Solid State NMR Structural Analysis of Oligomeric Alzheimers Beta-Amyloid Peptide

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Country

USA

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Solid State NMR Structural Analysis of Oligomeric Alzheimers Beta-Amyloid Peptide

Source of funding information

NIH (NIA)

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01/05/2014

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) research has traditionally focused on amyloid fibrils found in plaque deposits in the brain, but recent evidence suggests that oligomers of Alzheimer’s beta-amyloid peptides play a more significant role in initiating AD pathology. The long-term objective of this project is, through characterizing Abeta oligomer structures, answer fundamental questions about pathways of A beta self-assembly and how these pathways could be controlled as strategies for designing therapeutics. The proposed research addresses major challenges related to oligomer stability and structural homogeneity, which have hindered oligomer structural characterization to date. We will determine the structure of a 150 kDa Abeta (1-42) oligomer by integrating solid state nuclear magnetic resonance (ssNMR) spectroscopy with computational modeling. Specifically, we will 1) define secondary structure and sidechain proximity across the amino acid sequence; 2) Determine alignments between neighboring beta -strands and conformations of non- beta -strand regions; and 3) Model the structure of the Abeta (1-42) oligomer based on the ssNMR data. The structural information obtained in this project will help characterize early events in Abeta self-assembly and may lead to diagnostic tools for early detection of Alzheimer’s disease and therapeutic strategies that exploit differences in oligomer and fibril assembly pathways.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease results from death of neurons in the brain associated with deposition of plaques, composed largely of nanostructured protein assembles called amyloid fibrils. Mounting evidence now suggests that small molecular clusters, or oligomers, of Alzheimer’s beta -amyloid protein may be especially toxic to neurons. In this project, we will produce stabilized purified samples of a beta -amyloid oligomer and characterize its structure. These studies will help us understand the atomic details of Alzheimer’s disease related protein assembly and provide a structural basis for therapeutic strategies.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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