Granular tau oligomer is a key for understanding clinical progression of Alzheimer’s disease

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Development of neurofibrillary tangles (NFTs) is well-correlated with clinical progression of Alzheimer’s disease. NFTs formation in entorhinal cortex may be correlating with memory loss in brain aging, because entorhinal cortex is involved in memory formation, and NFTs in limbic and neocortex may cause dementia in AD, because limbic and neocortex serve higher order brain functions. These suggest that regional development of NFTs is correlated with decline of brain functions in aging and AD. Recent reports suggested that the process of NFT formation, but not NFT itself is involved in neuronal dysfunction. Normally tau binds to microtubules and stabilize them. Once tau receives hyperphosphorylation by activating tau kinases, tau dislodge from microtubules, and starts tau-tau interaction in cytoplasm, forming tau oligomers. When tau oligomers possess β-sheet structure, tau oligomer forms insoluble granular tau oligomer. Granular tau oligomers sticks together, and form tau fibrils. From analysis of tau Tg mouse, we found that hyperphosphorylated tau, and soluble tau oligomer are involved in synapse loss, and granular tau aggregate is involved in neuronal loss, which suggest that different tau aggregates induce synapse loss, and neuronal loss before NFT formation, leading to brain dysfunction in brain aging and AD. Indeed, tau aggregation inhibitor blocked neuronal loss with reducing sarcosyl insoluble tau aggregates in P301L tau Tg mouse. Therefore, inhibition of granular tau aggregation is expected to block a progression of AD symptom by preventing neuronal loss.