Amyloid ion channels to design therapeutics for neurodegenerative diseases

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Country

USA

Title of project or programme

Amyloid ion channels to design therapeutics for neurodegenerative diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,441,177.98

Start date of award

15/09/2006

Total duration of award in years

10

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... Prevention

Research Abstract

DESCRIPTION (provided by applicant): Abnormal (or mis-)folding alters protein's 3D conformation from native (soluble form) to non-native (insoluble from) polymorphic amyloid structures. Protein misfolding is linked to neurodegenerative (Alzheimer's, Huntington's, Parkinson's, familial dementia, prion encephalopathies), systemic (type II diabetes, light chain amyloidosis related cancer) and other (cystic fibrosis) diseases. Prevailing view suggests that protein misfolding-induced amyloids result into a gain-of-function and cause pathophysiologic cell response by destabilizing cell ionic homeostasis. Understanding protein misfolding and the resulting 3D conformations that induce pathophysiologic activity have been an important but challenging area of research. Mechanisms underlying amyloid fibril formation and its prevention are being studied extensively although amyloid fibers do not directly appear to cause neurodegenerative diseases; recent studies have shown that only globular amyloids are sufficient to cause pathophysiologic responses. The most direct mechanism of globular oligomer- mediated toxicity would involve their membrane poration as the key initial events. Our prevailing paradigm, therefore, is that protein misfolding diseases result from small globular amyloids forming ion channels to destabilize cell ionic homeostasis. Molecules and other interventions that modulate their channel structure and activity could thus be used for effective therapy. Indeed, amyloidogenic peptides induce ionic conductances in both native cell as well as artificial membranes. Structural study of membrane-bound amyloid complexes has been limited. Our studies have shown that amyloid peptides associated with several diseases form polymorphic ion channels. This continuing proposal primarily focuses on Alzheimer's disease (AD) linked amyloid beta (Ab) peptide that forms toxic channels. We intend to define the 3D structural polymorphism and identify amino acid (AA) epitopes in Ab peptide that can then be used as targets for designing effective therapeutics for AD. We will continue our multidimensional and complementary approaches of AFM imaging, ion conductance recording, molecular dynamics (MD) simulation, and cell Calcium uptake and degeneration to obtain a comprehensive understanding of amyloid ion channels. Our Specific Aims are 1) Image 3D structure of synthetic as well as tissue-derived amyloidogenic peptides and peptides with site-specific amino acid (AA) substitutions reconstituted in lipid membrane; 2) Image open-closed conformations, in response to pharmacologic agents, of channels made of peptides, normal as well as with site-specific amino acid (AA) substitutions, 3) Correlate open-close channel conformations with ion conductance using integrated ion conductance AFM and pharmacologic agents and site-specific AA substitutions, and 4) Examine the cellular effects (e.g., calcium uptake and degeneration) of amyloid peptides. Our study will define specific amyloid structures underlying Alzheimer's and other degenerative pathophysiology and will identify specific structural motif(s) in amyloid ion channels that can then be used for designing pharmacological intervention of therapeutic value.

Lay Summary

PUBLIC HEALTH RELEVANCE: Protein misfolding causes abnormal protein aggregates as amyloid plaques commonly associated with many devastating diseases, including Alzheimer's disease (AD). How these amyloids cause diseases is still unclear. Using complementary approaches of atomic force microscopy, electrophysiology, MD simulation and cell biology, our proposed work will identify the structural basis of AD pathology and define specific targets that can then be used for designing therapeutic and preventive strategies.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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