Fundamental membrane interactions of copper generated oligomers, profibrils and amyloid fibres

https://neurodegenerationresearch.eu/survey/fundamental-membrane-interactions-of-copper-generated-oligomers-profibrils-and-amyloid-fibres/

Principal Investigators

Dr J Viles

Institution

Queen Mary, University of London

Contact information of lead PI
Country

United Kingdom

Title of project or programme

Fundamental membrane interactions of copper generated oligomers, profibrils and amyloid fibres

Source of funding information

BBSRC

Total sum awarded (Euro)

€ 400,905

Start date of award

01/08/2015

Total duration of award in years

3

Keywords
Research Abstract

Background: There are a range of diseases including Mad-cow and Alzheimer's disease (AD) whose etiology involves proteins that self-associate into oligomers and amyloid fibers. It is this misassembly, of amyloid beta peptide (Ab), in the case of Alzheimer's disease, which causes a cascade of events culminating in cell-death and dementia. Ab is a small peptide 40 or 42 amino acids long. There is strong evidence that oligomers of Ab42, but not Ab40, are the most

cytotoxic. The mechanism by which the oligomers are toxic to cells is not clearly understood. One popular hypothesis involves oligomer and protofibre disruption of membrane integrity.

Interestingly metal ions alter Ab fibre formation. Animal models of AD implicate copper ion homeostasis in disease etiology. Furthermore Cu(II) is found bound to Ab within plaques. Cu(II) has a pico-molar affinity for Ab and is therefore capable of coordination Cu(II) at the synapse.

Aims: The broad aim of this proposal is to investigate the fundamental interaction of Ab oligomers, protofibres and fibres with lipid membranes. We will use metal ions, in particular Cu(II), which influence the distribution between these various forms, generating and stabilising the more cytotoxic oligomeric/protofibrillar form of Ab42.

Significance: Our preliminary observations suggest that differences in cytotoxicity between Ab40 and 42 may be due to the very different ways these two peptides misassemble in the presence of Cu(II) ions. The ability of Cu(II) to almost exclusively generate oligomers and protofibres of Ab42, rather than fibres, will facilitate studying this form of Ab42, which is otherwise quite transient in nature. The effect of Cu-Ab-oligomers on liposome models of the bi-layer will facilitate the first 3D structures of lipid membrane disruption by oligomers. Cellular studies of Cu-Ab-oligomer cytotoxicity will, for the first time, be related to measures of synaptic health in the presence of Cu-Ab42 oligomers.

Further information available at:

Types:
Investments < €500k

Member States:
United Kingdom

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A