Protein Aggregation and Neurotransmitter Deficits in Parkinson Disease

https://neurodegenerationresearch.eu/survey/protein-aggregation-and-neurotransmitter-deficits-in-parkinson-disease/

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Country

USA

Title of project or programme

Protein Aggregation and Neurotransmitter Deficits in Parkinson Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,394,511.93

Start date of award

01/08/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

protein aggregation, alpha synuclein, neocortical, Neurotransmitters, noradrenergic

Research Abstract

Abstract People with Parkinson disease (PD) frequently develop dementia, which is associated with neocortical deposition of alpha-synuclein (?-syn) in Lewy bodies and Lewy neurites. In

addition, neuronal loss and deposition of aggregated ?-syn also occurs in multiple subcortical nuclei including substantia nigra (dopaminergic), nucleus basalis of Meynert (cholinergic), locus coeruleus (noradrenergic) and dorsal raphe nuclei (serotonergic). Accumulation of ?-syn likely contributes to impaired function of cortical neurons, which may also be affected by widespread A? accumulation that occurs in approximately 60% of PD with dementia cases and widespread tau accumulation in fewer cases. However, the affected subcortical nuclei project rostrally to thalamic, striatal, limbic and neocortical regions, and the loss of innervation from these nuclei also may contribute to cognitive impairment in PD. We developed postmortem tissue analysis methods to quantify accumulation of fibrillar ?-syn, A? and tau, as well as the loss of innervating projections from dopaminergic, serotonergic, noradrenergic and cholinergic subcortical neurons. In this project we will collect autopsies from a longitudinal study of PD participants that measures cognitive, behavior, and gait function. We will sample thalamic, cerebellar, basal ganglia, limbic and neocortical regions from frozen brain tissue for each autopsy case and analyze the tissue with the following goals: 1) Determine the relationship between ?-syn, A? and tau deposition and the loss of dopaminergic, serotonergic, noradrenergic and cholinergic innervation. 2) Determine whether fibrillar protein deposition and loss of projections from subcortical nuclei relate to gait, global cognition and specific cognitive phenotypes, including: impaired attention, memory, visuospatial and executive function, fluctuations in attention, hallucinations and delusions. Defining the pathologic substrates for cognitive, behavior and gait impairment in PD will provide further guidance for therapeutic targets and outcome measures for therapeutic trials in PD.

Lay Summary
Project Narrative This project will improve our understanding of mechanisms underlying the development of cognitive impairment and gait difficulty in Parkinson disease, which is needed to guide the development of treatments for Parkinson disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
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Database Categories:
N/A

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