

NMR Structure of the A-beta Peptide Inside Living Cells

<https://neurodegenerationresearch.eu/survey/nmr-structure-of-the-a-beta-peptide-inside-living-cells/>

Principal Investigators

ZAGORSKI, MICHAEL GERARD

Institution

CASE WESTERN RESERVE UNIVERSITY

Contact information of lead PI

Country

USA

Title of project or programme

NMR Structure of the A-beta Peptide Inside Living Cells

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

379446.789

Start date of award

15/05/2016

Total duration of award in years

1

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

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is characterized by the abundance of intraneuronal neurofibrillary tangles and the extracellular deposition of the A β peptide (hereafter referred to as A β) into amyloid. In AD brains, the A β undergoes a conversion (monomer \rightarrow aggregate) and eventually precipitates as β -sheet like structures that have been

linked to neuronal death. The chemical mechanisms associated with these conversions remains largely unknown. Due to its high propensity to aggregate, the A β is extremely difficult to handle in the laboratory. Despite these difficulties, our research group was one of the first to perform solution NMR studies of the A β , which along with subsequent work from other labs established that the A β adopts a predominantly random, unfolded structure in aqueous solution at neutral pH. A major advantage of the NMR approach is that it can provide atomic level aspects of the structures and dynamics in solution that are not available with other low-resolution techniques. In this application, we will take the next important and novel step, and will use NMR to study the structural ensembles of the A β peptide inside living eukaryotic cells. This work will establish whether or not the A β structures in vitro are the same as those in living cells in vivo. This is extremely important, in that the A β is an "intrinsically disordered" protein, which is a major class of proteins that have a very flexible three-dimensional structure and are particularly sensitive to environmental perturbations, and that the complex, crowded environment of the cell could potentially alter the structure and function. We will perform two Specific Aims and attempt to determine the intracellular structure and dynamics in living cells using an array of NMR experiments. We will also explore the interactions between the A β and mitochondria. Furthermore, the classical view is that the A β is deposited extracellularly, although new data from transgenic mice and human patients demonstrates that the A β can likewise accumulate intraneuronally and contribute to AD progression, further emphasizing the importance of in-cell NMR studies.

Further information available at:

Types:

Investments < €500k

Member States:

United States of America

Diseases:

N/A

Years:

2016

Database Categories:

N/A

Database Tags:

N/A