Alzheimers BACE1 inhibition regulates neuronal contactin function

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Country

USA

Title of project or programme

Alzheimers BACE1 inhibition regulates neuronal contactin function

Source of funding information

NIH (NIA)

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15/08/1997

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18

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): While BACE1 has emerged as an effective drug target for the prevention and treatment of Alzheimer’s disease (AD); side effects of BACE1 inhibitors are not well characterized. To identify the neuronal surface proteins most affected by lack of BACE1 inhibition, we recently performed an unbiased screen of surface proteins in adult BACE1-null mouse brain slices. This screen and subsequent cell-based studies revealed those two GPI- anchored adhesion molecules, contactin-1 and -2, highly increased in the BACE1-null brain. Interestingly, contactin-1 is known to regulate the surface expression and localization of Nav1.2 channels while contactin-2 modulates Kv1.1/2 channels. Nav and Kv channels almost exclusively carry out the rising and falling phases of action potentials. Previously, we have also shown that BACE1 activity regulates mRNA, protein, and cell- surface levels of the pore-forming Nav1.1 ¿-subunit, a major CNS-specific voltage-gated sodium channel (Nav). Contactin-2 is also known to promote APP processing. In vitro analyses confirmed that BACE1 cleaves both contactin-1 and -2. In primary hippocampal/cortical neurons, we found that either BACE1 inhibitor treatment or overexpression of BACE1 dramatically alter surface levels of contactin-1 and -2. Interestingly, contactin-2 levels decrease by ~50% in AD brains with elevated BACE1. Nav1.2 surface levels are increased in BACE1- null neurons and the surface expression of Kv1.2 channels is dramatically modulated by BACE1 activity in brain slices and primary neurons. Importantly, overexpression of contactin-1 rescues impaired Nav channel ¿- subunit channel trafficking in neuroblastoma cells expressing BACE1. Therefore, our new findings suggest that BACE1 regulates Nav1.2 and Kv1.2 channel trafficking by modulating the surface expression of contactin-1 and -2. The overarching goals of this application are to explore how contactin-1 and -2 processing by BACE1 regulates ion channel metabolism and to elucidate non-amyloidogenic functions of BACE1 for developing a safe therapeutic protocol to inhibit BACE1 activity in AD patients. To this end, we propose to use an integrated approach of cell biology and in vivo animal models. We will first identify the BACE1 cleavage sites in contactin- 1 and -2, and characterize the effect of these cleavages on APP metabolism. We will then determine the functional role of BACE1-mediated contactin processing in Nav and Kv channel metabolism. We will also explore the effect of BACE1 inhibitors on non-amyloidogenic BACE1 functions, including contactin-regulated ion channels in adult mouse brains, and in 3D cultures of human neural cells. Collectively, the proposed studies will define how BACE1-mediated processing of contactin-1 and -2 regulates Nav1.2 and Kv1.2 channel metabolism and may also provide novel mechanistic insights on contactin-regulated A¿ generation. Since imbalance in ion channel function may lead to seizures, the overall goal of these experiments is to provide necessary mechanistic and in vivo data for further development of BACE1 inhibitors as a safe therapeutic strategy for AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Although BACE1 is a major therapeutic target for the prevention and treatment of Alzheimer’s disease, side effects of BACE1 inhibitors are not known. We have recently found that BACE1 inhibition dramatically increases levels of contactins 1 and 2, two proteins that regulate ?-amyloid precursor protein cleavage and ion channel levels. This proposal directly tests side effects of BACE1 inhibition mediated by contactins, using cells, animal models, and BACE1 inhibitor candidates for clinical trials.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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