Alpha-Galactosidase A: a novel target for reducing alpha-synuclein toxicity

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Research Abstract
PROJECT SUMMARY The pathological accumulation of alpha-synuclein (?-syn) is believed to play a major role in Parkinson’s disease (PD) pathogenesis. The autophagy-lysosome pathway (ALP) provides for the high-capacity clearance of ?-syn and its dysfunction is well-documented in PD. Inhibiting the ALP has been shown to induce ?-syn accumulation. Conversely, excess ?-syn has been shown to inhibit the ALP. Because the lysosome is critical for ?-syn clearance we believe its continued investigation will further delineate mechanisms of PD pathogenesis and

foster development of PD therapeutics. Alpha-Galactosidase A (?-Gal A) is a soluble lysosomal enzyme, with mutations causing the rare lysosomal disorder Fabry disease. While it is unknown if ?- syn accumulates in Fabry patients, our analysis of postmortem PD brains indicates a decrease in ?-Gal A activity specific to specimens with increased ?-syn pathology. Our preliminary data also indicate reduced ?-Gal A activity in neuroblastoma cells following the conditional over-expression of ?-syn. Together with our report of ?-syn pathology and altered ALP markers in ?-Gal A-deficient mouse brain, these findings suggest a strong link between ?-Gal A deficiency and ?-syn accumulation. However, whether ?-Gal A deficiency exacerbates the neurotoxic potential of ?-syn is unknown. Increasing ?-Gal A activity via enzyme replacement therapy (ERT) is clinically approved therapy for Fabry disease. Because ERT has limited CNS bioavailability, there is a critical gap in understanding its potential for treating PD. To help bridge this gap we developed novel research tools to increase ?-Gal A activity in neuronal systems, including its dose-responsive increase in neuronal cells via ERT, and transgenic mice that exhibit two-fold increases in ?-Gal A brain activity. Our preliminary data in neuroblastoma cells shows that ?-Gal A ERT enhances the clearance of over-expressed ?-syn. However, whether increasing ?-Gal A activity attenuates ?-syn-associated neurotoxicity has not been tested. Taken together, we hypothesize that ?-syn-associated neurotoxicity is exacerbated by ?-Gal A deficiency and is attenuated by increasing ?-Gal A activity. In Aim 1 we will determine if ?-Gal A-deficiency in primary neuron cultures exacerbates neurotoxicity resulting from the exogenous addition of ?-syn pre-formed fibrils (PFFs) in a manner concomitant with ALP disruption. We will also determine if ?-Gal A–deficient mice exhibit exacerbated loss of tyrosine hydroxylase (TH)-positive neurons in the substantia nigra following AAV2-mediated over- expression of human wild-type ?-syn. In Aim 2 we will determine if ?-syn PFF-mediated neurotoxicity in primary neuron cultures is attenuated by ?-Gal A ERT or the transgenic over-expression of ?-Gal A and if this protection is regulated by the ALP. We will also determine if ?-Gal A over-expressing mice exhibit a reduction in TH-positive neuron loss resulting from AAV2-?-syn. If our hypothesis is correct, it would suggest that ?-Gal A deficiency regulates ?-syn pathogenesis, a mechanism worthy of future investigation, and would accelerate the development of therapeutics for PD that act by increasing CNS ?-Gal A activity.

Further information available at:

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