Mimicry of Amyloid Oligomers

https://neurodegenerationresearch.eu/survey/mimicry-of-amyloid-oligomers/

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Contact information of lead PI
Country

USA

Title of project or programme

Mimicry of Amyloid Oligomers

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,209,270.64

Start date of award

01/04/2011

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

mimicry, Amyloid, Amyloid beta-Protein, beta pleated sheet, abeta oligomer

Research Abstract

Project Summary/Abstract: Mimicry of Amyloid Oligomers Amyloid oligomers now thought to be the damaging molecular species in Alzheimer’s disease, Parkinson’s disease, and many other amyloid diseases. Understanding the structures of these oligomers is essential to understanding their mechanism of action, and quite possibly to developing drugs to prevent or treat these diseases. Studying the structures of the oligomers at high resolution is challenging, because the

oligomers are heterogeneous and dynamic, forming a variety of sizes and structures that can interconvert. The oligomers are metastable, with fibrils being the more thermodynamically stable species. Only a few studies have provided glimpses of amyloid oligomers at atomic resolution. Thus far, the there are no atomic-resolution structures of oligomers of the beta-amyloid peptide, Abeta, the 40 or 42 amino acid polypeptide closely associated with Alzheimer’s disease. This proposal aims to determine the structures of oligomers formed by Abeta by incorporating key fragments of Abeta into macrocyclic beta-sheet peptides designed to mimic the key beta-hairpin building blocks that are thought to make up Abeta oligomers. The PI has determined X-ray crystallographic structures at atomic resolution of trimers formed macrocyclic beta-sheet peptides containing fragments from the central and the C-terminal regions of Abeta. The trimers have a hitherto unprecedented structure consisting of a triangular arrangement of beta-hairpins that pack together at the three vertices. The trimers further assemble to form hexamers and dodecamers. This proposal aims to build on the discovery of these trimers and higher-order oligomeric assemblies. The broad overarching goal is to understand the relationship between the atomic-resolution structures of the oligomers and their biological and biophysical properties. To achieve these goals, the PI will synthesize macrocyclic beta-sheet peptides that incorporate different aspects of Abeta structure, determine the X-ray crystallographic structures of the oligomers that these peptides form, measure their cytotoxicity, elucidate their mechanisms of cytotoxcity, and correlate their cytotoxicity and their crystallographic structure by means of biophysical studies of their solution-phase properties.

Lay Summary
Project Narrative: Mimicry of Amyloid Oligomers Oligomers of peptides and proteins are involved in many devastating neurodegenerative disorders, including Alzheimer’s disease and the prion diseases. This proposal seeks to understand and control oligomer formation through the use of chemical model systems. The knowledge that is gained through these studies may eventually lead to new therapies for these 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