Modeling synaptic vesicles: how does alpha-Synuclein inhibit fusion?

https://neurodegenerationresearch.eu/survey/modeling-synaptic-vesicles-how-does-alpha-synuclein-inhibit-fusion/

Principal Investigators

SACHS, JONATHAN N

Institution

UNIVERSITY OF MINNESOTA

Contact information of lead PI
Country

USA

Title of project or programme

Modeling synaptic vesicles: how does alpha-Synuclein inhibit fusion?

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,651,573.39

Start date of award

30/09/2013

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Synaptic Vesicles, alpha synuclein, Vesicle, Membrane, membrane model

Research Abstract

DESCRIPTION (provided by applicant): Our goal is to develop a mechanistic understanding of the inhibition of synaptic vesicle fusion by monomeric alpha-Synuclein (alphaS). This research will establish the foundation for new therapeutic strategies in the treatment of Parkinson’s

disease (PD). There is growing consensus that monomeric alphaS is a central regulatory component of synaptic vesicle trafficking. Although the formation of Lewy bodies, mediated by the aggregation of alphaS into insoluble fibrils, is commonly associated with PD, high levels of alphaS have also been shown to disrupt normal vesicle trafficking and markedly inhibit neurotransmitter release without the formation of alphaS aggregates. Our approach will involve quantitative studies of the biophysical and mechanical properties of synaptic vesicle membranes for which we will combine coarse-grained molecular dynamics simulations with a panel of complementary biophysical experiments. A precise understanding of the native interactions between monomeric alphaS and synaptic vesicle membranes will position us to evaluate the protein's role in vesicle trafficking defects as they relate to PD. Limited biophysica data have yielded conflicting views on how alphaS over-expression inhibits vesicle trafficking and fusion in the absence of fibril formation. In multiple model systems from yeast to rodents, an overabundance of alphaS has been shown to stall proper synaptic vesicle cycling at the plasma membrane. One view is that this pathology may be driven by interactions between alphaS and other synaptic or plasma membrane proteins (e.g. SNARES). We propose an alternate view based on recent work both from our labs and others. According to this view, alphaS can directly alter the physical properties of lipids within membranes – namely membrane rigidity and phase. This is achieved in the absence of specific interactions with other proteins. We therefore reason that alphaS might have an intrinsic capacity to control synaptic vesicle fusion. This hypothesis is motivated by our preliminary data and published result from biophysical experiments, which show that alphaS reduces a membrane's rigidity, can alter membrane curvature, and can inhibit fusion of synthetic (otherwise protein-free) lipid vesicles. Our proposed research intimately combines computational modeling with experimental x-ray scattering and atomic force microscopy to bridge a critical gap in understanding how alphaS creates physical barriers to vesicle fusion. The proposed research avenue will provide critical information about PD associated trafficking defects. Ultimately, our work will lead to better understanding of normal and abnormal functions of alphaS and position the community to develop new therapeutic strategies that exploit the native state of the protein (i.e., restoring proper vesicle trafficking.

Lay Summary

PUBLIC HEALTH RELEVANCE: We will understand a new role for the protein alpha-Synuclein (alphaS) in the pathology of Parkinson's disease. Our multi-disciplinary research team will use a battery of approaches to obtain a molecular level picture of how overabundant alphaS aberrantly alters the physical properties of synaptic vesicles and thus has the potential to disrup normal neuronal function. Our proposal aims to identify a new and relevant target for the development of therapeutics to treat this debilitating disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A