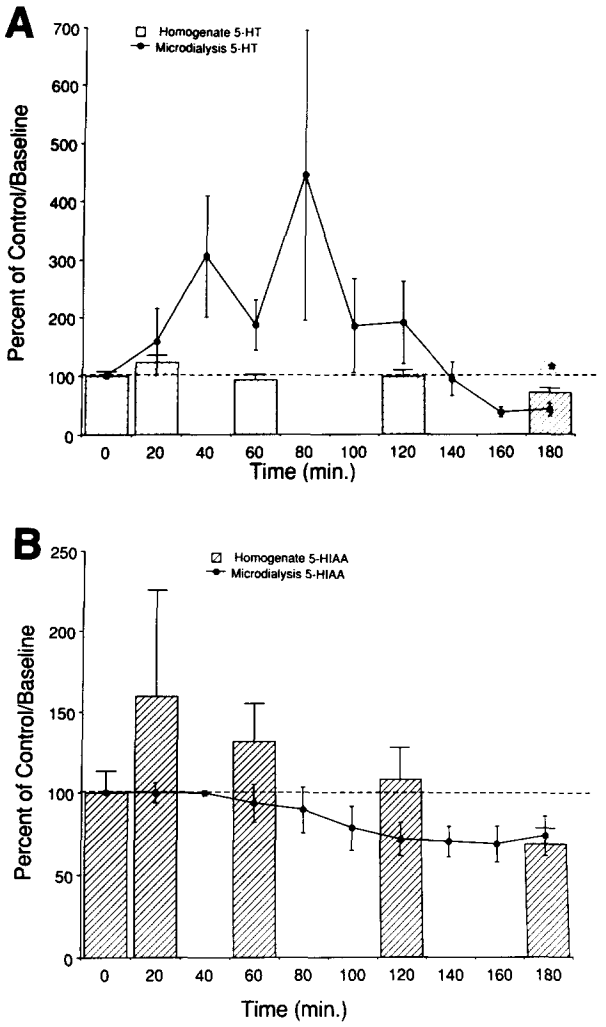

FIG. 2. MDMA-induced changes in serotonin and metabolites. Line represents results of microdialysis; bars represent content of caudate homogenate. Both are shown as percentage of baseline/control, ±SEM. *Indicates points that are significantly different from respective control/baseline. (A) Serotonin. Control values for homogenate were 1.35 ng/mg; dialysis baseline content was 28 pgm/10 μl. (B) 5-HIAA. Control values for homogenate were 0.036 ng/mg: dialysate baseline content was 636 pgm/10 μl.

sue monoamine concentrations. In either case, MDMA had an amphetamine-like effect, enhancing release of dopamine and serotonin, while blocking formation of their major metabolites (4, 12, 16, 18, 26, 27). p-Chloroamphetamine, another amphetamine analog with serotonin-specific neurotoxicity, also is reported to have similar amphetamine- or MDMA-like effects on caudate release of dopamine and serotonin (17). However, there were interesting differences in the time course of these drug effects in caudate homogenates as compared to dialysates. Dopamine levels in homogenates peaked considerably later than in dialysates, an effect that might be attributed to enhanced DA synthesis following MDMA-induced release. Serotonin levels, on the other hand, showed a small peak in homogenates at 20 minutes, well before the maximum rise in dialysate levels. This initial spike in serotonin tissue content was also reported by Stone and colleagues (22). Although not significant, tissue content of 5-HIAA also showed an early increase not seen in dialysates. Further, by three hours, serotonin levels in both dialysates and homogenates had fallen below baseline, unlike dopamine levels. Both the early serotonergic response to MDMA in homogenates and the late depletion may be indicative of the selective serotonergic toxicity seen in rats at MDMA doses in the range used in this study (14, 15, 19, 22).

In comparing these findings to other published reports, it is evident that our single 10-mg/kg MDMA dose did not deplete caudate serotonin levels at three hours in our rats to the 40–50% reported by two other laboratories (14, 15, 19, 22, 23) at the same MDMA dose. These differences may be attributable to strain differences in sensitivity to MDMA. Thus Logan et al. (8) failed to obtain a sizeable decline in serotonin levels three hours after a 25-mg/kg dose and also attributed this failure to strain differences. Even larger differences in MDMA sensitivity exist between mice and rats (8,19).

These results certainly demonstrate that MDMA acutely has similar amphetamine-like effects on both dopaminergic and serotonergic neurotransmitters in the neostriatum. Yet high doses of methamphetamine are toxic to both serotonergic and dopaminergic nerve endings (2, 3, 24), while MDMA toxicity is restricted to the serotonin system. The differences between these closely related drugs may be a function of the relative magnitude of drug-elicited serotonin and dopamine release. In caudate slices, MDMA release of serotonin is reportedly greater than for dopamine (13,10). While such comparisons are difficult with the techniques used here, the fact that only serotonin was depleted at three hours in these experiments could indicate that MDMA has a greater depleting effect on 5-HT than on DA in vivo as in vitro. If so, this might also suggest that acute depletion is nec-

TABLE 1

METABOLITE/NEUROTRANSMITTER RATIOS IN CN HOMOGENATE ARE DECREASED FOR DA BUT NOT 5-HT

	Time Post-MDMA (minutes)				
	0	20	60	120	180
DOPAC/DA	9.05 ± 0.47* (12)	5.68 ± 0.38† (7)	5.0 ± 0.28† (7)	6.36 ± 0.66† (7)	5.24 ± 0.29† (7)
HVA/DA	4.98 ± 0.29 (12)	4.54 ± 0.28 (7)	3.50 ± 0.25† (7)	3.89 ± 0.46† (7)	3.33 ± 0.24† (7)
5-HIAA/5-HT	3.03 ± 0.58 (12)	3.09 ± 1.05 (7)	3.72 ± 0.63 (7)	2.84 ± 0.26 (7)	2.71 ± 0.48 (7)

*Mean ± SEM.
‡Indicates significant difference from time 0.
Numbers in parentheses indicate the number of animals in each group.

essary for long-term toxicity of amphetamine analogs.

In summary, several conclusions may be drawn from these findings. First, these experiments demonstrate that the acute effect of MDMA in the caudate is similar to that of amphetamine. Second, it is possible that there are substantial differences between rat strains to MDMA serotonergic toxicity, although this conclusion is based on circumstantial evidence and awaits direct demonstration with several rat strains in a single laboratory. Finally, it is possible that differences between methamphetamine and MDMA toxicity are a function of their relative effects on dopamine and serotonin release. This possibility is currently under investigation.

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