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p-Methylthioamphetamine is a potent new non-neurotoxic serotonin-releasing agent

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p-Methylthioamphetamine (MTA), was compared to p-chloroamphetamine (PCA) in a number of pharmacological assays. MTA was about 2-fold more potent than PCA at inhibiting synaptosomal uptake of [^{3}H]5-hydroxytryptamine ([^{3}H]5-HT), and about 7-fold and 10-fold less potent than PCA at inhibiting synaptosomal uptake of [^{3}H]dopamine and [^{3}H]norepinephrine, respectively. In drug discrimination assays, MTA was nearly equipotent to PCA in animals trained to discriminate saline from 3,4-methylenedioxymethamphetamine (MDMA), or two related analogues S-(+)-N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (S-MBDB) or 5-methoxy-6-methyl-2-aminoindan (MMAI). MTA caused dose-dependent increases of tritium efflux from superfused rat frontal cortex slices preloaded with [^{3}H]5-HT, comparable to that induced by an equal molar concentration of PCA. The potential neurotoxicity of MTA was examined by measuring monoamine and metabolite levels at one week following an acute dose. A 10 mg/kg dose of PCA caused a 70–90% decrease of cortical, hippocampal and striatal 5-HT and 5-hydoxyindoleacetic acid (5-HIAA) levels, while twice the molar dose of MTA (21.3 mg/kg) had no effect. Thus, MTA is a potent, selective, serotonin releaser, apparently devoid of serotonin neurotoxic effects. This work also supports the idea that catecholamine systems may play a critical role in the neurotoxicity of PCA-like compounds.

p-Chloroamphetamine; p-Methylthioamphetamine; Drug discrimination; Uptake inhibition; Superfusion; 5-HT (5-hydroxytryptamine, serotonin); Neurotoxicity; Brain slices

1. Introduction

Substantial efforts in our laboratory over many years have been made to understand the structure-activity relationships of substituted amphetamines which exert a variety of pharmacological actions. Amphetamine derivatives such as 3,4-methylenedioxymethamphetamine (MDMA), and p-chloroamphetamine (PCA) cause central serotonin neurotoxicity which is marked by persistent reductions in brain 5-hydoxytryptamine (5-HT), 5-HT uptake sites, and tryptophan hydroxylase activity (e.g. Schmidt et al., 1986; Battaglia et al., 1987; 1988; Fuller and Snoddy, 1974). This persistent reduction in serotonin markers seems to correlate with the degeneration of certain serotonin axonal projections in brain (O'Hearn et al., 1988; Mamounas and Molliver, 1988). Developing less neurotoxic MDMA and PCA analogues which preserve desired behavioral effects will not only give a needed safety factor for any potential clinical use of this type of compound but also will provide tools for studying the mechanisms of behavior and neurotoxic activity of these types of compounds.

Data from recent research in our laboratory and others have provided evidence that drug-induced 5-HT release is important in the discriminative cue of MDMA-like drugs (Oberlender and Nichols, 1988; Nichols et al., 1986; Schechter, 1988; Nichols and Oberlender, 1990; Nichols et al., in press). 5-Methoxy-6-methyl-2-aminoindan (MMAI), which possesses a more potent in vitro serotonergic effect than MDMA and has almost no dopaminergic effect, fully substitutes for MDMA and S-(+)-N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (S-MBDB) in drug discrimination experiments (Johnson et al., 1991a). Recently, in our laboratory, MMAI has been used as a training drug in drug discrimination experiments because of its greater serotonergic specificity and decreased neurotoxic effects (Nichols et al., in press).

Recent work suggests that non-vesicular dopamine release plays a very important role in drug-induced serotonergic toxicity of these drugs. Compounds such

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as MMAI, 5,6-methylenedioxy-2-aminoindan (MDAI), MBDB and 1-(4-chlorophenyl)-2-aminobutane (CAB) which have little dopaminergic effect produce little or no serotonergic toxicity (Johnson et al. 1990; 1991a; Nash and Nichols, 1991; Nash and Brodkin, 1991). Serotonin neurotoxicity induced by the combination of the non-neurotoxic MDMA analogs MDAI or MMAI and the dopamine releasing agent (+)-amphetamine (Johnson and Nichols, 1991; Johnson et al., 1991b) gives additional strong support to the hypothesis of dopamine involvement in the serotonin neurotoxicity induced by these types of drugs.

Based in part on the above studies, further exploration of new MDMA and PCA analogs with increased serotonergic effects and/or decreased dopaminergic effects (i.e. highly selective serotonergic agents) was warranted. Most monoamine releasing amphetamine derivatives are 3,4-disubstituted compounds (e.g. MDMA) or are simply monosubsituted at the para position. For the latter, small electronegative groups such as methoxy, and chloro or other halogens give neurotoxic compounds. It should be noted however, that the halogens other than chlorine and bromine give compounds that are less neurotoxic (Fuller et al., 1975; 1980). Thus, we reasoned that a larger, less electronegative group would be an interesting candidate. In particular, a sulfur atom substitution seemed an appropriate choice. Sulfur is hydrophobic, in the same family of the periodic table as oxygen, and much less electronegative than oxygen or chlorine. Following this reasoning, p-methylthioamphetamine (MTA), was synthesized in our laboratory. This report discusses the pharmacology of MTA in a number of assays. The structures of PCA and MTA are shown in fig. 1.

As a simple screening procedure, the ability of MTA to substitute for MDMA, S-MBDB, MMAI, (+)-amphetamine and (+)-lysergic acid diethylamide (LSD) in a drug discrimination paradigm was first determined. Synaptosomal monoamine uptake inhibition experiments were then used to assess the relative potency of the new compound to affect serotonin, dopamine, and norepinephrine uptake and release. Superfusion experiments were utilized to test its serotonin releasing properties. Finally, the ability of the compound to cause long-term depletion of monoamines in different rat brain regions (frontal cortex, hippocampus and striatum) was determined.

2. Materials and methods

2.1. Materials

MTA and PCA were synthesized in our laboratory using standard methods. HPLC standards were purchased from Sigma Chemical Co. (St. Louis, MO). [^{3}H]5-HT, [^{3}H]dopamine and [^{3}H]norepinephrine were purchased from Amersham (Arlington Heights, IL) at a specific activity of 12.3, 5 and 13.8 Ci/mmol respectively. (+)-Amphetamine sulfate was purchased from Smith Kline & French Laboratories (Philadelphia, PA). MDMA, S-MBDB, MMAI, as their hydrochlorides, and LSD tartrate were synthesized in our laboratory (Nichols et al., 1986; Johnson et al., 1991). With the exception of drug discrimination experiments, all drugs were injected subcutaneously. In drug discrimination experiments, all drugs were dissolved in 0.9% saline and were injected intraperitoneally in a volume of 1 ml/kg, 30 min before the session.

2.2. Animals

Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 175–200 g were used in all experiments. Animals were either group housed six per cage or individually caged in a temperature controlled room with a 12/12 h lighting schedule. With the exception of rats used in the drug discrimination experiments, food and water were available ad libitum at all times. In drug discrimination experiments, 62 male rats were used as subjects and divided into five groups (N = 9–15 per group), trained to discriminate MDMA (1.75 mg/kg), S-MBDB (1.75 mg/kg), MMAI (1.71 mg/kg), (+)-amphetamine (1.0 mg/kg) or LSD (0.08 mg/kg) from saline. None of the rats had previously received drugs or behavioral training. Water was freely available in the home cages and a sufficient amount of supplemental feeding (Purina, Lab Blox) was made available after experimental sessions so as to maintain them at approximately 80% of free feeding weight, compared with control rats housed under the same conditions. In neurochemical studies, rats were killed by decapitation, the brains were removed and rapidly dissected on ice according to the procedure of Glowinski and Iversen (1966). In neurotoxicity studies, the frontal cortex, hippocampus and striatum were frozen with liquid nitrogen. The samples were stored separately at −70°C until assay using HPLC-EC methods.

2.3. Drug discrimination

Six standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound-attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the cage, which was also equipped with two response levers, separated by a food hopper, all positioned 2.5 cm above the floor. Solid state logic in an adjacent room, interfaced through a Coulbourn Instruments Dynaport to an IBM PC, controlled rein-

forcement and data acquisition with a locally written program.

A fixed ratio (FR) 50 schedule of food reinforcement (Bioserv 45 mg dustless pellets) in a two-lever paradigm was used. The drug discrimination procedure details have been described elsewhere (Oberlender and Nichols, 1988; 1990; Nichols et al., in press). Half of the rats were trained on drug-L (left), saline-R (right) and the other half on drug-R, saline-L to avoid positional preference. Training sessions lasted 15 min and were conducted at the same time each day. Training sessions were continued until an accuracy of at least 85% (number of correct presses $\times 100$/number of total presses) was attained for eight of ten consecutive sessions. Once criterion performance was attained, test sessions were interspersed between training sessions, either one or two times per week. At least one drug and one saline session separated each test session. Rats were required to maintain the 85% correct responding criterion on training days in order to be tested. In addition, test data (less than 5%) were discarded when the accuracy criterion of 85% was not achieved on the two training sessions following a test session. Test drugs were administered i.p. 30 min prior to the sessions; test sessions were run under conditions of extinction, with rats removed from the operant chamber when 50 presses were emitted on one lever. If 50 presses on one lever were not completed within 5 min, the session was ended and scored as a disruption. Treatments were randomized at the beginning of the study.

2.4. *In vitro [^{3}H]5-HT, [^{3}H]dopamine and [^{3}H]norepinephrine uptake inhibition*

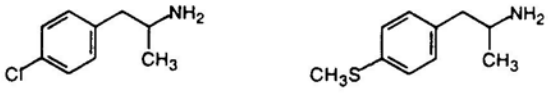
A modified procedure of Steele et al. (1987) was employed. Briefly, whole brain minus cerebellum was homogenized in 15 volumes of ice cold 0.32 M sucrose using a glass mortar with a motor driven pestle. The homogenate was centrifuged at $1086 \times g$ for 10 min at 4°C. The supernatant was then recentrifuged at $17800 \times g$ for 10 min and the resulting pellet was resuspended in the same volume of sucrose solution. Incubations were carried out in a shaking incubator under an atmosphere of 95% O_2-5% CO_2 at 37 or 0°C to measure total tissue uptake and non-specific uptake, respectively. A 5 min preincubation was begun by adding 0.2 ml of the synaptosomal preparation to test tubes containing 1.65 ml of O_2-saturated Krebs-Henseleit buffer (mM: 118 NaCl, 4.8 KCl, 1.3 $CaCl_2$, 1.2 KH_2PO_4, 25 $MgSO_4$, 25$NaHCO_3$, 10 glucose, 0.06 ascorbic acid and 0.03 Na_2EDTA), 50 μl of drug solution and 50 μl of pargyline HCl solution (final concentration of 100 μM). Then either [^{3}H]5-HT, [^{3}H]dopamine or [^{3}H]norepinephrine was added in a 50 μl aliquot (final concentration of 10 nM), and incubations were continued for 5 min more. Incubations were terminated by cooling in ice and were then rapidly filtered through Whatman GF/B filters with a Brandel Cell Harvester (Brandel, Gaithersburg, MD). The filters were washed with ice cold buffer and allowed to air dry before placing them in plastic scintillation vials. Scintillation cocktail (10 ml) was added and the vials were sealed and allowed to sit overnight before counting at an efficiency of 54%.

2.5. *[^{3}H]5-HT release experiments*

Rat frontal cortex was chopped coronally into 0.3 mm slices. The slices were immediately transferred into O_2-saturated Krebs-Henseleit buffer (pH 7.4) containing 100 μM of pargyline. After incubation with [^{3}H]5-HT (100 nM) for 30 min at 37°C, one slice was placed into each of 12 superfusion chambers (Brandel, Gaithersburg, MD). The slices were superfused at a rate of 0.5 ml/min with fresh oxygenated modified Krebs-Henseleit buffer (mM: 118 NaCl, 4.8 KCl, 1.2 $MgSO_4$, 25 $NaHCO_3$, 1.2 KH_2PO_4, 12 glucose, 0.01 ascorbic acid, 0.03 Na_2EDTA, and 0.1 pargyline). After a 40 min wash serial 2 min fractions were collected. Buffer solution containing the test compound was administered only for 4 min, during the collection of fractions 5 and 6. At the end of the experiment, 5 ml of Ecolite Scintillation cocktail (ICN, Cleveland, OH) was added to all fractions of superfusate. Slices were recovered and transferred to vials containing 5 ml of scintillation cocktail. After vigorous shaking, radioactivity was counted with a Packard Scintillation Counter.

2.6. *HPLC with electrochemical detection*

High pressure liquid chromatography (HPLC) with electrochemical detection was used to determine biogenic amines and metabolite levels. A mobile phase containing 50 mM NaH_2PO_4, 30 mM citric acid, 0.1 mM Na_2EDTA, 0.034% sodium octyl sulfate and 23% v/v methanol was used. The brain samples were prepared by homogenizing the weighed brain areas from one hemisphere in 0.5 ml of HPLC mobile phase without sodium octyl sulfate, using a motor-driven Teflon pestle and Eppendorf 1.5 ml centrifuge tube. An internal standard of 100 ng/ml of 3-(3,4-dihydroxyphenyl)propionic acid (DHPPA) was used. The samples were then centrifuged at $14000 \times g$ for 4 min with a table top centrifuge. The supernatant was assayed for monoamines and their metabolites by injection of 50 μl onto a Brownlee C18 analytical cartridge column (Anspec, Ann Arbor, MI) with a flow rate of 0.7 ml/min. The HPLC-EC system consisted of a refrigerated autosampler (TosoHaas, Philadelphia, PA), and a model 400 EG and G Princeton electrochemical detec-



p-Chloroamphetamine (PCA)

p-Methylthioamphetamine (MTA)

Fig. 1. The structures of p-chloroamphetamine (PCA) and p-methylthioamphetamine (MTA).

tor (EG & G PARC, Princeton, NJ) with a dual electrode potential set at $E_1 = -200$ mV and $E_2 = 850$ mV versus the Ag/AgCl reference electrode.

2.7. *Statistical analysis*

Data from the drug discrimination studies were scored in a quantal fashion, with the lever on which the rat first emitted 50 presses in a test session scored as the 'selected' lever. The percentage of rats selecting the drug lever (%SDL) for each dose of test compound was determined. The degree of substitution was determined by the maximum %SDL for all doses of the test drug. 'No substitution' (N.S.) is defined as 59% SDL or less, and 'partial' substitution is 60–79% SDL. If the drug was one which completely substituted for the training drug (at least one dose resulted in a %SDL = 80% or higher), the ED50 values and 95% confidence intervals (95% C.I.) were then determined from quantal dose-response curves according to the procedure of Litchfield and Wilcoxon (1949).

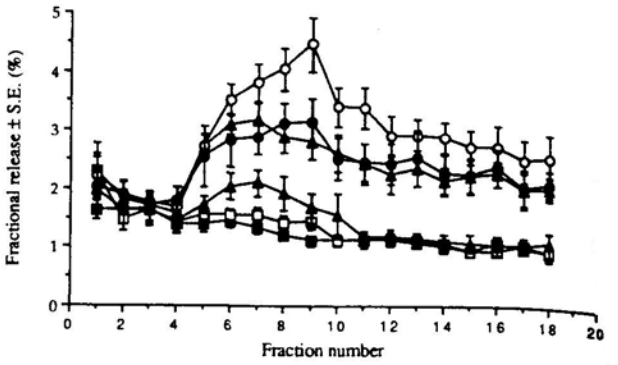


Fig. 2. The fractional release of tritium from rat frontal cortex slices preloaded with 100 nM [^{3}H]-5-HT induced by plain KRP buffer (■), 0.1 (□), 1.0 (▲), 10 (△), 100 (○) μM MTA and 10 μM PCA (●). The slices were continuously superfused at 37°C with modified Krebs-Henseleit buffer as discribed in methods. 2 min fractions were collected after a 40 min wash. At the fifth and sixth collected fraction, PCA and MTA were administered in the superfusion fluid followed by a return to drug-free buffer from fraction 7 to the end of the experiment. The superfusion flow was 0.5 ml/min. The results are the means of five experiments run on different days.

Percent uptake inhibition was defined as the difference between specific tritium uptake in control and drug test tubes divided by control uptake, times 100% as described in Steele et al. (1987). The IC_{50} values

TABLE 1

Drug discrimination data from (A) MDMA-trained, (B) S-MBDB-trained or (C) MMAI-trained rats. The ED_{50} values for substitution were calculated according to the method of Litchfield and Wilcoxon (1949).

Drug	Dose		N [a]	D [b]	%SDL [c]	ED_{50} (95% C.I.)	
	mg/kg	μmol/kg				mg/kg	μmol/kg
(A)							
MDMA						0.64 [d]	2.79 [d]
MTA	0.11	0.5	5	0	20	0.21	0.95
	0.22	1.0	7	0	29	(0.14–0.32)	(0.62–1.45)
	0.33	1.5	9	0	78		
	0.44	2.0	9	0	100		
PCA						0.17 [e]	0.84 [e]
(B)							
S-MBDB						0.79 [d]	3.25 [d]
MTA	0.11	0.5	11	2	22	0.18	0.83
	0.22	1.0	11	2	44	(0.13–0.25)	(0.61–1.15)
	0.33	1.5	12	1	91		
	0.44	2.0	12	0	92		
PCA						0.17 [e]	0.82 [e]
(C)							
MMAI						0.56 [f]	2.64 [f]
MTA	0.11	0.5	13	1	8	0.21	0.96
	0.22	1.0	13	1	50	(0.16–0.27)	(0.44–1.08)
	0.33	1.5	13	1	75		
	0.44	2.0	14	0	100		
PCA						0.14 [e]	0.82 [e]

[a] Number of animals tested. [b] Number of animals disrupted (50 presses not completed in 5 min). [c] Percentage of non-disrupted animals that selected drug lever. Values included for comparison, taken from: [d] Nichols et al., 1990; [e] Johnson et al., 1990; [f] Nichols et al., in press.

reported are the average of three experiments as determined from graded dose-response curves, according to the procedure of Tallarida and Murray (1981). To compare IC_{50} values for [^{3}H]5-HT or [^{3}H]dopamine uptake inhibition between PCA and MTA, a Student's t-test was employed.

Tritium efflux into the superfusate was calculated as the percentage of the tritium content of the slice at the beginning of the collection of that fraction. Each point in the tritium efflux curve (fig. 1) is the average of five experiments, performed on five different days.

For HPLC-EC assays, the concentrations of norepinephrine, dopamine, homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were determined using the Dynamax Method Manager software (Rainin, Woburn, MA) implemented on an Apple Macintosh SE computer. All comparisons utilized an analysis of

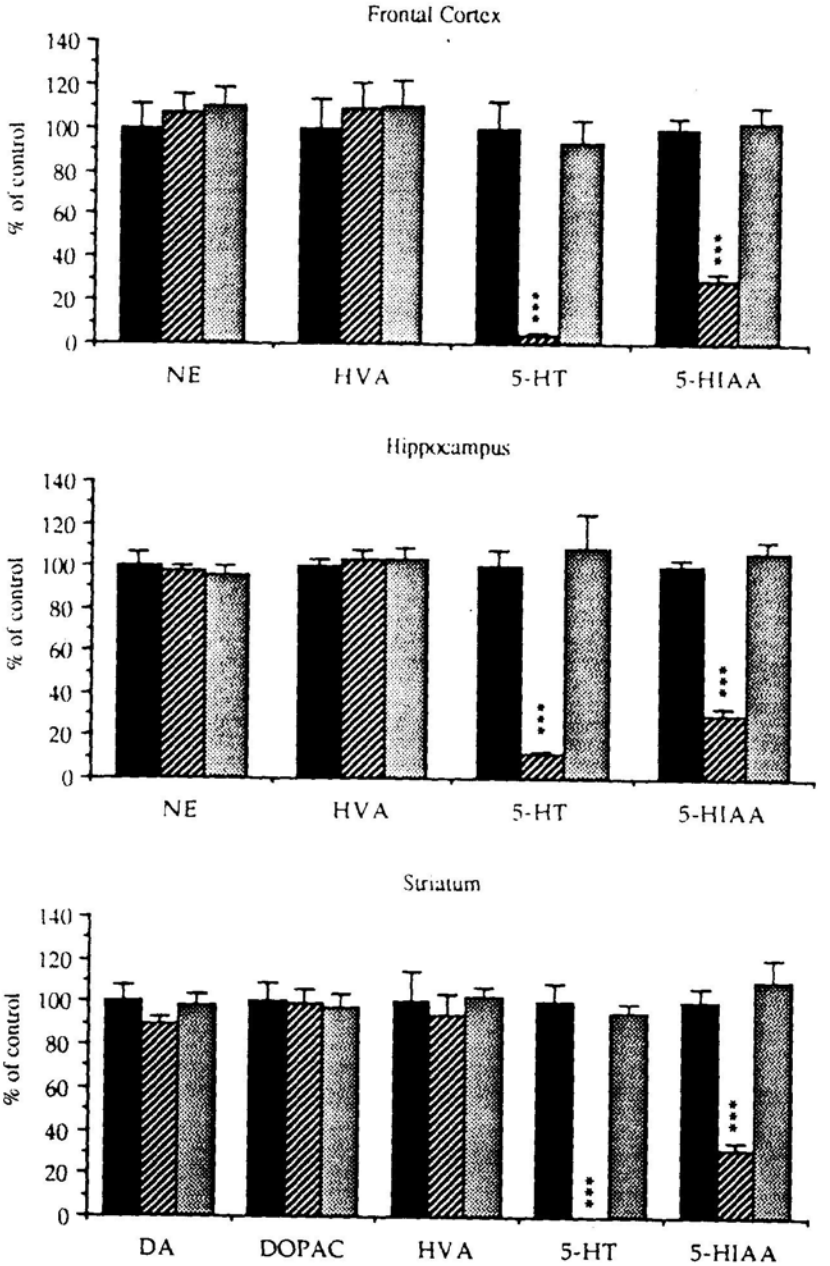


Fig. 3. Saline (■), PCA 10 mg/kg (▨), or MTA 21.3 mg/kg (▩) was injected s.c. and animals were killed one week later. Brain 5-HT, 5-HIAA, dopamine, DOPAC, norepinephrine and HVA levels were determined in frontal cortex, hippocampus and striatum using HPLC-EC techniques. Values are represented as the means ± S.E.M. for n = 6. Saline control values were as follows with units of pg/mg wet weight: cortical NE, 538 ± 59; HVA, 239 ± 31; 5-HT, 441 ± 54; 5-HIAA, 399 ± 20; dopamine and DOPAC were too low to be stably detected. Hippocampal NE, 1267 ± 77; HVA, 544 ± 19; 5-HT, 941 ± 171; 5-HIAA, 1099 ± 42; dopamine and DOPAC were too low to be detected. Striatal dopamine, 11612 ± 869; DOPAC, 1898 ± 177; HVA, 1652 ± 244; 5-HT, 1109 ± 102; 5-HIAA, 1218 ± 89. *** Significantly different from saline control value ($P < 0.001$, ANOVA).

TABLE 2

The inhibition of [^{3}H]5-HT, [^{3}H]dopamine and [^{3}H]norepinephrine uptake was examined in rat whole brain synaptosomes. The IC_{50} values represent the means ± S.E.M. of three separate experiments. Each experiment utilized five concentrations, run in triplicate. The IC_{50} values were determined from the linear portion of graded dose-response curves, according to the procedure of Tallarida and Murray (1981).

	IC_{50} (nM) to inhibit monoamine uptake		
	[^{3}H]5-HT	[^{3}H]dopamine	[^{3}H]norepinephrine
PCA	182 ± 16	424 ± 55	207 ± 14
MTA	74 ± 10 [a]	3073 ± 407 [a]	2375 ± 121 [a]

[a] Significantly different from PCA IC_{50} ($P < 0.005$, Student's t-test).

variance followed by a post hoc comparison as embodied in the computer program EPISTAT (EPISTAT Services, Richardson, TX).

3. Results

Results of drug discrimination studies shown in table 1 indicate that MTA fully substituted in MDMA-trained, S-MBDB-trained and MMAI-trained rats. Both MTA and PCA were potent in producing disruption in (+)-amphetamine-trained and LSD-trained rats. Neither compound substituted in (+)-amphetamine-trained or LSD-trained rats which were not disrupted (data not shown). These results indicate that behaviorally, MTA acts like PCA and has neither amphetamine-like nor LSD-like properties.

In synaptosome monoamine uptake inhibition experiments, MTA is about two times more potent than PCA in the inhibition of [^{3}H] 5-HT uptake but about seven and ten times less potent than PCA in the inhibition of [^{3}H]dopamine and [^{3}H]norepinephrine uptake, respectively (table 2).

The superfusion experiments (fig. 2) show that MTA can induce a dose-dependent increase of tritium efflux from rat frontal cortex slices preloaded with [^{3}H]5-HT. The degree of radioactive efflux induced by 10 μM of MTA is not different from that induced by 10 μM of PCA.

Neurotoxcity studies (fig. 3) show that 10 mg/kg of PCA causes a dramatic long-term decrease of both 5-HT and 5-HIAA. By contrast, 21.3 mg/kg of MTA, twice the molar dose of PCA, caused no changes in serotonin markers. Neither compound produced effects on other monoamine levels (fig. 3).

4. Discussion

Previous studies in our laboratory, and others, have provided strong evidence that the primary discriminative cue of MDMA, S-MBDB and MMAI is probably a consequence of release of endogenous serotonin (Nichols et al., 1986; Oberlender and Nichols, 1988; Schechter, 1988; Nichols and Oberlender, 1990; Nichols et al., in press). We have previously shown that another para-substituted amphetamine, PCA, completely substituted in animals trained to discriminate MDMA, S-MBDB or MMAI from saline (Johnson et al., 1990; Nichols et al., in press). The present studies show that MTA, another para-substituted amphetamine, also completely substituted for MDMA, S-MBDB or MMAI with potency comparable to PCA in the drug discrimination paradigm (table 1). The high doses of MTA (21.3 mg/kg; used in our neurotoxicity study) produced typical serotonergic behaviors that included hindlimb abduction, flat body posture, reciprocal forepaw treading, and salivation (data not shown). These behavioral syndromes induced by MTA are similar in their nature and intensity to those evoked by PCA, although there are also certain differences. For instance, MTA did not induce lateral head weaving and Straub tail, identified as a component of the serotonin syndrome which is characteristic of PCA (Jacobs, 1976; Trulson and Jacobs, 1976). Thus, both the drug discrimination experiments and direct behavioral observations suggest that MTA is a behaviorally active PCA analogue.

Synaptosome monoamine uptake inhibition experiments showed MTA to be a very selective serotonergic agent compared to PCA. Its potency in this regard is at least as high as that of PCA. It is however, much less potent as a catecholaminergic agent (table 2). The superfusion experiments were employed to investigate further the properties of MTA on serotonin systems. This work established that MTA can cause a dose-dependent serotonin release, with a potency no less than that of PCA (fig. 2). Thus, MTA is a potent serotonin releaser, and is less pharmacologically complex than PCA. The present results support our previous proposal that serotonin release is the primary discriminative cue of MDMA, S-MBDB and MMAI (Nichols et al., 1986; Oberlender and Nichols, 1988; Schechter, 1988; Nichols and Oberlender, 1990; Nichols et al., in press).

Previous work in our laboratory, and others, has also suggested that non-vesicular dopamine release plays an important role in drug-induced serotonin neurotoxicity of amphetamine-like compounds (e.g. Johnson et al., 1990; 1991a; Johnson and Nichols, 1991). If this hypothesis were true, then MTA, which is relatively inert as a catecholaminergic agent, should also lack serotonin neurotoxicity. Based on this rationale, long-term effects of MTA on monoamine levels in frontal cortex, hippocampus and striatum were determined. These studies showed that MTA, in contrast to PCA, had no long-term serotonin marker depleting effects (fig. 3). This result is consistent with the hypothesis that cate-

cholamine systems may play a critical role in the neurotoxicity of PCA-like compounds. The question of which catecholamine – dopamine or norepinephrine – is more important could not be answered by the present studies.

PCA currently seems to be the 'standard' serotonin releasing agent used in most research studies. Its effects on dopamine and norepinephrine systems confound interpretation of behavioral studies of PCA. MTA, as a potent and 'purer' serotonin releasing agent provides a new and better tool for researchers interested in understanding the importance of 5-HT in animal behavior and the mechanism of the serotonin releasing effects of amphetamine-like compounds.

To summarize, the initial behavioral characterization of MTA indicates that it is about equipotent to PCA. Synaptosome uptake studies show that it is slightly more potent than PCA as a serotonin uptake inhibitor, but considerably less potent than PCA as a catecholaminergic agent. Superfusion experiments further confirmed it to be equipotent to PCA as a serotonin releaser. Unlike PCA, MTA appears to lack serotonin neurotoxicity at behaviorally relevant doses. The present studies also support previous conclusions regarding the critical role of 5-HT but not dopamine in the discriminative stimulus properties of MDMA and similar compounds (Oberlender and Nichols, 1988). The lack of serotonin neurotoxicity for MTA suggests that effects on catecholamine systems are a necessary condition for the expression of serotonin neurotoxicity of PCA-like compounds.

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