Orb2 a functional amyloid in long-term memory: Its structure and how it forms

https://neurodegenerationresearch.eu/survey/orb2-a-functional-amyloid-in-long-term-memory-its-structure-and-how-it-forms/

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Country

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Title of project or programme

Orb2 a functional amyloid in long-term memory: Its structure and how it forms

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,509,747.71

Start date of award

01/09/2015

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease and other dementias

Keywords

long term memory, Amyloid, solid state nuclear magnetic resonance, Amyloid Fibrils, Electron Spin Resonance Spectroscopy

Research Abstract
? DESCRIPTION (provided by applicant): The mechanisms that lead to toxicity in

neurodegenerative amyloid disease as well as the mechanisms that enable other amyloid fibrils to carry positive functions are some of the most important unsolved questions in amyloid biology. The long-term goal of our research is to understand what structurally distinguishes functional amyloids from disease causing amyloid and how amyloid fibril formation can act as a switch to control the native function of a protein. Towards this goal, we are working on Orb2 a functional amyloid that has been shown to be a key translation regulator important for long-term memory in Drosophila, but also has interesting similarities to huntingtin exon-1 (HDx1) important in Huntington's disease. The objective of this proposal is to determine a structural model of the Orb2 amyloid fibril and test the functional implications of this structure with mutations and functional assays. Our central hypothesis is that the N-terminus of Orb2A initiates amyloid core formation regulated by membrane interaction. The predominant isoform Orb2B, which has an N-terminus different from Orb2A, only forms fibrils when interacting with Orb2A. We will test this hypothesis in three specific aims: In aim 1 we will determine a structural model of the Orb2A amyloid fibril core. We will use cloning, solid-state NMR, and EPR experiments to identify the core of the Orb2A amyloid fibril and determine a structural model of this core using solid-state NMR and EPR spectroscopy. In aim 2 we will map Orb2B's amyloid core and interface with Orb2A. We will measure solid-state NMR and EPR experiments on Orb2B alone and mixed Orb2A and Orb2B aggregates that will map the Orb2A-Orb2B binding interface and characterize the structure of the amyloid fibril formed by the two Orb2 isoforms. In aim 3 we will determine the function of Orb2A-membrane interaction. We will test our hypothesis that membrane interaction is a regulator of amyloid formation and function by determining how Orb2A interacts with membranes of different lipid compositions and to which extend it forms amyloid under these conditions. We will also characterize the structure of the membrane bound form. All these structural studies will be accompanied by functional assays in which we test mutants derived from our structural findings as well as lipid compositions found in aim 3 for their ability to regulate Orb2 dependent protein translation. This contribution will be significant since it will bea major step towards understanding how amyloids can function as a molecular switch in translation regulation and will advance our knowledge of the structure and formation of glutamine-rich amyloids. The proposed research is innovative because we will combine solid-state NMR and EPR experiments to determine a structural model of an amyloid fibril. Furthermore, by choosing a functional amyloid that resembles the domain structure of HDx1 we will advance our understanding of what structurally distinguishes toxic from functional amyloids.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyloid fibrils are found in many neurodegenerative diseases but their mechanism of toxicity is currently not understood. Furthermore, an increasing number of non-toxic, functional amyloids have been described, including proteins that are important for neuronal growth and long-term memory. The proposed research is relevant to public health because knowing the structure of functional amyloids and understanding how their aggregation is regulated will also lead to a better understanding of toxic amyloids and might ultimately help find a cure for neurodegenerative amyloid diseases.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A