Neuroinflammation-mediated Degradation of NMDA receptors and Tau Dephosphorylation Mechanisms Related to Alzheimer's Disease

Current Alzheimer’s disease (AD) research highlights the importance of neuroinflammation and tau accumulation as drivers of AD onset and progression. To better understand the role of neuroinflammation in tau phosphorylation mechanisms in neurodegeneration, we used in vitro primary cortical rat neurons treated with conditioned media (CM) generated from A\(\beta\)-oligomer challenged macrophages. Following time course experiments to optimize the length of CM treatment, Western blot biochemical analysis of primary cortical neuron lysate with and without CM was performed to investigate changes in protein expression levels of NMDA receptors (NMDAR), AMPA receptors (AMPAR), tau epitopes, and other synaptic proteins. Subsequently, we used pharmacological inhibitors to dissect the molecular mechanisms of observed biochemical changes. The phosphatase inhibitor okadaic acid appears to prevent CM-induced tau dephosphorylation. Meanwhile, inhibiting phosphatases does not protect NMDARs from being degraded under the neuroinflammatory insult of CM. NMDAR antagonist D-AP5 prevents NMDAR degradation from the neuroinflammatory and excitotoxic effects of CM, yet tau dephosphorylation still occurs in neurons treated with CM and D-AP5. These results indicate that acute neuroinflammatory insult via CM treatment induces degradation of NMDARs and tau dephosphorylation. Whether the NMDAR and tau degradation mechanisms under neuroinflammatory insult are independent or through some unknown mechanistic link has yet to be determined. The neuroinflammatory factors secreted from macrophages challenged with A\(\beta\)-oligomers clearly impact both NMDAR and tau, linking AD behavioral pathology (e.g., memory impairments and cognitive deficits) with neuronal physiology. Further investigation of the mechanistic link between NMDAR and tau could be instrumental in identifying treatments for AD.