Probing the role of membrane and cholesterol on APP-C99 structure and dynamics

https://www.neurodegenerationresearch.eu/survey/probing-the-role-of-membrane-and-cholesterol-on-app-c99-structure-and-dynamics/

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Country

USA

Title of project or programme

Probing the role of membrane and cholesterol on APP-C99 structure and dynamics

Source of funding information

NIH (NIA)

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€ 1,100,687.16

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01/03/2015

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5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid beta-Protein Precursor, Cholesterol, dimer, monomer, Membrane

Research Abstract

? DESCRIPTION (provided by applicant): Aggregation of proteins of known sequence is linked to a variety of neurodegenerative disorders. Familial mutations in the Amyloid Precursor Protein

(APP), from which the amyloid ß (Aß) protein associated with Alzheimer’s Disease (AD) is derived, have been linked with the early onset of amyloid disease. In this computational and theoretical research proposal, augmented by synergistic experimental research collaborations, we will determine the structure and dynamics of the 99 amino acid transmembrane fragment of APP (APP-C99) in membrane environments in order to address fundamental biophysical questions articulated in three Specific Aims. (1) We will explore how length, sequence, and membrane composition influence the structure of the APP-C99 monomer. (2) The structures of APP-C99 dimers and the associated stability as well as the monomer-dimer equilibrium are also influenced by membrane composition and C99 sequence. We will investigate the influence of these environmental factors on the structure and dynamics of dimer formation. (3) We will also determine how APP-C99 interacts with cholesterol and cholesterol-analogs, as well as how those interactions influence APP-C99 structure and dimerization. The proposed coordinated studies will lead to a fundamental molecular-level understanding of the network of interactions of APP-C99 monomer and dimer, and cholesterol, which are recognized to be essential components of our understanding of APP-C99 processing, the Aß aggregation pathway, and potentially in the design of knowledge-based therapy for AD.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer’s Disease (AD) accounts for nearly 50% of all cases of senile dementia, is the third leading cause of death in the elderly population, and is presently incurable. The proposed computational studies and experimental collaborations will explore the structure and function of the C-terminal fragment of Amyloid Precursor Protein (APP-C99) to gain much-needed quantitative insight into its processing to form Aß protein, critical to AD. Our results will elucidate the role of familial AD mutations and environmental conditions, including cholesterol levels, in the processing of APP and the onset of AD, with the goal of informing the future development of preventive or early stage therapeutics.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
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