Mechanisms of rotenone-induced neuroinflammation and Parkinsonism in aging mice

https://www.neurodegenerationresearch.eu/survey/mechanisms-of-rotenone-induced-neuroinflammation-and-parkinsonism-in-aging-mice/

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Country

USA

Title of project or programme

Mechanisms of rotenone-induced neuroinflammation and Parkinsonism in aging mice

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,588,962.39

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01/08/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Rotenone, Parkinsonian Disorders, neuroinflammation, Aging, Parkinson Disease

Research Abstract

? DESCRIPTION (provided by applicant): The goal of this project is to characterize newly discovered cellular mechanisms of environmental toxin- induced neuroinflammation and determine if neuroinflammation is required and sufficient for the development of Parkinsonism in aging mice. In the large-scale Farming and Movement Evaluation Study (FAME), led by the National Institute of Environmental Health Sciences (NIEHS), exposure to the metabolic toxin rotenone has been identified as a risk factor in the development of Parkinson's disease (PD). With the goal of developing animal models recapitulating long-term occupational exposure to epidemiologically relevant environmental toxins, we exposed mice to low doses of rotenone using intra-gastric gavage, 5 days per week, continuously, for 5 months. Planned experiments build on our characterization of central nervous system (CNS) pathologies in rotenone treated mice during which we identified progressive neuroinflammatory changes occurring in association with the development of classical PD symptomology. Ongoing studies implicate the Nlrp3 inflammasome, an intracellular mediator of inflammation, in rotenone-induced neuroinflammation and suggest that prodromal anti-inflammatory treatment can block the progression of PD symptoms in rotenone treated mice. Our proposed aims will test key predictions made by our ongoing studies to determine the cellular origins of the rotenone-induced pro-inflammatory chemokine Cxcl1. In a second aim, we will use in vivo genetic and pharmacologic approaches to test the prediction that the Nlrp3-dependent neuroinflammation is required for the development of Parkinsonism in mice ingesting rotenone. In so doing, we will evaluate the specificity and efficacy of an investigational anti-inflammasome drug, BAY 11-7082, to determine if prodromal anti-Nlrp3 intervention can block the progression of Parkinsonism in aging rotenone-treated mice. Simultaneously, we will comprehensively characterize post-translational modification and aggregation of a-synuclein protein in the context of chronic rotenone exposure using a longitudinal approach. Using advanced biochemical and proteomic approaches, these studies will test the prediction that Nlrp3-mediated neuroinflammation can initiate a-synuclein aggregation and thereby cause Parkinsonism in aging mice. The completion of these studies is expected to have broad reaching implications for our understanding of neuroinflammation occurring as the result of long-term exposure to environmental toxins. Findings will inform the development of preventative treatments for neurologic disorders in at risk populations such as the elderly, agricultural workers and military personnel.

Lay Summary

PUBLIC HEALTH RELEVANCE: Detecting age-related neurodegenerative disorders at their earliest stages will allow scientists and clinicians to develop and implement neuroprotective therapies. We have identified novel cellular mechanisms of progressive neuroinflammation occurring in the brains of mice exposed to chronic low-doses of a pesticide known to increase the risk of developing Parkinson's disease in agricultural workers. Proposed studies will focus on characterizing mechanisms of neuroinflammation during the earliest stages of sporadic Parkinsonism in pesticide-exposed mice seeking pathways of importance for the development of preventative therapies for age-related neurodegenerative disorders.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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