Membrane interaction and disruption by the Alzheimers amyloid-beta peptide

https://neurodegenerationresearch.eu/survey/membrane-interaction-and-disruption-by-the-alzheimers-amyloid-beta-peptide/

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USA

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Membrane interaction and disruption by the Alzheimers amyloid-beta peptide

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01/08/2016

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1

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

Abstract Alzheimer’s disease (AD) is a neurodegenerative condition that currently affects more than 5 million Americans. AD is characterized by decreasing memory, loss of cognitive function and an eventual reduction in brain mass. The disease state can be linked to the cleavage of the amyloid precursor protein into smaller fragments – amyloidogenic peptides known as amyloid-? (A?). In fact, the formation of amyloid fibrils of the two most common alloforms of A?, A?1-40 and A?1-42, had previously been associated with disease pathology; however, mounting evidence points to misfolded intermediates being responsible for cell death in the Alzheimer’s brain. There are a number of theories as to how A? elicits toxicity including the generation of free radicals, interaction with metal ions, activation of cell surface receptors, and the disruption of cell membrane integrity. The interaction of A? with the cellular membrane is especially significant given the ability of lipid- A? interactions to accelerate fibril formation, facilitate the formation of ion channel-like pores, and cause the fragmentation of the lipid membrane. While understanding and characterizing the formation of misfolded intermediates of A? in solution is very important (and ongoing), the interaction of A? peptides with the membrane has remained elusive and controversial. A lack of data surrounding A?-membrane studies is largely due to the difficulties associated with carrying out biochemical and biophysical studies in the presence of lipids, although much insight has been gained by molecular dynamics simulations which have provided a strong basis for experimental studies. In order to determine the mode of membrane-associated toxicity, there remains a need to further characterize the interactions of A? with the lipid membrane, determine how these interactions drive membrane disruption, and define the structures formed in the presence of the membrane. Therefore, we propose to investigate the membrane interaction of A? through the following aims: 1) Characterization of A? misfolding and aggregation in the presence of lipid membranes; 2) Atomistic resolution structure determination of A? in a membrane environment by solid-state NMR spectroscopy. In addition to a variety of biophysical experiments, a combination of solution and solid-state NMR techniques and molecular dynamics simulations will be used to successfully accomplish the goals of the proposed study. High-resolution insights gained from the proposed studies will guide the development of drugs to stop the neuronal death. Although the proposed study is focused on A?, the outcome will be of importance to other amyloid-linked diseases such as Parkinson’s disease and Type II diabetes which have similar proteinopathies.

Lay Summary

Project Narrative: Neurodegenerative disorders such as Alzheimer’s disease (AD) place devastating financial and emotional burdens on patients, their families, communities, and societies worldwide. Studies have shown that aggregates of the amyloid-? (A?) protein are responsible for neuronal cell death in the Alzheimer’s brain. In order to develop drugs to treat AD, it is essential to fully understand how A? aggregates form and attack brain cells. The proposed study is aimed at developing a better understanding of this process through insights into the mechanism of interactions with cellular membranes and structural insights into the membrane-associated aggregates. Since the method by which A? attacks brain cells is similar to the way other amyloid proteins exert toxicity in diseases like Parkinson’s and Type II diabetes, this research may help in understanding these diseases as well.

Further information available at:

Types:

Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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