Alzheimers Brain-Seeded Abeta Fibrils

https://neurodegenerationresearch.eu/survey/alzheimers-brain-seeded-abeta-fibrils/

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Country

USA

Title of project or programme

Alzheimers Brain-Seeded Abeta Fibrils

Source of funding information

NIH (NIA)

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15/09/2015

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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

Research Abstract

DESCRIPTION (provided by applicant): The polymorphism of amyloid fibrils is well-established, but little is known how these various structures relate to disease pathogenesis. Our overall goal is to understand possible structure-malfunction relationships, i.e., relationship between the Aß

aggregate structure and disease phenotype. This proposal is based on our previous work on Alzheimer’s Disease (AD) brain-seeded fibrils (two papers, in PNAS (1), and in Cell (2)), the main findings of which were: 1) Brain Aß fibrils can be examined using amyloid from AD patients to seed isotopically labeled Aß solutions, thus producing replicate fibrils for solid-state NMR. 2) We obtained unprecedented structural detail, comparable to crystallography in resolution, of an AD brain- seeded Aß fibril. 3) Aß fibrils seeded from AD brain amyloid hav unique structures, which are providing startling new insights into AD pathogenesis. Remarkably (given the usual polymorphism of amyloid fibrils (4)), three different brain regions (from each of two individual patients) each yielded seeded fibrils with only one structure, i.e., identical in al three anatomic sites. But the fibrils from one patient were clearly of different structure from those of a second patient. As described in the proposal, our results raise a host of questions, including the possibility that during the development of AD, aggregated material might spread throughout the brain, seeding fibril formation in different regions. In the proposed studies, we wil examine replicate fibrils made by seeding with Alzheimer Disease (human and mouse model) brain amyloid. There are two specific aims: Aim 1) To study the structure of brain-seeded amyloid fibrils from patients with “”classical”” AD and clinically atypical forms of AD, including Cerebral Amyloid Angiopathy (CAA). (Further sub-aims are described in the proposal.) We will use brain amyloid from patients with AD and its variants to produce replicate Aß fibrils for study by solid-state NMR and other methods. Aim 2): A) To compare the structure of brain-seeded amyloid fibrils from AD patients to those from mice with five select models of cerebral amyloidosis/AD. These mice have cerebral amyloidosis, but have a range of neurological deficits. B) To compare human AD brain-seeded Aß40 fibrils to: human AD brain-seeded Aß42 fibrils, and Aß40 fibrils seeded by synthetic Aß42 fibrils. Through these studies, we will obtan critical information on the range of fibrils occurring in patients and mouse models of AD, and probe the possibility of a relationship between aggregate type and symptomatology, which will go beyond straightforward assessments of quantity of Aß deposits. These studies also have important implications for individualizing therapies and early diagnostic procedures (see 3).

Lay Summary

PUBLIC HEALTH RELEVANCE: ß-amyloid aggregates into polymorphic soluble oligomers and fibrils, but little is know how these various structures relate to disease pathogenesis. This proposal is based on the overarching hypothesis of a structure-malfunction relationship, i.e., between aggregate structure and pathogenicity. The specific aims will use solid-state NMR and other biophysical techniques to examine replicate fibrils made from seeding isotopically labeled ß-amyloid solutions with Alzheimer Disease (human and mouse model) amyloid.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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