Glucocerebrosidase chaperones in Parkinson’s

https://www.neurodegenerationresearch.eu/survey/glucocerebrosidase-chaperones-in-parkinsons/

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Country

United Kingdom

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Glucocerebrosidase chaperones in Parkinson's

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Parkinson's UK

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3

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Research Abstract

Glucocerebrosidase (GBA) mutations are the most important risk factor for Parkinson disease (PD) identified to date. The mechanisms by which these mutations increase PD risk potentially include a reduction in glucocerebrosidase enzyme (GCase) activity and/or endoplasmic reticulum (ER) trapping, unfolded protein response (UPR) and ER stress initiated by the misfolded mutant GCase.
Evidence from in vitro cell, in vivo animal models and human cell and human post mortem brain studies indicate that there is a reciprocal relationship between GCase and alpha-synuclein (SNCA) levels: a reduction in GCase activity increases SNCA levels, and increased SNCA reduces GCase levels. This forms the basis for a self-amplifying cycle leading to SNCA aggregation and lysosomal dysfunction that will promote PD-related pathology.
The use of small molecule chaperones to enhance GCase activity, reduce GCase trapped in the

ER and increase transit through the Golgi to the lysosome has attracted attention as a potential means to decrease SNCA. This strategy both reduces ER stress and increases lysosomal function. We have confirmed chaperones increase GCase in PD patient fibroblasts, and shown they reduce levels SNCA in cell model systems. We now propose to extend these studies to mouse models of GBA-SNCA mutations to test the effects in vivo.
We have developed both double mutant SNCA-L444P, and N370S mutant mice to act as the platform to determine in vivo if small molecule chaperones can enhance lysosomal function and reduce alpha-synuclein levels in brain. If positive, these studies will form the basis for translating this therapeutic strategy into humans.

Further information available at:

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