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Mechanisms of Axonal Transport Defects in a Cellular Model of Alzheimer's Disease

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Venue: 2nd floor Seminar Room (#A207) Main Building
iCeMS Complex 1, Kyoto University

The architecture of the neuron is such that the tip of the axon can be quite distant from the cell body where many of the cell's components are made. Thus, neurons rely on an elaborate microtubule-based transport system to allow for the shipping of cellular components, such as membrane and secreted proteins, to distal sites within the cell. Emerging evidence suggests that fast axonal transport (FAT) defects are early pathological manifestations of several neurodegenerative diseases including Alzheimer's disease (AD). We have previously shown that soluble amyloid beta oligomers (AβOs), a causative agent of AD, impede FAT of dense core vesicles (DCVs) and mitochondria in cultured hippocampal neurons through a NMDA-glutamate receptor mechanism that is mediated by a tau kinase, glycogen synthase kinase 3β (Decker et al., 2010). AβOs induce hyperphosphorylation of the axonal microtubule-associated protein, tau; however, it remains unclear how this modification disrupts transport. Notably, in our studies, transport defects occurred without concomitant microtubule destabilization, which is usually associated with hyperphosphorylated tau. To determine if tau is required for AβO-induced transport defects, we treated hippocampal neurons from wild type and tau knockout mice with nanomolar concentrations of AβOs and determined that transport defects of DCVs containing brain-derived neurotrophic factor (BDNF) indeed persist in the absence of tau. Thus, transport deficits may result from dysregulation of intracellular signaling cascades that are implicated in AD pathogenesis. Current work in our laboratory is geared towards identifying the signaling mechanisms that negatively affect axonal transport in AβO-treated neurons.

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