【論文の内容の要旨】

Alzheimer’s disease (AD) is characterized by two neuropathological hallmarks of extracellular senile plaques and intracellular neurofibrillary tangles. Senile plaques mainly consist of amyloid β peptide (Aβ) which is released from amyloid precursor protein (APP) by β- and γ-secretase cleavage. Neurofibrillary tangles mainly consist of hyperphosphorylated tau protein. In some familial forms of AD, mutations in the APP gene, which influence Aβ production, have been reported. So, abnormal production and deposition of neurotoxic Aβ has been believed to be the primary cause of AD, as amyloid cascade hypothesis. Tau is a microtubule-associated protein that stabilizes microtubules and promotes their assembly. Distributions of tau pathologies in AD have been shown to correlate with clinical phenotype. Furthermore, the pathologies appear to spread during the course of the disease in a stereotypical temporal and topological manner. Although many studies have attempted to show the associations between Aβ and tau, it remains unknown whether these two
pathologies are directly linked each other.

In recent studies, Aβ vaccination has been shown to result in clearance of amyloid plaques in patients with AD, but fail to prevent progressive neurodegeneration, suggesting that inhibition or clearance of Aβ may not influence tau pathologies. In addition, Braak et al (1991) reported that tau aggregation precedes diffuse plaque deposition, and presented a hypothesis that Aβ may be released from non-junctional varicosities of axons generated from abnormal tau-containing brainstem nuclei in sporadic AD. Furthermore, recent studies have demonstrated that intracellular tau aggregates propagate from cell to cell in a prion-like phenomenon in vitro and in vivo. Therefore, it is reasonable to speculate that APP, but not Aβ, may accelerate the spreading of tau pathologies.

In this study, I investigated whether the expression of APP influences uptake of tau fibrils and seed-dependent intracellular tau accumulation in culture cells. Treatment of SH-SY5Y cells expressing tau with recombinant tau fibrils and Aβ42 fibrils did not induce intracellular tau aggregation. This result suggests that Aβ42 does not influences uptake of tau fibrils and seed-dependent intracellular tau accumulation. On the other hand, the treatment with tau fibrils or sarkosyl-insoluble tau from AD brains induced intracellular tau aggregation in cells expressing both of tau and APP. The seed-dependent intracellular tau aggregation was not induced by the expression of mutant APP lacking an extracellular domain. The amount of phosphorylated tau aggregates in cultured cells was dose-dependently elevated by increased level of APP on cell membrane. Furthermore, FAD mutations of APP affected the formation of intracellular tau aggregates. The present results clearly indicate that extracellular domain of APP accelerates uptake of tau fibrils into cells and
promote intracellular aggregation of tau. APP, but not Aβ, may influence cell-to-cell spreading of tau pathologies in AD.