Soluble aSyn is a modulator of AD pathophysiology

https://www.neurodegenerationresearch.eu/survey/soluble-asyn-is-a-modulator-of-ad-pathophysiology/

Principal Investigators

LESNE, SYLVAIN E.

Institution

UNIVERSITY OF MINNESOTA

Contact information of lead PI
Country

USA

Title of project or programme

Soluble aSyn is a modulator of AD pathophysiology

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,400,933.94

Start date of award

15/09/2014

Total duration of award in years

3

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): The long-term goal of this project is to better

understand the contribution of soluble form(s) of alpha-synuclein (?Syn) in Alzheimer’s disease (AD). Our recently published findings suggest that (i) intraneuronal soluble ?Syn is abnormally elevated in AD brains in absence of deposited ?Syn, (ii) soluble ?Syn is a quantitatively better correlate of cognitive function than soluble amyloid-beta (Aß) and tau in humans, (iii) overexpression of ?Syn leads to cognitive impairment in mice, (iv) elevation of ?Syn leads to decreases in selected synaptic vesicle proteins and an alteration of the protein composition of synaptic vesicles and (v) a synergism between Aß/APP and human tau appears to be responsible for the abnormal elevation of soluble ?Syn in transgenic mice. In this study, we propose to determine whether soluble non-fibrillar forms of ?Syn are modulating cognitive decline in mice and to unravel the synaptic mechanism by which ?Syn might be impairing memory. The overall objective of this application is to identify the role of soluble ?Syn molecule(s) and its(their) relative contribution(s) to AD. Altogether, our observations suggest that AD might not be a two-protein disorder (i.e. Aß and tau) but instead a three-pronged attack of neuronal synapses by Aß, tau and soluble ?Syn. To test this provocative hypothesis, three questions regrouped under three aims are proposed: 1) Does deleting the ?Syn gene SNCA from APP mice improve behavior, pathology and synaptic vesicle composition? 2) What form(s) of soluble ?Syn is/are associated with cognitive impairment in brains of ?Syn transgenic animals and in subjects with AD? 3) What is the mechanism(s) by which soluble ?Syn species alter presynaptic vesicle composition?

Lay Summary
PUBLIC HEALTH RELEVANCE: Soluble ?-synuclein is a modulator of Alzheimer’s disease pathophysiology Project Narrative If our hypothesis is correct, Alzheimer’s disease (AD) would not be considered a neurological disorder involving two key proteins, i.e. amyloid-ß (Aß) and tau, but instead a disease triggered by abnormal changes in three key proteins: Aß, tau and ?-synuclein (?Syn). In addition, our findings could explain why drugs effective in current AD mouse models, which harbor amyloid plaques without human wild-type tau or wild-type ?Syn, do not work in humans.

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