Structural Markers for Alzheimers Disease and Cerebral Amyloid Angiopathy

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USA

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Structural Markers for Alzheimers Disease and Cerebral Amyloid Angiopathy

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NIH (NIA)

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11

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

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

Research Abstract

? DESCRIPTION (provided by applicant): There are two distinct processes involved in the deposition of amyloid in the brain during aging. Accumulation of the amyloid ?-protein (A?) in the brain parenchyma is the hallmark of Alzheimer's disease (AD), while accumulation of the A? protein in the cerebrovascular network is a condition known as cerebral amyloid angiopathy (CAA). There are familial mutations associated with both conditions. For AD, many of the mutations reside in the A? amyloid precursor protein and are responsible for the increased production of A?42 over the more prevalent A? 40 form of the peptide. For CAA, familial CAA disorders result from specific mutations in the A? peptides themselves, including the Dutch-type (E22Q) and Iowa-type (D23N) mutations. Despite the highly fibrillogenic nature of Dutch and Iowa mutant A? peptides, fibrillar A? is restricted to the cerebral vasculature in these familil disorders. Recent evidence suggests the parenchymal plaque amyloid is distinct from cerebral vascular amyloid. However, there is a poor understanding as to why either amyloid forms, and it is not known whether there are unique structural motifs that promote the distinct pathological consequences leading to dementia. The focus of this proposal is to fill this critical void in knowledge. Accordingly, the overall hypothesis of this proposal is that the A? peptides forming parenchymal and vascular amyloid have distinct structures that determine their location and pathology. To address this hypothesis we propose four specific aims. First, we plan to isolate parenchymal plaque amyloid and cerebral vascular amyloid from post mortem brain tissue of AD and familial CAA cases. Parallel studies will be undertaken on unique transgenic mouse models of AD and CAA. The studies on transgenic mice provide a direct method to assess the level of parenchymal and vascular amyloid, and the ability to engineer mutations. The isolated amyloid will serve as seeds to nucleate fibril growth for in vitro studies in Aim 2, which will reval the distinct structural signatures of cerebral vascular and parenchymal plaque amyloid deposits. Next, we will generate a collection (library) of homogeneous fibrils isolated from brain tissue. Fluorescence, infrared and NMR spectroscopy will be used to determine the structural features of these fibrils. Preliminary results show the A? peptides in parenchymal amyloid adopt ? – sheet structure with parallel, in-register ?-strands, whereas the ?-sheets in vascular amyloid have anti-parallel structure. Third, differences in cell toxicity and activation of different fibri (and oligomer) forms will be assessed using neuronal, vascular and microglial cell cultures. Preliminary results reveal profound differences of different A? fibrils on microglial activation. Fourth, we will assess the influence of A? inhibitors on different A? fibril structures. We wil first test the ability of known inhibitors to dissociate the different fibril structures isolated from brin tissue. Next, we will design dual-site inhibitors that combine elements of known inhibitors starting with designed, synthetic inhibitors that target the GxxxG sequences in the hydrophobic C-terminus of A? and inhibitors based on fragments of the myelin basic protein that interact with the N-terminus of A?.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyloid ?-protein assembly and deposition in the brain parenchyma and in brain blood vessels are key pathological features of Alzheimer's disease and related disorders. Different forms of the amyloid ?-protein can assemble into different structures. We propose to establish a library of different fibril structures that exist in amyloid deposits in the brain to be used for diagnostic and therapeutic purposes.

Further information available at:

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Investments > €500k

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United States of America

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