The ability of several 3,4-methylenedioxymethamphetamine (MDMA) analogues to inhibit the uptake of $[^3]H$ serotonin (5-HT), dopamine (DA) and norepinephrine (NE) into synaptosomes was examined. In addition, the ability of the compounds to inhibit the uptake of $[^3]H$-5-HT and DA into synaptosomes from rats pretreated with reserpine (5 mg/kg i.p., 16 h pretreatment) was compared to control experiments. All of the test compounds were found to be potent releasers of non-vesicular 5-HT (the reserpine IC$_{50}$ was significantly smaller than the control IC$_{50}$). The range of 5-HT inhibitory activity corresponds well to the small range of ED$_{50}$ values of the test compounds to substitute in drug discrimination experiments with animals trained to discriminate MDMA or S( + )-N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane (S-MBDB) from saline. In contrast, there was a wide range of potency for the inhibition of NE and DA uptake. In addition, several of the analogues appeared to be pure uptake inhibitors of DA while others were found to be releasers of non-vesicular DA. Several of the compounds were very selective for 5-HT over DA or NE uptake inhibition, including 3-methoxy-4-methylamphetamine (MMA) and 5-methoxy-6-methyl-2-aminoindan (MMAI). A correlation was noted between the 5-HT neurotoxic potential of some of the test compounds and their relative ability to induce a release of non-vesicular DA. The potential catechol metabolites of the methylenedioxy-substituted compounds also showed potent monoamine releasing properties, suggesting that metabolism may play a role in the neurotoxic actions of some of these drugs. The present data support the hypothesis that drug-stimulated non-vesicular 5-HT release is primarily responsible for the discriminative cue of MDMA.

1. Introduction

The recent research interest in the pharmacology of 3,4-methylenedioxymethamphetamine (MDMA) and its analogues has centered on two areas: their behavioral activity and the apparent serotonin (5-HT) neurotoxicity of these substituted amphetamines. The latter has been most well studied. For example, it is known that MDMA and the primary amine, 3,4-methylenedioxymethamphetamine (MDA), cause long-term reductions in the levels of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) (Ricaurte et al., 1985; Schmidt et al., 1986; Stone et al., 1986), and in the number of 5-HT uptake sites (Battaglia et al., 1987; 1988; Commins et al., 1987; Schmidt et al., 1987). This is similar to the reductions seen with p-chloroamphetamine (PCA) (Fuller and Snoddy, 1974; Harvey et al., 1975). These effects of MDA, MDMA, and PCA have been attributed to a selective degeneration of the serotonergic fine axon projections ascending from the dorsal raphe nucleus (O’Hearn et al., 1988; Mamounas and Molliver, 1988). A number of animal models have been utilized to assess the behavioral activity of MDMA, including the acoustic startle response (Mansbach et al., 1989) and locomotor and exploratory behavior in rats (Gold et al., 1988; 1989; Callaway et al., 1990). One routinely used method is the drug discrimination paradigm, where rats are trained to discriminate the effects of a drug from saline. This approach has been used extensively to study the discriminative properties of MDA and MDMA (Glennon et al., 1982; Oberlender and Nichols, 1988; Nichols et al., 1986; Nichols and Oberlender, 1990; Schechter, 1989). Utilizing this technique, several analogues of MDMA with similar discriminative cues have been identified. For example, it has been found that MDA and the a-ethyl analogue of MDMA, N-methyl-1-(1,3-benzodioxol-5-yl)-2-aminobutane...
(MBDB), substitute in MDMA- and S-MBDB-trained rats (Nichols et al., 1986; Oberlender and Nichols, 1990). Similarly, PCA and p-iodoamphetamine (PIA) also substitute for MDMA and S-MBDB (Johnson et al., 1990; Nichols et al., 1991). Also, 3-methoxy-4-methylamphetamine (MMA) has similar activity in these paradigms (Johnson et al., 1991).

Several rigid amphetamine analogues (fig. 1) have also been found to substitute for MDMA and S-MBDB in the drug discrimination paradigm, including 5,6-methylenedioxy-2-aminoindan (MDA) (Nichols et al., 1990), 5-methoxy-6-methyl-2-aminoindan (MMA) (Johnson et al., 1991), 6-chloro-2-aminoindan (6-CAT) (unpublished results), and 5-iodo-2-aminoindan (5-IA) (Nichols et al., 1991). Interestingly, these analogues show widely varying abilities to cause serotonin neurotoxic effects characteristic of PCA, MDMA, or MDA. For example, MBDB and PIA appear to be neurotoxic but are less potent than MDMA and PCA, respectively (Johnson and Nichols, 1989; Nichols et al., 1991). The rigid analogues 6-CAT (Fuller et al., 1974; 1977), MDA (Nichols et al., 1990), or 5-IA (Nichols et al., 1991) are markedly less potent or are not serotonin neurotoxins. Finally, neither of the methoxy-methyl-substituted analogues (MMA and MIA) were found to cause long-term decreases in 5-HT or 5-HIAA, even after multiple high doses (Johnson et al., 1991). Thus, we had available a series of ten amphetamine analogues that had behavioral properties similar to MDMA but very different neurotoxic potentials.

2. Materials and methods

2.1. Inhibition of $[^3]$H monoamines

The procedure of Steele et al. (1987) was utilized with minor modification. Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 175–200 g, were group-housed and maintained on a 14 h light (06:00)/dark (20:00) cycle. Food and water were provided ad lib. Animals were injected i.p. with either vehicle or 5 mg/kg of reserpine (dissolved in a minimum amount of acetic acid and diluted to 2.5 mg/ml with 5% ethanol/H$_2$O) 16 h before killing.

For each experiment two rats were killed by decapitation and their cortex, hippocampus and caudate nucleus were removed (Glowinski and Iversen, 1966), combined, and homogenized in 15 volumes of 0.32 M sucrose using a motor-driven teflon pestle and a glass mortar. The homogenate was centrifuged for 10 min at 17000 x g. The pellet was resuspended in the same volume of sucrose and the homogenate was placed on ice until assay.

Solutions of each test compound were prepared by serial dilution and 50 μl of each concentration was added to each of three test tubes. Tubes intended to measure total and non-specific binding received 50 μl of double-distilled water. Each tube contained 1.7 ml of Krebs-Ringer phosphate buffer mM: 118 NaCl, 25.0 NaHCO$_3$, 10.0 glucose, 4.8 KCl, 1.3 CaCl$_2$, 1.2 KH$_2$PO$_4$, 1.2 MgSO$_4$, 0.06 ascorbic acid, 0.03 Na$_2$EDTA) with pargyline (final concentration 100 μM). The assay was commenced by adding a 200 μl aliquot of the tissue homogenate to each test tube.
Test tubes were then subjected to a 5 min pre-incubation at 37°C under a 95% O₂-5% CO₂ atmosphere. Immediately following this, 50 µl of the appropriate radioligand ([³H]5-HT, [³H]DA or [³H]NE; final concentration 10 nM) was added to each tube (final volume of 2 ml). All tubes were then incubated for an additional 5 min. Synaptosomal uptake of radioligand was terminated by cooling the tubes on ice. Synaptosomes were collected by suction filtration through Whatman GF/B filters (Brandel Cell Harvester Model M-12R, Brandel). After drying, the filters were placed into plastic scintillation vials, filled with 10 ml of scintillation counting fluid (Budget-solve; Research Products International) and left overnight prior to counting at an efficiency of 54%. Specific uptake was defined as that occurring at 37°C minus the uptake at 0°C.

2.2. Drugs

PCA HCl and pargyline HCl were purchased from Sigma Chemical Company (St. Louis, MO). 6-CAT HCl was kindly provided by Eli Lilly Laboratories (Indianapolis, IN). All other test compounds were synthesized according to standard procedures. [³H]5-HT, [³H]DA and [³H]NE were purchased from New England Nuclear (Boston, MA) at a specific activity of 15.1, 13.8 and 20.5 Ci/mmol, respectively.

2.3. Statistical analysis

Percent uptake inhibition was defined as the difference between specific uptake in control and drug test tubes divided by control uptake times 100% (Steele et al., 1987). The values reported were determined by combining the data from three to four experiments and utilizing the procedure of Tallarida and Murray (1981) to determine the IC₅₀ from graded dose-response curves. Comparisons between IC₅₀ values from control and reserpinized animals utilized a Student’s t-test. Multiple linear regression for the uptake inhibition: potencies versus substitution in either MDMA- or 3-MBDB-trained animals was attempted utilizing routines in the computer program EPISTAT (EPISTAT Services, Richardson, TX).

3. Results

3.1. Amphetamine analogues

As seen in table 1, all of the test compounds were potent inhibitors of [³H]5-HT uptake into synaptosomes. In addition, the reserpine IC₅₀ was significantly lower than the control IC₅₀ value for each drug, giving ratios of control IC₅₀/reserpine IC₅₀ significantly greater than unity. In contrast, some but not all of the test drugs were potent inhibitors of [³H]DA and [³H]NE uptake. Also, several of the test compounds appear to be DA uptake inhibitors rather than non-vesicular DA releasers (including MDAI, MMA, MMAI and PIA) as indicated by their control IC₅₀/reserpine IC₅₀ value. Since the reserpine technique utilized in this study has been previously shown to be ineffective when examining NE uptake inhibition versus non-vesicular release (Ross, 1979), the relative ability of the test drugs to release NE, as opposed to inhibition of uptake cannot be commented upon.

<table>
<thead>
<tr>
<th>Drug</th>
<th>[³H]5-HT</th>
<th>[³H]DA</th>
<th>[³H]NE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Reserpine</td>
<td>Control</td>
</tr>
<tr>
<td>MDA</td>
<td>177 ± 9 d</td>
<td>2.70</td>
<td>384 ± 20 d</td>
</tr>
<tr>
<td>MDMA</td>
<td>76 ± 6 d</td>
<td>5.59</td>
<td>571 ± 36 d</td>
</tr>
<tr>
<td>MBDB</td>
<td>152 ± 16 d</td>
<td>5.16</td>
<td>4615 ± 668 d</td>
</tr>
<tr>
<td>MDAI</td>
<td>140 ± 3.3 d</td>
<td>3.66</td>
<td>5155 ± 559</td>
</tr>
<tr>
<td>MMA</td>
<td>52 ± 4 d</td>
<td>2.62</td>
<td>16293 ± 1878</td>
</tr>
<tr>
<td>MMAI</td>
<td>77 ± 5 d</td>
<td>2.76</td>
<td>25778 ± 3035</td>
</tr>
<tr>
<td>PCA</td>
<td>56 ± 3 d</td>
<td>3.30</td>
<td>304 ± 39</td>
</tr>
<tr>
<td>6-CAT</td>
<td>35 ± 2.4 d</td>
<td>3.41</td>
<td>1181 ± 127 d</td>
</tr>
<tr>
<td>PIA</td>
<td>43 ± 2 d</td>
<td>1.89</td>
<td>542 ± 69</td>
</tr>
<tr>
<td>5IAI</td>
<td>40 ± 4 d</td>
<td>6.05</td>
<td>286 ± 34 d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>[³H]5-HT</th>
<th>[³H]DA</th>
<th>[³H]NE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Reserpine</td>
<td>Control</td>
</tr>
<tr>
<td>MDA</td>
<td>478 ± 40</td>
<td>177 ± 9 d</td>
<td>890 ± 100</td>
</tr>
<tr>
<td>MDMA</td>
<td>425 ± 41</td>
<td>76 ± 6 d</td>
<td>1442 ± 120</td>
</tr>
<tr>
<td>MBDB</td>
<td>784 ± 52</td>
<td>152 ± 16 d</td>
<td>7825 ± 888</td>
</tr>
<tr>
<td>MDAI</td>
<td>512 ± 38</td>
<td>140 ± 3.3 d</td>
<td>5920 ± 690</td>
</tr>
<tr>
<td>MMA</td>
<td>136 ± 22</td>
<td>52 ± 4 d</td>
<td>16317 ± 2173</td>
</tr>
<tr>
<td>MMAI</td>
<td>212 ± 20</td>
<td>77 ± 5 d</td>
<td>19793 ± 2404</td>
</tr>
<tr>
<td>PCA</td>
<td>184 ± 12</td>
<td>56 ± 3 d</td>
<td>383 ± 46</td>
</tr>
<tr>
<td>6-CAT</td>
<td>120 ± 13</td>
<td>35 ± 2.4 d</td>
<td>3137 ± 248</td>
</tr>
<tr>
<td>PIA</td>
<td>82 ± 8</td>
<td>43 ± 2 d</td>
<td>589 ± 32</td>
</tr>
<tr>
<td>5IAI</td>
<td>241 ± 21</td>
<td>40 ± 4 d</td>
<td>992 ± 90</td>
</tr>
</tbody>
</table>

* Ratio of the IC₅₀ in control synaptosomes over the IC₅₀ in reserpinized synaptosomes. * Values included for comparison. Taken from Johnson et al. (1991). * Values included for comparison. Taken from Nichols et al. (1991). * Significantly lower than the control IC₅₀.
3.2. Potential metabolites of methylenedioxy-substituted amphetamines

Previous experiments have indicated that MDA and MDMA are metabolized to α-methyldopamine and α-methylepine, respectively (Steele et al., 1990; Cho et al., 1990; Midha et al., 1978; Marquardt and DiStefano, 1974; Marquardt et al., 1978b). Furthermore, Marquardt et al. (1978a) have reported that α-methyldopamine is a potent uptake inhibitor and releaser of non-vesicular NE. Therefore, the potential catechol metabolites of MDA, MDMA, MBDB and MDA1 (namely α-methyldopamine, α-Me-DA, α-methylepine, α-Me-Ep; α-ethylepine, α-Et-Ep; and 5,6-dihydroxy-2-aminoindan, DHAI; respectively) were examined. The rigid analogue DHAI had relatively low potency as an inhibitor of monoamine uptake, although a moderate selectivity for NE uptake inhibition was found (table 2). In contrast, α-Me-DA, α-Me-Ep and α-Et-Ep are very potent releasers of non-vesicular DA and inhibitors of NE uptake. They showed much lower potencies as releasers of non-vesicular 5-HT.

3.3. Linear correlation to drug discrimination potencies

Multiple linear regression with the reciprocals of the IC₅₀ values for inhibition of 5-HT, DA and NE uptake, versus the reciprocal of the ED₅₀ in MDMA- or S-MBDB-trained rats (listed in table 3) was not possible due to the high degree of covariance between the IC₅₀ values. For example, the r value for linear regression of 1/(5-HT IC₅₀) on 1/(DA IC₅₀) was 0.70, while r values of 0.4 or less are generally required to ensure independence of variables in multiple linear regression analysis. This high degree of covariance for uptake inhibition of each monoamine probably explains the similarity in the r values reported in the legend of table 3. Therefore, no conclusions could be drawn regarding the relative importance of 5-HT, DA or NE systems in drug discrimination, utilizing linear regression.

4. Discussion

Despite the inability to determine the relative importance of 5-HT, DA and NE in the discriminative cue of MDMA or MBDB using regression analysis, a careful examination of the data indicates that non-vesicular 5-HT release may be of primary importance. This is perhaps best illustrated by comparing the range of drug discrimination ED₅₀ values to the range of IC₅₀ values for inhibition of 5-HT, DA and NE uptake. For instance, the 50-fold range in IC₅₀ values for DA
uptake inhibition does not correspond well to the only 5-fold range of ED$_{50}$ values for MDMA substitution or the 4-fold range for S-MBDB substitution. Similarly, the range of NE potencies is much larger (over 40-fold) than is seen in the drug discrimination experiments. This is not surprising considering the high degree of correlation between potency for inhibition of DA and NE uptake ($r = 0.85$, reciprocal IC$_{50}$ linear regression). However, it should be noted that all of the test drugs are either equipotent or selective for NE over DA uptake inhibition, suggesting that NE might be of relatively greater importance than DA in any catecholamine mediation of the discriminative cue.

In contrast to the catecholamine data, the 10-fold range in potency for 5-HT uptake inhibition corresponds more closely to the small range of ED$_{50}$ values for drug discrimination. In addition, some of the test drugs are quite selective for 5-HT over DA or NE neurons. For example, MMA has 120- and 30-fold selectivity for 5-HT over DA and NE, respectively. Its rigid analogue MDAI has 100- and 50-fold selectivity for 5-HT over DA and NE, respectively. Therefore, the present data suggest that 5-HT modulation is more important than DA or NE for the discriminative cue of MDMA and S-MBDB. This is in agreement with a previous report by Scheechter (1989) where the discriminative cue at short time periods after MDMA administration was serotonergic in nature.

Any simple relationship between the present data and the relative serotonergic neurotoxicity of these compounds is complicated by several factors. First, the reserpinized synaptosome technique cannot be used to differentiate uptake inhibition from release of non-vesicular NE (Ross, 1979). Although many of the test drugs are moderately potent inhibitors of NE uptake, there is no clear trend for either the neurotoxic or the non-neurotoxic compounds to be more potent inhibitors of NE. For example, PIA, MBDB, MDAI and 6-CAT are all approximately equipotent NE uptake inhibitors, but only PIA and MBDB are known to be serotonin neurotoxins.

Similarly, there are no clear trends in the 5-HT data. All of the test drugs, including the neurotoxic and non-neurotoxic analogues were potent non-vesicular 5-HT releasers. However, this does not exclude a role for serotonin release in the toxicity associated with some of these compounds. For example, it may be that the short-term depletion of 5-HT induced by release, coupled with inhibition of tryptophan hydroxylase (Stone et al., 1986; 1989; Johnson et al., 1986; Schmidt, 1987b; Schmidt and Taylor, 1987) might play a critical initial role in the selective serotonin neurotoxicity. However, the data strongly suggest that release of non-vesicular 5-HT cannot be the only factor involved in the neurotoxicity of some of these drugs. This is supported by the observation that the non-neurotoxic analogues MDAI, MMA, and MDAI also deplete levels of 5-HT at 3 h after a single high dose (Johnson et al., 1991; Johnson and Nichols, unpublished results).

A second complication of the data stems from the finding that some of the test compounds appear to be DA uptake inhibitors rather than non-vesicular releasers. For instance, while MDA and MDMA appear to be non-vesicular DA releasers, the very potent neurotoxin PCA would appear to be a DA uptake inhibitor. However, it is known that PCA is a non-vesicular releaser of DA at higher doses (Schmidt, 1987b). Therefore, it is possible the test compounds that resemble DA uptake inhibitors may actually be releasers of non-vesicular DA at slightly higher concentrations.

A further complication in interpreting the results is the inability to take into account in vivo pharmacokinetic parameters. Although all the test drugs are structurally similar, there is evidence that some of these have widely different pharmacokinetic properties. For example, it has previously been noted that the in vitro potency of PIA is greater than PCA, while the opposite relationship is seen in vivo. That is, PIA in vivo is a less potent depleter of 5-HT (Fuller et al., 1980) and a substantially less potent serotonin neurotoxin (Fuller et al., 1980; Nichols et al., 1991). Also, PIA and 5-IAI are substantially less potent in substituting for MDMA and S-MBDB in drug discrimination experiments than might be anticipated from the in vitro data (tables 1 and 3; Nichols et al., 1991).

There is now considerable evidence to implicate the involvement of DA in the neurotoxicity of MDMA. For example, depletion of DA with either reserpine or the decarboxylase inhibitor, monofluoromethyl-DOPA, led to an attenuation of the neurotoxic actions of MDMA (Stone et al., 1988; Schmidt et al., 1990). Similarly, the tyrosine hydroxylase inhibitor a-methyl-p-tyrosine partially blocks the toxic actions of MDMA (Stone et al., 1989; Schmidt, 1991). The DA uptake inhibitor GBR-12909 attenuates (Stone et al., 1988) and the D$_2$ antagonist haloperidol blocks the neurotoxicity of MDMA (Schmidt et al., 1990). DA lesions generated by bilateral but not unilateral injections of 6-OH-DA into the substantia nigra result in decreased MDMA neurotoxicity (Stone et al., 1988; Schmidt et al., 1990). Taken together, these data strongly implicate DA in the neurotoxic actions of MDMA.

The relative potency of the test drugs to inhibit DA uptake (shown in table 1) further supports the involvement of DA in MDMA's neurotoxicity. For instance, the most potent neurotoxins (PCA, MDA and MDMA) cause toxicity after a single high dose, and also have the greatest inhibitory effect on DA uptake (less than 1.5 µM). Those drugs that do not result in toxicity after a single dose and are, or may be, toxic only after multiple dosing (6-CAT, MBDB and MDAI) have a moderate potency for DA uptake inhibition (3-8 µM).
Finally, the two drugs (MMA and MMAI) that completely lack any apparent neurotoxic actions even after multiple high dosing have the lowest potency for DA uptake inhibition (greater than 15 μM). This structure-activity relationship linking dopaminergic potency and serotonin neurotoxicity is similar to that noted earlier for the stereoisomers of MDA and MDMA, as well as for the MDMA analogue, N-ethyl-3,4-methylenedioxyamphetamine (Schmidt, 1987a,b; Johnson et al., 1988; Stone et al., 1987).

The possibility of DA involvement in serotonin neurotoxicity also opens a plausible role for the catechol metabolites of some of these drugs. Previous work has indicated α-Me-DA to be a primary metabolite of MDA both in vitro and in vivo (Midha et al., 1978; Marquardt and DiStefano, 1974; Marquardt et al., 1978b). Similarly, it has been suggested that α-Me-Ep is a metabolite of MDMA (Steele et al., 1990; Cho et al., 1990). This metabolite can be formed in vitro by both liver and brain microsomes. Furthermore, the catechol metabolites of the neurotoxic methylenedioxy analogues were potent non-vesicular DA releasers. In fact, these compounds are some 8- to 10-fold more potent than the parent drugs, suggesting that their formation could contribute to any non-vesicular DA release that occurs in vivo. It should also be noted that these catechols are 10- to 20-fold selective for DA over 5-HT release.

A more direct assessment of the neurotoxicity of α-Me-Ep has been reported by Steele et al. (1990). In this study, i.c.v. injections of up to 600 μg failed to produce any long-term effects on the levels of 5-HT or its metabolite, suggesting α-Me-Ep alone is not neurotoxic. However, it is possible that both the pharmacological actions of the parent drug MDMA and its catechol metabolite are required for this neurotoxic response. As cited previously there is more than sufficient evidence to suggest an involvement of DA in this toxic response. However, recent work has also implicated the importance of 5-HT release in the neurotoxic effects of MDMA-like drugs (Johnson and Nichols, in press). Therefore, it is conceivable that both the DA-releasing properties of α-Me-Ep and the 5-HT-releasing properties of MDMA may be required for the induction of a serotonergic neurotoxicity.

In contrast to the other catechols, the metabolite of the non-neurotoxic MDAI (DHAI) is substantially less potent than the parent drug for inhibition of monoamine uptake. Also, like its parent drug, DHAI appears to be a pure uptake inhibitor rather than a releaser of non-vesicular DA. Therefore, if catechol metabolites can play a role in neurotoxicity, this may partially explain the decreased neurotoxic potential of MDAI compared to MDA. Therefore, the available data do not exclude the possibility that metabolism of the methylenedioxy ring to a catechol may play a contributory role in the neurotoxicity of MDA, MDMA and MBDB.

To summarize, the present report characterized the monoamine-releasing and uptake inhibition properties of several substituted amphetamine analogues. Both the serotonin neurotoxic and the non-neurotoxic analogues were potent releasers of non-vesicular 5-HT, with varying degrees of selectivity over DA and NE. The ability to release 5-HT corresponds well to the ability of the test drugs to substitute in drug discrimination experiments with MDMA- and S-MBDB-trained rats. In addition, there is some evidence to suggest that non-vesicular DA release may be important for the amphetamine analogues that have selective serotonin neurotoxic activity. The corresponding potential catechol metabolites of the methylenedioxy-substituted analogues are potent and selective non-vesicular DA releasers, and may contribute to the neurotoxicity of these derivatives.

Acknowledgement

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