Pathogenic mechanisms of gene-environment interactions in Parkinsons disease

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Principal Investigators

BURTON, EDWARD ALAN

Institution

UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Contact information of lead PI
Country

USA

Title of project or programme

Pathogenic mechanisms of gene-environment interactions in Parkinsons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,580,977.06

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01/12/2013

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

synuclein, gene environment interaction, Rotenone, dopaminergic neuron, Parkinson Disease

Research Abstract

DESCRIPTION (provided by applicant): The long-term objective of this work is to develop effective treatments for the common sporadic form of Parkinson’s disease (PD) by elucidating

pathogenic mechanisms, thereby facilitating identification of neuroprotective interventions. PD is characterized by degeneration of groups of neurons in the central, autonomic and enteric nervous systems with formation of eosinophilic intracellular inclusion, Lewy bodies, in surviving neurons; the prominent motor symptoms of PD are attributable to severe loss of substantia nigra dopaminergic neurons. Convergent genetic, biochemical and pathological evidence implicates (i) alpha-synuclein, a presynaptic protein and a major component of Lewy bodies, and (ii) abnormalities of mitochondrial function, oxidative stress and resulting oxidative damage, in pathogenesis. In preliminary studies, we showed that these factors are mechanistically interdependent. Chronic exposure of rats to rotenone, a pesticide that is epidemiologically linked to PD, causes systemic mitochondrial complex I inhibition, resulting in specific neuropathology closely resembling PD (including alpha-synuclein aggregate formation). Abrogation of alpha-synuclein gene expression in the substantia nigra of rats prevented neurodegeneration, demonstrating that the PD-like neuropathology resulting from this etiologically-relevant environmental trigger is dependent on endogenous alpha-synuclein. Interactions between alpha-synuclein and mitochondria have been suggested previously, but the mechanisms whereby alpha-synuclein is necessary for susceptibility of dopamine neurons to etiologically-relevant mitochondrial toxins in vivo are not known. In order to address this question, we will employ a range of innovative models and tools, including: viral vectors that abrogate SNCA expression in vivo; transgenic zebrafish models in which neurodegeneration triggered by mitochondrial toxins is dependent on human alpha-synuclein; and novel transgenic zebrafish lines that express fluorescent reporters, allowing detection of dynamic changes in reactive oxygen species, glutathione oxidation, ATP levels, and mitochondrial fission, fusion and transport, in live dopamine neurons in vivo. Using these unique tools, we will determine how alpha- synuclein affects ROS production and oxidative stress (aim 1), cellular respiration and bioenergetics (aim 2) and mitochondrial dynamics (aim 3) following exposure to mitochondrial toxins implicated in PD pathogenesis, in mammalian and zebrafish dopamine neurons in vivo. In aim 4, we will exploit automated behavioral measurements in zebrafish larvae housed in 96-well plates to discover small molecule modifiers of alpha-synuclein-dependent toxicity of mitochondrial inhibitors in dopamine neurons. These data will elucidate the mechanisms underlying alpha-synuclein-dependent degeneration of dopamine neurons in response to mitochondrial toxins implicated in PD pathogenesis. The unique array of model systems and the team of investigators will enable us to understand the mechanistic link between the two most prominent pathological abnormalities in sporadic PD and thereby address a critical roadblock in the development of PD therapeutics.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) affects more than 1 million Americans; no current treatments prevent disease progression, and patients become increasingly disabled over time. In this project, we will determine how two of the factors thought important in causing PD – accumulation of a protein called alpha-synuclein and abnormalities of cellular components called mitochondria – interact to make nerve cells become sick and eventually die. We will use a series of unique models to understand this interaction in living nerve cells and to identify new targets for drug treatments.

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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