Effects of 3,4-Methylenedioxyamphetamine and 3,4-Methylenedioxymethamphetamine Isomers on Central Serotonergic, Dopaminergic and Nigral Neurotensin Systems of the Rat[1]

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ABSTRACT

This study demonstrates that the isomers of 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) are different in their ability to induce changes in serotonergic parameters and nigral concentrations of neurotensin-like immunoreactivity. With five successive doses (3.5 mg/kg) the *d*-MDA isomer was more potent than the *l*-MDA in its ability to decrease the concentrations of serotonin in the frontal cortex and hippocampus. The same difference occurred in the ability to decrease the hippocampal activity of tryptophan hydroxylase as well as the hippocampal and neostriatal 5-hydroxyindoleacetic acid concentrations. However, both isomers of MDMA were equipotent in their ability to decrease serotonergic parameters in the brain areas examined. When the doses were increased to 5 and 10 mg/kg, both isomers of MDA were equipotent in their effects on the serotonin system, whereas the *l*-MDMA was significantly less potent than its *d* isomeric counterpart in causing a decrease in serotonergic parameters of the different brain areas. In contrast, treatments with any of the isomers appeared to have a minimal impact on neostriatal dopaminergic parameters. However, treatment with MDA or MDMA caused increases in the nigral concentrations of neurotensin, with the *d* isomer of both compounds having substantially greater effects on this neuropeptide system. These increases are suspected to result from drug-released dopamine. This study demonstrates that at selected doses, the *d* isomers of MDA and MDMA are more potent than their *l* forms in affecting neurochemical systems, whereas high doses of either isomer of MDA share a common ability to induce changes in the serotonergic system that are likely associated with neuronal damage.

Although MDA was first synthesized at the beginning of the century, only recently has it been shown that its potency as a serotonergic neurotoxin is similar to that of PCA, another amphetamine-related compound (Ricaurte *et al.*, 1985; Stone *et al.*, 1986a). Treatment with high concentrations of PCA produces a dramatic depletion in TPH activity and 5-HT concentrations (Sanders-Bush *et al.*, 1975), decreases the rate of 5-HT uptake for at least 90 days (Sanders-Bush *et al.*, 1975; Sanders-Bush and Steranka, 1978), and produces selective neuronal degeneration in the serotonergic system (Harvey, 1978; Massari *et al.*, 1978). Similar neuronal changes have been reported 2 wk after treatment with multiple toxic doses of MDA (Ricaurte *et al.*, 1985). Recently, the N-methyl analogue of MDA, MDMA, has also been shown to produce changes in central TPH activity and 5-HT concentrations (Schmidt *et al.*, 1986; Stone *et al.*, 1986a). Destruction of 5-HT nerve terminals produced by this compound appears to be similar to that induced by MDA (O'Hearn *et al.*, 1986).

Some biochemical and psychotomimetic effects of MDA and MDMA appear to be stereoselective. For example, *d*-MDA is a more potent stimulant than its *l* isomer, whereas the *l* isomer of MDA is the most potent hallucinogen (Marquart *et al.*, 1978a,b). In humans, the *l*-MDA isomer is considered a more effective psychotomimetic agent than its *d* counterpart (Anderson *et al.*, 1978); however, the N-methylation of MDA removes the hallucinogenic properties of this compound (Shulgin and Nichols, 1978), and the *d* form of the resulting drug, MDMA, becomes the most potent form (Anderson *et al.*, 1978). As demonstrated with PCA, the neurotoxic properties of amphet-

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ABBREVIATIONS: DOPAC, dihydroxyphenylacetic acid; DA, dopamine; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; HVA, homovanillic acid; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; METH, methamphetamine; NT, neurotensin; NTLI, neurotensin-like immunoreactivity; PCA, *p*-chloroamphetamine.

amine-related compounds can also be stereoselective (Sekerke *et al.*, 1975).

Despite the reports of preferential behavioral effects by the isomers of MDA and MDMA, there has been little investigation of these amphetamine-like analogues on the central nervous transmitter systems. In the present study, the effects of the isomers of MDA and MDMA on monoaminergic and neuropeptidergic systems of the rat brain have been evaluated. We assessed and compared the changes induced by *d*- and *l*-MDA and MDMA on 1) the activities of TPH and TH, the biosynthetic enzymes of 5-HT and dopamine respectively; 2) the concentrations of 5-HT, dopamine, and their major metabolites, and 3) the nigral concentrations of NT, whose pathway is regulated by monoaminergic systems (Letter *et al.*, 1987).

Methods

Treatment and dissection. Male Sprague-Dawley rats (180–250 g) were housed six per cage in a room with controlled lighting (12-hr light/dark cycle) and temperature (24°C). They had access to food and water *ad libitum*. The animals were given five doses of either isomer of MDA or MDMA (3.5, 5, or 10 mg/kg s.c., expressed in terms of the free base) at 6-hr intervals and decapitated 18 hr after the last injection. The brain was quickly removed and placed on a cold plate. Frontal cortex, neostriatum, and hippocampus were removed, frozen on dry ice, and stored at −80°C until used for evaluation of monoaminergic systems. The bilateral substantia nigras were excised from frozen sections using an extra-fine dissecting scalpel, pooled, and stored frozen as above until assayed for NT.

Determination of monoaminergic parameters. Frontal cortex, hippocampus, and neostriatum were separately homogenized in 80, 200, and 125 μl, respectively, of 50 mM HEPES buffer (pH 7.4) containing 0.2% (v/v) Triton X-100 and 5 mM dithiothreitol. After centrifugation at 40,000 × *g* (4°C) for 15 min, duplicate 7.5-μl aliquots were removed and assayed for TPH activity by a modified CO_2-trapping procedure as described by Hotchkiss *et al.* (1979). Aliquots (10 μl) from homogenized neostriatum were assayed for TH activity according to the method of Nagatsu *et al.* (1964) after dilution to 50 μl with glass-distilled water; *dl*-6-methyl-5,6,7,8-tetrahydrobiopterin was used as cofactor.

Contralateral brain tissues were used to measure the concentrations of dopamine, 5-HT, and their metabolites, DOPAC, HVA, and 5-hydroxyindoleacetic acid using high-performance liquid chromatography and electrochemical detection (model LC-4B, Bioanalytical Systems, West Lafayette, IN) according to a modification of the method described by Nielsen and Moore (1982). Briefly, tissues were weighed, homogenized in 0.3–0.5 ml mobile phase buffer (0.15 M monochloroacetic acid buffer, 2 mM EDTA, 0.1 mM 1-octanesulfonic acid sodium salt, and 12.5% methanol, pH 2.9), centrifuged at 4,000 × *g* for 15 min (4°C). The supernatant fractions were filtered with a 0.2-μm Microfilter system (Bioanalytical Systems), and 50 μl were injected onto a 10-cm Microsorb reverse-phase column (Rainin Instrument, Woburn, MA). The eluent was monitored using a glassy carbon electrode with a potential set at +0.73 V (*vs.* Ag/AgCl reference electrode). Tissue levels were quantitated by comparison with standards of known concentration.

Determination of nigral NT concentrations. Nigral tissues were homogenized in 0.3 ml 0.01 N HCl in 12 × 75-mm silanized glass tubes with a Ultra-Turrex homogenizer (Tekmar, Cincinnati, OH) for 15 sec, and 20 μl were removed for protein determination (Bradford, 1976). The homogenate was heated in boiling water for 10 min, after which the samples were centrifuged 30 min at 4,000 × *g*, and the resulting supernatant was removed for lyophilization. Samples were reconstituted in 0.5 ml phosphate-buffered saline with 0.1% gelatin (0.1 M monobasic sodium phosphate, 0.9% sodium chloride, and 0.1% sodium azide, pH 7.4). NT concentrations were determined by radioimmunoassay as previously reported (Letter *et al.*, 1987). The concentrations are expressed as picograms per milligram protein of NTLI. The NT specific antiserum was prepared in our laboratory by Dr. Anita A. Letter (see Letter *et al.*, 1987).

Materials. The *d*-3,4-methylenedioxyamphetamine hydrochloride, *l*-3,4-methylenedioxyamphetamine hydrochloride, *d*-N-methyl-3,4-methylenedioxyamphetamine hydrochloride, and *l*-N-methyl-3,4-methylenedioxyamphetamine hydrochloride were generously supplied by the National Institute on Drug Abuse (Rockville, MD). The *dl*-6-methyl-5,6,7,8-tetrahydrobiopterin was purchased from Sigma (St. Louis, MO).

Statistical analysis. All results were analyzed by a one-way analysis of variance with a Student-Newman-Keuls multiple comparisons test with the level of significance set at $P < .05$.

Results

Effects of MDA and MDMA isomers on 5-HT concentrations in frontal cortex, hippocampus, and neostriatum. At some doses, the *d* isomers of MDA and MDMA were more potent in their ability to decrease central nervous system concentrations of 5-HT than their respective *l* isomers. As shown in figure 1, this difference in potency between the MDA isomers is apparent only with the 3.5 mg/kg treatment in the frontal cortex and hippocampus, whereas the discrepancy between the two isomers of MDMA is significant with the 5 and 10 mg/kg doses in all brain areas examined. The lower dose of the isomer of each drug produced a significant decrease of 5-HT concentrations in the hippocampus (59–85% of control) and in the neostriatum (68–90% of control) while only the *d* isomer of MDA significantly decreased the transmitter concentration in the frontal cortex (78% of control). Usually, the injection of higher doses of the isomers (5 or 10 mg/kg) induced greater decreases in 5-HT concentrations in a dose-dependent fashion. At these higher doses (5 and 10 mg/kg), the difference in potency between the MDA isomers observed at the 3.5 mg/kg dose disappeared, whereas the *l* isomer of MDMA was significantly less potent than its *d* isomer in all three tissues.

Effects of MDA and MDMA isomers on brain 5-HIAA concentrations. The effects of the isomers of MDA and MDMA on 5-HIAA concentrations were very similar to the effects of these isomers on 5-HT concentrations. Figure 2 illustrates that the hippocampi and neostriata from rats treated with the *d*-MDA isomer (3.5 mg/kg) contained a lower concentration of 5-HIAA than rats treated with *l*-MDA. This was also true for *d*-MDMA in the hippocampus. The treatments with 5 and 10 mg/kg *d*-MDA, *l*-MDA, and *d*-MDMA similarly decreased the 5-HIAA concentration in the three brain areas examined, reaching 29–30% of control with the 10 mg/kg dose in a dose-dependent fashion. At these higher doses, the *l* isomer of MDMA was significantly less potent than its *d* isomer in all brain regions.

Effects of the MDA and MDMA isomers on TPH activity. A difference in the ability of MDA isomers to decrease TPH activity was observed in the hippocampus of rats treated with the 3.5 mg/kg dose, whereas a difference between the two isomers of MDMA was detectable in the three brain structures after either the 5 or 10 mg/kg treatment (figure 3). At the lower dose, *d*-MDMA was the only isomer to decrease the TPH activity in the frontal cortex. At this same dose, only the MDA isomers significantly decreased the hippocampal and neostriatal TPH activity, with the *d*-MDA isomer being more potent than the *l*-MDA in the hippocampus. At the higher doses, the *d*-MDA, *l*-MDA, and *d*-MDMA were relatively equipotent in causing the decrease in enzymatic activity. This decrease was

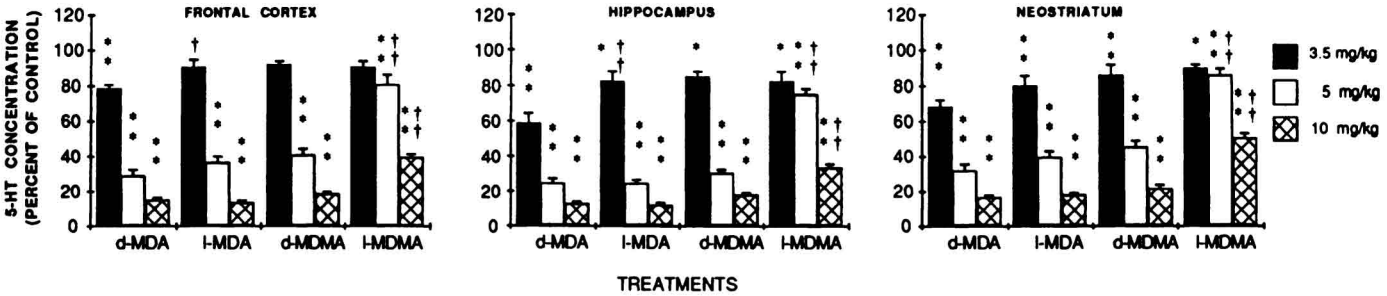

Fig. 1. Effects of MDA and MDMA isomers on 5-HT concentrations within frontal cortex, hippocampus, and neostriatum. The different isomers of MDA or MDMA (3.5, 5, or 10 mg/kg s.c.) were administered for five doses at 6-hr intervals, and animals were killed 18 hr later. Results are expressed in percentage of control values (saline treatment) and represent means ± S.E. of 6–18 rats/group. Actual control values for the 10 mg/kg treatment follow: frontal cortex, 0.61 ± 0.02 μg/g tissue; hippocampus, 0.36 ± 0.01 μg/g tissue; neostriatum, 0.56 ± 0.02 μg/g tissue. *P < .05, **P < .01 *vs.* respective control; †P < .05, ††P < .01 *vs.* corresponding *d* isomer group.

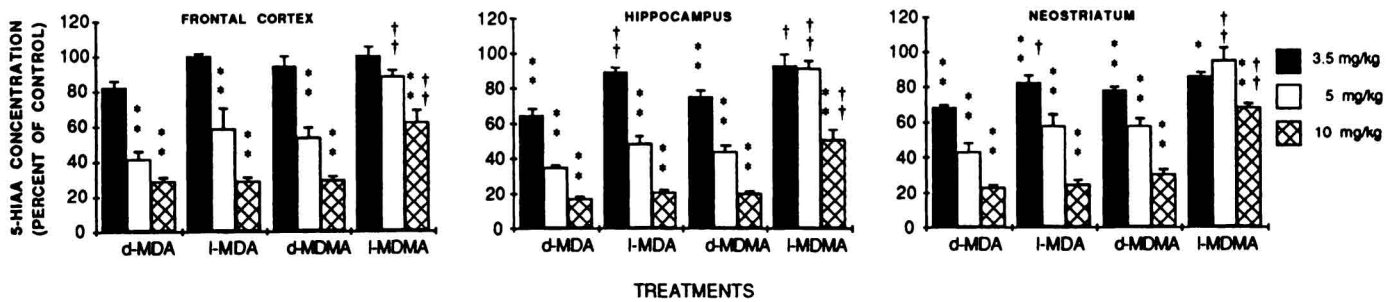

Fig. 2. Effects of MDA and MDMA isomers on 5-HIAA concentrations within frontal cortex, hippocampus, and neostriatum. Treatment protocol is the same as described in figure 1. Results are expressed in percentage of control values (saline treatment) and represent means ± S.E. of 6–18 rats/group. Actual control values for the 10 mg/kg treatment follow: frontal cortex, 0.21 ± 0.01 μg/g tissue; hippocampus, 0.36 ± 0.02 μg/g tissue; neostriatum, 0.53 ± 0.02 μg/g tissue. *P < .05, **P < .01 *vs.* respective control; †P < .05, ††P < .01 *vs.* corresponding *d* isomer group.

dose-dependent except in the hippocampus where the 5 and 10 mg/kg doses diminished the enzyme activity to the same extent. In all brain areas studied, the *l* isomer of MDMA was less potent than the *d* isomer.

Effects of MDA and MDMA isomers on the dopaminergic parameters of the neostriatum. In contrast to the changes produced in the serotonergic system, the different isomers had only a modest effect on the neostriatal dopaminergic system (table 1). The TH activity remained unaffected by any dose of the drugs used. The dopamine concentrations were unaltered by the 3.5 mg/kg doses, whereas the 10 mg/kg dose of *d*-MDMA slightly decreased the concentration of this catecholamine to approximately 85% of control. Neither MDA isomer changed the DOPAC concentrations, whereas the 3.5 mg/kg treatment with the MDMA isomers slightly decreased the concentration of this metabolite. This change did not occur with higher doses except for *l*-MDMA, which increased DOPAC concentrations after the 5 mg/kg treatment. HVA concentrations remained unaffected after the 3.5 mg/kg treatment, whereas treatment with 5 mg/kg of the *l* isomer of either drug produced approximately a 30% increase. However, such increases occurred with the MDMA isomers only after treatment with the highest dose treatment.

Effects of MDA and MDMA isomers on nigral neuropeptide concentrations. The data presented in figure 4 demonstrate that the *d* forms of MDA and MDMA were more potent than their *l* isomers in their ability to induce changes in concentrations of nigral NTLI. The nigral concentrations of NTLI were increased to 227 and 292% of control after treatment with 3.5 and 10 mg/kg *d*-MDA, respectively, whereas treatment with *d*-MDMA at either dose increased NTLI concentrations to about 210% of control (fig. 4). The lower dose of *l*-MDA isomer did not change the nigral NTLI concentration, whereas treatment with 10 mg/kg increased the concentration to 173% of control. However, the *l* isomer of MDMA had no significant effect on the NTLI concentration at either concentration.

Discussion

The results presented in this study suggest that the effects of the *d* isomer of MDA on central nervous system transmitter systems are greater than its *l* counterpart, although this stereoselectivity appears to be lost at higher doses. In contrast, *d*-MDMA is more potent than its *l* isomer only at high doses (5 and 10 mg/kg). The greater potency of the *d* isomeric form of these designer drugs is characteristic of amphetamine-related compounds. Thus, the *d*-isomer of amphetamine induces greater locomotion (Scheel-Krüger, 1972; Thornburg and Moore, 1972; Franklin and Robertson, 1980), causes greater stereotypic behavior (Scheel-Krüger, 1972), releases more 5-HT (Holmes and Rutledge, 1976), produces a more exaggerated 5-HT syndrome (Sloviter *et al.*, 1980), and decreases neostriatal DA concentrations further (Steranka, 1981) than the *l* form of this drug. As previously mentioned, behavioral studies also demonstrate that the *d* isomer of MDA is the most effective form for inducing stereotypic behavior and locomotion (Marquardt *et al.*, 1978a; Marquardt *et al.*, 1978b). However, *l*-MDMA is more potent than its *d* counterpart in its ability to decrease neostriatal 5-HT concentrations 3 hr after a single administration (Schmidt *et al.*, 1987). The present study suggests that the *d* isomers of MDA and MDMA induce greater changes associated with the neurotoxic properties of these drugs than their *l* counterparts, although this is dependent on the

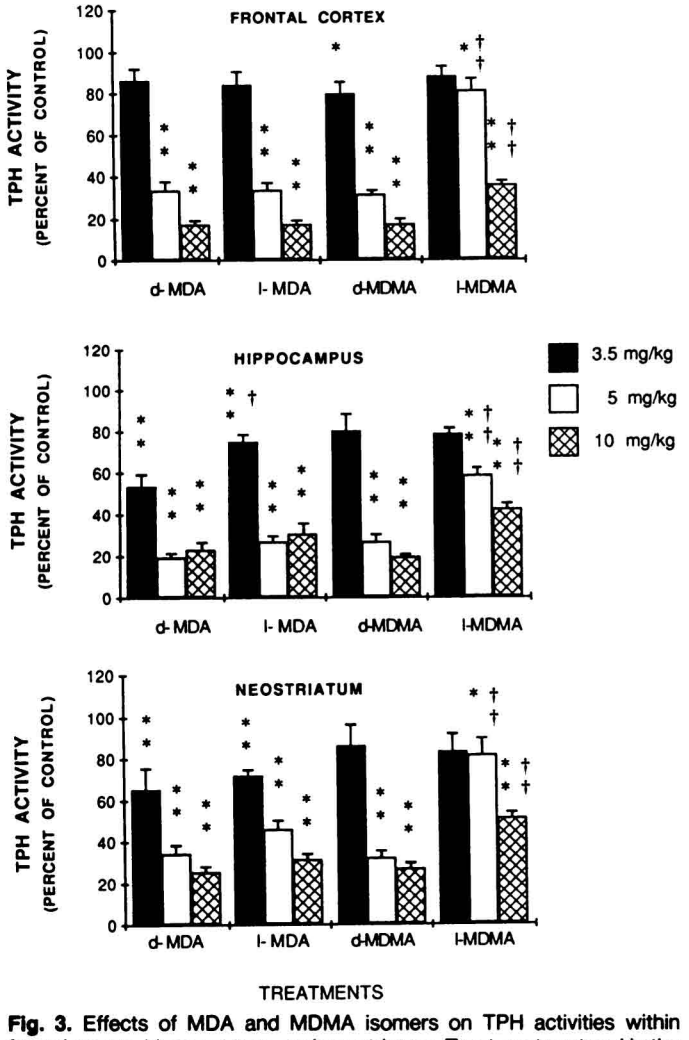

Fig. 3. Effects of MDA and MDMA isomers on TPH activities within frontal cortex, hippocampus, and neostriatum. Treatment protocol is the same as described in figure 1. Results are expressed in percentage of control values (saline treatment) and represent means ± S.E. of 6–18 rats/group. Actual control values for the 10 mg/kg treatment follow: frontal cortex, 66.5 ± 1.9 nmol tryptophan oxidized/hr/g tissue; hippocampus, 54.5 ± 2.9 nmol tryptophan oxidized/hr/g tissue; neostriatum, 49.5 ± 2.4 nmol tryptophan oxidized/hr/g tissue. *$P < .05$, **$P < .01$ *vs.* respective control; †$P < .05$, ††$P < .01$ *vs.* corresponding *d* isomer group.

dose used and the brain structure studied. Moreover, because the *l* isomer is thought to be the hallucinogenic form of MDA (Anderson *et al.*, 1978), this study also suggests that the hallucinogenic component of MDA is not associated with the reduction of the central serotonergic parameters by this compound.

The effects of the individual isomers of MDA and MDMA observed in this study are similar to those caused by their respective racemic mixtures (Stone *et al.*, 1986a). Multiple injections of *dl*-MDA or *dl*-MDMA (10 mg/kg) produce long term decreases in the serotonergic parameters that are likely the consequence of drug-related neurotoxicity (Stone *et al.*, 1987). These similarities between the changes observed 18 hr and 2 wk after a multiple dose treatment suggest that the changes observed in the serotonergic system in the present experimental conditions reflect the neurotoxic effects of these isomers. Previous findings demonstrate that *dl*-MDMA is slightly less potent than *dl*-MDA. The present study explains this difference by demonstrating the lower potency of *l*-MDMA in affecting the serotonergic parameters when injected at 5 or 10 mg/kg while the *d* and *l* forms of MDA are equipotent. The absence of a difference between the MDA isomers in affecting the serotonergic system after a high dose indicates that this drug is less dependent than MDMA on isomeric forms to induce neurotoxicity. This confirms the recent observation of Schmidt (1987) who reported that MDA loses its stereoselectivity for inducing neurotoxicity at higher doses.

The mechanism by which these amphetamine-related compounds decrease the central serotonergic parameters is not yet understood. Decreases in 5-HIAA concentrations may be related to the decrease in 5-HT concentrations that in turn are influenced by TPH activity and the drug-induced release. Because a single injection of *dl*-PCA or multiple injections of *dl*-METH or *dl*-MDA produce a decrease of 5-HT uptake associated with degeneration of 5-HT nerve terminals (Ricaurte *et al.*, 1980; Ricaurte *et al.*, 1985; Sanders-Bush *et al.*, 1975), the decreases in the serotonergic parameters observed in the present study are also assumed to result from neurotoxicity. Since the effects of MDMA, METH, or PCA on the serotonergic parameters are prevented by the blockade of the 5-HT uptake carrier, it is assumed that a toxic compound must be taken up into the neuronal terminal by this carrier to produce the neuronal changes (Fuller *et al.*, 1975; Hotchkiss and Gibb, 1980; Schmidt and Gibb, 1985a; Schmidt and Lovenberg, 1986). The amphetamine-related compounds do not seem to be the toxic agents because they diffuse freely into the neuronal terminals without the aid of an uptake system (Fuller and Snoddy, 1979; Ross and Ask, 1980; Schmidt and Gibb, 1985b; Schmidt *et al.*, 1987). However, there is significant evidence that dopamine is involved in the decrease of 5-HT parameters after single or multiple injections of METH (Commins and Seiden, 1986; Hotchkiss and Gibb, 1980; Johnson *et al.*, 1987; Schmidt *et al.*, 1985). Dopamine also appears to play a role in the toxic effects of MDA and MDMA on the serotonergic system (Stone *et al.*, 1986b).

Unlike METH (Hotchkiss and Gibb, 1980), multiple injections of MDA or MDMA have a minimal impact on the dopamine parameters 18 hr after the last injection (table 1); however, the increase in nigral NT concentrations provides evidence that both MDA and MDMA still affect the dopaminergic system *in vivo*. These increases in nigral NTLI concentrations are dependent on dopamine release, as demonstrated with METH treatment (Letter *et al.*, 1987), and the alteration of nigral concentrations of this peptide by *d*-MDA, *l*-MDA, and *d*-MDMA suggests that these drugs release enough dopamine to affect other transmitter systems. Interestingly, *l*-MDMA, which is the least potent isomer to induce changes in the serotonergic system, did not affect the NT levels at either the low or high doses. Thus, the changes in the NT system parallel those observed in the serotonergic system.

The dramatic effect of MDA and MDMA on the nigral NT pathway shows several patterns of response by this system. First, the *d* isomers of both drugs are significantly more effective than their *l* counterparts in increasing nigral NTLI levels. Second, for MDA, the changes induced in NTLI concentration were dose-dependent, whereas with MDMA, this did not appear to be the case. Third, the data suggest that MDA is more effective than MDMA in elevating nigral NTLI levels at the higher doses. Because the *l* isomer of MDA is the hallucinogenic form of the amphetamine-like compound, just as for other hallucinogenic substances (Anderson *et al.*, 1978), the present

TABLE 1

Effects of MDA and MDMA isomers on neostriatal TH activity and DA, DOPAC, and HVA concentrations

Dose	Treatments				
	Control	*d*-MDA	*l*-MDA	*d*-MDMA	*l*-MDMA
mg/kg			*μmol/h/g tissue*		
TH					
3.5	2.99 ± 0.17 (6)	2.59 ± 0.26 (6)	2.86 ± 0.13 (6)	2.76 ± 0.16 (6)	2.54 ± 0.24 (6)
5	2.76 ± 0.20 (7)	2.47 ± 0.13 (7)	2.88 ± 0.22 (6)	2.69 ± 0.24 (6)	2.89 ± 0.18 (6)
10	3.05 ± 0.14 (18)	2.69 ± 0.14 (10)	2.76 ± 0.20 (12)	2.84 ± 0.17 (12)	2.91 ± 0.18 (14)
			μg/g tissue		
DA					
3.5	9.88 ± 0.60 (6)	8.98 ± 0.28 (6)	9.71 ± 0.54 (6)	9.32 ± 0.27 (6)	8.64 ± 0.46 (6)
5	9.06 ± 0.38 (7)	9.72 ± 0.35 (7)	9.57 ± 0.75 (6)	9.31 ± 0.32 (6)	10.02 ± 0.53 (6)
10	10.86 ± 0.34 (18)	9.46 ± 0.37 (10)	9.42 ± 0.36 (10)	9.18 ± 0.34 (12)**	10.08 ± 0.28 (15)
DOPAC					
3.5	0.85 ± 0.04 (6)	0.74 ± 0.04 (6)	0.83 ± 0.05 (6)	0.72 ± 0.03 (6)*	0.70 ± 0.04 (6)*
5	0.74 ± 0.02 (7)	0.86 ± 0.05 (7)	0.85 ± 0.07 (6)	0.83 ± 0.06 (6)	0.91 ± 0.05 (6)*
10	1.07 ± 0.06 (18)	1.17 ± 0.09 (10)	1.05 ± 0.11 (12)	1.05 ± 0.06 (12)	1.09 ± 0.17 (15)
HVA					
3.5	0.63 ± 0.04 (6)	0.62 ± 0.03 (6)	0.68 ± 0.05 (6)	0.53 ± 0.04 (6)	0.61 ± 0.03 (6)
5	0.61 ± 0.03 (7)	0.79 ± 0.05 (7)	0.82 ± 0.09 (6)*	0.68 ± 0.05 (6)	0.79 ± 0.06 (6)*
10	0.63 ± 0.02 (18)	0.67 ± 0.04 (10)	0.66 ± 0.05 (12)	0.77 ± 0.06 (12)*	0.77 ± 0.03 (15)*

Statistical analysis was performed with a one-way ANOVA test followed with a Student-Newman-Keuls multiple comparisons test: * $P < .05$; ** $P < .01$ *vs.* respective control group.

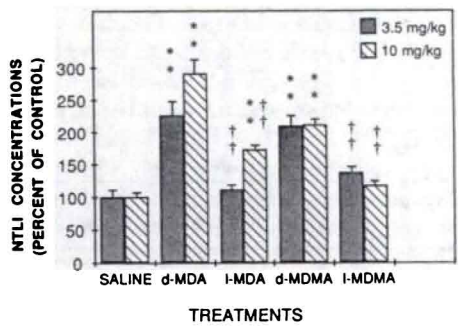

Fig. 4. Effects of MDA and MDMA isomers on NTLI concentrations within substantia nigra. Different isomers of MDA or MDMA injected at 3.5 (■) or 10 mg/kg (□) were administered for five doses at 6-hr intervals, and animals were killed 18 hr later. Results are expressed in percentage of control values (saline treatment) and represent means ± S.E. of 6–18 rats/group. Actual control values for the 10 mg/kg treatment follow: 955 ± 70 pg/mg protein. **$P < .01$ *vs.* respective control; ††$P < .01$ *vs.* corresponding *d* isomer group.

study suggests that increases in nigral NTLI are unrelated to the hallucinogenic property of MDA.

The significance of the changes in the peptide systems after these drug treatments is not yet fully understood. NT has properties similar to the dopaminergic receptor blocker, haloperidol (Nemeroff *et al.*, 1980). Since nigral concentration of NT is affected by dopamine release, it is likely that the increases in concentration of this peptide are the result of a feedback mechanism by the nigrostriatal dopaminergic pathway.

In summary, at certain doses, the *d* forms of the amphetamine analogues MDA and MDMA are the more active isomers on the central nervous system serotonergic, dopaminergic, and neuropeptidergic systems. The precise mechanisms responsible for these effects are not totally elucidated; however, at least for the NT system, it is likely that these drugs exert their effects *via* their dopamine releasing properties. This would suggest that the *d* isomers of MDA and MDMA are more potent than their *l* counterparts in releasing dopamine, which is supported by the *in vitro* findings of Schmidt *et al.* (1987). The mechanism that mediates MDA- or MDMA-induced decreases in 5-HT parameters is not as apparent but could involve dopamine release (Stone *et al.*, 1986b). Even so, the changes in the 5-HT system were greater with *d* isomers, although the trends were dose-dependent.

Acknowledgment

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