Depolarization-induced tau and exosome release from synapses in AD

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Research Abstract

Project Summary Extracellular tau has been shown to be toxic and evidence supports regional trans-synaptic spread of tau pathology but the process is poorly understood. Moreover, tau immunotherapeutic approaches have been shown to be effective but progress is slow because the exact peptide released is not known. Based on recently published evidence that C-terminal

truncated and intact tau is released by depolarization in Alzheimer’s disease (AD) synaptosomes, the present project has the goal of understanding how synaptic release and accumulation of tau contributes to disease progression and whether tau release is modulated by A?. The general hypothesis is that synaptic C-terminal truncated tau peptides impact synaptic function and regional spread of tau pathology, and that released tau is carried on exosomes. Synaptosomes from cryopreserved AD and aged control cases will be studied; cases are staged and genotyped and will include a high pathology control group. A tauopathy mouse model that expresses human tau will also be studied. Aim 1 will characterize the specific tau peptides that are released along with neurotransmission and endocytic mechanisms, and will determine stage and APOE effects on release. Aim 2 will quantify exosome release from synapses and determine its association with disease stage and APO, and will determine the extent of tau association with exosomes and other pathology-related cargos. This proposal will directly address mechanisms related to synaptic release of tau peptides in AD.

Further information available at:

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