Mechanisms of brain phenotypes caused by FAD-linked Presenilin-1 Mutations

https://neurodegenerationresearch.eu/survey/mechanisms-of-brain-phenotypes-caused-by-fad-linked-presenilin-1-mutations/

Principal Investigators

KELLEHER, RAYMOND J

Institution

MASSACHUSETTS GENERAL HOSPITAL

Contact information of lead PI
Country

USA

Title of project or programme

Mechanisms of brain phenotypes caused by FAD-linked Presenilin-1 Mutations

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,301,744.04

Start date of award

01/07/2011

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

presenilin-1, familial Alzheimer disease, gamma secretase, presenilin, Knock-in

Research Abstract

Project Summary/Abstract Mutations in the PSEN1 and PSEN2 genes encoding Presenilin-1 (PS1) and Presenilin-2 (PS2) are the most common cause of familial Alzheimer’s disease

(FAD), highlighting the importance of Presenilin function in disease pathogenesis, but the underlying mechanisms remain unresolved. Aberrant APP processing by ?- secretase and ?-secretase-independent activities of PS1 have been implicated in FAD pathogenesis. Our recent work has shown surprisingly that pathogenic mutations in PS1 can inactivate its function as the catalytic subunit of the ?-secretase complex and produce FAD-related phenotypes through a loss-of-function mechanism. To assess the effects of FAD mutations in vivo, particularly in the brain where the pathogenic process occurs, we generated two independent lines of Psen1 knock-in (KI) mice that precisely reproduce chromosomal PSEN1 mutations identified in FAD patients. Our analysis revealed phenotypes in the resulting homozygous KI mice indistinguishable from those caused by a Psen1 null mutation, accompanied by essentially complete loss of ?-secretase activity in the brain. Heterozygosity for the Psen1 L435F KI mutation produced deficits in hippocampal short- and long-term synaptic plasticity and hippocampal learning and memory reminiscent of those caused by conditional inactivation of Presenilins in the adult brain. Intriguingly, heterozygous KI mice also displayed elevation of the cortical A?42/A?40 ratio and exacerbation of cortical A? deposition on a mutant APP transgenic background. Moreover, the Psen1 L435F KI mutation was unable to support neuronal survival in the aging brain, triggering widespread cerebral cortical neurodegeneration. In this competing renewal application, we propose to investigate the important questions of whether and to what extent these synaptic, behavioral, and neurodegenerative phenotypes caused by the FAD mutation are attributable to aberrant APP processing and impaired ?-secretase activity, or alternatively to APP-independent and/or ?-secretase-independent functions of PS1. We propose to perform multidisciplinary molecular, synaptic, behavioral, and histological analysis using novel mouse models to understand the contributions of APP processing and ?-secretase-independent activity to Presenilin function and FAD-related dysfunction in the adult brain. The results of our studies will have significant impact on understanding of FAD pathogenesis and strategies to devise effective therapies.

Lay Summary

Project Narrative Alzheimer’s disease (AD) is the most common neurodegenerative disorder, and mutations in the Presenilin genes are the most common cause of inherited or familial AD (FAD). Results from our recent generation and multidisciplinary analysis of novel mouse models point to an important role for loss of Presenilin function in FAD pathogenesis. In this application, we propose to investigate the mechanisms by which Presenilin mutations impair synaptic function, learning and memory, and neuronal survival in the adult brain. Completion of these studies will advance efforts to understand FAD pathogenesis and devise effective therapies.

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

Database Tags:
N/A