GABAergic Control of Network Activity in an in vitro Model of Alzheimer Pathogenesis

Alzheimer's Disease (AD) is a neurodegenerative disease resulting in irreversible gradual cognitive dysfunction, which currently has no disease-modifying treatment available. Two hallmarks of AD are cytotoxic aggregation of amyloid-beta (AŒ≤) oligomers and intraneuronal neurofibrillary tangle (NFT) formed by the abnormally phosphorylated microtubule associated protein, tau. For decades, AŒ≤ aggregation was thought to be the primary event of AD pathogenesis, but recent developments in the field suggest that tau modification occurs early in the pathogenesis, thus making it a viable target for therapeutics. Early AD pathogenesis involves inflammation, cytoskeletal damage, and synaptic loss. Prominent theories of pathogenesis indicate that GABAergic neuron loss from inflammatory damage causes neuronal hyperactivation associated with excitotoxicity and other phenotypes of early AD pathogenesis. This study investigates whether neuronal hyperactivity is associated with the development of tau tangles. By measuring electrophysiology of neurons, we are able to see for the first time if the hyperactivity model of AD pathogenesis aligns with the activity of neurons that have tangle formation on a network level. Multielectrode arrays (MEAs) were used to measure the electrophysiology of WT neurons in two groups: 1) neurons infected with the PLSF lentiviral construct that induced tau tangle formation, and 2) neurons treated with the GABAergic inhibitor, as well as a neuroinflammatory agent in order to mimic the inflammatory damage induced on neurons during AD pathogenesis. Neuronal interspike intervals (ISIs), interburst intervals (IBIs), and firing rates were analyzed via Python. Immunostaining confirmed tau tangle formation in the PLSF-infected neurons. ISI, IBI, and firing rates of the neurons indicated gradual network dysfunction post-infection. However, early tau pathology created in vitro via PLSF lentiviral constructs did not exhibit enhanced excitatory activity, and also did not mimic effects of inflammation. Instead, there was a disruption of normal bursting patterns suggesting that the neurons could no longer synchronize their activity efficiently. Thus, treatments designed to restore normal activity in AD patients will require more than correction of GABAergic activity.