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Short communication

3,4-Methylenedioxyethylamphetamine (MDE), a novel analogue of MDMA, produces long-lasting depletion of serotonin in the rat brain

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The present study was carried out to asses possible toxic effects of 3,4-methylenedioxyethylamphetamine (MDE) on serotonergic, dopaminergic or noradrenergic neurons in the rat brain. It was found that MDE produced a long-lasting, dose-related depletion of serotonin (5HT). However, even at high dosage, MDE did not reduce the concentration of either dopamine (DA) or norepinephrine (NE) on a long-term basis. When compared to 3,4-methylenedioxymethylamphetamine (MDMA), MDE was approximately one fourth as potent as producing a long-term depletion of 5HT. These results suggest that MDE, like MDMA, may be selectively toxic to central serotonergic neurons.

Amphetamines (and analogues); Serotonergic neurons; Neurotoxicity

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA), a derivative of 3,4-methylenedioxyamphetamine (MDA), has recently received a great deal of attention in the United States. In July of 1985 the United States Drug Enforcement Agency (DEA) invoked its powers under the Controlled Substances Act of 1984 and, on an emergent basis, temporarily placed MDMA on schedule I of controlled substances, a category generally reserved for compounds with high abuse liability and no documented medical utility. In taking this action, the DEA cited the rising incidence of non-medical use of MDMA and expressed concern that MDMA might induce serotonergic nerve terminal degeneration similar to that produced by MDA (Ricaurte et al., 1985), a compound that has been on schedule I for some time.

Since the banning of MDMA, another derivative of MDA has appeared on the street (Sapienza, personal communication). The new compound is 3,4-methylenedioxyethylamphetamine (MDE or 'Eve'). MDE appears to be the latest in a line of controlled substance analogues ('designer drugs') to surface on the illicit drug market. Structurally, MDE differs from MDMA (also known as 'Adam') only in that it contains an ethyl instead of a methyl substituent on the nitrogen (fig. 1). Subjectively, the effects of MDE are reported to be similar, but not identical, to those of MDMA. The pharmacological actions of MDE also appear to resemble those of MDMA (Boja et al., 1986; Johnson et al., 1986). Unfortunately, virtually nothing is currently known about the neurotoxic potential of MDE. We have therefore assessed the long-term effects of MDE on central serotonin (5HT)-, dopamine (DA)- and norepinephrine (NE)- containing neurons, and compared them to those of MDMA.

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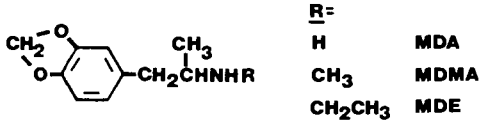

Fig. 1. Structure of 3,4-methylenedioxyamphetamine (MDA) and its analogues.

2. Materials and methods

2.1. Drugs and chemicals

Racemic mixtures of MDE hydrochloride and MDMA hydrochloride were synthesized using previously described methods (Braun et al., 1980). The hydrochloride salts of DA and NE and the creatinine sulfate salt of 5HT were purchased from the Sigma Chemical Company, St. Louis, USA.

2.2. Subjects and drug treatments

Male albino Sprague-Dawley rats weighing 250-300 g were used. MDE hydrochloride was administered subcutaneously at the following doses: 10, 20 and 40 mg/kg (dose expressed as base). Each dose was tested in a separate group of five animals. For comparative purposes, separate groups of rats (n = 5) were given identical doses of MDMA hydrochloride. Both MDE and MDMA were injected every 12 h for 4 consecutive days. This schedule of drug administration was employed because it has previously been shown to be useful in detecting toxic activity of other amphetamine derivatives (Ricaurte et al., 1985).

2.3. 5HT, DA and NE determinations

Two weeks after drug treatment, rats were killed and the hippocampus and striatum and rest of brain were isolated as detailed elsewhere (Ricaurte et al., 1983). 5HT, DA and NE concentrations in these brain regions were determined by reverse phase liquid chromatography coupled with electrochemical detection as previously described (Ricaurte et al., 1985).

3. Results

MDE produced a long-lasting, dose-related depletion of 5HT in the rat brain (table 1A). The 20 and 40 mg/kg dose regimens of MDE reduced 5HT concentrations by 29 and 54%, respectively (table 1A). The 10 mg/kg dose regimen of MDE did not lower 5HT concentrations (table 1A). Neither DA nor NE levels were altered on a long-term basis by the high dose regimen (40 mg/kg) of MDE (table 1A).

To compare the effects of MDE with those of MDMA, separate groups of rats were subjected to 10, 20 and 40 mg/kg dose regimens of MDMA. MDMA also produced a dose-related depletion of 5HT (table 1B). It is of note that the 10 mg/kg dose regimen of MDMA reduced hippocampal 5HT content by approximately the same amount as the 40 mg/kg dose regimen of MDE (see table 1A,B).

TABLE 1

(A) Effect of various dose regimens of MDE on 5HT, DA and NE concentrations in the rat brain measured 2 weeks after the last drug injection. Each dose of MDE was given every 12 h for 4 days. 5HT and NE were measured in the hippocampus. DA was measured in the striatum. Values are expressed in micrograms per milligram of tissue. N.M., not measured because higher dose regimen produced no effect. * Significantly different from saline control ($P < 0.05$).

MDE dose	n	5HT	DA	NE
10 mg/kg	5	0.40 ± 0.04	N.M.	N.M.
20 mg/kg	5	0.29 ± 0.03 *	N.M.	N.M.
40 mg/kg	5	0.19 ± 0.02 *	11.3 ± 0.3	0.67 ± 0.04
Control (saline)	5	0.41 ± 0.01	11.8 ± 0.3	0.70 ± 0.03

(B) Effect of various dose regimens of MDMA on 5HT concentration in the rat hippocampus measured 2 weeks after the last drug injection. Each dose was given every 12 h for 4 days. Values are expressed in micrograms per milligram of tissue. * Significantly different from saline control ($P < 0.05$).

MDMA dose	n	5HT	% Depletion
10 mg/kg	5	0.23 ± 0.02 *	44
20 mg/kg	5	0.15 ± 0.02 *	64
40 mg/kg	5	0.11 ± 0.01 *	73
Control (saline)	5	0.41 ± 0.03	–

4. Discussion

The major finding of this study is that MDE induces a prolonged depletion of 5HT in the rat brain. Since a long-lasting depletion of 5HT appears to be a good predictor of 5HT neurotoxicity (Ricaurte et al., 1985; Schmidt et al., 1986; Stone et al., 1986; Commins et al., in press), this finding suggests that MDE, like MDMA and MDA, may be toxic to central 5HT neurons.

The toxic effect of MDE on 5HT neurons appears to be selective. Even at high dosage (40 mg/kg), MDE failed to alter the concentration of either DA or NE on a long-term basis (table 1A). This selectivity of MDE for 5HT neurons is reminiscent of that of MDA and MDMA. Neither of these compounds exerts a major long-term effect on DA or NE nerve terminal markers (Ricaurte et al., 1985; Schmidt et al., 1986; Stone et al., 1986; Commins et al., in press).

When compared to MDMA, MDE appears to be less toxic. This is indicated by the fact that approximately 4-fold higher doses of MDE are required to produce a comparable effect as MDMA (see Results). Since the only difference between MDE and MDMA is the length of the carbon chain attached to the nitrogen (fig. 1), it would appear that this substituent is a key determinant of 5HT neurotoxic activity of the MDA molecule. A similar decline in activity has been noted when considering the hallucinogenic activity of various N-substituted analogues of MDA (Braun et al., 1980).

At first glance, the present results would appear to be at odds with those recently reported by Schmidt and Lovenberg (1986). These investigators found that MDE did not produce a long-lasting reduction in cortical 5HT content or in the number of 5HT uptake sites. It should be noted, however, that the highest dose tested by these investigators was 20 mg/kg dose, and that this dose was given only once. By contrast, in this study the 20 mg/kg dose was given repeatedly (twice a day for 4 days), and a higher dose (40 mg/kg) was also tested. To the best of our knowledge, no other studies have yet examined the long-term effects of repeated high doses of MDE on 5HT neurons. Additional studies are needed to determine if drug regimen differences mentioned above account for the differing findings. Johnson and colleagues (1986) have recently reported that repeated doses of MDE reduce markers for 5HT terminals when these are measured 18 h after the last dose of MDE.

In summary, the present study has shown that repeated doses of MDE produce a prolonged, selective, dose-related depletion of 5HT in the rat brain. Given prior findings with MDA and MDMA, it seems reasonable to suspect that MDE produces this long-lasting depletion of 5HT by destroying serotonergic nerve terminals. In view of this, the same caution that is currently being exercized in the use of MDA and MDMA seems warranted in the use of MDE.

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