PGC-1alpha and Pitx3 as individual and combined targets for neuroprotection

https://neurodegenerationresearch.eu/survey/pgc-1alpha-and-pitx3-as-individual-and-combined-targets-for-neuroprotection/

Principal Investigators

SIMON, DAVID K

Institution

BETH ISRAEL DEACONESS MEDICAL CENTER

Contact information of lead PI
Country

USA

Title of project or programme

PGC-1alpha and Pitx3 as individual and combined targets for neuroprotection

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,718,270.64

Start date of award

01/04/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

neuroprotection, Parkinson Disease, Substantia nigra structure, Gene therapy trial, overexpression

Research Abstract
DESCRIPTION (provided by applicant): Mitochondrial dysfunction and oxidative stress play

important roles in Parkinson’s disease (PD). PGC-1alpha, a transcriptional coactivator, upregulates mitochondrial biogenesis and antioxidant defenses, and thus is an attractive target for neuroprotection in PD. Susceptibility to MPTP, a mitochondrial toxin, is increased in mice lacking PGC-1alpha, whereas overexpressing PGC-1alpha protects against an oxidative challenge in cell lines. Levels of expression of genes regulated by PGC-1alpha are low in substantia nigra (SN) neurons in early PD. Two important genetic causes of PD now have been linked to low PGC-1alpha. First, a recent study showed that loss of Parkin function leads to increased levels of novel protein called “”PARIS”” which transcriptionally inhibits expression of PGC-1alpha. And recently it was demonstrated that alpha-synuclein binds to the PGC-1alphha promoter and also suppresses its transcription. Together, these data strongly implicate a pathogenic role for low PGC-1alpha activity in PD, and raise the hope that correction of the PGC-1alpha deficit in PD will be neuroprotective. However, unexpectedly, we and others find that overexpressing PGC-1alpha at very high levels leads to reduced Bdnf and suppression of the dopaminergic phenotype. Our preliminary data suggest that this may result from suppression of Pitx3, a transcription factor that is critical for maintaining the dopaminergic phenotype and also for expression of Bdnf. Vulnerability to MPTP is increased by the very high levels of PGC-1alpha achieved using our AAV-PGC-1alpha vector. Thus, either low or very high levels of PGC-1alpha can be deleterious. Together, these data reveal that maintenance of PGC-1alpha activity levels within a “”therapeutic”” range is critical for the survival and function of dopaminergic neurons. We hypothesize that very high levels of PGC-1alpha lead to suppression of Pitx3, leading to loss of the dopaminergic phenotype and to enhanced vulnerability to MPTP due to loss of Bdnf. We further hypothesize that it will be possible to harness the neuroprotective potential of viral vector- mediated increases in PGC-1alpha activity while avoiding the potentially deleterious effects associated with very high levels of overexpression. We propose to test this by studying the impact in dopaminergic neurons on mitochondrial function, oxidative stress, the dopaminergic phenotype, and susceptibility to MPTP following more modest levels of upregulation of PGC-1alpha, or following co-expression of Pitx3 to prevent the deleterious effects of higher PGC-1alpha levels. The potential neuroprotective effects of Pitx3 on its own also will be studied. These experiments will test our hypothesis that suppression of Pitx3 mediates the PGC-1alpha-induced downregulation of Bdnf and of the dopaminergic phenotype. In addition, multiple gene therapy trials have been conducted in PD patients, and thus the proposed studies also will serve as initial tests of therapeutic strategies with translational potential.

Lay Summary

PUBLIC HEALTH RELEVANCE: Impaired function of mitochondria (the energy producing parts of cells) and the resulting oxidative stress contribute to Parkinson’s disease, and may result from low levels of PGC-1alpha, a molecule that regulates mitochondrial biogenesis and antioxidant defenses. However, very high levels of PGC-1alpha also have deleterious effects, potentially by suppressing levels of Pitx3, a molecule important for the maintenance and survival of dopamine-producing neurons. We propose to test 2 gene therapy approaches, alone and in combination, in animal models of Parkinson’s disease to assess the potential to harness the neuroprotective potential of upregulating PGC-1alpha and/or Pitx3 while avoiding potentially deleterious effects.

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

Database Tags:
N/A