Knockin Mouse Models of Alzheimers Disease

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Country

USA

Title of project or programme

Knockin Mouse Models of Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,446,655.96

Start date of award

01/04/2002

Total duration of award in years

15

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is an age-related neurodegenerative disorder defined by the deposition of ¿- amyloid (A¿) plaques and

neurofibrillary tangles (NFT), of which the principal components are A¿ peptides derived from the amyloid precursor protein (APP) and hyper-phosphorylated tau, respectively. The relationship between the extracellular A¿ and intracellular NFT pathologies and how they mediate synaptic dysfunction, which is regarded as a causal event in AD, remain poorly understood. Mutations in APP and presenilin (PSEN) genes lead to early onset of familial AD (FAD), establishing their critical roles in AD pathogenesis. Based on the genetic evidence, we have established APP and PS1 knockin mouse models (APP/hA¿/PS1) in which the disease-causing mutations and human A¿ sequence are introduced into the endogenous APP or PSEN1 loci such that the pathogenic effects of the FAD mutations and A¿ can be investigated under their physiological context. Analysis of the knockin mice show that they exhibit profound anxiety phenotypes, likely mediated by impaired inhibitory neuronal function. We have now developed a second generation of the knockin mice which allow us to express the APP/PS1 mutations and A¿ in specific neurons and brain regions. Equipped with these powerful mouse models, the application seeks to gain mechanistic and functional understanding of AD pathogenesis by addressing the following fundamental questions: 1) What is the relationship between anxiety/stress and dementia? 2) How does the specific impairment of excitatory or inhibitory neurons contribute to synaptic dysregulation and whether they differentially mediate cognitive and stress-related behaviors? 3) What are the molecular and cellular mechanisms mediating mutant APP/hA¿/PS1-induced NFT pathology? Our proposal will reveal unprecedented insights into AD pathogenesis and we are equipped with innovative and sophisticated mouse models to address these questions.

Lay Summary
The objective of the application is to decipher AD pathogenesis at the cellular and network levels using novel and disease-relevant mouse models. It will lead to the mechanistic understanding of the pathways contributing to the neuropathological, synaptic and behavioral phenotypes and the identification of effective cellular targets for therapeutic intervention.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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