Regulation of SNARE-dependent synaptic vesicle fusion

https://www.neurodegenerationresearch.eu/survey/regulation-of-snare-dependent-synaptic-vesicle-fusion/

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Country

USA

Title of project or programme

Regulation of SNARE-dependent synaptic vesicle fusion

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,074,931.19

Start date of award

01/08/1994

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

SNAP receptor, Synaptic Vesicles, Vesicle, alpha synuclein, nanodisk

Research Abstract
? DESCRIPTION (provided by applicant): The neuron is remarkable in that upon the influx of Ca2+ it synchronizes vesicle fusion, and releases many quanta of neurotransmitters to the synaptic cleft in less than 1 msec. The fast synchronization is orchestrated by interactions

between the core fusion machinery SNAREs and auxiliary proteins including a major Ca2+-sensor synaptotagmin 1 (Syt1) and a clamping factor complexin (Cpx). Because release underlies cognition and behavior, toxic agents that undermine the release of neurotransmitter might lead to the symptoms of neurodegenerative diseases such as Parkinson’s and Alzheimer’s. In this project we use innovative approaches to investigate the mechanism whereby the fusion machinery achieves the synchronization of vesicle fusion. To mimic the native membrane environment we prepare a nanodisc sandwich that harbors a single trans SNARE complex in the middle. Single molecule (sm)FRET and site-directed spin labeling (SDSL) EPR are used to characterize the interactions of SNAREs with auxiliary proteins in the chasm of two nanodiscs. In addition, the drastically improved single vesicle-vesicle fusion assay that can resolve docking, lipid mixing, fusion pore opening, and pore expansion steps, is used to delineate the intervention of regulatory factors onto individual fusion steps. Taken altogether, a comprehensive picture of how synchronization of vesicle fusion is choreographed by the interactions among individual components of the fusion machinery would emerge. For neurodegenerative diseases such as Parkinson’s there is an emerging theme of pathophysiology that toxic misfolded oligomers are tampering with the vesicle fusion machinery, leading to disease symptoms. We use EPR to investigate the interaction between ?-synuclein and vesicle (v-)SNARE VAMP2 that takes place on the membrane surface. The outcomes of these investigations are expected to reveal new therapeutic targets for treating symptoms of the Parkinson’s disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: Neurons release chemical messengers called neurotransmitters to synapses via the pathway called vesicle fusion when stimulated by the action potential. Communication among neurons constitutes the fundamental basis for cognitive activities. This project is aimed at elucidating the mechanism, at a molecular level, by which vesicle fusion is regulated. The study will ultimately provide important insights into mental illnesses. Furthermore, toxic misfolded proteins cause altercation of vesicle fusion, leading to symptoms of neurodegenerative diseases such as Parkinson’s and Alzheimer’s. The study is also directed toward the understanding of molecular interactions that cause neurodegenerative diseases, which will identify new drug targets for treating these diseases.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

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N/A

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