

BRI2 Familial British and Danish Dementias and Alzheimers Disease

<https://www.neurodegenerationresearch.eu/survey/bri2-familial-british-and-danish-dementias-and-alzheimers-disease/>

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Country

USA

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BRI2 Familial British and Danish Dementias and Alzheimers Disease

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NIH (NIA)

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01/12/2008

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8

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... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's Disease (AD) is the most common cause of ageing-dependent dementia in the world and is associated with cerebral amyloid plaques, mostly composed of A β peptides. These peptides are produced by a double cleavage of the amyloid precursor protein (APP). BACE1 cleavage produces the C-terminal fragment, β -CTF, which is then processed into several A β isoforms by γ -secretase. Genetic data suggest that regulation of APP processing contributes to AD, which lead us to perform genetic screens for regulators of APP processing. We isolated ITM2B/BRI2, a gene mutated in AD-like familial Danish and British dementias (FDD and FBD), and found that it tightly binds APP and inhibits its cleavage by BACE1. To address the hypothesis that alterations of APP processing participate in dementia we generated knock-in models of Danish and British dementias. These FDDKI and FBDKI mice showed synaptic plasticity/memory deficits due to loss of BRI2 function and increased processing of APP by BACE1. Surprisingly however, we found that β -CTF and not A β , is the main synaptotoxic APP metabolite in these mice. The simplest explanation of our observations is that AD and FDD/FBD are pathogenically different. Alternatively, our observation may reflect the model systems we use. The pathogenic centrality of A β has been shown in mouse models over-expressing mutant forms of human AD-associated genes (APP and PS) and thus human A β , whereas our results stem from model systems that rely on endogenous, murine APP expression coupled to loss of an APP processing regulator. In this context, it is important to note that ITM2B/BRI2 has been recently identified as a master regulator of the common patterns of gene expression shared by healthy ApoE4 carriers and LOAD patients who do not carry the ApoE4 allele. This evidence establishes a direct connection in humans between ITM2B/BRI2 and ApoE4, the strongest genetic risk factor for AD, as well as ITM2B/BRI2 and sporadic AD, supporting the idea that FDD and FBD are genetic variants of FAD. Regardless of which explanation is correct, two points are worth noting; 1) a therapeutic approach inhibiting BACE1 cleavage of APP would be efficacious in all scenarios; 2) γ -secretase inhibition, an aggressively sought-after therapeutic approach for AD, would result in accumulation of β -CTF so it is vital to determine if this intermediate contributes to pathogenesis. In this application, we will further characterize the mechanisms by which APP processing mediates memory deficit. These studies are likely to shed light on the pathogenesis of AD, as well as to unveil novel targets for disease-modifying AD drugs.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mutations in genes that regulate the processing of APP cause Familial Dementias in humans. BRI2 is one of these genes. We have generated a mouse model that faithfully represents the human dementias caused by the mutation in BRI2. In addition, we have also generated mice in which we can inactivate BRI2 in the brain of adult mice. The mice we made have shown that when BRI2 is mutated or eliminated, APP processing is increased and causes memory loss. The models of Danish and British dementia that we made reproduce accurately the genetic defects of patients. Therefore, they are ideal systems to dissect the pathogenic mechanisms that cause dementia in humans and to test therapies for human dementias, including Alzheimer's disease. These studies will also serve as a proof of concept to development BRI2-like drugs that reduce APP processing without inhibiting the enzymes that mediate processing of APP.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

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