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± 0.004	0.070 ± 0.005[c]	+
± 0.005	0.095 ± 0.010[c]	+
± 0.024[c]	0.214 ± 0.013[c]	+++
± 0.008	0.003 ± 0.006[d]	–
± 0.020	0.054 ± 0.011[c]	+
± 0.021[c,d]	0.095 ± 0.013[c,d]	++
± 0.027[c]	0.185 ± 0.028[c]	+++
± 0.020[c]	0.185 ± 0.034[c]	+++
± 0.029[c,d]	0.042 ± 0.005[c,d]	+
± 0.008[c,d]	0.011 ± 0.010[d]	+

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Neurotoxic Amphetamine Analogues: Effects in Monkeys and Implications for Humans[a]

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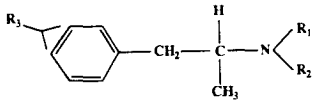
The neurotoxic potential of amphetamine and some of its analogues has come to light over the last two decades. The first clue that amphetamines possess neurotoxic activity came in 1972, when Sanders-Bush and colleagues[1] noted that rats given a single dose of *p*-chloroamphetamine (PCA) developed depletions of presynaptic serotonergic neuronal markers which lasted for months beyond the period of drug exposure. These findings, coupled with subsequent observations,[2-8] established PCA as a potent serotonergic neurotoxin, and provided the first suggestion that amphetamines possess neurotoxic activity.

The fact that neurotoxicity is not unique to PCA, but is also a property of the parent compounds (amphetamine and methamphetamine) surfaced in 1976, when Seiden and colleagues[9] found that rhesus monkeys given repeated high doses of methamphetamine developed marked and persistent depletions of caudate dopamine. That same year (1976), Gibb and coworkers[10] made similar observations in methamphetamine-treated rats and, shortly thereafter, Ellison and coworkers[11] extended findings with methamphetamine to amphetamine. Along with a number of subsequent studies,[12-21] these early reports established the neurotoxic potential of amphetamine and methamphetamine. Further, these early reports sparked a series of studies which led to the discovery that methylenedioxy amphetamine analogues were particularly toxic to brain serotonin neurons[22-30] (TABLE 1). Since some of these analogues are recreationally abused[30-33] [e.g., 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDEA), *N*-methyl-3,4-methylenedioxyethylamphetamine (MBDB)], much effort has been devoted to the characterization of their pharmacologic properties and assessment of the risks they might pose to humans.

This chapter will focus on the neurotoxicity of one methylenedioxy amphetamine derivative in particular, MDMA ("Ecstasy"), and emphasize recent findings in nonhuman primates. MDMA is highlighted for several reasons. First, MDMA is one of

[a] This work was supported by NIDA Grants DA05707 and DA05938 from the NIH.

TABLE 1. Amphetamine Analogues with Neurotoxic Activity



	Substituent			Toxicity	
	R_1	R_2	R_3	DA	5-HT
Amphetamine	H	H	H	++	–
Methamphetamine	CH_3	H	H	++	+++
Dimethylamphetamine	CH_3	CH_3	H	+	–
MDA	H	H		–	++++
MDMA	CH_3	H	"	–	++++
MDEA	CH_2CH_3	H	"	–	++
MBDB	CH_2CH_3	CH_3	"	–	++

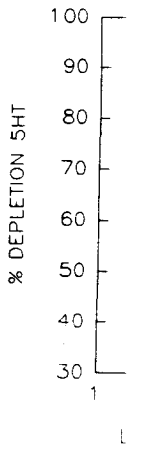
the most frequently abused amphetamine analogues, both in the United States[30–33] and abroad.[34–36] Second, MDMA is the prototype methylenedioxy amphetamine; as such, information on MDMA may shed light on properties of other members of the group (MDA, MDEA, MBDB). Third, MDMA is one of the few amphetamine derivatives that has been tested in both rodents and nonhuman primates. Interspecies comparisons are therefore possible, and these can help gauge the risks that MDMA and related drugs might pose to humans.

WHY PRIMATES?

Given existing data in rodents,[22–30] and the expense and difficulty of carrying out studies in primates, it seems appropriate to specify a rationale for conducting studies of MDMA in monkeys. Monkeys, like humans, metabolize amphetamines chiefly by means of side-chain deamination, whereas rats metabolize amphetamines mainly through ring hydroxylation.[37] As such, findings in nonhuman primates are more likely to predict MDMA's effects in humans. In addition, there is the precedent of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was only after MPTP was tested in primates that its toxic behavioral effects became apparent,[38] and the first primate model of Parkinson's disease was developed.[39] Indeed, a major impetus for undertaking studies of MDMA in monkeys was to develop a primate model of central serotonin deficiency. Such a model might be used to elucidate the role of serotonin in the primate central nervous system (CNS).

EFFECTS IN PRIMATES MORE PRONOUNCED THAN IN RODENTS

One of the first findings to emerge from studies of MDMA in primates was that MDMA's neurotoxic effects are more pronounced in the monkey than in the rat.[40–43]



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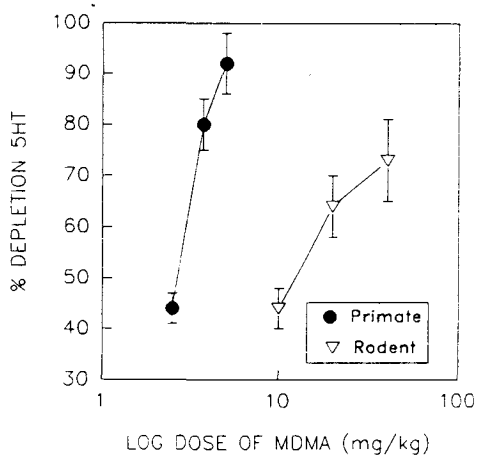


FIGURE 1. Effect of MDMA in the primate versus the rodent.

FIGURE 1 summarizes the results of a representative study in which MDMA was given to rats and squirrel monkeys subcutaneously twice daily (at 0900 and 1700 hours) for 4 days. Two weeks later, the animals were killed and cortical serotonin levels were determined. As shown in FIGURE 1, monkeys are more sensitive than rats to the 5-HT-depleting effects of MDMA. In addition, the maximal effect of MDMA in the squirrel monkey is greater than that in the rat. These results, which are in accord with those of others,[41-42] indicate that MDMA produces greater neurotoxic effects in primates than in rodents. Whether the greater effects in the monkey are related to pharmacokinetic or pharmacodynamic factors remains to be determined.

NERVE CELL BODIES IN PRIMATES AFFECTED

Until recently, the neurotoxic effects of amphetamines have been thought to be limited to monoaminergic axon terminals, sparing monoaminergic nerve cell bodies in the brain stem.[21,29,44,45] In evaluating these data, however, it is important to bear in mind that virtually all of the studies have been carried out in rodents, and it may be that rodents do not sustain sufficient axonal damage to cause retrograde degeneration of the nerve cell body.[21] Because of this consideration, the status of nerve cell bodies was evaluated in MDMA-treated primates,[40] which develop larger serotonin deficits than do MDMA-treated rodents (FIG. 1). Squirrel monkeys treated with a regimen of MDMA that causes severe axonal damage (5 mg/kg twice daily for 4 days) were killed for anatomic studies of nerve cell bodies two weeks later. In hematoxylin-eosin (H&E)-stained sections, no evidence of cell loss was found in the raphe nuclei. However, in sections stained with luxol fast blue (LFB)-cresyl violet many of the neurons in the dorsal raphe nucleus (DRN) were found to contain brownish red spherical cytoplasmic inclusions which displaced the nucleus to the periphery of the cell perikaryon. Additional studies showed that the inclusions contained lipofuscin. The presence of lipofuscin suggested that inclusions arose from lipid peroxidation of cell components and subsequent phagolysosomal activity. While the exact sequence of events remains

to be confirmed, the cytopathologic changes described provide one of the first suggestions that amphetamine neurotoxicity can involve the nerve cell body, at least in the primate.

LASTING EFFECTS IN PRIMATES

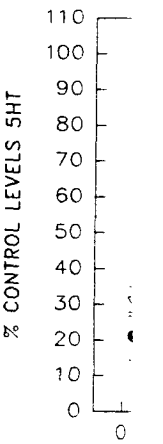
If nerve cell bodies in primates are damaged, MDMA's effects in the monkey might be anticipated to be longer lasting than in the rat, where gradual recovery is the rule,[44,46] presumably because nerve cell bodies are spared.[29,44,45] To test this hypothesis, a time-course study was undertaken in primates.[47] Squirrel monkeys were treated with MDMA (5 mg/kg twice daily for 4 days) and examined 2 weeks, 10 weeks, 8 months, and 18 months after MDMA treatment. In each animal, three presynaptic markers of serotonin neurons were measured (serotonin, [^{3}H]paroxetine-labeled serotonin uptake sites, and 5-hydroxyindoleacetic acid [5-HIAA]), and compared with those of controls. These studies revealed that by 10 weeks, there was a trend toward recovery, but that by 18 months, serotonergic deficits were as severe as at 2 weeks (FIG. 2). Together with previous findings in methamphetamine-treated monkeys,[9,48] these results suggest that the neurotoxic effects of amphetamines in primates are longer lasting than in rodents. Further, these results are consistent with the view that damage of nerve cell bodies impairs the ability of neuronal perikaryon to support axonal recovery. Recent findings provide further support for this view.[49]

TOXIC DOSES IN MONKEYS CLOSELY APPROACH DOSES USED BY HUMANS

In view of MDMA's lasting effects in monkeys, long-term effects in humans become a concern. However, before generalizing the present results to man, it is important to emphasize that MDMA regimens in monkeys differed from typical human-use patterns in two key respects: (1) monkeys received multiple MDMA doses over a 4-day period, whereas humans generally take single doses, usually weeks apart; (2) monkeys received MDMA subcutaneously, whereas humans generally take the drug orally. Because of these differences, studies have been performed to assess the influence of route and frequency of MDMA administration on the expression of MDMA neurotoxicity.[30,50–52] These studies have shown that the oral route of administration does not afford significant protection against MDMA neurotoxicity. Further, one of the studies has shown that a single oral dose of MDMA (5 mg/kg) produces a depletion of brain serotonin two weeks later.[50] Similar observations have recently been made in monkeys treated with dexfenfluramine,[53] an amphetamine derivative used clinically in the treatment of obesity. Hence, at least two amphetamine analogues produce neurotoxic effects in monkeys at doses that closely approach those used by humans.

5-HIAA IN CEREBROSPINAL FLUID REFLECTS DAMAGE IN CNS

Before proceeding with studies in humans, it was important to determine whether CSF 5-HIAA could serve as a marker for MDMA neurotoxicity in living nonhuman



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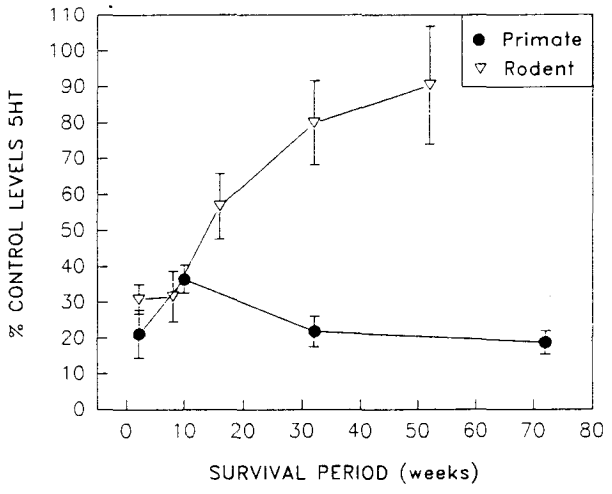

FIGURE 2. Recovery after MDMA in the primate versus the rodent.

primates. If it could, CSF 5-HIAA might be useful for detecting MDMA neurotoxicity in humans. Squirrel monkeys were treated with toxic doses of MDMA (5 mg/kg twice daily for 5 days); two weeks later, the animals were lightly anesthetized and samples of CSF were obtained at a cervical level. Shortly after CSF was removed, the monkeys were sacrificed, and the brain and cervical spinal cord were removed and measured for serotonin and 5-HIAA. These studies, which allowed changes in the CSF to be directly correlated with changes in the CNS, showed that monkeys with 73–94% depletions of serotonin and 5-HIAA in brain and 42–45% depletions of serotonin and 5-HIAA in the cervical spinal cord had a 60 ± 7% depletion of 5-HIAA in cervical CSF.[54] These results indicate that CSF 5-HIAA levels can be used to detect the MDMA neurotoxicity in the brain of living primates. Further, these results indicate that 5-HIAA in cervical CSF underestimates serotonergic deficits in brain, and overestimates serotonergic deficits in the cervical spinal cord.

PRELIMINARY FINDINGS IN HUMANS

With this information in hand, 33 individuals with a history of extensive MDMA use were evaluated.[55] Volunteers agreed to undergo lumbar puncture, and to refrain from using MDMA or any other drug for 2 weeks prior to study. CSF was collected at a lumbar level (L4–L5 interspace) and analyzed for its monoamine metabolite content. Compared to age- and sex-matched controls (n = 24), recreational MDMA users showed a significant reduction in 5-HIAA levels, but no change in the values for homovanillic acid (HVA) or 3-methoxy-4-hydroxy-phenylglycol (MHPG). While consistent with findings in nonhuman primates,[54] these data should be interpreted with caution

for a number of reasons. First, diet, activity and other factors reported to influence CSF 5-HIAA[56] were not controlled in this exploratory study. Second, subjects were not formally screened for psychiatric disease, which could influence CSF 5-HIAA (e.g., as in depression[57]). Third, while the reduction in CSF 5-HIAA could have been caused by MDMA, it could have been caused by other drugs, since most of the participants were polydrug users. Fourth, reduced CSF 5-HIAA levels may have predated the use of MDMA. Finally, another study[58] involving five subjects found no alteration in CSF 5-HIAA, although a larger study,[59] which used a neuroendocrine approach to measure serotonin function, did find evidence suggestive of impaired serotonin function in recreational MDMA users. For all these reasons, we are currently conducting a controlled study of recreational MDMA users.

OTHER CLINICAL OBSERVATIONS

While the neurotoxic effects of MDMA in humans remain to be documented, a number of recent case reports merit attention because they describe a variety of neuropsychiatric sequelae in recreational MDMA users, some of which may be linked to serotonin dysfunction. Thus far, neuropsychiatric syndromes reported after MDMA use include panic disorder with secondary depression,[60] depression with suicidality,[61,62] chronic paranoid psychosis,[63] recurrent acute paranoid psychosis,[64] and chronic memory disturbance.[60] Notably, these syndromes have often occurred in individuals using MDMA repeatedly, and usually at high dosage. Further, while all of these cases occurred in individuals healthy at the time of MDMA ingestion, several of the reported cases involved individuals with prior psychiatric histories. As such, it appears that risk factors for the development of neuropsychiatric disturbance after MDMA ingestion include a high dose of MDMA (either cumulative or acute) and a prior history of psychiatric illness.

Although the functional role of serotonin in the human brain is not well understood, it is intriguing that a number of the neuropsychiatric syndromes mentioned above have been linked to serotonin dysfunction. For example, serotonin has been implicated in the regulation of mood,[57] anxiety,[65] impulse control,[66] aggression,[66] memory,[67] sleep,[68] and appetite.[69] To what extent, if any, the clinical disturbances mentioned above are due to MDMA-induced neurotoxicity is unknown. However, since a number of the subjects had psychiatric histories suggestive of pre-existing serotonergic impairment, it is tempting to speculate that MDMA, in these individuals, may have altered an already compromised level of serotonergic function.

The aforementioned case reports highlight the potential hazards of MDMA in humans. However, it should be emphasized that lingering functional deficits in healthy individuals after sporadic use of moderate doses of MDMA are extremely rare. At first glance, the paucity of adverse consequences is reassuring. However, many of the functions in which serotonin has been implicated are subtle and subjective, and abnormalities in these functions may be difficult to detect unless specific and sensitive methods are used. Aside from CSF and neuroendocrine studies, strategies that may be employed to detect subclinical serotonergic damage in humans include pharmacologic challenges and positron emission tomography (once a suitable ligand is developed). Using such strategies, it may be possible to obtain converging lines of evidence regarding the occurrence of MDMA neurotoxicity in humans.

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SUBSTITUTED AMPHETAMINES IN THE STUDY OF NEUROPSYCHIATRIC DISEASE

As discussed by Fuller[70] in this volume, amphetamines with dopaminergic neurotoxic properties (e.g., amphetamine and methamphetamine [TABLE 1]) may be useful for studying Parkinson's disease. In particular, a better understanding of how amphetamines damage dopaminergic neurons may yield insights regarding the process(es) underlying nerve cell degeneration in Parkinson's disease. Studies of amphetamine neurotoxicity could be relevant to Parkinson's disease in one other respect. If amphetamine and methamphetamine are found to cause dopaminergic damage in humans (as in animals[9-21]), studies of individuals with a history of amphetamine abuse may help determine whether an insult to CNS dopamine systems during early life is associated with an increased risk for developing Parkinson's disease at a later age. These studies would be analogous to those in progress with the MPTP cohort,[71] and could help test the Calne and Langston hypothesis.[72]

Along similar lines, MDMA may be useful in the study of serotonin and its role in neuropsychiatric illness. However, unlike the clear-cut relationship between dopamine and Parkinson's disease, the role of serotonin in neuropsychiatric illness is less well defined. Further, although serotonin neurotoxicity is well established in animals, it is not yet known whether MDMA is neurotoxic in humans. Therefore, for MDMA animal models to become more useful in the study of neuropsychiatric illness, it is important to first determine whether MDMA induces neurotoxicity in humans, and if it does, to identify functional consequences. If this can be accomplished, preclinical MDMA models can be developed to study neuropsychiatric disorders in which impaired serotonin function is suspected.

MECHANISMS

The mechanisms by which MDMA and related drugs damage dopamine and serotonin neurons are poorly understood. However, mechanisms under consideration will be briefly mentioned because of their possible relevance to neurodegenerative disorders. These include: (1) involvement of a toxic drug metabolite[73-77]; (2) formation of a toxic neurotransmitter metabolite [e.g., 6-hydroxydopamine (6-OHDA)[78] or 5,6-dihydroxytryptamine (5,6-DHT)[79]]; (3) increased dopamine release somehow leading to dopaminergic and serotonergic neurotoxicity[80,81]; (4) involvement of excitatory amino acids[82]; (4) oxidative stress[83]; and, possibly as a terminal event, (5) calcium-mediated cell injury.[84] Given the wide range of potential mechanisms under investigation, it seems safe to predict that studies of amphetamine neurotoxicity will contribute to our understanding of neurodegenerative disorders.

SUMMARY AND CONCLUSION

A wealth of evidence has accrued over the last 20 years indicating that certain amphetamine analogues have the potential to damage central monoaminergic neurons. For example, amphetamine has been shown to be toxic to dopamine neurons, MDMA to serotonin neurons, and methamphetamine to both (TABLE 1). In rodents, the toxic

effects of amphetamines appear to be limited to axon terminals, and regenerative sprouting tends to be the rule. By contrast, in primates, nerve cell bodies appear to be affected, and the deleterious effects of amphetamine derivatives tend to be longer lasting, and possibly permanent (FIG. 2). Although findings in animals are compelling, observations in humans are less clear. In particular, it remains to be determined whether amphetamine analogues damage central monoaminergic neurons in humans and, if they do, whether functional consequences ensue. Also, the mechanism by which amphetamines damage monoaminergic neurons remains to be defined. Further insight into these basic and clinical aspects of amphetamine neurotoxicity should enhance our understanding of central monoaminergic systems in normal brain function, and their role in the pathophysiology of neuropsychiatric disorders.

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