

SYNJ1 Mediates a Novel Signaling Pathway in Parkinsons Disease

<https://www.neurodegenerationresearch.eu/survey/synj1-mediates-a-novel-signaling-pathway-in-parkinsons-disease/>

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Country

USA

Title of project or programme

SYNJ1 Mediates a Novel Signaling Pathway in Parkinsons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

427637.6147

Start date of award

30/09/2015

Total duration of award in years

1

Keywords

synaptojanin, LRRK2 gene, Synaptic Vesicles, dopaminergic neuron, Parkinson Disease

Research Abstract

? DESCRIPTION (provided by applicant): The goal of our project is to investigate pathogenic mechanism underlying Parkinson's disease (PD) based on inherited forms of PD. We and two other groups have identified the same mutation in SYNJ1 gene on chromosome 21q22 that is associated with early onset Parkinsonism. As one of the most important inositol phosphatases in the brain, synaptojanin1 (encoded by SYNJ1) is involved in many aspects of membrane trafficking and has been implicated in a number of brain disorders including Alzheimer's disease

and Down's syndrome. However, its pathogenic mechanism in PD has not been studied. Emerging evidence reveals the convergence of pathogenic pathways for α -synuclein, LRRK2 and other PD-related genes in deregulating synaptic vesicle (SV) cycling in the early stage of PD. Our preliminary study shows shared phenotypes in SV endocytosis and dopaminergic transmission in SYNJ1 heterozygous mice and LRRK2-G2019S mice. SYNJ1 heterozygous mice develop abnormal dendritic morphology and lipid composition selectively in substantia nigra. Given that synaptojanin1 forms a protein complex with endophilin A, which was identified as a putative LRRK2 substrate, we propose a "LRRK2-endophilinA-synaptojanin1?" signaling axis for the regulation of SV cycling, which is deregulated in PD. We will test the hypothesis using state-of-art optical tools and genetic animal models. Completion of our project is expected to provide insight into the pathogenic mechanism for PD and open new avenues for identification of novel therapeutics.

Further information available at:

Types:

Investments < €500k

Member States:

United States of America

Diseases:

N/A

Years:

2016

Database Categories:

N/A

Database Tags:

N/A