Understanding PDI-related neurotoxicity and advancing preventative approaches

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Country

USA

Title of project or programme

Understanding PDI-related neurotoxicity and advancing preventative approaches

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

405206.422

Start date of award

08/07/2016

Total duration of award in years

4

Keywords

SNCAIP gene, Protein Disulfide Isomerase, Ellagic Acid, Lewy Body Variant of Alzheimer's Disease, alpha synuclein

Research Abstract
? DESCRIPTION (provided by applicant): Protein disulfide isomerase (PDI) is an endoplasmic reticulum (ER)-resident oxidoreductase chaperone that catalyzes the maturation of disulfide-bond-containing proteins. S-nitrosylated PDI (SNO-PDI), which is the chemical modification of its catalytic cysteine in response to nitrosative stress, has been found in post-mortem brains of Parkinson’s and Alzheimer’s disease victims along with synphilin-1:alpha-synuclein protein

aggregates (called Lewy Bodies). Additional studies in cells revealed that levels of SNO-PDI formation directly co-related with the aggregation and accumulation of the minor but critical Parkinsonian biomarker synphilin-1 in a NO-sensitive manner. While SNO-PDI formation leads to the accumulation of polyubiquitinated proteins, expression of native PDI (non-SNO-PDI) attenuates these effects in a Parkinsonian cell model. These data show that PDI is neuroprotective and underscore the need for functional preservation of PDI's catalytic activity as a key preventative approach to pathogenesis of nitrosative-stress-related Parkinson's. The data also suggest the involvement of PDI dysfunction in the pathogenesis of neuropathies such as the Lewy Body Variant of Alzheimer's (LBVAD) and Alzheimer's. However, there is still a gap in studies designed to determine whether other neurotoxicity-related biomarkers accumulate as a function of SNO-PDI formation. We hypothesize that SNO-PDI formation may provoke aggregation of alpha-synuclein, the major Parkinsonian and LBVAD biomarker protein and Lewy-body constituent. As a corollary to our hypothesis, it is possible that strategies designed to prevent SNO-PDI formation are neuroprotective and prophylactic to Parkinson's. The hypothesis will be tested by examining the aggregation of alpha-synuclein as a function of nitrosative insult in a cell line model. Furthermore, the translational feasibility of ellagic acid, Na-betahydroxybutyrate and Ferrostatin-1 analogs, which our lab has preliminarily demonstrated as being neuroprotective, will be assayed in a rotenone rat Parkinson model. The overall objective of this project it to lay the foundation for long-term work involving the development of pharmacologically relevant small molecule therapies that are neuroprotective by mitigating the effects of oxidative and nitrosative stress.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A