LRRK2-mediated molecular and synaptic events in the striatum

https://www.neurodegenerationresearch.eu/survey/lrrk2-mediated-molecular-and-synaptic-events-in-the-striatum/

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Country

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Title of project or programme

LRRK2-mediated molecular and synaptic events in the striatum

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NIH (NINDS)

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€ 1,775,504.59

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15/08/2016

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Cyclic AMP-Dependent Protein Kinases, Corpus striatum structure, Synapses, Parkinson Disease

Research Abstract
Project Summary Parkinson's disease (PD) is the second most common neurodegenerative disease of aging. Mutations in LRRK2 are associated with both inherited and sporadic forms of

PD. LRRK2 is highly enriched in spiny projection neurons (SPN) in the dorsal striatum. However, the physiological role of LRRK2 in SPNs remains elusive. Our previous observations suggest a linkage between the pathogenic R1441C mutation and aberrant PKA signaling in SPNs. However, the analyses were limited by the inherent resolution provided by conventional biochemical approaches and microscopy. In this proposal, we seek to provide more precise information about the pathophysiological consequences of LRRK2 mutations in SPNs. In particular, it is our central hypothesis that LRRK2R1441C mutation leads to aberrant dopaminergic signaling in SPNs. The resultant striatal dysfunction, in turn, contributes to the symptomatology of PD. To pursue this, we will examine if LRRK2R1441C mutation alters dopamine signaling, corticostriatal transmission, corticostriatal plasticity, and excitability in SPNs through PKA signaling dysregulation. Moreover, assessment of striatal-dependent motor learning along with pharmacological manipulations will provide insight on the effects of LRRK2R1441C mutation in a whole-animal setting. In conjunction with standard cellular, molecular, and electrophysiological approaches, our investigations will capitalize on a combination of cutting-edge approaches that overcome obstacles that have impeded progress to date. These include, LRRK2 mutant mice, striatal pathway-specific (Cre and reporter) mice, viral gene delivery, and super-resolution imaging. The successful achievement of these aims will significantly advance our understanding of the mechanisms underlying PD, and in doing so, will promote the development of new therapies for PD patients in the future.

Lay Summary
Project Narrative The proposed research aims to determine the cellular alterations of striatal projection neurons harboring pathogenic LRRK2 mutations. The knowledge gained will provide a framework for novel therapeutic strategies.

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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