Cortical Lewy Pathology Leads to Opposing Effects on Intrinsic Excitability Based On Presence of Pathology

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Aggregation of alpha-synuclein into high molecular weight, hyper-phosphorylated, ubiquitinated, and insoluble structures termed Lewy Bodies when in the cell body and Lewy Neurites when in the dendrites and axons is associated with neuronal dysfunction and cell death in multiple brain regions and cell types. Cortical alpha-synuclein aggregates are associated with Parkinson's Disease Dementia and Dementia with Lewy Bodies, encompassing the Lewy Body Dementias. How these intraneuronal aggregates lead to neuronal dysfunction and subsequent cell death are poorly understood. We have recently shown that injection of alpha-synuclein pre-formed fibrils to corrupt endogenous alpha-synuclein into Lewy like pathology quickly induces glutamatergic synaptic dysfunction at cortico-striatal synapses. Shockingly, this does not correlate with changes in cognitive function, and changes in synaptic efficacy appear to proceed changes in cognitive function temporarily. To try to understand this, we utilize a recently developed autofluorescent alpha-synuclein binder to selectively patch onto cortical neurons that do and do not have Lewy Like pathology. Using this tool compound to segregate neurons based on presence of pathology, we find that neurons with Lewy Like pathology rearrange their intrinsic properties to be hyperactive, and nearby cells without Lewy Like pathology are hypoactive compared to monomer injected controls. This dichotomous change in neuronal activity appears around 3 months pre-formed fibril injection, and closely correlates with the development of cognitive dysfunction in rodent tests of cognitive dysfunction. These results suggest that there are both cell autonomous and non-cell autonomous mechanisms for changes in cortical physiology induced by alpha-synuclein aggregation that cause cognitive dysfunction.

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