MDMA

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(±)3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy," E, Adam, X, XTC) is a methamphetamine analogue. It has hallucinogenic, psychostimulant, and multiple behavior-altering activities (Green et al., 1995). Although it was discovered serendipitously in 1912 by Merck Pharmaceuticals, its use as a psychotherapeutic/recreational drug was unknown until the late 1970s. By the early 1980s, as the popularity of the "rave party" increased so did use of MDMA. In 1985, prior to its classification as a Schedule I drug, it was being evaluated for its use in psychotherapy. A fearful Congress and Drug Enforcement Administration (DEA) successfully petitioned for its classification as a Schedule I compound with no evidence that it was at all harmful.

Recreational use of MDMA has been on the rise for the past 20 years (Peroutka, 1987; Schuster et al., 1998; Pope et al., 2001). Increases in the rate of MDMA use have continued despite reductions in the use of other substances (Johnston et al., 2001a,b). This is an international trend (Abraham et al., 1998; Hibell et al., 2000; McPherson and Afsarifard, Chapter 3 of this book).

Although there have been occasional deaths indirectly caused by the use of MDMA (Henry et al., 1992), it is widely considered by its users to be a "safe" drug. The illusion of safety stems from lack of the obvious negative effects that other amphetamine-type compounds induce. MDMA does not cause an increase in aggressive behavior, and its users do not experience paranoid schizophrenia. According to the Drug Abuse Warning Network (DAWN) less than 0.3% of drug-related emergency room visits are due to MDMA. In fact, most users are normal adolescents. The problems with MDMA are far subtler than those associated with methamphetamine. MDMA is neurotoxic, and the observable long-term behavioral effects seem to be specifically linked to impairments of memory and attention in a subpopulation of individuals, which are difficult to detect.

Myths about MDMA Use

Before discussing the known and suspected effects of MDMA it is important to dispel the myths about its use:

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1. MDMA drains your spinal fluid.
2. MDMA causes Parkinson's disease (PD).
3. MDMA is an aphrodisiac.
4 MDMA is a "date rape drug."

First, no known pharmacological agent drains spinal fluid.

Second, MPTP is the chemical agent that was featured in the film *The Frozen Addict*. When made improperly, that drug becomes a very potent neurotoxin that can cause brain damage that may cause a syndrome similar to PD. Because it has four letters and starts with an *M*, MPTP is often confused with MDMA. There has never been a single research report that suggests that MDMA causes PD.

Third, MDMA is not an aphrodisiac. Although MDMA use is correlated with high-risk sexual behavior (Klitzman et al., 2002) it is not known to be causal. In fact, it may reduce sexual functioning (Milani, et al., 2000).

Fourth, a date rape drug is difficult to define. There are certain drugs (alcohol, barbiturates, benzodiazepines, and disassociate anesthetics) that have been used by certain unscrupulous individuals or groups to intoxicate a woman to the point where she could not defend herself from, or even remember, a rape. MDMA does not have the characteristics of any of these compounds. Users are conscious and aware. There is no reason to believe that MDMA is a "date rape" drug.

Neurotoxic Properties of MDMA in Nonhuman Animals

Accumulating evidence has documented that MDMA is a selective serotonergic neurotoxin in rodents and nonhuman primates (Stone et al., 1986; Battaglia et al., 1988; Ricaurte et al., 1992). MDMA has been shown to be neurotoxic in rats (Stone et al., 1986; Schmidt and Taylor, 1987), pigeons (LeSage et al., 1993), and nonhuman primates (Ricaurte et al., 1992). MDMA-induced serotonergic neurotoxicity exhibits with four characteristic features:

1. Reduced levels of serotonin and its metabolite, 5-hydroxyindole acetic acid (5-HIAA) (Schmidt and Taylor, 1987) indicate that serotonin is being both released and "turned over" (broken down and reused) less frequently.
2. Reduced numbers of serotonin reuptake transporters (Battaglia et al., 1988) indicate that at the same time serotonin release and reuse is inhibited the molecular mechanism that recycles it is also inhibited.

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3. Reduction in tryptophan hydroxylase (TPH) activity (Stone et al., 1986) indicates that the enzyme that synthesizes serotonin is also inhibited.
4. MDMA produces a loss of serotonin-containing neurons (Commins et al., 1987; Slikker et al., 1988).

Similar to the mechanism by which methamphetamine is neurotoxic, there is evidence that MDMA may indirectly cause neurodegeneration by promoting dopamine (DA) release. In Chapter 5 we discuss the mechanisms by which methamphetamine causes DA release. These are calcium-dependent and calcium-independent processes: Ca^{2+}-dependent release is regulated by the firing of an action potential; Ca^{2+}-independent release is spontaneous. MDMA can also release DA by the same two mechanisms, a calcium-dependent process (Gudelsky et al., 1994) and a calcium-independent nonvesicular transporter-mediated process (Nash and Brodkin, 1991; Shankaran et al., 1999). Drugs that block DA transmission have been shown to be effective in attenuating the neurotoxic effects of MDMA. For example, depletion of DA stores by inhibiting the enzyme that makes DA, tyrosine hydroxylase, and blockade of the protein that transports DA both protect serotonergic terminals from MDMA neurotoxicity (Nash and Brodkin, 1991).

The exact mechanism responsible for MDMA-induced neurotoxicity is not known. The two prominent theories are that it may be induced by oxidative stress caused by the increased DA release (Sprague and Nichols, 1995) or by hyperthermia (Malberg et al., 1996).

Neurotoxic Properties of MDMA in Humans

The evidence for a neurotoxic effect of MDMA in humans has been much more controversial than for methamphetamine. Ethical and methodological problems have made evaluation of the effects of MDMA on humans difficult. These difficulties include the inability of researchers to be sure what drug was taken, and how much of it was taken, by a research participant. Ecstasy tablets can contain from 40 to 150 mg of MDMA as well as a variety of other psychotropic compounds. Researchers have to rely on self-report by subjects, which can be contaminated by misdirection (the user could be lying), problems with recall (the user may not remember how much drug he or she took), or simply misinformation (the user may be misinformed about what drug he or she took).

Perhaps the most important methodological issue has to do with studies that include poor control groups. Most MDMA users also use other drugs. For this reason, any study that tries to evaluate the effect of MDMA on human

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subjects should have two control groups. One of these groups should be a traditional control group of individuals that use no drugs. The other should be a polydrug-use group of individuals that use a variety of drugs but not MDMA. This way the effects of MDMA could be separated from the effects of other drugs. Very few studies of the effects of MDMA have been appropriately controlled. A recent review identified three types of studies that have been used to examine the neurotoxic effects of MDMA in humans (Curran, 2000).

The first type is neurobiological research. Consonant with the animal research described above, the concentration of 5-HIAA in the cerebrospinal fluid of MDMA users is reduced compared with that of non-MDMA-using controls (Ricaurte et al., 1990; McCann et al., 1994). This indicates reduced serotonergic turnover as described above. Further, the literature on humans has also provided a measure of reduced serotonergic reuptake transporters. In one such study (the most direct connection between MDMA and altered serotonergic function in humans) the PET scans of 14 self-affirmed MDMA users who had been abstinent from the drug for 21 days were compared with those of 15 non-drug-using controls. This study indicated that there were fewer serotonin transporters (the molecules that are responsible for serotonergic reuptake into the presynaptic neuron; see Chapter 5) in the brains of the drug users than in the brains of the control group. Human studies that examine the effect of MDMA on tryptophan hydroxylase (TPH) activity and serotonergic cell loss have not been conducted.

The second type of research focuses on psychological functioning. Acute effects of MDMA tend to be positive (Greer and Tolbert, 1986). These effects include intimacy with others, euphoria, heightened sensual awareness, and increased physical and emotional energy. Prior to concerns about the potential neurotoxicity of MDMA, it was hoped that the drug could be used for couples therapy. However, the long-term effects may be very negative. Frequent recreational users of MDMA exhibit poor performance on neurocognitive measures (McCann et al., 1999; Morgan, 1999; Rodgers, 2000; Gouzoulis-Mayfrank et al., 2000; Bhattachary and Powell, 2001; Verkes et al., 2001). Specifically, memory and attention seem to be impaired by MDMA use (for review, see Morgan, 2000; Parrott, 2000). Chronic MDMA abuse has been shown to cause deficits in the following areas: recall (Morgan, 1999); visual and verbal memory in low intellectually functioning males, but not in females or in high intellectually functioning males (Bolla et al., 1998); working memory (Wareing, Fisk, and Murphy, 2000); and complex tests of attention (McCann, 1999). These deficits may (McCann et al., 1999; Morgan, 1999; Gouzoulis-Mayfrank et al., 2000; Bhattachary and Powell, 2001) or may not (Fischer et al., 1995) be permanent. Special note should be made of the work by Bolla et al. (1998). In that study the sex and IQ of the

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participants were measured. The authors determined that the negative effects of MDMA use may be observed only in lower intellectually functioning males. Females and higher intellectually functioning males may be protected.

The third type of research focuses on psychiatric symptomatology. Serotonin is involved in most psychopathology, and MDMA alters the serotonergic system. Thus, MDMA should have some effect on psychiatric functioning. This literature, however, is impossible to evaluate because most studies have examined only polydrug users with inappropriate control groups, completely confounding the effects of MDMA with those of other drugs.

Conclusions

There have been numerous criticisms of the research that has evaluated the effects of MDMA. One such criticism is that the doses of MDMA given to animals for experimental purposes are far higher than the doses taken by recreational users (Saunders, 1995). However, when the metabolic rates of the animals tested were taken into account, it was determined that the dosages that were neurotoxic to animals were equivalent to the dosages used recreationally by humans (Ricaurte et al., 2000). Some drugs do affect human and nonhuman animals differently. The only way to know is through experimentation.

The available evidence from studies of human MDMA users suggests but cannot prove conclusively that there is a direct relationship between MDMA use and alterations of serotonergic neurotransmission and cognitive impairment. The MDMA users who are typically studied are polydrug users. They have used drugs prior to, during the time of, and after the studies that have evaluated their performance. Many of the drugs that are commonly used (marijuana, alcohol, and methamphetamine, to name but a few) by today's adolescents can cause both serotonergic alterations and cognitive deficits. Recent studies provide conflicting evidence about the relative contributions of MDMA and cannabis to both serotonergic alterations and cognitive deficits (Rodgers, 2000; Croft et al., 2001). Because of ethical concerns (we cannot give humans drugs that we believe may cause neurodegenerative damage), it has been impossible to design a study that would prove conclusively that MDMA causes this type of damage. We have had to rely on correlational studies and analogous animal models to elucidate the effects of MDMA. These studies have tended to support the role of MDMA as a neurotoxin.

Many proponents of MDMA still argue that the potential benefits of its controlled use outweigh any negative effects that it may have (J. Holland, Congressional testimony, 2001). These proponents suggest that under controlled clinical use the drug is not neurotoxic. They suggest that the negative

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effects occur only after repeated chronic use. However, there is a growing body of evidence that suggests that observable (i.e., behavioral) deficits occur much later than physiological deficits (i.e., brain alterations) (Frederick et al., 1998; Taffe et al., 2001; Winsauer et al., 2002).

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