Neuroprotective effect of acetylcholinesterase inhibitors

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Alzheimer's disease (AD) is the most common cause of dementia among people age 65 and older. Prevalence of AD is predicted to increase worldwide, and financial and social impact of AD is likely to explode. In Japan, donepezil, an acetylcholinesterase inhibitor (AChEI), is the only one approved for the treatment of AD. It has been indicated that donepezil and other AChEIs may slow the rate of cognitive decline in people with AD. Donepezil was reported to inhibit the progress of brain atrophy in AD, indicating the attenuation of neuronal death in the brain of the patients. A slower rate of whole brain shrinkage in galantamine-treated patients was also found.

It has been suggested that beta amyloid (Aβ), a major component of senile plaques found in the brains of AD patients, leads to cell death in cultured neuron. We found that Aβ not only induces neuronal death but enhances glutamate-induced excitotoxicity. Excessive amount of glutamate would cause NMDA receptor-mediated Ca^{2+} overload, disrupt homeostasis, and induce neuronal death. Aβ may increase the vulnerability of neuron to glutamate.

Using primary cultured rat cortical neurons, donepezil and galantamine exert neuroprotective effect against Aβ- or glutamate-induced cell death. The protective effect was mediated via nicotinic acetylcholine receptor (nAChR). Stimulation of α7 nAChR up-regulates phosphatidylinositol-3 kinase (PI3K)-Akt-Bcl-2 cascade or defensive system. AChEI-induced protection was also mediated via the pathway.

We would show the neuroprotective effect of AChEI, and discuss the effect of nAChR stimulation as a target for the treatment of AD.