NMR Based Studies of Alpha-Synuclein Aggregation and Inhibition

https://neurodegenerationresearch.eu/survey/nmr-based-studies-of-alpha-synuclein-aggregation-and-inhibition/

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Contact information of lead PI
Country

USA

Title of project or programme

NMR Based Studies of Alpha-Synuclein Aggregation and Inhibition

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,173,554.13

Start date of award

01/08/2015

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, synuclein, dimer, monomer, Homo

Research Abstract

? DESCRIPTION (provided by applicant): The mechanism of aggregation in neurodegenerative disease has been investigated by numerous laboratories and although the process is still elusive, significant progress has been made in defining different stages of the process. To fight

these debilitating illnesses it is not only critical to characterize aggregation processes but alsoto understand the mechanisms of aggregation inhibition. N-terminally acetylated a-synuclein (Ac-aS) is a small neuronal intrinsically disordered protein (IDP) that self-associates in pathological ways to oligomers and fibrils in the brains of patients with Parkinson’s disease. In contrast, a highly homologous IDP protein, acetylated ß- synuclein (Ac-ßS) that co-localizes with Ac-aS, does not self-associate into fibrils but can act as a neuro-protector of Ac-aS toxicity in vivo to inhibit pathological Ac-aS fibrillation. In light of the incredible importance of neurodegenerative diseases and their threat to global health in the ageing population, a detailed understanding of the molecular mechanism of inhibition is critical. At this stage very little known about these processes and about the specific inter-molecular interactions that guide inhibition versus aggregation. The goal of this proposal is to use NMR and other biophysical techniques, in conjunction with cell toxicity studies, to provide the first molecular description of the complexes that exist at the different stages of inhibition. In this grant we will: (1) characterize the influnce of different aS/ßS sequences, or structural units, on the potential to accelerate/inhibit fibril formation by the natural inhibitor ßS and its toxic mutants; (2) map interactive regions that define the earliest stages of inhibition; and (3) undertake the molecular characterization and toxicity studies of aS, ßS and hetero aS/ßS oligomers. The outcome of the proposed work will be to advance our fundamental understanding of the ‘structure-toxicity’ relationship of aS/ßS inhibition and to address more global questions about the location, nature and specificity of inhibitory interactions. These studies will provide a framework for identifying specific interactios that are important for disrupting toxic oligomers and for proposing novel targets for therapeutic intervention in Parkinson’s disease. The approaches developed here can be more widely applied to other cross amyloid interactions that have been shown to play a critical role in neurodegenerative disease, such as the interaction between aS and amyloid-ß-protein, or aS and tau.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease affects over 7-10 million people worldwide and has been closely linked to a-synuclein fibril formation. We use NMR and other biophysical approaches to understand, at the molecular level, the mechanism by which ß-synuclein can serve as a neuro-protector of a-synuclein and prevent its fibril formation. These studies will provide new insight into drug therapy approaches to inhibit the progression of this debilitating disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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N/A