

ALPHA 1-ADRENOCEPTOR ANTAGONIST AMELIORATES AGING-INDUCED MEMORY IMPAIRMENT THROUGH INCREASING OF NEUROGENESIS IN THE HIPPOCAMPUS OF RATS

Hypothesis / aims of study

Alpha 1-adrenoceptor (α 1-AR) antagonists have widely been used for the treatment of LUTS, and other actions of α 1-AR antagonists, such as memory-related effects and inhibitory effects on behavioral activation, have been reported. In the present study, we investigated the effect of tamsulosin on aging-induced memory impairment in relation with neurogenesis in the hippocampus of rats.

Study design, materials and methods

4 months old Fisher 344 rats (n = 40) were used as the young-aged (YA) group and 25 months old Fisher 344 rats (n = 40) were used as the old-aged (OA) group. The rats were randomly divided into 10 groups (n = 8 in each group) as the YA control group, the YA and 0.001 mg/kg, 0.01 mg/kg, 0.1 mg/kg, 1 mg/kg tamsulosin-treated group, the OA control group, the OA and 0.001 mg/kg, 0.01 mg/kg, 0.1 mg/kg, 1 mg/kg tamsulosin-treated group. The tamsulosin-treated groups received orally tamsulosin once a day for 35 days at respective dose in total volume 1 ml and the control groups received 1 ml distilled water for the same duration. Step-down avoidance task and radial 8-arm maze test were conducted for the determination of memory function. In the hippocampus, immunohistochemistry for 5-bromo-2'-deoxyuridine (BrdU) was performed for the evaluation of neurogenesis and Western blot analysis for the expressions of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) were performed. Patch clamp recording was used for the evaluation of the effects of tamsulosin on ionotropic glutamate receptors, such as N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainite receptors.

Results

In step-down avoidance task, latency of the OA group was shorter than that of the YA group. Tamsulosin treatment increased the latency in both the OA and YA groups as dose-dependently. In radial 8-arm maze test, OA group showed lower number of correct choice and higher number of error than those in the YA group. Neurogenesis and expressions of BDNF and TrkB proteins were significantly decreased in the OA rats, whereas those were remarkably increased in both the YA and OA groups treated by tamsulosin. The NMDA-induced ion current was significantly increased as tamsulosin dose-dependently. However, AMPA-induced and kainate-induced ion currents were not affected by tamsulosin.

Interpretation of results

Tamsulosin decreased the frequency of spontaneous inhibitory postsynaptic currents without affecting the amplitude. Also, increasing of cell proliferation can be ascribed to the enhancing effect on apoptotic neural cell death by drug. This study showed that α ₁ AR antagonists may overcome aging-induced neuronal cell death in the hippocampus.

Concluding message

Alpha 1-AR antagonist treatment alleviated aging-induced memory impairment through increasing of neurogenesis in the hippocampus of the rats. The possible underlying mechanism might ascribe to the enhancing effect of NMDA-induced ion current.

References

1. The phosphodiesterase type-5 inhibitor, tadalafil, improves depressive symptoms, ameliorates memory impairment, as well as suppresses apoptosis and enhances cell proliferation in the hippocampus of maternal-separated rat pups. Baek SB, Bahn G, Moon SJ, Lee J, Kim KH, Ko IG, Kim SE, Sung YH, Kim BK, Kim TS, Kim CJ, Shin MS. *Neurosci Lett.* 2011 Jan 13;488(1):26-30.

Specify source of funding or grant	No funding
Is this a clinical trial?	No
What were the subjects in the study?	ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	Yes
Name of ethics committee	Kyung-hee University Institutional Animal Care and Use Committee