

## Ecstasy Neurotoxicity

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Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA), is a synthetic amphetamine derivative and an illicit drug of abuse which is primarily consumed by young people in dance and music environments. Generally, MDMA causes elevated mood and a heightened sense of empathy (1). It is capable of producing both reversible and irreversible brain changes, such as expression of microglia cells, hypertrophy of astrocytes and neuronal degeneration in various areas of the brain (2). It has been reported that degenerating pyramidal and non-pyramidal neurons are localized within the parietal cortex, teniatecta and thalamic nuclei (3). MDMA can also result in degenerating neurons in the insular and perirhinal cortex (4). The neurotoxicity associated with MDMA exposure may be the result of oxidative stress leading to the formation of hydroxyl radicals (5, 6), lipid peroxidation (7, 8) and an increase in the number of tunnel positive cells in the hippocampus (9). The imbalance between reactive oxygen species (ROS) and the internal antioxidants result in oxidative stress. Oxidative stress is generated by an imbalance between reactive oxygen species (ROS) and antioxidants and may contribute to the neurotoxicity of MDMA in the brain (5). 3, 4-methylenedioxymethamphetamine (MDMA) or ecstasy has excitatory effects on the central nervous system as an amphetamine derivative, particularly on hippocampus, neostriatum and cerebellum (5, 10, 11). MDMA has excitatory effects on the central nervous system, mostly on the serotonergic, dopaminergic and noradrenergic synaptic endings. The highest affinity is noted for serotonin transporter (SERT) and 5-hydroxytryptamine 2 (5-HT<sub>2</sub>) receptors (12).

### MDMA and Memory

3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity is characterized by functional impairment in memory and depression (13, 14). Our previous studies showed that MDMA causes learning memory

impairment and apoptosis in the brain (14). Exposure to 3,4-methylenedioxymethamphetamine (MDMA) leads to spatial memory impairment and hippocampal cell death. The hippocampus is one of the most important brain structures associated with learning memory and cognition (15).

Many studies have demonstrated that MDMA is neurotoxic to serotonergic neurons of the hippocampus (16, 17). These effects seem to be dose-dependent, leading to memory impairment (18) and apoptosis in the hippocampus (19).

### MDMA and Apoptosis

MDMA induces cell death through an apoptotic pathway by releasing cytochrome C and activating the caspases cascade (20). Apoptosis is a gene-regulated phenomenon that occurs under both physiological and pathological conditions. This mechanism is regulated by several sets of genes, the best characterized being the Bcl-2 family (21). The Bcl-2 family consists of anti-apoptotic (Bcl-2, Bcl-xL and Bcl-w) and proapoptotic (Bax, Bak, Bid and Bad) members (22). It has been stated that MDMA can induce neural apoptosis and expression of apoptosis-related factors, such as caspase 3 and cytochrome C in rat brains (23). A study by Upreti et al. showed that MDMA induces activation of c-Jun protein, N-terminal protein kinase, and p38 kinase, which phosphorylate the anti-apoptotic Bcl-2 protein and promote apoptosis in MDMA-exposed tissues (24). Our previously published study suggests that multiple doses of MDMA can induce cell death through an apoptotic pathway, resulting in the up-regulation of Bax and down-regulation of Bcl-2 (19). We also showed that nonacute apoptotic effects of this drug are dose-dependent. To prove the anti-apoptosis effects of MDMA, more assays on the caspase family and other members of the Bcl-2 family need to be performed (19, 25). We showed that MDMA administration caused an

increase in caspase 3 expression in the hippocampus (25). Taken together it seems that MDMA-induced memory impairment is caused by ROS production and apoptosis in the hippocampus.

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