Age-related expression and activity profile of glucoc in brain and the association with phosphorylated alpha-synuclein implicated in Parkinson's disease

Yasine Malki[1], Zoe Yuen Kiu Choi[1], Philip Wing-Lok Ho[1], Hui-Fang Liu[1], Chi-Ting Leung[1], Eunice Eun Seo Chang[1], Shirley Yin-Yu Pang[1], David Boyer Ramsden[2], **Shu-Leong Ho***

[1]Division of Neurology, Department of Medicine, The University of Hong Kong, Hong Kong

[2]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

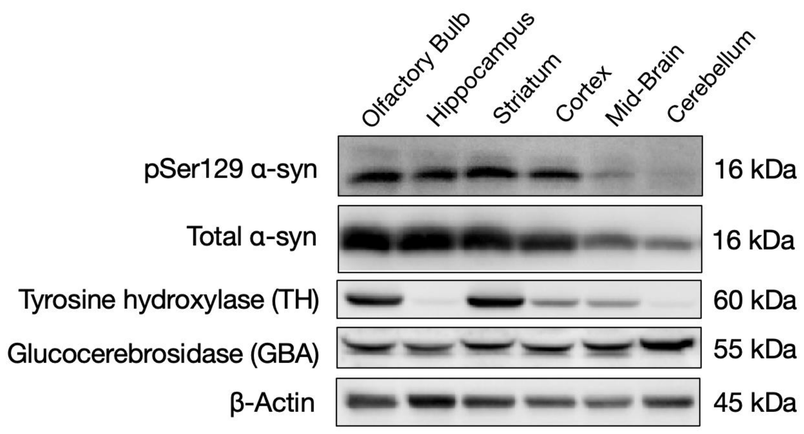
Introduction

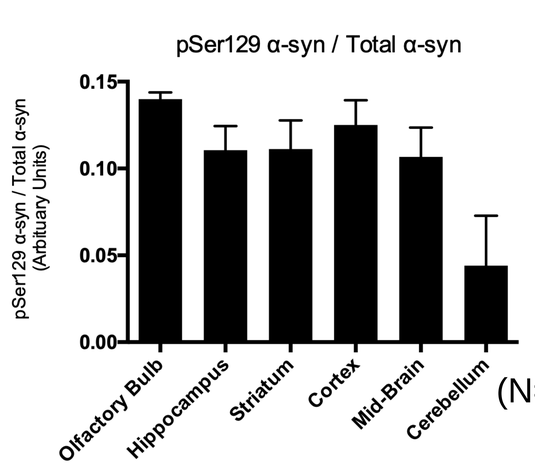
The aggregation and inter-neuronal propagation of misfolded alpha-synuclein determines the progression and severity of Parkinson's disease (PD). Reduced lysosomal enzyme glucocerebrosidase (GCase) activity may be linked to alpha-synuclein accumulation in PD. Different brain regions may have varied susceptibility to developing alpha-synuclein pathology, due to the difference in cellular composition and proteomes. We aim to establish a brain region profile for the levels of phosphorylated serine-129 (pSer129) alpha-synuclein, the pathogenic form of alpha-synuclein, as well as GCase expression and activity, in both young and aged mouse brains.

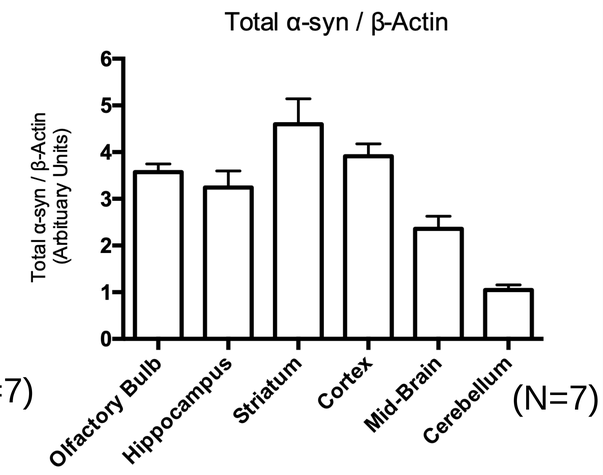
Method

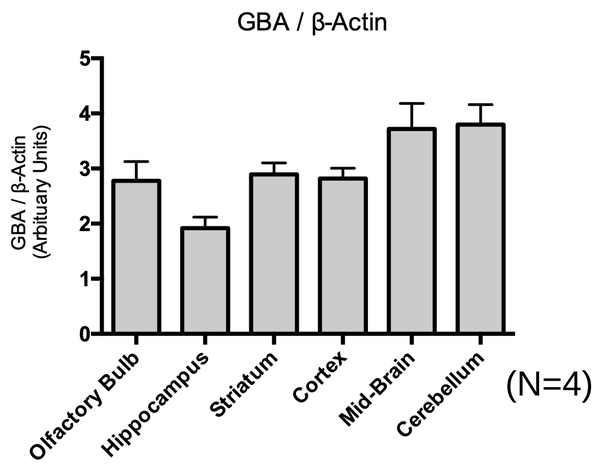
Total lysates from freshly isolated brain regions of young (3-month-old) and aged (26-month-old) wild-type mice were subjected to immunoblotting. GCase activity was measured through an established fluorescence assay.

1. Brain Region Profile for pSer129 α-syn and Glucocerebrosidase (GBA) in 26-month-old mice





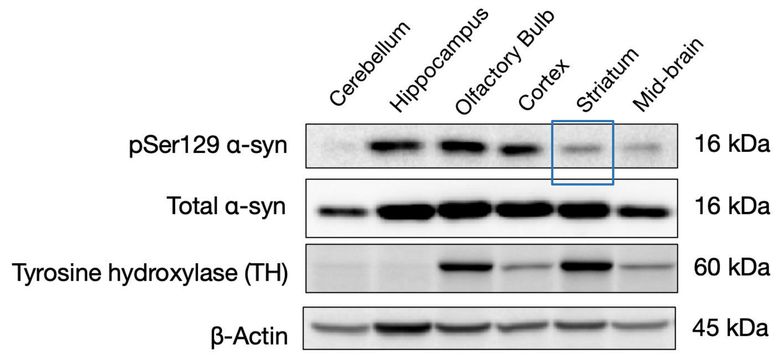


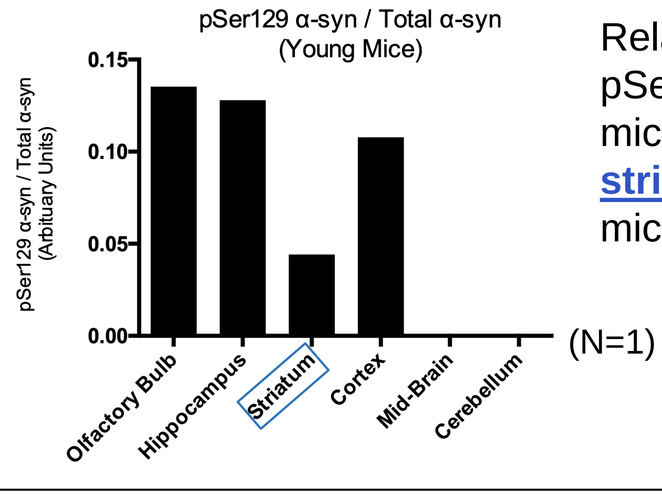


pSer129 α-syn / Total α-syn ratio from highest to lowest:

- Olfactory Bulb
- Cortex
- Striatum
- Hippocampus
- Mid-brain

2. Decreased pSer129 α-syn in the striatum of young 3-month-old mice compared to aged mice

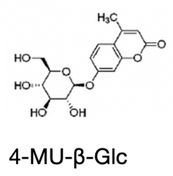


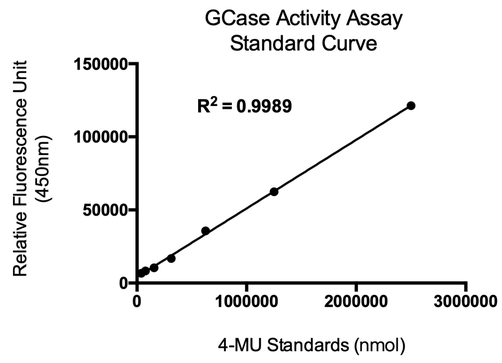


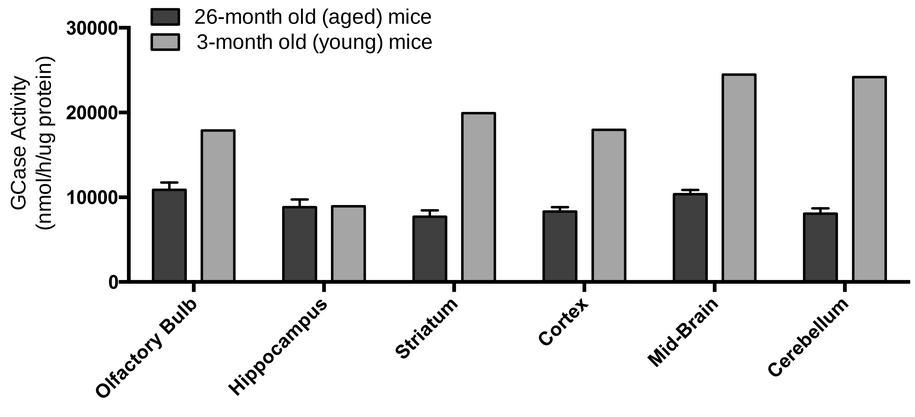
Relatively lower levels of pSer129 α-syn in young mice (3-month-old) in the **striatum** compared to aged mice.

3. Glucocerebrosidase Activity Brain Region Profile and the decrease in activity with aging

Fluorescence assay:







Conclusion

Varied levels of pSer129/total alpha-synuclein and GCase activity exist in different brain regions, possibly in age and cell-type dependent manner. The age-dependent accumulation of pSer129 alpha-synuclein, and relatively lower GCase activity specifically in the **striatum** may underlie its selective vulnerability to neurodegeneration in PD.

Acknowledgements

- Tai Hung Fai Charitable Foundation–Edwin S H Leong Research Programme for Parkinson's Disease
- Henry G. Leong Endowed Professorship in Neurology (SLH)
- Health and Medical Research Fund (HMRF; 07183516)

Contact Details: ymalki@hku.hk