Mechanisms of Aggregated Alpha-Synuclein Induction and Progression

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Country

USA

Title of project or programme

Mechanisms of Aggregated Alpha-Synuclein Induction and Progression

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,481,431.19

Start date of award

15/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, prion-like, Parkinson Disease, Brain Tissue Transplantation, neurofilament

Research Abstract

DESCRIPTION (provided by applicant): Parkinson disease (PD) is the most common movement disorder affecting over one million people in North America alone and results in an insidious

reduction in the quality of life and ability to function. A hallmark of PD is the brain accumulation of neuronal cytoplasmic inclusions comprised of the protein a-synuclein, but the presence of ?-synuclein brain aggregates is observed in a spectrum of neurodegenerative diseases, including dementia with Lewy body. Several findings suggest that ?-synuclein amyloid pathology may spread during disease progression by a self-templating alteration in protein conformation mechanism, however other alternative and/or synergistic biological mechanisms, as supported by our data, could also lead to progression of ?-synuclein pathology. From a therapeutic aspect it is critical to determine the relative importance, mechanisms and physiological consequences of the spread of ?-synuclein aggregation in disease. It this proposal, two major specific aims are proposed to inform on ?-synuclein induced and spread of disease: 1) Using both wild-type and disease causing mutant forms of ?-synuclein with unique aggregation properties, we will directly investigated that a-synuclein aggregation can spread within the central nervous system and from the periphery with specific conformational characteristics. 2) We will assess the importance of alternative biological mechanisms including perturbation of the protein network homeostasis, neuronal intermediate filament integrity, neurotoxicity and age-related changes in the induction and propagation of ?-synuclein pathology by exogenous a-synuclein challenges. These studies will provide critical insights on the mechanisms and the involvement of ?-synuclein aggregation in PD disease progression with the objective of guiding the development of novel therapeutics.

Lay Summary
PUBLIC HEALTH RELEVANCE: Parkinson disease is an insidious neurodegenerative disease, affecting ~1% of the population over 65 years of age. Progressive aggregation and inclusion formation of the protein ?-synuclein is a hallmark of this disorder and the planned research project focuses on understanding the underlying biological and molecular mechanisms involved in the development of disease with the objective of guiding novel therapeutic interventions.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

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N/A

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