Understanding the Origins of Amyloid Deposition in Cerebral Amyloid Angiopathy

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Contact information of lead PI
Country

USA

Title of project or programme

Understanding the Origins of Amyloid Deposition in Cerebral Amyloid Angiopathy

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NIH (NIA)

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€ 1,630,733.94

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01/04/2016

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Cerebral Amyloid Angiopathy, Amyloid deposition, Familial Cerebral Amyloid Angiopathy, Amyloid, Vascular Cognitive Impairment

Research Abstract

? DESCRIPTION (provided by applicant): Cerebrovascular accumulation of the amyloid ß-

protein (Aß), a condition known as cerebral amyloid angiopathy (CAA), is an important driver of vascular cognitive impairment and dementia (VCID) and is a common comorbidity of patients with Alzheimer's disease (AD). CAA can promote VCID through a number of mechanisms including chronic inflammation, hypoperfusion and ischemia, loss of vessel wall integrity and hemorrhage. In addition to its prevalence in AD, several related familial CAA disorders result from specific mutations that reside within the Aß peptide sequence of the Aß precursor protein including the Dutch-type (E22Q) and Iowa-type (D23N) mutations. Despite the highly fibrillogenic nature of Dutch mutant and Iowa mutant Aß peptides, fibrillar Aß is restricted to te cerebral vasculature in these familial disorders. Recent evidence suggests the cerebral vascular amyloid is distinct from parenchymal plaque amyloid. However, there is a poor understanding as to why cerebral vascular amyloid forms and its unique structural features that promotes distinct pathological consequences leading to VCID. Thus, the focus of this proposal is to fill this critica void in knowledge. Accordingly, the overall hypothesis of this proposal is that fibrillar amyloid i cerebral blood vessels possesses distinct structural features compared to parenchymal fibrillar amyloid and unique anti-parallel structures, enhanced by CAA mutations, drives the cerebral vascular specific deposition of amyloid in brain. To address this hypothesis we propose three specific aims. First, we will determine the structure, assembly and membrane interactions of wild-type and the Dutch and Iowa CAA mutants of Aß in solution and model membrane systems that drive their compartmental deposition. Second, we will determine how familial CAA variants of Aß chronologically influence the structural features and assembly of wild-type Aß in the brains of transgenic mice. Third, we will isolate parenchymal plaque amyloid and cerebral vascular amyloid from post mortem brain tissue of AD cases, sporadic CAA cases and familial CAA cases and investigate their ability to promote assembly of wild-type and CAA mutant Aß peptides. These important studies will reveal the distinct structural signatures of cerebral vascular and parenchymal plaque amyloid deposits in human disease. Presently, there are no reliable biomarkers or effective therapies specifically for CAA and VCID. These deficiencies are complicated by our lack of understanding of the unique structural attributes of cerebral vascular amyloid and its early-stage oligomeric precursors, and their distinctive features and processes compared to parenchymal plaque amyloid. The present proposal will seek to fill this critical void in our knowledge and will advance our understanding of the pathogenesis of CAA and provide the basis for the future development of novel therapeutic interventions and diagnostic markers for CAA and VCID.

Lay Summary
PUBLIC HEALTH RELEVANCE: Eposition in brain blood vessels is the key pathological feature of cerebral amyloid angiopathy and associated vascular cognitive impairment & dementia. Different forms of Aß can assemble into different structures. The purpose of this proposal is to investigate if the different structures of Aß dictate whether the protein deposits n brain blood vessels rather than parenchymal plaques. Distinct Aß structures in the blood vessels may dictate their unique pathological consequences.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:

Alzheimer's disease & other dementias

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2016

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