DOI: 10.1002/alz.078491

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

MOLECULAR AND CELL BIOLOGY

Extracellular Tau Oligomers Damage the Axon Initial Segment by an Endogenous Tau-Dependent Mechanism

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Abstract

Background: Neuronal polarity and synaptic connectivity are compromised in Alzheimer's disease (AD) and other tauopathies. The axon initial segment (AIS) is a key structure for regulating polarity and functions of neurons. It occupies the first 20-60 μm of the axon, comprises a diffusion barrier that segregates axon-enriched from somatodendritic-enriched molecules, and has a high concentration of voltage-gated ion channels that generate action potentials. Extracellular amyloid-β oligomers compromise AIS integrity. However, effects on the AIS of toxic tau species, including extracellular oligomers (xcTauOs) that spread tau pathology from neuron to neuron by a prion-like process, whereas unknown. Therefore, we wanted to test the hypothesis that AIS structure is sensitive to xcTauOs.

Method: Primary cortical neurons derived from either wild type (WT), or tau knock-out (KO) mice were exposed to xcTauOs or vehicle. Quantitative western blotting and immunofluorescence microscopy with an antibody against the AIS-enriched protein TRIM46 was used to monitor effects on the AIS. The same methods were also used to compare TRIM46 and two other AIS proteins, ankyrin-G and neurofascin-186 in human hippocampal tissue obtained from AD and age-matched non-AD donors.

Result: In cultured WT, but not TKO neurons, xcTauOs cause a trend toward AIS shortening and reduce the concentration of the resident AIS protein, TRIM46, without affecting total TRIM46 levels. Lentiviral-driven human tau expression in tau KO neurons rescues TRIM46 sensitivity to xcTauOs. In human AD hippocampus, AIS length and TRIM46 concentration within the AIS are reduced in neurons containing neurofibrillary tangles (NFTs), without affecting the overall protein levels of multiple resident AIS proteins.

Conclusion: These collective findings demonstrate that in cultured neurons, xcTauOs cause partial AIS damage by a mechanism dependent on intracellular tau, thereby raising the possibility that AIS reduction in AD is caused by xcTauOs working in concert with endogenous neuronal tau.