Pretreatment with memantine prevents Alzheimer-like alterations induced by intrahippocampal okadaic Acid administration in rats.

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Introduction: Cerebral okadaic acid (OA) administration induces Alzheimer's disease (AD)-like phenotype in rats. Alterations in glutamate levels associated with hyperactivation of cyclin dependent kinase 5 (Cdk5) signaling pathway downstream Tau phosphorylation may participate in the genesis of this pathological phenotype. Material and Methods: Here, we examined the efficacy of memantine (MN, 20mg/kg) pretreatment on reducing OA-induced AD-like phenotypes in rats. Wistar rats were given daily intraperitoneal injections of MN for 3 days and then given an intrahippocampal infusion of OA (100ng). Animals were divided into four groups: control (CO), MN, OA and MN/OA. Spontaneous locomotion and spatial memory performance were assessed by open field and Morris water maze respectively. Additionally, we measured glutamate levels in the cerebrospinal fluid (CSF) and the immunocontent of Cdk5, p35, p25 and phosphorylated Tau (pTauSer199/202) in the hippocampus. Results and Discussion: Spontaneous locomotion did not differ between groups. The OA group showed a significant decrease in spatial memory performance compared to all groups. The OA infusion also increased CSF glutamate levels and the immunocontents of Cdk5, p25 and pTauSer199/202 in the hippocampus. Conversely, pretreatment with MN prevented OA-induced spatial memory deficits and the increment of CSF glutamate level; which paralleled with normal immunocontents of Cdk5, p25 and pTau-Ser199/202 proteins. There were positive correlations between spatial memory performance and the neurochemical parameters. Conclusions: In summary, pretreatment with MN prevents spatial memory deficits induced by intrahippocampal OA administration in rats. The prevention of increase CSF glutamate levels, along with the reduced hippocampal phosphorylation of TauSer199/202 by Cdk5/p25 signaling pathway, are the mechanisms proposed to participate in the prophylactic effects of MN in this AD-like model.

Keywords: Alzheimer’s disease, okadaic acid, memantine, glutamate, Cdk5, tau, learning and memory, neurotransmitter, aberrant phosphorylation, Liquid Chromatography, Western Blotting

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