Regulation of Protein Trafficking in Neurodegeneration

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Country

USA

Title of project or programme

Regulation of Protein Trafficking in Neurodegeneration

Source of funding information

NIH (NIA)

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€ 1,793,463.30

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01/07/2003

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

nexin, protein transport, Sorting - Cell Movement, Amyloid beta-Protein Precursor, Nerve Degeneration

Research Abstract

DESCRIPTION (provided by applicant): Dysregulated trafficking of the ¿-amyloid precursor protein (APP) and glutamate receptors contributes to the pathogenesis/pathology of Alzheimer’s

disease (AD). The SorL1 protein interacts with APP and changes in SorL1 expression or function affects the subcellular distribution and thus the processing of APP. The retromer complex is composed of VPS35, VPS29, VPS26 and Sorting Nexins 1 and 2, and regulates retrograde sorting from the endosome to the trans-Golgi network (TGN). Deficits in retromer transport are implicated in sporadic AD but most studies propose a link between the retromer complex and ¿-secretase (BACE1) transport. Although VPS35 and VPS26 interact with SorL1, how retromer regulates APP trafficking and processing is largely unknown. Sorting Nexin 27 (SNX27) belongs to the Sorting Nexin family whose members regulate protein endocytosis and recycling. Our recent findings published in Nature Medicine demonstrate that SNX27 directly mediates glutamate receptor sorting to the plasma membrane, and attenuated SNX27 expression in Down syndrome (DS) brain contributes to synaptic dysfunction and neurodegeneration. Significantly, we find that SNX27 re-expression can ameliorate neuropathological and behavioral phenotypes in a DS mouse model. We attempt to further establish molecular mechanisms underlying SNX27-mediated neurodegeneration through the trafficking and homeostasis of glutamate receptors and APP. Our preliminary results indicate that SNX27 interacts with VPS26 and VPS35, components of the retromer complex. In addition, we find that SNX27 regulated cell surface glutamate receptor levels in a retromer-dependent manner and downregulation of VPS26 or VPS35 abolished the effect of SNX27 overexpression on promoting cell surface levels of glutamate receptors. Additionally, we find that overexpression and downregulation of SNX27 reduced and increased A¿ levels, respectively, further suggesting that SNX27 can also regulate trafficking and processing of APP. Our results also show that SNX27-mediated APP trafficking potentially occurs through direct interactions with the APP trafficking receptor SorL1 since overexpression and downregulation of SNX27 can increase and decrease SorL1 levels, respectively. Therefore, we hypothesize that interactions between SNX27, SorL1 and the retromer complex play important roles in AD by coordinating APP endocytic and golgi retromer trafficking pathways that attenuate A¿ generation, and by maintaining proper cell surface homeostasis of glutamate receptors. In this proposal, we will ascertain whether SNX27, SorL1 and the retromer complex coordinately regulate APP trafficking/processing and cell surface homeostasis of glutamate receptors and synaptic function. Moreover, as deficiencies in VPS35 and SorL1 may accelerate onset of disease-like phenotypes in AD mice, we will study whether overexpression of SNX27 can delay early-onset neuropathological and cognitive phenotypes in AD mice bearing VPS35- or SorL1-haploinsufficiencies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Dysregulation of intracellular trafficking of APP and glutamate receptors may promote A generation and impair synaptic functions, thus contributing to the pathogenesis/pathology of Alzheimer’s disease (AD). Our preliminary results suggest that SNX27, SorL1 and retromer interact with each other and coordinately regulate the retrograde transport of APP and the cell surface recycling of glutamate receptors; further ascertaining the role of SNX27-SorL1-retromer in AD and elucidating the underlying pathways will not only reveal new mechanisms responsible for disease pathogenesis/pathology, but also provide new targets for disease intervention.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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