Roles of SN27 in regulating glutamate receptors during neurodegeneration

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USA

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Roles of SN27 in regulating glutamate receptors during neurodegeneration

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Down Syndrome... Intellectual and Developmental Disabilities (IDD)... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Dysregulation of glutamate receptors (GluRs) has been observed in various neurodegerative diseases such as Alzheimer's disease (AD) and Down Syndrome (DS). However, the underlying mechanisms responsible for the changes in GluRs and the contribution of GluR dysregulation to neurodegeneration have remained largely elusive. In our preliminary studies, we found that the Sorting Nexin 27 (SNX27) protein can interact with GluRs and govern their trafficking to the plasma membrane for recycling. SNX27 is abundantly expressed in the brain and SNX27 homozygous knockout (KO) mice exhibit severe neuropathologies resembling those found in AD and DS patients. SNX27 heterozygous KO mice have memory deficits and their neurons have reduced GluR levels and synaptic dysfunction. DS is caused by an extra copy of chromosome 21 which results in over- dosage of the genes on this chromosome. We found that in DS patient brains, a microRNA gene on chromosome 21, miR-155, which negatively regulates the transcription factor C/EBP¿, was upregulated, accompanied by a concomitant reduction of C/EBP¿ and SNX27. We also show that C/EBP¿ positively regulates SNX27 expression. These results reveal a miR-155/C/EBP¿/SNX27 pathway that leads to GluR dysregulation and synaptic dysfunction in DS. Since late stage DS patients develop AD-like pathologies and cognitive deficits, we studied the effect of SNX27 on the generation of ¿-amyloid (A¿), which is the primary culprit in AD pathogenesis and is derived from ¿-amyloid precursor protein through sequential cleavages by ¿- and ¿-secretases. We found that overexpression of SNX27 reduces A¿ production and the level and activity of ¿-secretase as well. Therefore, we hypothesize that SNX27 plays an important role in regulating GluRs and thus synaptic function, and that SNX27 deficiency may contribute to neurodegeneration in DS and AD. In this proposal, we will further ascertain the participation of SNX27 in DS by: (1) corroborating the regulation of GluRs by SNX27 and its modulators (miR155 and C/EBP¿) in primary neurons~ (2) using virus systems to modulate miR155, C/EBP¿, and SNX27 levels in SNX27 deficient mice and Ts65Dn mice, and study whether the impaired phenotypes in these mice can be ameliorated~ and (3) generating brain-specific SNX27 transgenic (Tg) mice and crossing them with Ts65Dn mice to study any amelioration of pathology through SNX27 overexpression. Moreover, we will explore the role of SNX27 in AD. We will: (1) modulate the levels of SNX27 and determine whether and how ¿-secretase level/trafficking/activity and APP processing/A¿ generation are affected~ (2) study whether SNX27 is affected by and involved in A¿-mediated neurotoxicity and examine any changes in SNX27 in AD brains~ and (3) cross SNX27 Tg mice with Tg2576 AD mice and attempt to rescue impaired phenotypes in AD mice. These results will elucidate the role of SNX27 in regulating GluRs and synaptic functions in DS and AD, providing novel molecular mechanisms for disease pathogenesis/pathology.

Lay Summary

PUBLIC HEALTH RELEVANCE: Dysregulation of glutamate receptors may impair synaptic functions and contribute to the pathogenesis/pathology of neurodegenerative diseases such as Alzheimer's disease (AD) and Down syndrome (DS). Our preliminary results suggest that SNX27 regulates the stability/trafficking of glutamate receptors, synaptic function and neuronal death, and is involved in DS and possibly AD. Further elucidation of the role of SNX27 in these diseases and discovering the underlying pathways will not only reveal a new mechanism responsible for disease pathogenesis/pathology, but also provide a new target for disease intervention.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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