glycoNOE signals in a mouse model of Parkinson's disease

Jannik Prasuhn[1,2,3,4,5], Jae-Jin Song[1,6,7], Fatih Akkentli[1,6], Tae-In Kam[1,6], Valina L. Dawson[1,6,7,8], Ted M. Dawson[1,6,7,9], Nirbhay N. Yadav[2,10]

[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [2]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, USA. [3]Department of Neurology, University-Medical Center Schleswig-Holstein, Campus Lübeck, Lübeck, Germany. [4]Institute of Neurogenetics, University of Lübeck, Lübeck, Germany. [5]Center for Brain, Behavior, and Metabolism, University of Lübeck, Lübeck, Germany. [6]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [7]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [8]Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [9]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [10]Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

INTRODUCTION: Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by changes in brain metabolism, including mitochondrial bioenergetics. Glycogen, a crucial glucose reserve in the brain, is understudied but likely plays a significant role in PD pathology as a potential compensatory mechanism. This study aims to explore the potential of neuroimaging-based brain glycogen mapping as a tool for understanding metabolic changes in PD and to evaluate the therapeutic implications of targeting glycogen metabolism.

METHODS: We used a PD mouse model (n = 6, three PD mice, and three control mice, 10 months of age) created by injecting pathological alpha-synuclein-preformed fibrils into the duodenal and pyloric muscular layer of the gut. Control mice underwent similar injections with a phosphate-buffered saline instead of alpha-synuclein fibrils.[1] The proposed mouse model is suitable for studying the pathophysiology of PD because it mimics the gut-to-brain propagation of pathological alpha-synuclein via the vagus nerve. This model replicates key aspects of PD, including the degeneration of dopamine neurons and the appearance of both motor and non-motor symptoms, which are consistent with the progressive spread of alpha-synuclein pathology observed in human PD cases. Glycogen rNOE (glycoNOE) experiments were performed on an 11.7T Bruker Biospec animal scanner. Full Z-spectra were acquired using a 0.7 μT, 4s long continuous wave (CW) saturation pulse followed by a fast spin echo readout (TR = 8 s). GlycoNOE signals were quantified by fitting the Z-spectral background using a Lorentzian and polynomial hybrid fitting model based on the $R_{1\rho}$ relaxation theory[2] and then integrating the residual spectrum between -0.7 to -1.4 ppm.

RESULTS: Here, we found increased glycoNOE signal intensities in the brain regions primarily affected by the ascending pathology observed in PD. These changes are more pronounced in the hind- and midbrain compared to the forebrain, where alpha-synuclein deposition and subsequent neurodegenerative changes are more likely to appear later in the disease propagation in this mouse model.

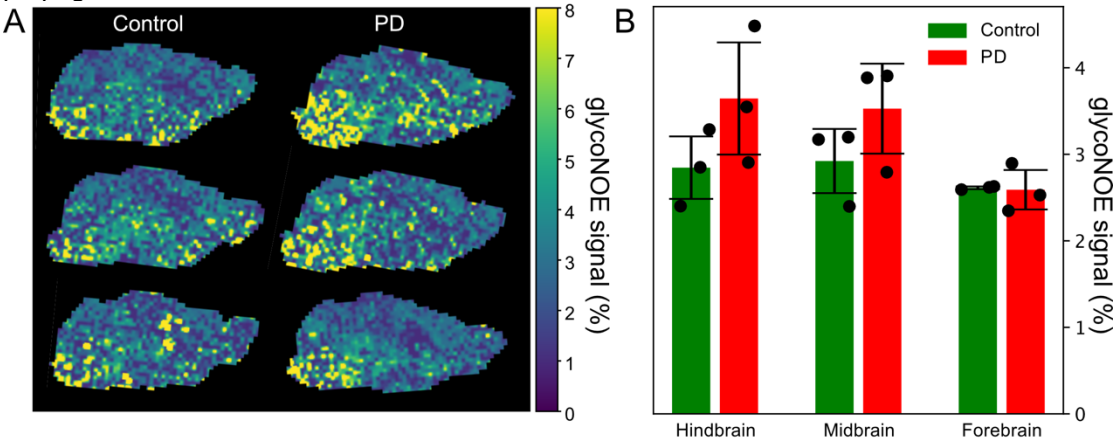

Fig 1. (A) Sagittal glycoNOE maps from each control and PD mice. (B) Mean glycoNOE signals across three different axial slices in each mouse. Mean signals in the hind brain were 2.8±0.4 (control) and 3.6±0.6 (PD), 2.9±0.4 (control) and 3.5±0.5 (PD) in the midbrain, 2.6±0.1 (control) and 2.6±0.2 (PD) in the forebrain.

DISCUSSION: Our results point toward PD-associated changes in the glycoNOE signals in neuroanatomical regions primarily affected in our disease model. However, we would expect an increased glycogen turnover to compensate for impaired mitochondrial bioenergetics (e.g., due to lower OXPHOS-related energy production). Even though these results are preliminary, they point toward unexpected changes in brain glycogen metabolism in a sophisticated mouse model of PD.

CONCLUSION: Brain glycogen metabolism might be a suitable target for yielding neuroprotective properties (as demonstrated by the disease-modifying nature of antidiabetic drugs in patients with PD), and therefore, our glycoNOE approach may shed light on the multifaceted nature of this disease mechanism in future studies.

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