A single neurotoxic dose of MDMA increases kynurenine pathway metabolism in plasma and hippocampus of rat

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Summary

Introduction: The kynurenine pathway is the main route of tryptophan metabolism and under physiological conditions, it is responsible for over 95% of tryptophan degradation in mammals. Tryptophan is converted into the first stable molecule of the pathway, kynurenine, through the action of the enzymes tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase. The pathway is divided into two branches, one of which forms kynurenic acid by means of kynurenine aminotransferases, and the other of which, by the action of kynurenine mono-oxygenase, gives rise to 3-hydroxykynurenine, a precursor of the neurotoxin quinolinic acid. Kynurenine, kynurenic acid and quinolinic acid have been implicated in various neurological and neurodegenerative disorders [1]. 3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is an amphetamine derivative that produces serotonergic neurotoxicity [2] and neuroinflammation manifested as increased production of interleukin-1β and microglial activation [3]. **Objective**: The aim of this study was to evaluate possible changes in the levels of major kynurenine pathway metabolites following MDMA administration. **Materials and methods:** Male Dark Agouti rats received a single neurotoxic dose of MDMA (12.5 mg/kg, i.p.) and were sacrificed 1 h, 3 h, 6 h, 24 h or 7 days later. Plasma and hippocampal concentrations of serotonin, tryptophan, kynurenine and kynurenic acid were measured by high pressure liquid chromatography. The ratios of serotonin/tryptophan and kynurenine/tryptophan were also calculated as an index of the activity of the enzymes involved in the metabolism of tryptophan. **Results:** MDMA increases hippocampal concentrations of tryptophan 1 h and 3 h after administration, returning to control concentrations at 6 h. No differences in plasma concentrations of tryptophan occur at any of the times measured compared with the control group. Kynurenine concentrations are also raised in hippocampus 1 h, 3 h and 6 h after MDMA as are the plasma concentrations 3 h and 6 h after drug administration. Furthermore, in hippocampus the kynurenine/tryptophan ratio is increased only 6 h after MDMA whereas in plasma, an increase is observed after 1 h, 3 h and 6 h. MDMA raises kynurenic acid concentrations at 6 h in hippocampus and at 3 h in plasma. Serotonin concentrations decrease in hippocampus at all the time-points evaluated, and in plasma at 3 h and 6 h. The serotonin/tryptophan ratio also decreases in hippocampus at all the times measured but only at 3 h and 6 h in plasma. **Conclusions:** Administration of a neurotoxic dose of MDMA in Dark Agouti rats leads to an imbalance of the kynurenine pathway, resulting in an increase in the kynurenine/tryptophan ratio in plasma and hippocampus reflecting an increase in IDO activity.

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