Mechanisms of synaptic dysfunction in Parkinsons and other synuclein-linked dise

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Country

USA

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Mechanisms of synaptic dysfunction in Parkinsons and other synuclein-linked dise

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NIH (NINDS)

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15/01/2012

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

synuclein, Synaptic Vesicles, Parkinson Disease, Clathrin, Synapses

Research Abstract

ABSTRACT The long term goal of this project is to identify the cellular and molecular mechanisms that give rise to the synaptic defects in patients with Parkinson’s disease (PD) and

other related neurological disorders. The pathological hallmark of these diseases includes abnormal levels of ?-synuclein at synapses and throughout the neuron. While it is generally agreed that synucleins participate in synaptic vesicle trafficking, the exact steps of the vesicle trafficking pathway that are perturbed by altered levels of synuclein remain unclear. Thus, at present, it is not possible to design targeted strategies for improving synaptic function in PD. Experiments proposed here take the first steps toward this by identifying the precise synaptic vesicle trafficking defects caused excess synuclein at synapses, the mechanisms giving rise to these defects, and new strategies for reversing them. The experiments take advantage of two model synapses that are ideally suited for studies of synaptic vesicle trafficking, using both acute and genetic perturbations. The combination of highly quantitative biochemical assays to measure synuclein interactions, design of reagents to perturb these interactions, and detailed ultrastructural analyses provides the best opportunity to identify the cellular and molecular mechanisms leading to synuclein-induced synaptic vesicle trafficking defects. In initial studies, excess wild type synuclein causes a loss of synaptic vesicles, increased cisternae, and altered clathrin-coated profiles, consistent with inhibiting clathrin-mediated synaptic vesicle recycling. Going forward, proposed experiments are aimed at identifying the cellular mechanisms by which excess wild type ?-synuclein and PD-related mutations (e.g. A30P, E46K, A53T) cause vesicle trafficking defects (Aims 1 and 2). Experiments will also investigate how synuclein interactions with specific synaptic binding partners (e.g. PI(4,5)P2 and the uncoating ATPase) contribute to the synaptic vesicle trafficking defects, and targeted strategies for disrupting these interactions will be assessed as a possible means for reversing synaptic defects (Aim 2 and 3). The proposed experiments are innovative because they are the first to use a combination of quantitative biochemical binding assays, acute perturbations, controlled stimulation conditions, and detailed ultrastructural analyses to identify the precise synaptic vesicle trafficking defects caused by excess synuclein or its mutations, which is ideally suited for the overall goal. The experiments are significant because they represent the first steps toward understanding the mechanisms giving rise to the synaptic defects, and they provide possible targeted, molecular strategies for improving synaptic function. Thus, these studies have direct implications for slowing or halting the neurodegeneration, cognitive deficits, and dementia in PD and other synucleinopathies.

Lay Summary

PROJECT NARRATIVE The proposed research on synuclein is relevant to public health because it provides direct insight into the cellular and molecular mechanisms that lead to synaptic defects in Parkinson’s and other related neurodegenerative diseases. By focusing on the molecular underpinnings of the synaptic defects, the work addresses an important and under-investigated topic that complements other ongoing studies. The results of the proposed studies will provide critical knowledge for designing novel, targeted therapies aimed at improving synaptic function in Parkinson’s disease, Lewy body dementia, Lewy variant of Alzheimers disease, as well as other synuclein-associated neurological disorders where synapse function is compromised, such as brain and spinal cord injury, neuromuscular disease, and stroke.

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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