Abeta-mediated toxicity in Alzheimer’s disease: delineating mechanisms of internalisation, cell-cell transmission and synaptic dysfunction

https://neurodegenerationresearch.eu/survey/abeta-mediated-toxicity-in-alzheimers-disease-delineating-mechanisms-of-internalisation-cell-cell-transmission-and-synaptic-dysfunction/

Principal Investigators

Professor L Serpell

Institution

University of Sussex

Contact information of lead PI
Country

United Kingdom

Title of project or programme

Abeta-mediated toxicity in Alzheimer's disease: delineating mechanisms of internalisation, cell-cell transmission and synaptic dysfunction

Source of funding information

MRC

Total sum awarded (Euro)

€ 553,022

Start date of award

11/11/2013

Total duration of award in years

3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Alzheimer’s disease is characterised by the abnormal association of Abeta (Ab) peptide to form oligomeric species, with catastrophic consequences for neuronal function and survival. However, clear understanding of the mechanisms by which Ab exerts toxicity remains elusive. Specifically, it is not known how Ab is transmitted around neural networks, how it internalises/accumulates in neurons, the nature of its cellular/molecular targets, or the mechanisms which underlie its disruption of critical neuronal synaptic processes. This proposal will exploit established and novel biochemical, imaging and ultrastructural approaches in cultured and native hippocampal neurons to examine these issues, providing fundamental new insights into the toxic mechanisms of Ab action. A key aim is to translate our recent findings from neuroblastoma cells, defining a pathway of Ab internalisation, into primary neurons. Ab will be tracked alongside cellular/organelle markers to examine endocytic processes and targeting to specific compartments, and followed by ultrastructural investigation. Ab transmission around neuronal networks will be assayed with genetically-encoded fusion constructs providing insight into the spreading of Ab pathology in Alzheimer’s patients. We will also examine Ab consequences on presynaptic function – specifically dynamic properties of vesicle pools. Our pilot data indicates striking Ab-induced effects on functional pool partitioning, lateral vesicle trafficking and vesicle endocytic efficiency. Alongside culture experiments we will use an established transgenic model to explore synapse-specific presynaptic deficits in acute slice. This approach also permits a function-ultrastructure readout of recycling vesicles in native tissue, offering unique insights into Ab-induced vesicle pool re-organisation. Our findings will shed new light on pivotal steps in the pathway of Ab action, providing important potential targets for the rational development of therapeutics.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A