Formation and Propagation of Tau Oligomeric Strains in Alzheimers Disease

https://www.neurodegenerationresearch.eu/survey/formation-and-propagation-of-tau-oligomeric-strains-in-alzheimers-disease/

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Country

USA

Title of project or programme

Formation and Propagation of Tau Oligomeric Strains in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,777,522.94

Start date of award

15/07/2016

Total duration of award in years

1

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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

The pathological aggregation of the microtubule-associated protein tau and its subsequent accumulation into neurofibrillary tangles (NFTs) and other hyperphosphorylated tau-containing inclusions are defining histopathological features of Alzheimer’s disease (AD) and several other neurodegenerative disorders collectively known as tauopathies. These diseases affect millions of people in the United States and exact enormous personal and financial costs on those afflicted and their loved ones. However, while amyloid-? (A?) and tau aggregates in the brain are the common pathological hallmarks of AD, the disease is heterogeneous with different comorbid pathologies and symptom progression rates. Recent studies suggest that NFTs are not the most toxic tau entities in tauopathies; rather tau oligomers—soluble intermediates between monomers and NFTs—have emerged as an important drug target due to their toxicity, seeding potency, and ability to propagate a specific abnormal tau conformation and thus initiate widespread tau pathology. Our data suggest that oligomers composed of different proteins might give rise to increased and diverse tau oligomerization, resulting in different pathologies and phenotypes that sometimes overlap with other neurodegenerative diseases. The dynamic and hydrophobic nature of tau oligomers allows for the formation of heterogeneous populations of aggregates that include distinct tau oligomeric conformers (strains). In this proposal we will test the tau oligomeric strain hypothesis in AD by defining strain characteristics and potential mechanisms of strain formation and propagation. Specific aim 1 will test the hypothesis that diverse tau oligomeric strains are found in AD brain and CSF. Specific aim 2 will test the hypothesis that brain-derived tau oligomeric strains arise from cross-seeding other amyloidogenic proteins and propagate pathology in vivo. This research proposal will yield useful results with great potential to advance the development of diagnostic and therapeutic applications to target toxic tau oligomers in AD. The elucidation of different tau oligomeric strains and their roles in disease progression may reveal novel therapeutic strategies and identify upstream drug targets for treating AD. Moreover, a better understanding of tau strains could help identify useful approaches for screening the best drug candidates. Finally, it could provide novel insights into the design of future clinical trials and introduce the exciting possibility of personalized medicine to treat AD and other tauopathies.

Lay Summary

Millions people in the United States are affected by Alzheimer`s diseases (AD) and the incidence of these diseases is on the rise and yet there is a paucity of effective therapies. We and others recently demonstrated e. tau oligomers, may constitute a distinct toxic species in AD and other tauopathies. The pathological protein aggregates in AD are heterogeneous which makes it hard for diagnosis and treatment. The elucidation of different tau oligomeric strains and their roles in AD will advance diagnostic applications and may also reveal new targets for novel therapeutic strategies which would improve the health and well-being of the growing aging population in the US.

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