

Molecular mechanisms of Abeta aggregation in Alzheimer Disease

<https://www.neurodegenerationresearch.eu/survey/molecular-mechanisms-of-abeta-aggregation-in-alzheimer-disease/>

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Title of project or programme

Molecular mechanisms of Abeta aggregation in Alzheimer Disease

Source of funding information

Swedish Research Council

Total sum awarded (Euro)

€ 228,509

Start date of award

01/01/2014

Total duration of award in years

3

Keywords

Research Abstract

We aim at a detailed understanding of the mechanism of aggregation of the Abeta peptide involved in Alzheimer's disease and neuronal cell death. We take an unbiased approach and set up a large number of kinetic experiments with variation of total peptide concentration. We use analytical solutions to the combined rate equations for sets of microscopic steps, and chose the minimal model that can fit all data. We challenge the found model by new experiments, the outcome of which has to agree with the prediction based on the fitted rate constants for the mechanism to be accepted. Such standard procedure to find a mechanism has not previously been used in the case of Abeta aggregation. By taking full control over peptide cloning,

production, purification, monomer isolation, inertness of all solutions and surfaces, we get unprecedented reproducibility in the kinetic data. Thus we can propose to not only solve the mechanism, but to find the molecular determinants of each step through systematic variation of intrinsic (sequence) and extrinsic (pH, salt, temperature, membranes, other proteins, crowding effects, body fluids) parameters. We also study which steps in the mechanism are retarded by known inhibitors. We study structure of rare intermediates and search for interactions with other proteins during the process. Full insight into the mechanism in terms of the underlying microscopic steps and their molecular driving forces will aid in rational design of inhibitors.

Further information available at:

Types:

Investments < €500k

Member States:

Sweden

Diseases:

N/A

Years:

2016

Database Categories:

N/A

Database Tags:

N/A