alpha-Synuclein Inhibition of Mitochondrial Protein Import

https://neurodegenerationresearch.eu/survey/alpha-synuclein-inhibition-of-mitochondrial-protein-import/

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Country

USA

Title of project or programme

alpha-Synuclein Inhibition of Mitochondrial Protein Import

Source of funding information

NIH (NINDS)

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€ 2,043,805.50

Start date of award

15/09/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Protein Import, alpha synuclein, Mitochondrial Proteins, Mitochondria, Outer Mitochondrial Membrane

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson disease (PD) is a common neurodegenerative disorder resulting in motor impairment, cognitive and psychiatric symptoms

and autonomic dysfunction. Genetic and environmental factors have been implicated in PD pathogenesis, and it appears that mitochondrial defects and accumulation of the synaptic protein, ?- synuclein, are common to most forms of the disease. Moreover, there is evidence of a bidirectional interaction between mitochondrial dysfunction and ?-synuclein accumulation. Inhibition of mitochondrial complex I leads to accretion and oligomerization of ?-synuclein, and increased levels of ?-synuclein cause mitochondrial impairment and production of reactive oxygen species (ROS). The nature of the interaction between ?- synuclein and mitochondria remains obscure, and it is unclear whether unmodified monomeric ?-synuclein is responsible for these effects, or whether posttranslational modifications which have been implicated in pathogenesis, such as oligomerization, dopamine modification, phosphorylation or nitration are important. Mitochondria contain their own genome, but it encodes only 13 proteins, so they must import about 99% of the >1000 proteins they contain. Mitochondrial protein import occurs through complex and highly regulated systems, the best understood of which recognizes N-terminal mitochondrial targeting signals (MTS) on proteins destined for import. While there is no consensus sequence, MTS characteristically form an amphipathic helix that is recognized by a receptor protein, TOM20, which is a subunit of the translocase complex of the outer mitochondrial membrane (TOM). Although monomeric ?-synuclein is an intrinsically disordered protein in solution, in association with anionic lipids in membranes, it forms an amphipathic helix similar to known MTS motifs. In this context, we have strong evidence that certain forms of posttranslationally-modified ?-synuclein bind specifically to TOM20 and interfere with import of mitochondrially-targeted proteins. We propose to study the interaction of ?-synuclein with mitochondrial import machinery in the following aims: (1) Define the specific forms of ?-synuclein that inhibit mitochondrial protein import; (2) Define key binding partners and binding parameters; (3) Determine functional consequences of ?-synuclein-induced impairment of mitochondrial protein import; (4) Investigate whether blockade of mitochondrial protein import causes nigrostriatal neurodegeneration similar to ?-synuclein overexpression; and (5) Examine the potential for genetic manipulation of mitochondrial import to protect against AAV2-mediated ?-synuclein overexpression in substantia nigra.

Lay Summary
PUBLIC HEALTH RELEVANCE: Two key factors in the causation of Parkinson’s disease are (i) a protein called ?-synuclein and (ii) impairment of the cells’ power plants – the mitochondria. We have discovered a novel mechanism by which these 2 factors are directly related: ?-synuclein blocks a key maintenance function needed by mitochondria – protein import. This proposal seeks to better define this mechanism and to develop therapeutic strategies to combat it.

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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