Water-soluble Abeta and its role in Alzheimers disease

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Contact information of lead PI
Country

USA

Title of project or programme

Water-soluble Abeta and its role in Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,618,832.11

Start date of award

15/05/2014

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... Immune System... Immunization... Neurodegenerative... Neurosciences... Vaccine Related

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) represents a personal and

societal tragedy that demands an accelerated effort to develop effective therapies. Strong genetic evidence links the amyloid precursor protein (APP) and its proteolytic derivatives to AD. A leading hypothesis proposes that a small amphipathic fragment of APP, amyloid b-protein (Ab), self-associates to form assemblies loosely referred to as “”oligomers””, and that these trigger a complex pathogenic sequence of events that culminate in dementia. However, the toxic forms of Ab in human brain, and their relationship to disease have not been rigorously studied. Given the unsustainable burden that AD is placing on healthcare systems worldwide, it is essential that scientific doubts about the role of Ab and how it is best targeted are dealt with directly and swiftly. More than a decade ago, we and others proposed that certain non-monomeric, non-fibrillar forms of Ab are potent neurotoxins and may be the precipitating agent in AD. Yet the precise biochemical identity of these “”toxic oligomers”” remains unclear. Moreover, while the vast bulk of studies of Ab structure and activity have used synthetic Ab peptides, it is now apparent that brain-derived Ab preparations are much more damaging to neurons and much better seeds for amyloidogenesis than are Ab assemblies formed in vitro. We hypothesize that the enhanced toxic activity of brain-derived oligomers is related to the presence of mixtures of different Ab sequences, post-translational modifications and/or formation of covalent cross-links, all of which act to increase the stability of toxic assemblies. s appears to be true in prion diseases, we predict that the size, conformation and stability of Ab assemblies strongly influence their toxic activity. Using aqueous extracts of AD brains, and based on substantial preliminary data, we propose to investigate rigorously: (i) the assembly size, (ii) conformations and (iii) dynamic nature of toxic Ab species. Then we propose to purify them to homogeneity and to elucidate their composition. Throughout our experiments, we will constantly link our physical analyses with measures of neurobiological activity directly relevant to AD. Thereafter, we will analyze postmortem tissue to compare the quantity and quality of toxic oligomers in brains of demented subjects vs. cognitively normal humans with high plaque burdens. Using the same human tissues, we will also measure the levels of other APP fragments to see if any of these better relate to disease than does Ab. Then we will examine brain tissue and plasma from AD patients that received the AN1792 vaccination. The goal of this particular experiment is to ascertain how vaccination affects the levels and forms of Ab in the human brain and whether some immunized patients develop antibodies capable of targeting the toxic oligomers. Finally, from a selection of 20 candidate antibodies in hand, we will identify one that preferentially recognizes toxic oligomers. Then we expect to learn whether it can protect against Ab species in AD mouse models better than does the current lead therapeutic antibody, mAb266.

Lay Summary

PUBLIC HEALTH RELEVANCE: Substantial data indicate that the amyloid b-protein (Ab) may be a cause of Alzheimer’s disease (AD). However, most trials of drugs that target Ab have proved disappointing and there is significant concern about the involvement of Ab in this tragic disorder. The primary goals of this project are: (1) to identify from human brain toxic forms of Ab, (2) to use this information to rigorously test fundamental unresolved questions about Ab’s role in AD, and (3) to determine whether antibodies that specifically target toxic forms of Ab have therapeutic potential.

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