Advancing Our Understanding of Oligomer Toxicity in Age-Related Amyloid Disorders

https://neurodegenerationresearch.eu/survey/advancing-our-understanding-of-oligomer-toxicity-in-age-related-amyloid-disorders/

Principal Investigators

EISELE, YVONNE SIMONE

Institution

SCRIPPS RESEARCH INSTITUTE

Contact information of lead PI
Country

USA

Title of project or programme

Advancing Our Understanding of Oligomer Toxicity in Age-Related Amyloid Disorders

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

165091.7431

Start date of award

15/09/2015

Total duration of award in years

2

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Amyloid diseases are a group of highly diverse degenerative disorders, named after the cross-ß-sheet aggregates or amyloid fibrils that are the histopathological hallmarks of these maladies. Prominent examples include Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, as well as the systemic

transthyretin and light chain amyloidoses. Amyloid fibrils in a given disease generally comprise one specific protein. Aggregation of one of more than 30 different proteins is linked to a spectrum of pathologies. Typically, these proteins are expressed throughout the lifetime of an individual, but misfold, aggregate and accumulate only at an older age. The invariant presence of amyloid structures in affected tissue has led to the formulation of the “”amyloid hypothesis””, i.e., the idea that the process of protein aggregation causes tissue degeneration by a toxic gain-of-function mechanism. However, the mechanistic connection between protein aggregation and tissue degeneration is not understood yet. Amyloid structures can be present in fairly large quantities in affected individuals without causing symptoms. Therefore, the leading, but still highly controversial hypothesis postulates that small, soluble oligomeric aggregates of the misfolded proteins are drivers of the toxicity cascade. The objective of the proposed project is to scrutinize the oligomer toxicity hypothesis and to gain insight into the mechanism of oligomer toxicity by studying oligomers isolated from patients with transthyretin amyloidosis. Importantly, this is the only amyloid disease where a regulatory agency approved anti-amyloidogenic drug that halts disease progression is available. It is therefore possible to repeatedly obtain blood samples from presymptomatic and symptomatic patients, as well as from patients undergoing anti-amyloidogenic treatment. I will immunoisolate and characterize patient-derived transthyretin oligomers and decipher the cytotoxicity pathways activated in primary tissue cultures using transcriptomics and proteomics (K99). The next step will then be to probe these findings in vivo, to expand the knowledge gained to the most common age-related neurodegenerative disorders, namely Alzheimer’s and Parkinson’s diseases, and to evaluate the therapeutic potential of interference with the disclosed pathways (R00). The outcomes are expected to have an important positive impact because they comprehensively delineate the contribution of oligomeric protein aggregates to tissue degeneration and are anticipated to guide the field in its endeavor to develop effective, targeted and successful therapeutics for age-related amyloid disorders.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A