The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxymethamphetamine (MDA) on monoaminergic systems in the rat brain

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The effects of two amphetamine-like designer drugs, 3,4-methylenedioxymethamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA), on dopaminergic and serotonergic systems in the rat brain were investigated and compared to those of methamphetamine (METH). Like METH, single or multiple 10 mg/kg doses of either drug caused marked reductions in both tryptophan hydroxylase (TPH) activity and concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid, in several serotonergic nerve terminal regions. In all regions examined, the reduction in 5-HT content corresponded to the depression of TPH activity. Unlike multiple METH administrations, which induced pronounced deficits in dopaminergic neuronal markers, repeated doses of MDA or MDMA did not alter striatal tyrosine hydroxylase (TH) activities or reduce striatal dopamine concentrations. A single dose of MDA or MDMA significantly elevated striatal dopamine content; however, after repeated drug administrations dopamine concentrations were comparable to control values. At this time, striatal levels of homovanillic acid were significantly elevated suggesting that both drugs influence dopamine turnover. The effects of MDA or MDMA administration in the rat brain are reminiscent of those elicited by p-chloroamphetamine, a presumed serotonergic neurotoxin.

3,4-Methylenedioxymethamphetamine; 3,4-Methylenedioxymethamphetamine; Tryptophan hydroxylase; Tyrosine hydroxylase; Serotonin; Dopamine

1. Introduction

MDA and MDMA are synthetic amphetamine analogs which have attracted recent public attention, as well as growing interest and concern in the scientific and medical communities. As substituted phenylethylamines, they are structurally related to a wide variety of other synthetic and naturally occurring compounds including amphetamine, a classical psychomotor stimulant; mescaline, a potent hallucinogen; and catecholamines. Variations in the location and identity of substituent groups, both on the phenyl ring and the ethylamine side chain, profoundly alter the potency and ability of these compounds to elicit stimulatory or psychotomimetic effects (Anderson et al., 1978; Shulgin et al., 1969); this characteristic renders them valuable tools with which to investigate the relationship between biochemistry and behavior.

MDA produces a combination of sympathomimetic stimulation and perceptual alterations (Gunn et al., 1939), and its clinical toxicity parallels that of amphetamine (Simpson and Rumack, 1981), whereas its N-methylated derivative, MDMA ('ecstasy'), is neither a true hallucinogen nor a potent stimulant; rather, it induces a unique state of enhanced emotional and sensory awareness (Adler et al., 1985). Although both compounds have been advocated as aids to psycho-
therapy (Adler et al., 1985; Naranjo et al., 1967), and MDA has been evaluated as a possible anorexigenic or antidepressant agent (Smith, Kline and French laboratories, 1957, Report on clinical evaluation of SKF No. 5 (amphetadonamine), Philadelphia, PA), there is, currently, no legitimate therapeutic use for either compound.

Recent findings by Ricaurte et al. (1985) suggest that MDA is selectively toxic to serotonergic neurons in the rat brain. These investigators found morphological evidence of nerve terminal degeneration in brain regions corresponding to those in which MDA had produced selective long-lasting reductions in three serotonergic neuronal markers. Although the toxicity of MDMA has not previously been assessed, its high abuse liability, increasingly widespread recreational use, and structural similarity to MDA prompted the Drug Enforcement Administration to place MDMA under a temporary 'Schedule I' controlled substance classification (Lawn, 1984, Federal Register 50 (150), 23118) along with MDA, LSD and heroin.

In this study we have focused on the responses of the serotonergic and dopaminergic neurotransmitter systems to MDA and MDMA. Effects of these two designer drugs were compared to those of METH, a structural analog which is known to cause long-lasting reductions in the brain concentrations of both dopamine and serotonin and their major metabolites (Koda and Gibb, 1973; Ricaurte et al., 1980; Wagner et al., 1980), as well as significant decreases in TH and TPH activities, the rate limiting enzymes for dopamine and serotonin synthesis, respectively (Hotchkiss and Gibb, 1980).

We now report that single or multiple doses of MDA or MDMA cause neurochemical deficits in serotonergic pathways which are similar to those induced by METH; in contrast, the response of dopaminergic pathways to these agents and METH are very different.

2. Materials and methods

2.1. Drug administration

Male Sprague-Dawley rats weighing 200-275 g were housed 5 per cage and maintained in a temperature controlled room (26°C) with a 12 h alternating light-dark cycle. They were allowed free access to standard laboratory food and water. All drugs, as their hydrochloride salts, were dissolved in 0.9% saline and administered by subcutaneous injection; doses are expressed in terms of the free base. Subacute drug treatment consisted of 5 sequential doses at 6 h intervals of either d-METH (15 mg/kg), dl-MDA (10 mg/kg) or dl-MDMA (10 mg/kg). Acute treatment consisted of a single injection of drug (MDA or MDMA, 10 mg/kg). Control animals received similar injections of saline vehicle alone.

Rats were killed by decapitation 18 h (subacute) or 3 h (acute) after the last dose (within a 3 h period at mid-day), and the brains were immediately removed and placed on ice. The neostriata, hippocampi, and frontal cortex regions were removed bilaterally by dissection, frozen on dry ice, and stored at −70°C until assayed. One filtered, anorexigenic or antidepressant agent (Smith, Kline and French laboratories, 1957, Report on clinical evaluation of SKF No. 5 (amphetadonamine), Philadelphia, PA), there is, currently, no legitimate therapeutic use for either compound.

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Male Sprague-Dawley rats weighing 200-275 g were housed 5 per cage and maintained in a
with hyamine hydroxide. Details of the assay are described by Hotchkiss et al. (1979).

2.3. Determination of monoamine and monoamine metabolite concentrations

Tissue levels of dopamine (DA) and its primary metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and 5-hydroxytryptamine (5-HT) and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), were measured by high-performance liquid chromatography (HPLC) with electrochemical detection. Tissues were weighed and homogenized in 0.3-0.5 ml mobile phase buffer containing 0.15 M monochloroacetic acid, 2.0 mM disodium EDTA and 25 mg/1 1-octanesulfonic acid in 12.5% methanol at pH 2.9. After centrifugation at 4080 x g for 15 min the supernatant fractions were filtered through a 0.2 μm microfilter system (Bioanalytical Systems, Inc., West Lafayette, IN). Fifty microliter volumes were injected by a WISP automatic sample processor (Millipore Corp., Millford, MA) onto a 3 μm reverse phase Microsorb C18 column (Rainin Instrument Co., Woburn, MA). Samples were run on a LC-154 liquid chromatograph equipped with a model LC-4B amperometric detector (Bioanalytical Systems, Inc.). The detector potential was set at +0.73 V. Monoamines and their metabolites were quantitated by measurement of peak heights and comparison with those of standards of known concentration prepared in mobile phase buffer.

3. Results

3.1. Subacute effects of MDA, MDMA and METH

Eighteen hours after termination of subacute treatment with MDA, MDMA or METH, TPH activity was markedly decreased in all brain regions examined (fig. 1). After MDA treatment, remaining enzyme activity ranged from 14% of control in the neostriatum to 9% of control in the cerebral cortex. Slightly less dramatic reductions were consistently observed after MDMA treatment (remaining TPH activity ranged from 25% of control in the neostriatum to 15% of control in the cerebral cortex). METH-induced decreases in TPH activity were comparable to those induced by either MDA or MDMA.

Figure 2 presents the results of HPLC determinations of 5-HT and 5-HIAA concentrations in selected brain regions following subacute drug treatment. Levels of 5-HT and 5-HIAA were decreased to less than 30% of controls by both MDA and MDMA in all regions examined. These results correlate with the regional depression of TPH activity induced by either drug. METH treatment resulted in reductions of a similar magnitude; values were consistent with previous reports (Hotchkiss and Gibb, 1980).

Of the three compounds only METH significantly affected neostriatal TH, as evidenced by a 56% reduction in enzyme activity (fig. 3); this response to subacute METH treatment has been characterized previously (Koda and Gibb, 1973). MDA or MDMA, even when administered in higher doses (15 mg/kg, data not shown), did not significantly alter TH activity.

The effects of drug treatments on DA and DA metabolite levels are depicted in fig. 4. Although repeated MDA or MDMA administrations did
not significantly alter neostriatal DA or DOPAC concentrations, both drugs significantly increased the levels of HVA in this region, to 124 and 116% of controls, respectively. In contrast, neostriatal DA, DOPAC and HVA were all significantly decreased after METH treatment, to 26, 39 and 50% of controls, respectively. The METH-induced reduction in DA content was consistent with the decrease in TH activity observed in this region. In the two other brain regions examined, control levels of DA and its major metabolites were too low for accurate measurement.

**3.2. Acute**

Three doses of MDMA, less than the dose used for saline (10 mg/kg), were administered to rats. The saline control group received 0.2 ml of saline (pH 7.4) i.p., and the MDMA group received 10 mg/kg of MDMA i.p. These doses were calculated on the basis of the number of animals indicated in parentheses. Experimental conditions are described in fig. 1. Control values (in µg/g tissue) were: DA, 8.2; DOPAC, 1.19; HVA, 0.582. **P < 0.001, * P < 0.005 versus control, by the two-tailed Student's t-test. Abbreviations used are: DA, dopamine; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.
3.2. Acute effects of MDA and MDMA

Three hours after a single injection of MDA or MDMA, neostriatal TPH activity was reduced to less than 50% of control (fig. 5). Significant reductions occurred also in other brain regions (for MDA the values were: hippocampus 60% of control, cortex 49% of control; for MDMA: 52 and 30% of control in the hippocampus and cortex, respectively). Corresponding decreases in 5-HT and 5-HIAA levels were observed in all regions (fig. 6).

Although neostriatal TH activity was not affected by acute administration of either MDA or MDMA (fig. 5), DA levels were significantly elevated after a single injection of either drug (fig. 7). However, the effects of the two drugs on neostriatal concentrations of DA metabolites dif-

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**Fig. 5.** Effect of acute drug treatments on neostriatal tyrosine hydroxylase and tryptophan hydroxylase activities. Rats were killed 3 h after a single 10 mg/kg injection of drug. Results are presented as the means ± S.E.M. (n = 6) and expressed as percent control. Control values for TH and TPH activities were 2178.8 and 38.2 nmol/g tissue per h, respectively. * P < 0.001 versus control, by the two-tailed Student's t-test.

**Fig. 6.** Effect of acute drug treatments on 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations. Experimental conditions are described in fig. 5. The means ± S.E.M. from 6 animals are presented as percent of control. Control values (in µg/g tissue), with 5-HT concentration listed first, were: neostriatum, 0.421 and 0.517; hippocampus, 0.277 and 0.375; cortex, 0.487 and 0.267. * P < 0.001, † P < 0.005 versus corresponding control, by the two-tailed Student's t-test.

**Fig. 7.** Effect of acute drug treatments on neostriatal concentrations of dopamine and its metabolites. Results are the means ± S.E.M. (n = 6), expressed as percent control. Experimental conditions are described in fig. 5. Control values were: DA, 8.5; DOPAC, 1.09; HVA, 0.615 µg/g tissue. ** P < 0.005, * P < 0.025 versus control, by the two-tailed Student's t-test. Abbreviations used are: DA, dopamine; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.
fered. Concentrations of DOPAC were decreased following MDA treatment, while HVA levels remained unchanged. In contrast, MDMA treatment did not significantly alter DOPAC concentrations, but significantly increased those of HVA (fig. 7).

4. Discussion

The present study provides evidence to suggest that high doses of either MDA or its N-methylated derivative, MDMA, are selectively ‘toxic’ to serotonergic neurons in the rat brain. Single or multiple doses of either drug dramatically reduced both 5-HT concentrations and TPH activities in three serotonergic nerve terminal regions. Histological examination has revealed MDA-induced nerve terminal damage in hippocampal and striatal regions of the rat brain (Ricaurte et al., 1985); the similarities of the neurochemical deficits resulting from both MDA and MDMA treatments indicate that, like MDA, MDMA is also neurotoxic. Two mechanisms which are thought to be involved in the serotonergic effects elicited by other amphetamine analogs, namely drug-induced 5-HT release, and inhibition of 5-HT reuptake (Sanders-Bush and Massari, 1977; Wong et al., 1973), might contribute to the lowered serotonin levels observed after MDA or MDMA treatments. In this regard, both MDA and MDMA are potent inducers of 5-HT release in vitro (Nichols et al., 1982).

The neurochemical alterations induced by MDA or MDMA in the rat brain are strikingly similar to those observed following the administration of p-halogenated amphetamine derivatives such as p-chloroamphetamine (PCA). A single dose (10 mg/kg) of PCA in the rat causes rapid and long-lasting reductions (up to 4 months) in the levels of brain serotonin and 5-HIAA (Sanders-Bush et al., 1972). Corresponding reductions in TPH activity, as well as decreases in the number of high affinity serotonin uptake sites in brain slices and synaptosomal fractions, have been reported (Carlson, 1970; Wong et al., 1973). These findings, in conjunction with histological evidence of nerve cell degeneration in the serotonin-rich B-9 cell region of the mesencephalon (Harvey et al., 1975), and ultrastructural evidence of degenerated axon terminals in the striatum (McGeer et al., 1975), have led several investigators to suggest that PCA, or some metabolite, exerts a specific neurotoxic action on serotonergic pathways. Like MDA and MDMA, PCA is not toxic to catecholamine neurons.

Although PCA has been extensively studied, the precise mechanism of its selective neurotoxic action is, as yet, unknown. However, its ability to lower brain content of 5-hydroxyindoles is blocked by fluoxetine (Fuller et al., 1975), an inhibitor of serotonin uptake, suggesting a requirement for transport into serotonergic neurons. Recently, a brief communication (Gehlert et al., 1985) reported that the serotonin deficits induced by PCA can be blocked by co-administration of the serotonin reuptake inhibitor citalopram, suggesting that the neurotoxic mechanism of MDMA may be similar to that of PCA. However, this report also indicated that MDMA was probably not concentrated in nerve terminals. Additional studies are required to determine the molecular events responsible for the serotonin-depleting effects of these agents.

Unlike METH, neither MDA nor MDMA are toxic to DA neurons. However, the alterations of DA and DA metabolite levels after single or multiple drug injections indicate that these agents do affect the dopaminergic system. Three hours after a 10 mg/kg dose of either drug, DA levels were significantly elevated, although TH activity was unchanged (figs. 7 and 5, respectively). However, this effect on DA concentrations was not observed after multiple drug administrations (fig. 4). Such an initial, transient elevation of striatal DA has been observed following acute administration of other amphetamine analogs, including amphetamine (Kuczenski, 1978), METH (Koda and Gibb, 1973; Kogan et al., 1976), and PCA (Leonard, 1976), and could reflect either an increase in DA synthesis, a decrease in DA catabolism or a combination of both actions. Since DA synthesis is thought to be regulated by TH, the enzyme which catalyzes the rate-limiting step in catecholamine biosynthesis, an activation of enzyme by some mechanism undetectable in our TH assay could
account for the observed increase in DA concentration; possible mechanisms include a decreased end-product inhibition (due, perhaps, to drug-induced DA release, see below) or an alteration of the enzyme molecule resulting in either an increased affinity of enzyme for the pteridine cofactor (Zivkovic et al., 1974), or a decreased affinity for the catechol inhibitor (Neff and Costa, 1966). Decreased DA catabolism could be attributed to monoamine oxidase inhibition, an effect observed with both MDA (Mann and Quastel, 1940) and MDMA (Fellows and Bernheim, 1950). Although it is conceivable that such a mechanism plays a role in the acute effects of these drugs, the MDMA-induced elevation of HVA (see fig. 7) appears inconsistent with such an interpretation.

Regarding the latter phenomenon, previous experiments in our laboratory have revealed an increase in the concentration of striatal HVA within the first few hours after acute METH treatment (unpublished observations); similar effects have been observed after a single dose of amphetamine (Jori and Bernardi, 1969). An elevated brain HVA content is often interpreted as evidence of enhanced DA turnover consequent to drug-induced DA release, and, indeed, acute amphetamine administration increases both the synthesis (Schwartz et al., 1980; Uretsky and Snodgrass, 1977) and release (Azzaro and Rutledge, 1973; Chiueh and Moore, 1975) of DA. The levels of HVA were significantly elevated following subacute treatment with either MDA or MDMA (fig. 4) suggesting, perhaps, that these two drugs also cause DA release.

The response of the catecholaminergic system to acute administration of MDA differed from that elicited by acute administration of MDMA, as evidenced by the inconsistent effects of the two drugs on striatal HVA concentrations (fig. 7). In this regard, it is of interest to note that MDA and MDMA have been proposed to act by different mechanisms. Evidence derives from studies performed in rats demonstrating a lack of cross tolerance between the two agents (Nichols et al., 1982); moreover, optical requirements for the central activity of MDA were reversed upon methylation (Anderson et al., 1978). This latter finding argues against the possibility that MDMA is activated in vivo by way of demethylation.

The ability of these drugs to influence the dopaminergic system might be an important determinant of long-term effects. Previous investigations in our laboratory have demonstrated that agents which preferentially influence dopaminergic activity, i.e. haloperidol, a DA receptor antagonist; α-methyl-p-tyrosine, an inhibitor of DA synthesis; or amfonelic acid, a specific DA uptake blocker, prevent the effects of METH on both dopaminergic and serotonergic neurotransmitter systems (Schmidt et al., 1985). It appears that the METH-induced alterations in the dopaminergic system are causally linked to changes in the serotonergic system, and that DA is the common mediator for toxic effects in both systems. Due to the similarity of the serotonergic effects elicited by METH, MDA and MDMA, it would be of interest to determine whether the 'neurotoxic' effects of the latter two agents are also linked to the dopaminergic system. This possibility is currently being explored in our laboratory.

In summary, our results demonstrate that both MDA and its N-methylated derivative, MDMA, cause selective neurochemical deficits in serotonergic pathways in the rat brain; these effects are observed after a single injection of either drug and become more pronounced with multiple drug administrations. In addition, we have shown that both MDA and MDMA appear to influence the dopaminergic system (at least initially), and this action may play an important role in their short-term behavioral, as well as long-term biochemical, effects.

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