MDMA (Ecstasy) Inhibition of MAO Type A and Type B: Comparisons with Fenfluramine and Fluoxetine (Prozac)

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3,4-Methylenedioxymethamphetamine (MDMA), a serotonin (5-HT) neurotoxin, has been shown to promote the release of serotonin (5-HT) and block its reuptake. The increased buildup of extracellular 5-HT should normally be degraded by monoamine oxidase (MAO). The effects of both enantiomers of MDMA were examined on MAO-A and monoamine oxidase-B (MAO-B) activity in rat brain homogenates. Both enantiomers competitively inhibited 5-HT catabolism by rat brain MAO-A. The K_i of MDMA for MAO-A was 22 μmol/L. A mixed type of inhibition by MDMA was observed for phenethylamine catabolism by MAO-B for both optical antipodes. Logistical analysis of concentration response curves for MDMA inhibition of MAO-A and MAO-B show an IC_{50} of 44 μmol/L for inhibition of MAO-A by MDMA. The IC_{50} value of MDMA inhibition of MAO-B was 370 μmol/L, showing a selective potency for MAO-A inhibition. The MAO inhibitory properties of fenfluramine (FEN) and fluoxetine (FLUOX) were compared to those of MDMA. The rank order potency of these drugs for MAO-A inhibition was MDMA>FLUOX>FEN, whereas for MAO-B inhibition, FLUOX>MDMA>FEN. A combination of FLUOX and MDMA at their respective IC_{50} did not inhibit MAO activity more than either drug alone at equivalent concentrations. These results indicate that the actions of FEN do not appear to involve MAO inhibition. MDMA (ecstasy) produced a preferential inhibition of MAO-A (IC_{50} = 44 μmol/L), which should increase extracellular 5-HT. This may explain its high toxicity potential. Finally, FLUOX (Prozac) showed an inhibition of MAO-B (IC_{50} = 80 μmol/L, which may increase the intracellular content of 5-HT. This may contribute to its therapeutic potential. In contrast, FEN appears to be a poor inhibitor of both MAO-A and MAO-B.
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KEY WORDS: *Serotonin; Phenethylamine; Enantiomer*

Monoamine oxidase (MAO) is an enzyme with two subtypes (E.C.1.4.3.4) characterized by their differential responses to the irreversible inhibitors clorgyline and deprenyl. Monoamine oxidase A (MAO-A) has a higher affinity for serotonin (5-HT) than MAO-B; the K_M of MAO-A for serotonin is 99 μmol/L, the K_M of MAO-B for serotonin is 1170 μmol/L (Fowler and Tipton 1982; Garrick and Murphy 1982). Monoamine oxidase A is inhibited by nanomolar concentrations of clorgyline (Johnston 1968). Monoamine oxidase B (MAO-B) has a higher affinity for phenethylamine than MAO-A and is inhibited by nanomolar concentrations of deprenyl (Garrick and Murphy 1982; Yang and Neff 1974). Dopamine (DA) is metabolized with equal affinity by both subtypes (Yang and Neff 1974). Further evidence for two molecular forms of MAO has been provided by the cloning of two distinct MAO genes (Bach et al. 1988) and their subsequent functional expression in COS cells (Lan et al. 1989).

Both neurons and glia contain monoamine oxidases that catabolize the classical monoamine neurotransmit-

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ters. Monoamine oxidase A is the predominant form in catecholaminergic neurons, whereas MAO-B is the prevalent form in glia (Levitt et al. 1982; Westlund et al. 1985). Although MAO-B has a higher affinity than MAO-B for serotonin, MAO-B is the major molecular form found within serotonergic neurons (Westlund et al. 1985).

3,4-Methylenedioxymethamphetamine (MDMA) binds with high affinity to the 5-HT transporter protein (Poblete et al. 1989) and has been shown to be a potent releaser of serotonin by a Ca^{2+}-independent mechanism (Berger et al. 1992; Gu and Azmitia 1989; Johnson et al. 1986; Schmidt 1987; Schmidt et al. 1987). MDMA has been demonstrated to produce a depletion of serotonin that may be reversed in acute stages by agents that bind to the serotonin transporter and block serotonin reuptake into presynaptic terminals (Azmitia et al. 1990; Schmidt 1987). It also inhibits the 5-HT reuptake system (Steele et al. 1987), resulting in an increased amount of extracellular 5-HT. However, little attention has been paid to the fate of extracellular 5-HT.

Parachloroamphetamine (PCA) is another substituted amphetamine that is a potent releaser of serotonin and has a biphasic depletion of serotonin similar to that observed with MDMA (Ask and Ross 1987; Berger et al. 1992; Fuller et al. 1975; Gu and Azmitia 1989; Gu 1993; Hwang and van Woert 1980; Mamounas and Molliver 1988; Poblete et al. 1989; Ross and Froden 1977). As with MDMA, the depletion of serotonin resultant from PCA may be reversed in its acute phase by serotonin uptake blockers (Fuller et al. 1975; Ross et al. 1977). Parachloroamphetamine has been shown to inhibit MAO-A activity in rat brain homogenates with a K_i value of 1.31 μmol/L (Fuller 1966). The toxicity of PCA is also affected by the amount of releasable serotonin into the extracellular space. For instance, if serotonin release is decreased by parachlorophenylalanine (pCPA) and reserpine, the level of toxicity is reduced (Berger et al. 1989).

The anorectic compound, fenfluramine (FEN), is a halogenated amphetamine that has actions in serotonergic axon terminals similar to those of MDMA and PCA (Mamounas and Molliver 1988; Molliver and Molliver 1990; O'Hearn et al. 1988). Like MDMA and PCA, FEN causes the release of 5-HT from presynaptic terminals (Borroni et al. 1983) and inhibits the reuptake of serotonin into its terminals (Belin et al. 1976; Kannengiesser et al. 1976). The effects of FEN are blocked by 5-HT uptake inhibitors, as in MDMA and PCA (Hekmatpanah and Peroutka 1990). These observations suggest that the carrier-mediated release of serotonin and the inhibition of its reuptake are critical components in the mechanism of these drugs. FEN, FLUOX, and MDMA bind to the serotonin transporter protein with high affinity; the rank order potencies for binding to the transporter for these agents is FLUOX>FEN = MDMA (Poblete et al. 1989).

The similar actions of FEN, FLUOX and MDMA on serotonin transporter binding suggest they may possess common effects upon other serotonergic parameters, such as monoamine oxidase activity, in vitro. The present report examines the effects of both enantiomers of MDMA on catabolism of [^{3}H]-serotonin and [^{14}C]-phenethylamine by rat brain monoamine oxidase in vitro. In addition, we compared the effects of fluoxetine (FLUOX) and fenfluramine (FEN) to MDMA on rat brain MAO activity. Our results suggest that inhibition of MAO-A by MDMA may contribute to an accumulation of extracellular 5-HT. The inhibition of MAO-B activity by FLUOX may increase intracellular 5-HT, whereas the actions of FEN do not appear to involve MAO inhibition.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 200 to 250 g (Taconic Farms, Germantown, NY) were housed two per cage and given free access to food and water. The animals were maintained on a 12-hour light/dark cycle. Animals were euthanized with CO_2 and decapitated according to a protocol approved by the NYU Animal Welfare Committee. Brains were rapidly removed and placed on ice in 0.32 mol/L sucrose. After removal of the cerebellum, brains were homogenized in 10-fold volume/weight in 0.32 mol/L sucrose using 10 strokes with a Teflon/glass homogenizer. P_1 pellets were prepared by sedimentation of homogenates at 800 × g for 10 minutes at 2°C in a Sorvall RC5C centrifuge (Sorvall Instruments, DuPont, Chadds Ford, PA). Supernatants were resedimented at 14,000 xg at 2°C for 15 minutes to obtain a crude mitochondrial P_2 pellet. Resultant pellets were resuspended in 500 μL 0.32 mol/L sucrose and stored at −70°C until use.

Prior to the MAO assay, homogenates were thawed and brought up to 10× volume/original weight 0.01 mol/L sodium phosphate buffer (PB), pH 7.4 and dialyzed to remove endogenous monoamines by a modification of the method described by Patterson, et al. (1973). Briefly, homogenates were dialyzed in 2 mL aliquots using 3500 mw cutoff dialysis tubing (Spectrapor) against 0.01 mol/L PB, pH 7.4 at 4°C for 2 hours with three successive changes of 1L buffer. MAO assays were performed immediately following this dialysis.

Monamine oxidase activity was assayed using [^{3}H]-5-HT (25Ci/mmol, 1 μCi/mL, New England Nuclear, Boston, MA) as a substrate for MAO-A at final concentrations ranging from 12.5 μmol/L to 400 μmol/L. [^{14}C]-phenethylamine at a final concentration of 5

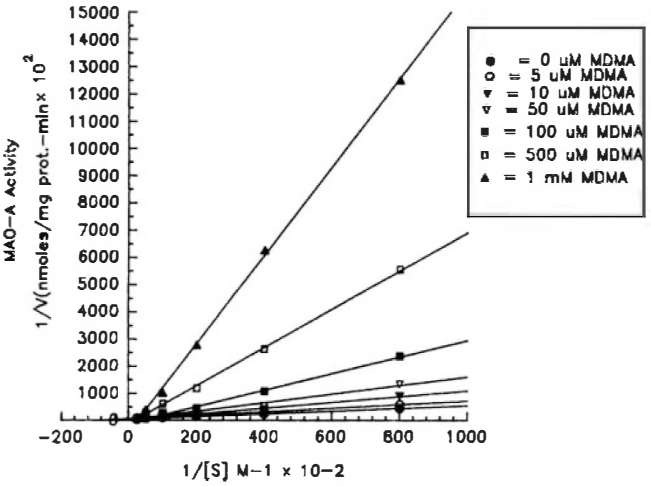

Figure 1. Inhibition of serotonin oxidation by (+) MDMA. All data points represent the average of three experiments. Nonspecific values (0.15 nmoles product/mg protein-minute) were subtracted from total activity. Error bars represent the standard error of the mean.

μmol/L to 50 μmol/L (50.8 mCi/mmol, 0.1 μCi/mL, New England Nuclear, Boston, MA) served as substrate for MAO-B. The assay procedure was a modification of the method described by Pintar et al. (1981) and Lan et al. (1989).

Competition Studies

A 15 μL portion of rat brain homogenate suspended in 75 μL 0.01 mol/L PB was treated with 20 μL (+) or (−) MDMA (National Institute on Drug Abuse, Bethesda, MD) at final concentrations ranging from 10 μmol/L to 1 mmol/L, 10 minutes in a 37°C water bath. Samples then received a 90 μL aliquot of [^{14}C]-PEA or [^{3}H]-5-HT and were further incubated in a 37°C water bath for 30 minutes. At the end of this time, the reaction was terminated by adding a 90 μL aliquot 1.2 mol/L HCl. Each sample point was assayed in quadruplicate. Radioactive product was measured by the addition of 3 mL 4% (vol/vol) Liquiscint (National Diagnostics, Bethesda, MD):toluene (HPLC grade, Aldrich Chemical Co., Milwaukee, WI) per sample followed by scintillation counting in Beckman LS 1801 scintillation counter (Fullerton, CA) with a counting efficiency of 40%.

Comparison of FEN, FLUOX, and MDMA

Fenfluramine, FLUOX, and each enantiomer of MDMA were assayed against MAO-A and MAO-B activity with substrate concentrations of 100 μmol/L 5-HT and 20 μmol/L PEA, respectively. Fenfluramine (Sigma Chemical Co., St. Louis, MO) and MDMA were tested at final concentrations of 1 μmol/L to 10 mmol/L, FLUOX (gift of Eli Lilly and Co., Indianapolis, IN) at concentrations of 1 μmol/L to 1 mmol/L. MAO activity was then assayed as described above.

Additive Effects

To determine whether MDMA and FLUOX share a common mechanism for MAO inhibition, homogenates were treated with FLUOX and (+) MDMA in combination at their IC_{50} or at $2 \times IC_{50}$ concentrations individually. Radiolabeled substrate was added and MAO activity was assayed as described above.

To determine nonspecific counts, a set of samples was preincubated with 1 mmol/L clorgyline or 1 mmol/L deprenyl, as appropriate, for 10 minutes at 37°C. Protein concentrations of homogenates were determined by the method of Lowry et al. (1951) with bovine serum albumin (Sigma Chemical Co., St. Louis, MO) as standard. Protein detection was determined at 540nm absorbance using a Titertek Multiskan spectrophotometer (EFLAB, Helsinki, Finland).

Analysis of data was conducted by employing Student's two-tailed *t*-test for two-sample comparisons. One-way analysis of variance (ANOVA) followed by Tukey post hoc analysis was performed for multisample comparisons (SYSTAT, Evanston, IL). IC_{50} values and Hill coefficients of concentration-response curves were determined by computer-assisted curve-fitting to a logistical equation (SigmaPlot 4.1, Jandel Scientific, San Rafael, CA). Kinetic constants for both subtypes of MAO were determined by the analysis of Lineweaver-Burk plots.

Table 1. Comparison of (+) and (−) MDMA against Deamination of Serotonin and PEA by MAO

Substrate of MAO	V_{max} (nmol/mg-minute)	K_M (μmol/L)	K_i (+) MDMA (μmol/L)	K_i (−) MDMA (μmol/L)
Serotonin	2.08 ± 0.03	100 ± 12	22.0 ± 3*	28.3 ± 5.0*
PEA	1.72 ± 0.20	20 ± 3	–	–

* No significance was determined between (+) and (−) MDMA with Student's two-tailed *t*-test. Values reported here represent the average of three experiments, plus or minus the standard error of the mean.

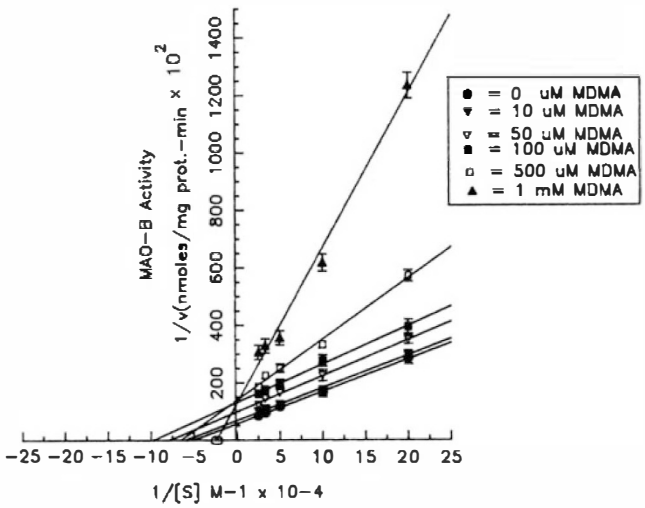

Figure 2. Inhibition of phenethylamine oxidation by (+) MDMA. All data points represent the average of three experiments. Nonspecific values (0.18 nmoles product/mg protein-minute) were subtracted from total activity. Error bars represent the standard error of the mean.

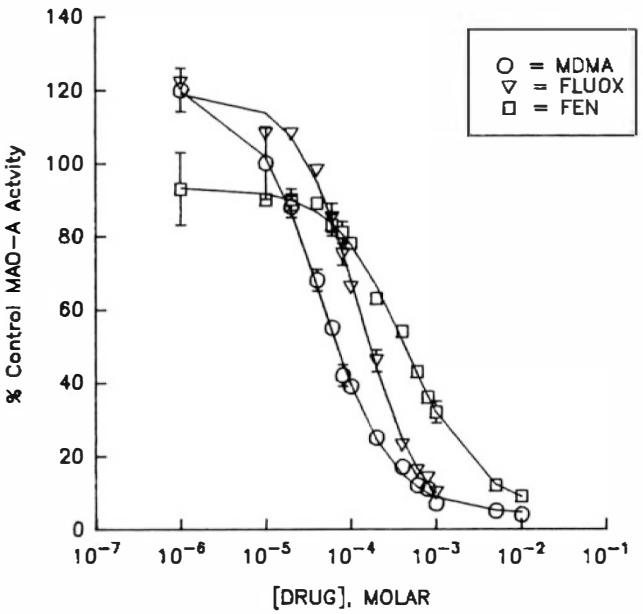

Figure 3. Concentration-response curve for the inhibition of MAO-A by FLUOX, FEN, and (+) MDMA. Control values = 2.08 nmoles product/mg protein-minute. Error bars represent the standard error of the mean.

RESULTS

In order to establish the kinetic parameters of MAO activity in this assay system, saturation studies were performed for MAO-A and MAO-B. MAO-A activity had a V_{max} of 2.08 nmoles product/mg protein-minute and a K_M of 100 μmol/L (Figure 1, Table 1). For MAO-B, a V_{max} of 1.72 nmoles product/mg protein-minute with a K_M value of 20 μmol/L was observed (Figure 2, Table 1). Both enzyme assay systems were responsive to the appropriate monoamine oxidase inhibitors; clorgyline with a K_i for MAO-A of 0.5 nmol/L and deprenyl with a K_i for MAO-B of 1 nmol/L.

Once these parameters were established, the effects of both enantiomers of MDMA were tested on MAO-A. A different K_M but no change in V_{max} was observed for MAO-A (Figure 1) with increasing concentrations of MDMA, indicative of a competitive inhibition. No stereospecific effect was observed (Table 1), that is (+) MDMA had a K_i value of 22.0 μmol/L against serotonin as substrate and (−) MDMA has a K_i value of 28.3 μmol/L (Table 1). A competitive inhibition of MAO-A was seen by both enantiomers of MDMA.

The effects of both enantiomers of MDMA were determined for MAO-B, the subtype of MAO localized within serotonergic neurons. MDMA produced a different type of inhibition with MAO-B than was observed for MAO-A (Figures 1, 2). In the case of MAO-B, both the V_{max} and K_M of the enzyme were changed by a range of MDMA concentrations; 10, 50, 100, and 500 μmol/L. At the highest concentrations, 1 mmol/L, the V_{max} remained the same whereas K_M has changed. The change in both the V_{max} and K_M shows a mixed-type inhibition of MAO-B by MDMA; the effect observed at the highest concentrations may reflect a saturation of all the available MAO-B active sites. A similar finding was observed with (−) MDMA (data not shown).

To compare the potencies of FEN, FLUOX, and MDMA on MAO-A inhibition, concentration-response curves were established that consisted of 14 points from 10^{-6} to 10^{-2} mol/L for MDMA and FEN. A concentration-response curve of 13 points from 10^{-6} to 10^{-3} mol/L was established for FLUOX. A representative curve obtained from the average of three experiments for FEN, FLUOX, and (+) MDMA had Hill coefficients of 1.02, 1.18, and 1.05, respectively (Figure 3). Their respective IC_{50} values (Table 2) show a rank order potency of MDMA>FLUOX>FEN (IC_{50} were 44, 130, and 440 μmol/L, respectively). The IC_{50} of (−) MDMA for MAO-A was 56 μmol/L (Table 2).

A similar study was performed for MAO-B with the drugs at the same concentrations as the MAO-A experiment. A representative curve obtained from the average of three experiments for FEN, FLUOX, and (+) MDMA had Hill coefficients of 1.13, 1.12, and 0.8182, respectively (Figure 4). Table 2 shows their respective IC_{50} values; 720, 80, and 370 μmol/L with FLUOX> MDMA>FEN. As was the case with MAO-A, no significant difference in IC_{50} was observed between (+) and (−) MDMA for MAO-B activity. The IC_{50} of (+) MDMA for MAO-B inhibition was roughly nine times greater than its IC_{50} for MAO-A, indicating that MDMA is selectively potent for MAO-A activity.

Table 2. IC_{50} Values (μmol/L) ± SEM

MAO Subtype	FEN	FLUOX	(+) MDMA	(−) MDMA
MAO-A	440 ± 23.09[ab]	130 ± 11.55[a]	44 ± 6.06	56 ± 8.24
MAO-B	720 ± 28.87[ab]	80 ± 10.55[a]	370 ± 4.68[ab]	378 ± 6.29

Values represent the average of three experiments ± standard error of the mean. MAO-A Data: One-way analysis of variance showed significant variance ($p = 1.02 \times 10^{-7}$, $F = 183.86$, $F_{crit} = 4.07$). MAO-B Data: One-way analysis of variance showed significant variance ($p = 6.16 \times 10^{-8}$, $F = 209.05$, $F_{crit} = 4.07$).

[a] $p < .001$ when compared to (+) MDMA with Tukey post hoc analysis.

[b] $p < .001$ when compared to FLUOX with Tukey post hoc analysis.

FLUOX showed a 60% greater inhibition of MAO-B than MAO-A activity, with an IC_{50} of 80 μmol/L for MAO-B. FEN showed poor inhibition of both MAO-A and MAO-B.

The additive effects of MDMA and FLUOX were tested. In this set of experiments, each drug was added to homogenates at its IC_{50} or 2 × IC_{50}. Another group had homogenates receiving a combination of both drugs at their respective IC_{50} values. In this way, we were able to test whether MDMA and FLUOX share a common mechanism for MAO-A and -B inhibition. A combination of FLUOX and MDMA at their IC_{50} did not inhibit MAO-A or MAO-B activity more than either drug alone at an equivalent concentration, which is indicative of a common mechanism for MAO inhibition (Table 3, Table 4).

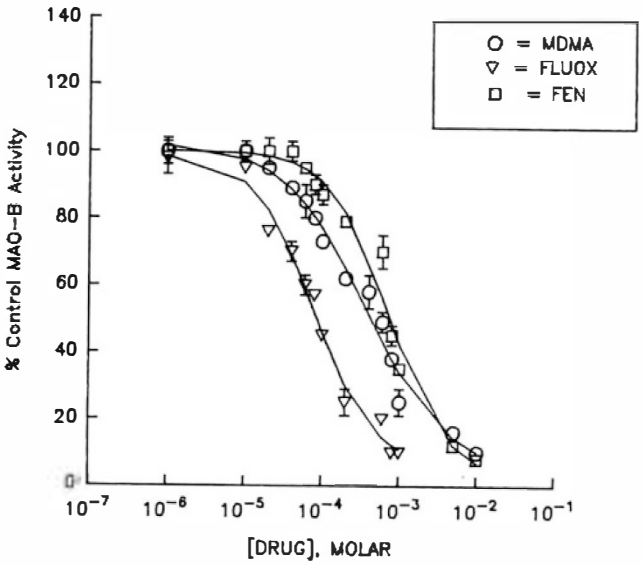

Figure 4. Concentration-response curve for the inhibition of MAO-B by FLUOX, FEN, and (+) MDMA. Control values = 1.74 nmoles product/mg protein-minute. Error bars represent the standard error of the mean.

DISCUSSION

Amphetamine has been reported as a competitive inhibitor of MAO-A activity (Mantle et al. 1976) and a mixed inhibitor of MAO-B, that is, both the V_{max} and K_M are changed (Pearce and Roth 1985). The results of this study show MDMA acts as a competitive inhibitor of MAO-A activity (see Results, Figure 1), whereas a mixed pattern of inhibition was observed for the MDMA inhibition of MAO-B (Figure 2). The kinetics of MAO-A and -B inhibition by MDMA reported here are therefore consistent with those previously described for amphetamine. A nine-fold difference was observed in the IC_{50} of MDMA for MAO-A and MAO-B activity, showing a selective potency of MDMA for MAO-A in rat brain homogenates (see Results, Figures 3 and 4, Table 2). This finding is consistent with studies showing the in vitro inhibition of MAO-A by amphetamine (Mantle et al. 1976) and its analogue, PCA (Fuller et al. 1965). A selective potency for the inhibition of the A subtype was also observed in vivo in rat brain homogenates 25 hours after the animals were injected with amphetamine followed by phenelzine, a nonselective MAO inhibitor (Miller et al. 1980).

The inhibition of MAO-A by amphetamine was found to be stereoselective for the (+) enantiomer in previous studies by other investigators (Mantle et al.

Table 3. Combined Effects of (+) MDMA and Fluoxetine on MAO-A Activity

	MDMA (44 μmol/L)	FLUOX (130 μmol/L)	MDMA (88 μmol/L)	FLUOX (260 μmol/L)	MDMA (44 μmol/L) + FLUOX (130 μmol/L)
% Control MAO-A	49 ± 5	50 ± 4	28 ± 3	34 ± 5	30 ± 2

Table 4. Combined Effects of (+) MDMA and Fluoxetine on MAO-B Activity

	MDMA (370 μmol/L)	FLUOX (80 μmol/L)	MDMA (740 μmol/L)	FLUOX (160 μmol/L)	MDMA (370 μmol/L) + FLUOX (80 μmol/L)
% Control MAO-B	55 ± 4	50 ± 3	35 ± 3	29 ± 3	31 ± 2

1976). We observed no significant difference between both enantiomers of MDMA with respect to oxidative deamination of serotonin and phenethylamine by monoamine oxidase (see Results, Table 1). This is in contrast to reports of a stereospecificity for MDMA on dopamine and serotonin release from striatum (Johnson et al. 1986; Schmidt et al. 1987). However, the observation that MDMA appears to lack stereospecificity for MAO inhibition is consistent with many of the acute properties of this drug both in vivo and in vitro. Release of serotonin observed in ^{3}H-serotonin-loaded rat hippocampal slices superfused with either enantiomer of MDMA did not show any significant stereoselectivity (Johnson et al. 1986). Treatment with both enantiomers of MDMA resulted in a decrease in rat striatal indoles in vivo 3 hours after injection. A nonstereoselective, acute depletion of serotonin following MDMA treatment in vivo was observed in rat cortex (Schmidt 1987). Finally, both the optical antipodes of MDMA were potent inhibitors of ^{3}H-serotonin uptake into rat hippocampal synaptosomes (Steele et al. 1987). The ability of MDMA to inhibit MAO-A would result in high extracellular levels of 5-HT.

Monoamine oxidase A is an enzyme whose preferred substrate is serotonin (Garrick and Murphy 1982) and is localized in dopaminergic neurons (Westlund et al. 1985). Serotonin has recently been reported to promote the release of DA through the dopamine transporter by an exchange-diffusion mechanism (Jacocks and Cox 1992). This effect would be enhanced by an increased level of 5-HT resultant from an inhibition of MAO-A activity.

Fenfluramine and MDMA share many neuropharmacologic characteristics. Both drugs bind to the serotonin transporter, with a similar affinity (Poblete et al. 1989). MDMA and FEN both release serotonin ($E.C._{50}$ = 2.92 and 7.90 μmol/L, respectively, Berger et al. 1992; Borroni et al. 1983; Buczko et al. 1975; Johnson et al. 1986; Kannengiesser et al. 1976; Schmidt et al. 1987), with FEN being more potent. In contrast, MDMA appears to be slightly more potent than FEN at inhibition of reuptake (0.42 μmol/L, Steele et al. 1987 and 0.876 μmol/L, Borroni et al. 1983, respectively). Finally, both drugs are toxic to serotonergic neurons (Appel et al. 1990; Azmitia et al. 1990; Battaglia et al. 1987, 1988; Molliver and Molliver 1990; O'Hearn et al. 1988), but MDMA has been shown to be a more potent toxic agent than FEN in both tissue culture experiments (Gu 1993) and in vivo (Sotelo and Zamora 1978). The fact that MDMA has greater toxicity is not due to its ability to induce release or bind to the serotonin transporter. However, a comparison between MDMA and FEN on MAO activity in this study showed MDMA to be approximately ten times more potent than FEN in the inhibition of MAO-A (see Results, Table 2). The inhibition of MAO-A may be a crucial variable for induced fiber degeneration. In support of this hypothesis, PCA, which is a more potent serotonergic toxin than MDMA (Gu 1993; Mamounas and Molliver 1988; O'Hearn et al. 1988) has a roughly 20-fold higher affinity for MAO-A than MDMA (K_i values of 1.33 μmol/L, Fuller 1966 vs. 22 μmol/L, this study).

Fluoxetine is a lipophilic, serotonin uptake blocker that is found in subcellular fragments prepared from brain tissue of FLUOX-treated rats (Caccia et al. 1990). Therefore, FLUOX may enter the cell and interact with monoamine oxidase. The IC_{50} of FLUOX was compared to that of MDMA and FEN with respect to MAO inhibition; the IC_{50} value of FLUOX for MAO-A was nearly three times higher than that of MDMA (see Results, Table 2). Interestingly, the IC_{50} of FLUOX for MAO-B, the subtype localized within serotonergic cells, was 80 μmol/L, a nine-fold difference from the IC_{50} of MDMA.

Finally, the additive properties of FLUOX and MDMA were tested on MAO activity (Results, Table 3, Table 4). Since both compounds bind to the serotonin transporter, we examined whether they share a common site for MAO inhibition. The addition of both drugs at their IC_{50} s produced effects that were equivalent to each drug on its own. We interpret this finding to be indicative of a competition of both compounds for the same site on MAO-A and MAO-B, respectively (Results, Table 3, Table 4).

In summary, these studies show that MDMA preferentially inhibits MAO-A in a reversible, nonstereospecific manner. Fluoxetine is significantly more potent than MDMA in the inhibition of MAO-B, whereas FEN does not significantly affect rat brain MAO-A or MAO-B activity. Like PCA, the greater toxicity of MDMA (Gu 1993) may be related to its ability to produce high levels of extracellular 5-HT by stimulating release, inhibiting reuptake and blocking the catabolism of serotonin by MAO-A. The therapeutic actions of Prozac may in-

volve a selective inhibition of MAO-B, which would result in a greater amount of 5-HT available for release. Finally, FEN has only weak effects on MAO-A and MAO-B activity.

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