Prefrontal cortical cholinergic signaling in models of α-synucleinopathy

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Progressive loss of basal forebrain cholinergic projection neurons is predictive of cognitive deficits in dementia with Lewy bodies and Parkinson's Disease dementia, and aggregates of α-synuclein robustly accumulates in the basal forebrain of patients. Aggregates of α-synuclein have been shown to impair synaptic transmission by disrupting vesicle recycling, SNARE complex function, and receptor trafficking, leading to reduced glutamate and dopamine release, excitotoxicity, and mitochondrial dysfunction. However, it remains unclear how a-synuclein aggregation impairs cholinergic neurons in the basal forebrain, acetylcholine release from basal forebrain neurons and postsynaptic cholinergic signaling. To address this, we use the preformed fibril model of α -synucleinopathies in rodents to induce robust α-synuclein aggregation like that seen in patients. We observe cholinergic fiber loss and accumulation of α-synuclein in basal forebrain projection neurons. Using whole-cell patch clamping electrophysiology we examine cholinergic dependent plasticity in the prefrontal cortex as well as cholinergic signaling in layer V pyramidal neurons. We observe increased long-term depression in layer V pyramidal neurons harboring Lewy like pathology. Additionally, we observe changes in cholinergic signaling and receptor expression. Taking together our data suggests α-synuclein aggregation leads to an anatomical rearrangement of basal forebrain cholinergic neurons that leads to altered plasticity and signaling in the prefrontal cortex, which may underlie executive function deficits in these disorders. We predict that, by selectively modulating muscarinic signaling in the prefrontal cortex, we may be able to normalize plasticity deficits and thereby normalize executive function, and that this may be a novel therapeutic approach for α-synuclein linked dementias.

Sponsored By: grant from NIH R01NS132293-03

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