

Short communication

METHYLENEDIOXYMETHAMPHETAMINE: A POTENTIALLY NEUROTOXIC AMPHETAMINE ANALOGUE

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The amphetamine analogue, methylenedioxymethamphetamine (MDMA) has received considerable attention recently as a novel and increasingly popular psychoactive agent. When administered acutely to rats in high doses, MDMA caused a selective and dramatic decrease in brain concentrations of serotonin and its metabolite, 5-hydroxyindoleacetic acid. The depletion of serotonin and its metabolite persisted for up to at least one week after a single injection of MDMA at approximately four to five times the acute dose reported for humans. These results are discussed in terms of the possible neurotoxic effects of MDMA.

Methylenedioxymethamphetamine Drug-induced neurotoxicity Hallucinogens Amphetamines
Serotonin

1. Introduction

The psychotomimetic agent, ($\pm$)-3,4-methylenedioxymethamphetamine (MDMA), has recently received considerable attention as one of the most popular members of the class of abused substances known as designer drugs. Chemically MDMA is related to both amphetamine-like stimulants and hallucinogens such as mescaline. The drug is reported to evoke a heightened sense of awareness with sensual and emotional overtones without interfering with normal thought processes in its users (Shulgin and Nichols, 1978). As such, MDMA has become one of the recreational drugs of choice among college students and young professionals and was being used by some analysts as an adjunct to psychotherapy.

Both because of its rapidly increasing popularity and a lack of detailed laboratory studies, the federal Drug Enforcement Agency has recently placed MDMA under an emergency one year Schedule I classification along with drugs such as LSD and heroin. Despite these measures there is little doubt that the illicit use of MDMA or 'Ecstasy', as it is known on the street, is still on the increase.

Repeated high doses of methamphetamine, a parent compound of MDMA, are known to induce persistent neurochemical alterations in the rat brain indicative of neurotoxicity (Bakhit and Gibb, 1981; Schmidt et al., 1985). Recently Ricaurte et al. (1985) demonstrated similar effects for methylenedioxamphetamine (MDA), a well studied hallucinogen which produces a qualitatively different intoxication than MDMA (Anderson et al., 1978). The neurotoxic effects of these closely related agents and the recent surge in the use of MDMA prompted us to begin experiments examining the effects of MDMA on those neurochemical parameters reportedly altered by

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methamphetamine and MDA. One of the early neurochemical effects of methamphetamine in the rat is the rapid loss of several parameters of central serotonergic function (Bakhit and Gibb, 1981). We have therefore examined acute effects of MDMA on neostriatal concentrations of the monoamines serotonin (5HT) and dopamine (DA) as well as their primary acid metabolites.

2. Materials and methods

Male Sprague-Dawley rats (200-250 g) were administered either saline or MDMA-HCl as the base. All animals were killed by decapitation and the brains were immediately removed on ice. The neostriata, cerebral cortex and hippocampus were dissected free, frozen on dry ice and stored at -70°C until assayed. Individual tissues were ho-

mogenized in 0.5 ml of 0.1 M HClO_4 containing 1% ascorbic acid and EDTA. After centrifugation ($19000 \times g$, 20 min) the supernatants were injected directly onto a μ -Bond-a-pak C-18 reverse phase column. The mobile phase was 0.15 M monochloroacetic acid, 75 mg/l EDTA and 1 g/l heptylsulfonic acid with 5% methanol (pH 2.9). Detection was by means of an ESA coulometric detector at +0.4 V. Quantitation was by comparison with standards of known concentration. N-Methyl-3,4-methylenedioxyphenylisopropylamine hydrochloride was prepared as described by Braun et al. (1980).

3. Results

As shown in fig. 1A, MDMA caused a dose-dependent reduction in neostriatal 5HT and 5-

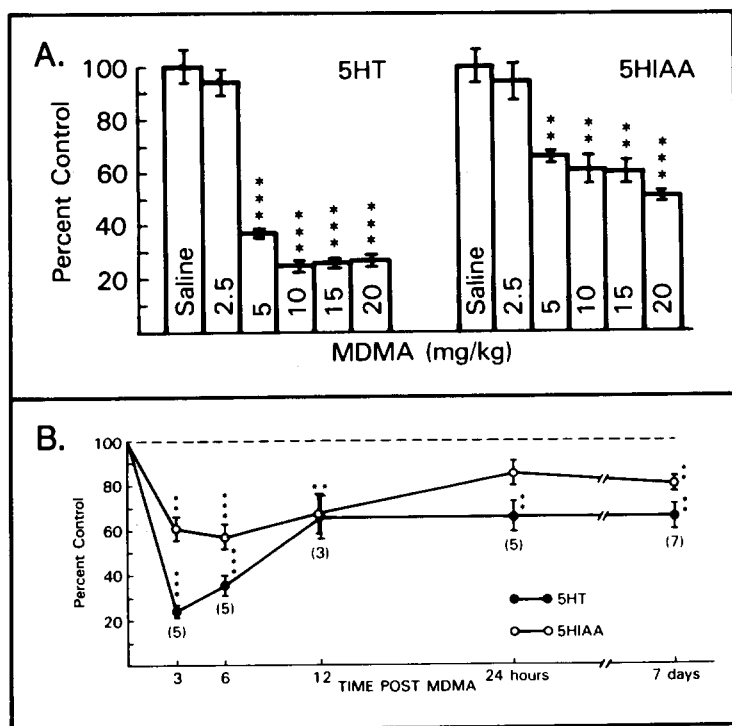


Fig. 1. (A) Dose-dependent depletion in neostriatal serotonin (5HT) and 5-hydroxyindoleacetic acid (5HIAA) 3 h after the acute administration of MDMA to rats. Values are the means with S.E.M. as a percent of control (saline) for five animals. (B) Time course of recovery of neostriatal 5HT and 5HIAA concentrations after the acute administration of 10 mg/kg MDMA. The number of animals is given beneath each value. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared to control by Student's t-test. Control values for 5HT and 5HIAA ($n = 16$) were 0.35 ± 0.01 and 0.42 ± 0.02 $\mu\text{g/g}$ tissue, respectively.

TABLE 1

Effect of acute administration of MDMA on neostriatal dopamine and metabolites. Each value is the mean with the S.E.M. for five animals given as a percent of control. Absolute values ($\mu\text{g/g}$ tissue) are given in parentheses. ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$ compared to saline by Student's *t*-test.

Dose mg/kg	(n)	Dopamine	Dihydroxyphenylacetic acid	Homovanillic acid
Saline	(5)	100 $\pm$ 3.1 (8.96 $\pm$ 0.28)	100 $\pm$ 5.2 (1.06 $\pm$ 0.06)	100 $\pm$ 4.2 (0.708 $\pm$ 0.030)
5	(5)	116.3 $\pm$ 3.8 ^b	96.0 $\pm$ 2.5	133.8 $\pm$ 7.5 ^b
10	(5)	123.1 $\pm$ 3.0 ^c	90.7 $\pm$ 5.0	156.9 $\pm$ 12.4 ^b
15	(5)	130.9 $\pm$ 4.2 ^c	75.8 $\pm$ 7.3 ^a	126.0 $\pm$ 7.5 ^a
20	(5)	127.9 $\pm$ 3.9 ^c	69.0 $\pm$ 2.6 ^c	128.7 $\pm$ 9.7 ^a

hydroxyindoleacetic acid (5HIAA) concentrations 3 h after its administration to rats. This effect became significant for both indoles at 5 mg/kg with a decline in 5HT and 5HIAA concentrations to approximately 40 and 70 percent of control, respectively. There was little additional effect beyond doses of 10 mg/kg MDMA which reduced 5HT concentrations by approximately 75 percent. Although there was some variability in the response to MDMA, acute reductions in neostriatal 5HT concentrations greater than 50 percent were consistently observed with drug doses of 10 mg/kg. Similar results were observed for indole concentrations in the cerebral cortex and hippocampus after MDMA administration (data not shown).

Table 1 contains the values for neostriatal concentrations of DA and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) 3 h after acute MDMA administration. Neostriatal DA concentrations were slightly but significantly elevated by MDMA to a maximum of approximately 130 percent of control at 15 mg/kg. Neostriatal DOPAC concentrations declined at the two highest drug doses while HVA levels rose to approximately 160 percent of control at 10 mg/kg then declined at higher doses of MDMA.

To determine if MDMA produced a reversible or more persistent effect on neostriatal 5HT neurons, rats were injected with 10 mg/kg of the drug and killed at various times after. The results of these experiments are shown in fig. 1B. Both 5HT and 5HIAA concentrations declined rapidly after MDMA, although the change in 5HIAA was less

dramatic. After a nadir at 3 h the concentration of both indoles began to recover somewhat to a plateau at 24 h. However, six days later or one week after the administration of a single dose of MDMA, 5HT and 5HIAA concentrations were still significantly depressed to 65 and 80 percent of control, respectively. Changes in neostriatal DA and its metabolites, corresponded to those previously observed (table 1) and by one week all three parameters were back within the range of control values (data not shown).

4. Discussion

The results of these experiments show that at the doses used here, MDMA can cause a persistent and selective depletion of transmitter in serotonergic neurons of the rat neostriatum. This depletion of 5HT is similar to that observed after the acute administration of the serotonergic neurotoxin, *p*-chloroamphetamine (Sanders-Bush et al., 1974). Although the dose of MDMA used here (10 mg/kg) was approximately four times the acute human dose (assuming 100-150 mg per tablet) (Shulgin and Nichols, 1978), cumulative daily doses of greater than 1 g have been reported in the popular press (Newsweek, April 15, 1985, p. 96). Therefore these results may have a bearing on the multiple doses of MDMA being taken by some abusers.

As would be expected from its amphetamine-like structure and reported mild stimulant effects (Shulgin and Nichols, 1978), MDMA is a potent

releasing agent for brain monoamines. Nichols et al. (1982) reported that the biologically active (+) isomer of MDMA released [^3H]5HT from brain synaptosomes suggesting 5HT release may play a role in the drug's psychotropic effects. The slight elevation of neostriatal DA observed following MDMA administration may reflect release of this monoamine as well. Similar elevations have been observed for other stimulants including amphetamine (Roberts and Patrick, 1979) and p-chloroamphetamine (Beck et al., 1984) which by releasing DA cause a reduction in feedback inhibition of the rate-limiting enzyme for DA synthesis, tyrosine hydroxylase. The acute elevation of the metabolite HVA similarly suggests some increase in DA turnover following MDMA treatment.

A number of amphetamine analogues such as methamphetamine and p-chloroamphetamine have been shown to deplete brain indoles after acute administration to laboratory animals. At single doses of 10 mg/kg or less this effect of methamphetamine is reversible by 24 h (Bakhit and Gibb, 1981) while 10 mg/kg of p-chloroamphetamine causes a persistent depletion of rat brain 5HT which is still present after four months. These long-term effects have been attributed to a cytotoxic action of p-chloroamphetamine toward 5HT neurons (Sanders-Bush et al., 1974). Harvey et al. (1977) have commented that amphetamine analogues causing 5HT depletions of less than 24 h duration are not associated with neurotoxic changes in 5HT neurons while those causing long-term depletions are associated with histological evidence of toxicity. The persistence of the depletion following acute MDMA administration suggests the mechanism responsible may be closer to that of p-chloroamphetamine than low doses of agents such as methamphetamine which cause a reversible depletion. Furthermore, the depletion of brain 5HT following treatment with methamphetamine has been linked to its ability to release large quantities of dopamine (Schmidt et al., 1985). In contrast to metamphetamine, MDMA and p-chloroamphetamine (Schmidt, unreported observation) are much more potent releasers of 5HT than DA. When considered with the persistent effects of the drug, it would appear that MDMA may be similar in its neurochemical effects to the halogenated amphetamines.

In conclusion, the results indicate that the psy-

chotomimetic agent MDMA can at high doses selectively induce persistent neurochemical deficits in the neostriatal serotonergic system of the rat brain. These alterations are reminiscent of the acute response of central serotonergic systems to the serotonergic neurotoxin, p-chloroamphetamine and the hallucinogen MDA. Our observations should be viewed in terms of the serious toxicological problems which may occur due to the wide spread abuse of MDMA and related compounds.

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