Determining how neural activity impairs bioenergetics in PD pathogenesis

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Country

USA

Title of project or programme

Determining how neural activity impairs bioenergetics in PD pathogenesis

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NIH (NINDS)

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€ 1,889,509.17

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01/04/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Bioenergetics, dopaminergic neuron, PINK1 gene, Parkinson Disease, relating to nervous system

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a progressive

neurological disorder in which dopamine (DA) neurons in the brain degenerate and die. A genetic form of PD is caused by mutations in the mitochondrial protein PINK1, which proves that DA neurons are selectively vulnerable to specific mitochondrial stressors. Interestingly, considerable evidence suggests that mitochondrial function is also disrupted in sporadic (rather than genetic) forms of PD, and these changes may also selectively kill DA neurons. So, why are DA neurons susceptible to mitochondrial dysfunction? Because a critical role of mitochondria is to produce energy, many researchers believe that DA neurons are susceptible to energy failure. For example, DA neurons may not be able to produce as much energy or they might require more energy than other types of neurons. Indeed, much of the brain's energy is dedicated to supporting neural activity, and the activity of DA neurons may increase in PD. However, although many believe that energy failure plays a central role in PD pathophysiology, we know remarkably little about energy levels in DA neurons; we don't know if energy failure even occurs in these cells. In order to investigate energy failure in DA neurons, we developed innovative assays to measure ATP and visualize mitochondria in individual neurons. With these methods, we can now test our central hypothesis that DA neurons intrinsically require more energy than other types of neurons to sustain their neural activity, making them particularly susceptible to insults that further increase their energy demands or compromise mitochondrial function. The overall objective of the proposed study is to understand if DA neurons have intrinsic differences in the way they produce or consume energy that make them susceptible to energy failure. We will accomplish these objectives in three specific aims. (1) We will determine if DA neurons have intrinsic deficits in mitochondrial bioenergetic function at the synapse. To do this, we will measure energy production and consumption in individual DA neurons with our newly developed assays to evaluate mitochondrial energy levels in individual synaptic boutons. (2) We will determine if and how loss of the PD protein PINK1 compromises bioenergetic function in DA neurons by determining how losing PINK1 affects these neurons' mitochondrial distribution and function. (3) We will determine if the level of neural activity makes DA neurons even more susceptible to energy failure by assessing their function and death after changing activity levels. Overall, these studies will advance our understanding of if and how energy failure develops in DA neurons, and they will provide insight into how we might therapeutically target energy failure in PD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Dopamine neurons may die preferentially in Parkinson's disease (PD) because they are uniquely susceptible to energy failure. However, we understand very little about energy levels in dopamine neurons: we don't know how they produce energy or how their energy levels change with respect to neural activity, which consumes most of the brain's energy. Thus, understanding if and how energy failure develops in dopamine neurons is critical for understanding why PD occurs and how we might target energy failure for PD therapy.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

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2016

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