Tau function in pre and postsynaptic plasticity of human cortical neurons

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Research Abstract

PROJECT SUMMARY Development, maintenance and plasticity of presynaptic axons and postsynaptic dendritic spines are essential for learning and memory and require proper regulation of the actin and microtubule (MT) cytoskeleton. Tau is a microtubule associated protein (MAP) that binds to and stabilizes MTs but also interacts with actin filaments and may

regulate actin/MT interaction. However, the normal functions of tau at the synapse are not well understood, which has hampered our understanding of tau pathology in neurodegenerative diseases such as Alzheimer's. In Alzheimer's Disease (AD) memory loss and cognitive decline are caused by synaptic loss in the cerebral cortex and hippocampus. The major hallmarks of AD are abnormal tau phosphorylation and accumulation of amyloid-?. In animal models hyperphosphorylated tau, mislocalized to postsynaptic hippocampal dendritic spines, caused impaired memory, synaptic dysfunction and disruption of physiological synaptic plasticity, even in the absence of overt neurodegeneration and spine loss. Phosphorylated tau also propagates transynaptically, causing presynaptic axon degeneration and synaptic loss. In cell free systems tau phosphorylation detaches tau from MTs, thereby decreasing MT stability and increasing MT dynamics. However, this has not been documented in living neurons. Thus it is not known whether a decrease in tau-MT binding induced by tau phosphorylation could contribute to impaired synaptic plasticity through changes in MT and actin dynamics. Given the importance of tau pathology in AD it will be important to address this question in human neurons expressing human forms of tau. Therefore, in this proposal we will use cortical neurons derived from human induced pluripotent stem cells (iPSCs) from normal subjects and from patients with AD to determine the role of tau phosphorylation in plasticity of pre and postsynaptic structures. We will ask how tau binding to the cytoskeleton regulates MT and actin dynamics in presynaptic axon terminals (using growth cones as a model) and postsynaptic dendritic spines of these neurons during plasticity induced by growth factors. We will determine how changes in tau phosphorylation affect interaction of tau with the MT and actin cytoskeleton and how these interactions regulate dynamic cytoskeletal reorganization required for structural plasticity of neuronal growth cones and dendritic spines. Results from this work will not only provide new information about the normal function of tau in synaptic plasticity of human neurons but also shed light on how abnormal tau phosphorylation may contribute to altered plasticity in AD.

Further information available at:

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