Evaluation of changes in GCase activity and substrate levels in human brain from PD

Lysosomal enzyme activities in postmortem brain tissue of patients with Lewy Body Diseases

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Research question and background

Lysosomal dysfunction is suggested to play a central role in the pathology of Lewy Body diseases (LBD), including Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB). Genetic associations have been identified between PD and different Lysosomal Storage disorders, for instance in Gaucher Disease, which is caused by a genetic deficiency of β-glucocerebrosidase (GCase). However, so far, the activity of lysosomal enzymes in selectively vulnerable brain regions in PD and DLB has not been investigated in detail. Our study aims to gain more insight into the activity of lysosomal enzyme activities in vulnerable brain regions in PD and DLB.

Methods and tissues used

Human postmortem brain tissue of 15 PD patients, 15 DLB patients and 15 age-matched non-demented controls was obtained from the Netherlands Brain Bank. Enzyme activities of three lysosomal enzymes - β-hexosaminidase, GCase and cathepsin D - and one endosomal enzyme - cathepsin E - were measured in the substantia nigra, putamen and superior frontal cortex using enzyme activity assays. In addition, neuronal loss and the load of α-synuclein pathology were quantified using a Stereo Investigator system.

Results and conclusion

Our results demonstrate that GCase enzyme activities are decreased in PD patients compared to controls specifically in the substantia nigra ($p= 0.04$); an effect that was more pronounced when comparing the total LBD group to controls ($p= 0.03$). No differences were observed between the DLB and PD groups. GCase activities in the SN were close to being significantly associated with the α-synuclein burden ($p= 0.08$) and with disease duration ($p= 0.08$). In addition to GCase, a trend was found for decreased cathepsin D activities in the frontal cortex of LBD cases ($p= 0.07$).
In conclusion, we have found a decrease in GCase activity in the substantia nigra of PD and LBD cases compared to controls, but not in the other brain regions. These findings support a role for decreased GCase functioning in synucleinopathies and suggest that this is associated with disease severity.