3,4-METHYLENDIOXYMETHAMPHETAMINE (ECSTASY) INDUCES FORMATION OF REACTIVE OXYGEN SPECIES AND TAU PROTEIN PHOSPHORYLATION IN THE HIPPOCAMPUS

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The psychostimulant 3,4-methylendioxymethamphetamine (MDMA, "ecstasy") is an amphetamine derivative that is widely abused in the Western society. Neuroimaging studies indicate that MDMA damages serotonin-containing fibres in the forebrain, which likely underlies changes in mood and behaviour that are frequently observed in chronic MDMA abusers. However, the occurrence of encephalographic (EEG) abnormalities and cognitive impairment in MDMA abusers suggests that MDMA toxicity is not restricted to monoaminergic neurons. We examined the neurotoxic effect of MDMA in the hippocampus and striatum of C57Black mice combining *in vivo* microdialysis, biochemical analysis, and immunohistochemistry. Three consecutive injections of MDMA (25 mg/kg, i.p., 2 hours apart) increased the formation of reactive oxygen species in the hippocampus, as assessed by the amount of 2,3-dihydroxybenzoate formed from salicylic acid in the dialysate. No formation of reactive oxygen species was observed in the striatum. MDMA also induced reactive gliosis and the expression of the glycoprotein, Dickkopf-1 (Dkk-1), in the hippocampus. Dkk-1 acts as an extracellular inhibitor of the canonical Wnt pathway, which protects neurons by inhibiting the enzyme glycogen synthase kinase-3β (GSK-3β). As tau protein is an established substrate of GSK-3β, we examined the levels of phosphorylated-tau in the hippocampus of mice treated with MDMA. MDMA induced an increase of tau phosphorylation, which peaked after one day and returned back to normal at 3 days. None of these changes were observed in the striatum. A chronic administration of MDMA (30 mg/kg/6 day, i.p.) induced an increased expression of Dkk-1 and phosphorylated tau which lasted for three days after the end of the treatment in the hippocampus, and only for one day in the striatum. Hyperphoshorylated tau loses the ability to bind to microtubules, inducing cytoskeletal abnormalities in neurons. Thus, our data suggest that MDMA induces neuronal dysfunction in the hippocampus, a region that is critically involved in spatial learning and episodic memory.