Role of LRRK2 in dopaminergic transmission

https://neurodegenerationresearch.eu/survey/role-of-lrrk2-in-dopaminergic-transmission/

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Country

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Role of LRRK2 in dopaminergic transmission

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Parkinson’s disease (PD) is the second most common neurodegenerative disease affecting millions of people. Many of the psychomotor symptoms are attributed to the degeneration of dopaminergic neurons innervating the striatum. Emerging evidence suggests that synaptic dysfunction is an early event in the pathogenesis of the disease occurring prior to the onset of symptoms. In order to develop more effective therapeutic strategies, we need a better understanding of the underlying mechanisms of synaptic dysfunction of PD. Mutations in Leucinerich-repeat-kinase 2 (LRRK2), the newly identified causative gene for PARK8 type PD

with autosomal dominant inheritance, are the MOST PREVALENT genetic causes in both familial and sporadic PD. Whereas plenty of effort is being directed to understand the role of LRRK2 in the pathogenesis of PD, little is known about the normal physiological functions of LRRK2 in DA neurotransmission and their contributions to PD. Recently a transgenic mouse model with over-expression of human LRRK2-R1441G has been shown to recapitulate robust motor behavioral, neurochemical and pathological features of PD. At the level of pathology, the early and most robust phenotype is the axonopathy of the nigrostriatal dopaminergic projection. Our preliminary data has shown age dependent progressive deficits of dopaminergic synaptic function in this model. Therefore, in this study, we plan to determine how LRRK2 affects dopamine release by comparing these processes in two mouse models with either high levels of mutated LRRK2 or no LRRK2. We hypothesize that pathogenic LRRK2 R1441G mutation 1) impairs synaptic vesicle recycling, which in turn increases cytosolic dopamine level in pre-synaptic terminals leading to axonal degeneration in the end, and 2) abolishes the maturation of the somatodendritic D2-autoreceptor response, which in turn lead to excitatory toxicity. We will further explore whether molecules of the endocytosis machinery mediate the dopamine synaptic transmission deficits and the axonal degeneration among all the aspects of LRRK2 induced pathogenesis. We will utilize a combination of electrophysiology, optical imaging, biochemistry, and mouse genetics to uncover mechanisms underlying the dopamine deficit in PD. These findings will likely provide new insights into pathogenesis of PD and open new avenues for therapeutic intervention.

Lay Summary

LRRK2 mutations are the most common genetic cause of Parkinson disease. In this study, we plan to determine how LRRK2 affects dopaminergic transmission and how dopaminergic transmission is altered by LRRK2 mutations which may lead to the neurites degeneration. These findings will help to develop early therapies for preventing and/or delaying onset of symptoms.

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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