Effects of chronic administration of memantine on okadaic acid induced spatial short-term memory impairment and hippocampal cell loss

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INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disease that causes progressive cognitive and behavior deterioration over age 65. Currently, the etiology and pathogenesis of AD remains unknown. It is critical to develop useful models to study the pathology of AD for pre-clinical testing of drugs. In spite of the limitations of animal model, the progress toward a cure for AD depends on the development of animal models.

In the present study, intracerebroventricular (ICV) injection of OA in rats was used as a memory impairment and hippocampal neurodegeneration animal model. The possible beneficial effect of memantine on the OA-induced spatial short-term memory impairment was examined in spatial alternation task, and the neuroprotective potential of memantine on OA-induced structural changes in the hippocampus was evaluated by Nissl staining. The effects of memantine have been studied in relation to cognitive function in animal models of long-term memory, but have rarely been tested in short-term memory paradigms. Chronic treatment with memantine in male rats at dose which produces a plasma level within the therapeutic range was used to verify whether blocking NMDA receptors may impair or improve spatial short term memory.

METHODS

Subjects. A total of 34 male rats, approximately 4 months of age and weighing 220-250 g at the start of experimentation served as subjects.

Surgery. Rats were anesthetized with i.p. injection of 4 % chloral hydrate (9 ml/kg) and placed in a stereotaxic apparatus. OA was dissolved in artificial cerebrospinal fluid (aCSF) and injected ICV (A: 0.2 mm from bregma; L: 1.1mm and V: 3.6mm) 200 ng in a volume of 10 μl bilaterally (OA group). Vehicle control received 10 μl of aCSF ICV bilaterally (Control). All injections were made with a 1-μl Hamilton syringe with a microinjection pump (CMA 402 Syringe Pump, Sweden). The rats were allowed to recover from the surgery for two weeks before starting the behavioral experiments.

Drug Treatment. Control and OA injected rats were divided into 2 subgroups: control rats injected i.p. with saline (n=8) or memantine (n=8) and OA injected rats treated i.p. with saline (n=8) or memantine (n=10). Memantine (5 mg/kg, i.p.; Sigma Chemical Co., St. Louis, MO) or saline were given daily for 13 days starting from the day of OA injection.

Spontaneous alternation behavior. Rats were trained in a four-arm plus-shaped maze with floor and walls made of black Plexiglas. Each rat was placed at the center of the maze and allowed to transverse the maze freely for 15 min. The number and sequence of arms entered were recorded to determine alternation scores. Alternation was calculated as follows: (Actual alternation/possible alternation) x 100; possible alternation sequences are equal to number of arm entries minus four.

Histology. At the end of the behavioral experiments OA treated and control rats were deeply anesthetized with pentobarbital and perfused through the ascending aorta with 300 ml saline followed by 600 ml 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The surviving pyramidal cells in the hippocampus of rats were visualized by Nissl staining. The number of the hippocampal pyramidal cells in Nissl staining sections was counted at X 400 magnification. Stained sections were analyzed with fluorescence optic microscope Leica MM AF.

RESULTS

ICV injection of OA significantly impaired SA performance. The one way ANOVA for spatial alternation score showed significant effect of group (F<sub>3,106</sub>=7.108, P<0.001). Post hoc (Tukey Test) analysis showed a significant difference between the saline and memantine treated control (P = 0.035) and between the saline and memantine treated OA injected rats (P = 0.034). The difference between the saline treated control and saline or memantine treated OA injected rats were not significant (P = 0.415; p = 0.6, respectively). Behavioral study showed that memantine treated control rats, relative to saline treated control rats, had a significantly lower level in the number of arms entered during the testing session.

SUMMARY

The one way ANOVA for the number of arms entered during the testing session showed significant effect of group (F<sub>3,106</sub>=8.057, P<0.001). Post hoc (Tukey Test) analysis showed a significant difference between the saline treated control and the saline treated OA injected rats (P < 0.001), but there was no significant difference between the saline and memantine treated control (P=0.467) and between saline treated control and memantine treated OA injected (P = 0.891) rats. Memantine treatment causes improvement of spontaneous alternation performance; the difference between saline and memantine treated OA injected rats is significant (P = 0.002).

The OA-induced spatial short-term memory impairment may be attributed, at least in part, to the hippocampal cell death caused by the OA. Chronic administration of memantine significantly attenuated the OA-induced spatial memory impairment.