Alpha-synuclein is crucial for neuronal function and survival-Characterization of a novel conditional alpha-synuclein knockout mouse model

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Research Abstract
PROJECT SUMMARY Our current understanding of the molecular etiology of Parkinson’s disease (PD) is incomplete and likely the product of multiple interacting factors. The best-validated participant in the molecular pathology of PD is alpha-synuclein (?-syn). Mutations in,

and multiplication of, the gene encoding ?-syn result in inherited forms of PD. In addition, the presence of ?-syn in Lewy bodies and neurites provides evidence for its association with idiopathic PD. A common hypothesis states that excess ?-syn and consequent aggregation causes neurotoxicity in a direct toxic gain-of-function event. Conversely, it has also been proposed that ?-syn aggregation may endanger neurons by removing the protein from its normal cellular location and diminishing its function in a toxic loss-of-function event. This issue remains a topic of debate. Despite this ambiguity, approaches that reduce ?-syn in the central nervous system represent an active area of research as a strategy for treating PD. Our published data in rats and nonhuman primates, and preliminary data in mice, supports the dissenting viewpoint, showing that eliminating ?-syn from mature dopamine (DA) neurons is not protective, but instead is toxic. Utilizing our newly developed conditional ?-syn knock-out mouse, our proposed studies will define the consequences that result from ablated/decreased expression of ?-syn in the nigrostriatal system. The use of rAAV to deliver CRE recombinase (iCRE) to dopamine neurons of adult mice carrying the floxed ?- syn allele will allow us to efficiently abolish ?-syn expression in mature neurons. This approach addresses the limitations of current germ-line mouse models by preventing the hypothesized compensatory adaptations that occur when ?-syn expression is abolished during development. The following proposal will utilize this new mouse model to: 1) Characterize the pattern, timing, and ?-syn dose-dependence of neurodegenerative effects on the nigrostriatal system and resultant impairment in motor behavior. 2) Define the characteristics of degeneration in its pattern and association with markers of cellular events previously implicated as participating in degeneration in PD (DA mishandling, oxidative/nitrative stress, proteasome/lysosome dysfunction, and microglial activation) at early and late stages of degeneration following removal of ?-syn. This proposal will answer the lingering question of whether ?-syn is crucial for the function and survival of mature DA neurons while also providing a new murine-based tool to study the importance of ?-syn induced DA neurodegeneration for the study of synucleinopathies. The successful completion of these aims will advance our knowledge and ability to develop therapeutic strategies aimed at halting neurodegeneration due to ?-syn dysfunction.

Further information available at:

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