Determining the Effect of Parkinson's Disease LRRK2 Mutations on Synaptic Vesicle Recovery

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Parkinson’s Disease (PD) is a progressive, degenerative neuromuscular disorder that affects nearly 2% of the population over 65. Despite its prevalence, little is known about the etiology of the disease and specifically about the molecular pathways that are altered to cause the dopaminergic neuronal (DN) degeneration. One commonly studied gene that has been associated with both sporadic and familial PD is LRRK2 (Leucine Rich Repeat Kinase 2). LRRK2 protein has been found to affect numerous pathways in neurons, such as dendritic length and synaptic vesicle (SV) recovery, thus making it difficult to isolate how mutations of this protein cause PD progression. Interestingly, SVs found in the DN of PD patients are reduced in number and are often times misshapen. Herein, I used in vitro biochemical assays and Fluorescence Fluctuation Spectroscopy (FFS) microscopy to monitor the effect of LRRK2 phosphorylation of Endophilin A1. EndoA1 was chosen as the most promising protein in the study with its finely regulated functions and it being the first precursor protein in the synaptic vesicle recycling pathway. My central hypothesis is that the increased phosphorylation of EndoA1, as a result of mutated LRRK2, causes deformed dopamine vesicles in the brain, which prevents the release of the dopamine neurotransmitter. Confirming that this mechanism is the causal pathway in LRRK2 mediated neurodegeneration in PD will allow for a more precise and quick search for novel targets for advanced therapeutics.

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