OR4-4 Oral session

α7 nicotinic acetylcholine receptor-specific stimulation ameliorates cognitive impairment in a mouse model of Alzheimer’s disease via suppression of neuronal γ-secretase activity and promotion of microglial amyloid-β phagocytosis

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The neuropathological hallmarks of Alzheimer’s disease (AD) are the presence of senile plaques and neurofibrillary tangles along with extensive neuronal loss. Senile plaques and neurofibrillary tangles consist mainly of amyloid-β (Aβ) peptides and intracellularly accumulated hyperphosphorylated tau proteins, respectively. The Aβ is derived from sequential proteolysis of amyloid precursor protein by β- and γ-secretases. Longitudinal studies in patients with AD suggest that Aβ deposition occurring through increased production or decreased degradation is the primary event before the emergence of brain atrophy, tau phosphorylation, and chronic symptoms. Thus, results have led to the acceptance of the amyloid hypothesis, which asserts that Aβ accumulation in the brain is responsible for the development of AD. Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels that play a central role in intercellular communication in the central nervous system by converting the binding of acetylcholine into an ion flux through the postsynaptic membrane of neurons and microglia in the brain.

We previously demonstrated that stimulation of nAChRs increases Aβ phagocytosis in rat microglia and is closely associated with the decrease of brain Aβ and amelioration of memory dysfunction in a transgenic mouse model of AD. However, it is not yet known which nAChR subtypes on microglia promote Aβ phagocytosis. We here examined the subtypes of nAChRs involved in these beneficial effects.

In primary cultures of rat microglia, the α7 nAChR subtype selective agonist 3-[(2,4-dimethoxy)benzylidene]-anabaseine dihydrochloride (DMXBA) promoted Aβ and fluorescent latex bead phagocytosis, whereas the α7 nAChR subtype selective antagonists suppressed the enhanced Aβ phagocytosis. In a transgenic mouse model of AD, administration of DMXBA attenuated brain Aβ burden and memory dysfunction. Moreover, DMXBA suppressed γ-secretase activity in solubilized fractions of human neuroblastoma cells and transgenic mouse brain. These results suggested that selective activation of α7 nAChR subtype promoted microglial Aβ phagocytosis and suppressed neuronal γ-secretase activity to contribute to the attenuation of the brain Aβ burden and cognitive impairment. Thus, we propose neuronal and microglial α7 nAChR subtype as new therapeutic targets in the treatment of AD.