Effects of chronic memantine treatment on okadaic acid induced memory impairment and changes in neurotransmitter activity in the septo-hippocampal system

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INTRODUCTION
Alzheimer’s disease (AD) is a complex multifactorial neurodegenerative disorder and hyperphosphorylated tau protein is a major pathological hallmark of AD. It is proposed that an imbalance between tau phosphorylation and dephosphorylation is critical to AD. This disturbance might be the result of either higher activities of tau kinases, lower activities of tau protein phosphatases (PPs), or both. May be suggested that breaking the balance between tau protein phosphorylation and dephosphorylation will lead to AD-like tauopathy. PP2A is reported the major tau phosphatase in brain, whose activity is reduced in AD brain and dephosphorylation of tau can be blocked in cells by Okadaic acid (OA). OA is a potent and selective inhibitor of protein phosphatase PP1 and protein phosphatase 2A (PP2A). Because of its property to inhibit phosphatase activity, OA is associated with protein phosphorylation and has been proved to be a powerful probe for studying the various regulatory mechanisms and neurotoxicity.

Objective: The present study was designed to explore involvement of neurotransmitter activity dysfunction in septo-hippocampal system in OA-induced memory impairment. The effects of chronic memantine treatment was also assessed on OA induced alterations in above parameters associated with memory deficit.

METHODS
The possible neuroprotective potential of memantine on OA-induced spatial memory and pathological changes in the hippocampus and MS was evaluated in 4 groups: control rats injected i.p. with saline [Contr(S)] or memantine [Contr(M)] and OA injected rats treated i.p. with saline [OA(S)] or memantine (OA(M)]. Memantine (5 mg/kg, i.p.) or saline were given daily for 13 days starting from the day of OA injection.

Animals were tested in a standard Morris water-maze, consisting of a circular (1.5 m in diameter and 0.5 m height) filled with opaque (white-colored) water.

The task was adapted from Bizon, at all. On days 1–9, rats received four trials per day, one from each of four equidistantly located start locations (N, S, E, W). On days 1 and 2, rats were trained to locate a visible platform in the southeast quadrant of the pool, followed by a third day in which the platform was submerged at the same location. This 3-day sequence was repeated twice on days 4–6 and 7–9 for a total of 36 trials. On day 10, a competition test was given in which the visible platform was moved to the northwest quadrant (opposite to its placement on the training days). Two trials were given with start points equidistant from the two platform locations (SE and NW).

RESULTS

Statistical analysis for differences in the platform reaching latency showed no significant difference between groups (P>0.05) in visible platform trials and significant difference between OA(S) and Contr(S) (P = 0.508), also between Contr(S) and Contr(M) (P = 0.710) groups in visible platform trials. In hidden platform trials differences in the platform reaching latency significant between OA(S) and Contr(S) groups (P = 0.014), also between OA(S) and OA(M) groups (P = 0.007), but no significant difference between Contr(S) and OA(M) groups (P = 0.998). This fact certifies for obvious deficit of the place learning performance strategy in rats of OA(S) group and chronic administration of memantine may prevent this deficit.

SUMMARY
Chronic administration of memantine significantly attenuated OA induced spatial memory impairment and the OA-induced neuropathological changes in the hippocampus and in the MS. It is suggested that IVC injection of OA may impair the hippocampus-dependent spatial memory through damaging the cholinergic and GABAergic projections between the MS and the hippocampus and the septo-hippocampal dysfunction may be at least part of the underlying mechanisms of OA induced spatial memory deficit.