Learning and Memory Impairments in Transgenic AD Models

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Country

USA

Title of project or programme

Learning and Memory Impairments in Transgenic AD Models

Source of funding information

NIH (NIA)

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01/12/2005

Total duration of award in years

9

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

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer disease (AD) impairs memory and causes cognitive and psychiatric deficits. Over 35 million people throughout the world are afflicted, including 5.4 million in the USA. All AD cases are marked by the accumulation of two lesions in the brain called plaques (consisting of a protein called Aß) and tangles (consisting of a protein called tau that becomes hyperphosphorylated. One of the most fundamental and unresolved questions in the field centers around elucidating the relationship between Aß and tau and their role in cognitive decline. It is critical to determine if Aß triggers pathology in human wild-type au, rather than the mutant used in previous models. Moreover, this proposal seeks to identify the interactions between these two critical proteins at the synapse using synaptoneurosomes, thereby enabling us to quantify Aß and tau levels in the synapse and other key markers of synaptic function. Lastly, the broad goal of this application is to understand how these synaptic changes lead to cognitive deficits, and whether therapies that remove either Aß or tau alone are sufficient to improve behavior. It is important to point out that research in the AD field can only progress if the tools evolve, hence there is an urgent need to develop and characterize new animal models until an effective treatment is discovered. Because the 3xTg-AD mice harbor mutant tau, addressing these issues necessitated the generation of innovative new transgenic models and viral vectors to manipulate gene expression in vivo. The first novel model we developed is a floxed human APP transgenic mouse that permits ablation of APP expression using Cre recombinase. We also created a novel human wild-type tau transgenic model that develops phosphotau pathology. After crossing these two lines, we can discover the impact Aß has on the development of tau pathology during various stages (i.e., before, during, and after tau pathology is established). Results from this study will reveal the conditions under which Aß induces wild-type tau pathology. Additionally, we will be uniquely positioned to determine if tau pathology continues to cause synaptic deficits even if Aß is suppressed using Cre. Using viral gene delivery to the CNS, we will determine whether intracellular and extracellular Aß plays a greater role in modulating tau pathology and cognitive decline. The development of the floxed human APP transgenic mice represents a significant advance for the field, as it enables abrogation of human APP gene expression using viral delivery of Cre recombinase during temporally-specified timepoints. Utilizing these novel models and innovative genetic approaches that add significantly to the research tool armatorium, we will unravel the distinctions between the cognitive loss due to Aß-dependent and -independent mechanisms, the pathological time point of Aß-induced tau dysfunction, and whether the presence of Aß intracellularly or extracellularly facilitates tau pathology and cognitive decline. Because a better understanding of these pathways is critical not only for academic reasons but also for helping to identify novel drug targets, the translational impact of this work is substantial and significant.

Lay Summary

PUBLIC HEALTH RELEVANCE: Project Narrative: Alzheimer's disease leads to severe memory loss and problems with activities of daily living, and will continue to be a significant public health problem that extolls a heavy burden on our society, particularly as the baby-boomers advance in age. The work proposed in this application utilizes newly developed animal models (floxed APP and wildtype human tau transgenic mice) to unravel the molecular connection between two hallmark Alzheimer's disease proteins and elucidate their relationship to cognitive decline. The translational impact of the proposed work is high and not only of major significance for academic reasons but because a better understanding of the relationship offers real and concrete opportunities to develop novel drug therapies for tackling the cognitive deficits associated with Alzheimer's disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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N/A