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Controlled studies in humans have shown that MDMA has potent effects on the cardiovascular system and on the body's ability to regulate its internal temperature. Of great concern is MDMA's adverse effect on the pumping efficiency of the heart - in the presence of MDMA, increased physical activity increases heart rate significantly, but the heart does not respond in its normal manner, which is to increase the efficiency with which it pumps blood. Since MDMA use is often associated with sustained, strenuous activity, such as dancing, MDMA's effects on the heart could increase the risk of heart damage or other cardiovascular complications in susceptible individuals.

Pharmacokinetic studies have shown that MDMA is rapidly absorbed into the human blood stream, but once in the body the metabolites of MDMA inhibit MDMA metabolism. As a result, subsequent doses of the drug produce unexpectedly high blood levels, which could worsen the cardiovascular and other adverse effects of this drug without increasing its "pleasurable" effects, which tend to peak about two hours after taking an initial dose. MDMA interferes with the metabolism of other drugs, including some of the adulterants in MDMA tablets.

### **Long-Term Consequences of MDMA: Neurochemical and Developmental**

Acute doses of MDMA produce marked changes in both dopamine and serotonin systems within the brain. Though the changes in dopaminergic neurons appear transient, the data suggest that the changes in the serotonergic system are longer-lasting. In addition, examinations of more global brain function have shown that the effects of acute doses of MDMA extend to regions of the brain that are thought to be involved in higher thought processes. These findings have raised concern about possible long-term effects on both infrequent and regular users of MDMA.

Several groups have shown that exposure to MDMA rapidly and persistently destroys a key marker of serotonergic function in regions known to have a high density of serotonin neurons, including the striatum and cortex. More detailed examination of this structural damage shows that MDMA appears to prune, or reduce in number, serotonin axons and axon terminals. Eighteen months after a short course of MDMA, investigators found that some brain regions had substantial loss of serotonin axon terminals, while a few others had more serotonin axon terminals. This pattern is a hallmark of axon pruning, since nerve cells will often grow replacement terminals upstream of the damaged terminals. These results, then, are evidence not only of MDMA's neurotoxicity, but of the brain attempting to rewire the serotonin system after damage.

Since younger brains may have an increased susceptibility to the neurotoxic effects of MDMA, it may be that the youngest, fastest developing brains - those of a developing fetus - could

be particularly vulnerable to the effects of this apparent serotonin neurotoxin. Since most MDMA users are young and in their reproductive years, it is possible that some female users may take MDMA when they are pregnant, either inadvertently or intentionally, because of the misperception that it is a safe drug. Studies in animals have shown that MDMA has little effect on the physical development of the young brain. Behavioral and cognitive studies in laboratory animals, however, have identified significant adverse cognitive effects from pre and neonatal exposure to MDMA. This effect was not due to serotonergic neurotoxicity; the mechanisms underlying the development of these cognitive deficits are not known yet. Though the rodent experiments have predictive value, it is not known whether human fetuses exposed to MDMA when their mothers abuse the drug will develop persistent and learning memory deficits.

### **Long-Term Functional Consequences of MDMA: Behavioral, Mood, Psychiatric, and Cognitive**

Because MDMA produces long-term deficits in serotonin function, and because serotonin function has been implicated in the etiology of many psychiatric disorders including depression and anxiety, investigators have suspected that MDMA users may experience more psychopathology than non-users. Indeed, a number of investigators have found that heavy MDMA users experience a constellation of psychiatric changes, scoring significantly higher on measures of obsessive traits, anxiety, paranoid thoughts, and disturbed sleep, among others. One study, aimed at developing reliable measures of diagnosing substance abuse disorders, found that 43 percent of MDMA users met DSM-IV criteria for dependence and 34 percent met the criteria for abuse of MDMA.

There is a large and growing body of evidence from a variety of studies with humans that MDMA use can have long-lasting effects on memory. None of these studies are perfect, as they all have methodological concerns such as concurrent use of other drugs (it is apparently impossible to find but a few MDMA users who do not use other illicit substances, particularly marijuana). In addition, results vary with the assessment used. Nonetheless, the general finding that emerges across all of the studies is that MDMA does impact memory abilities in ways that could adversely affect normal functioning on every day tasks. Moreover, the relationship between memory problems and MDMA use appears to have a dose-dependent relationship, that is, the more MDMA used, the greater the deficit.

Given that numerous studies have shown that the serotonin deficits caused by MDMA are persistent, lasting at least seven years in one study of nonhuman primates, it is important to determine if the psychological and memory deficits associated with even moderate use of MDMA recover after some period of time. This is a particularly important issue with MDMA because of the relatively young age of the majority of people who abuse this drug. So far, the majority of studies have focused on MDMA

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