Critical analysis of glycosphingolipid pathways in aging and Parkinsons disease

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Principal Investigators

HALLETT, PENELOPE JANE

Institution

MCLEAN HOSPITAL

Contact information of lead PI
Country

USA

Title of project or programme

Critical analysis of glycosphingolipid pathways in aging and Parkinsons disease

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NIH (NINDS)

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15/08/2015

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3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Glycosphingolipids, glucosylsphingosine, glucosylceramidase, synucleinopathy, Parkinson Disease

Research Abstract
? DESCRIPTION (provided by applicant): Glycosphingolipids are essential for many cellular

processes, are enriched in membranes, and undergo catabolism in endosomes and lysosomes through the action of acid hydrolases. GBA encodes the lysosomal enzyme glucocerebrosidase (GCase), which is responsible for the hydrolysis of the glycosphingolipid substrates glucosylceramide (GluCer) and glucosylsphingosine (GluSph). GBA gene mutations are the highest known genetic risk factor for developing Parkinson’s disease (PD) and related ?-synucleinopathies. Our preliminary data shows that levels of GluSph are increased in the human brain in sporadic PD. Moreover, we show that GCase activity is reduced, and glycosphingolipid levels are increased in the brain in normal aging. The consequences of increased glycosphingolipid levels on neuronal health in aging and in sporadic PD are not known. In this R01 application I have designed experiments to test the relevance of elevated glycosphingolipids in neural cells in aging and PD. In Specific Aim 1 we hypothesize that altered levels of glycosphingolipids induce neuronal dysfunction and susceptibility to degeneration. We will modulate levels of GluSph in mouse and human neurons in vitro to determine whether neuronal vulnerability to PD-stressors, including increased ?-synuclein loads, is altered. We will also establish whether reduced GCase and increased GluSph levels are detected in human PD patient fibroblasts and neurons as such alterations may represent novel bio- and pharmacodynamic- markers for PD. In Specific Aim 2 we hypothesize that reducing the accumulation of glycosphingolipids in aging and PD can prevent the aggregation and toxicity of ?-synuclein. We will determine how the homeostasis of glycosphingolipid pathways are altered in two rodent models of ?-synucleinopathy, and we will measure the effect of manipulating glycosphingolipid pathways by increasing neuronal GCase levels, in these same in vivo models. These experiments will provide critical analysis of the role of glycosphingolipid pathways in PD and related ?-synucleinopathies, and should provide new targets for the development of novel therapeutics to improve glycosphingolipid metabolism and prevent neurodegeneration.

Lay Summary
PUBLIC HEALTH RELEVANCE: Mutations in the gene encoding glucocerebrosidase (GBA), which is involved in glycosphingolipid metabolism, are the largest known genetic risk factor for Parkinson’s disease (PD) and related ?- synucleinopathies. Dysfunction of glycosphingolipid pathways may contribute to neuronal dysfunction and degeneration in aging and sporadic PD, and this study will test the contribution of glycosphingolipid pathways towards susceptibility of neurons in PD models. Modulation of these pathways may represent an important therapeutic approach in PD and related a-synucleinopathies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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