Mechanisms of synapse damage in Alzheimer disease

https://www.neurodegenerationresearch.eu/survey/mechanisms-of-synapse-damage-in-alzheimer-disease/

Principal Investigators

Gunnar Gouras

Institution

Lund University

Contact information of lead PI
Country

Sweden

Title of project or programme

Mechanisms of synapse damage in Alzheimer disease

Source of funding information

Swedish Research Council

Total sum awarded (Euro)

€ 228,509

Start date of award

01/01/2016

Total duration of award in years

3

Keywords
Research Abstract
Dementia is an increasingly feared disorder of progressive cognitive decline with age. The most common cause of dementia, Alzheimer’s disease (AD), is the only major disease that is growing in incidence but has no effective therapy. Therefore, it is essential to better understand the underlying molecular mechanisms that cause dementias in order to develop effective treatments. Multiple lines of evidence indicate that a small peptide called ?-amyloid (A?), which is the main constituent of the abnormal amyloid plaques that characterize brain pathology in AD, play a pivotal role in the development of the disease. Increasing evidence has shown that aggregation prone A? begins to accumulate in synapses, the sites of nerve cell communication that are central to our ability to think and remember. A? is formed from the larger amyloid

precursor protein, APP. Despite being ubiquitously expressed and abundant in cells, the function of APP remains unclear, although among others, cell adhesion and growth factor functions have been reported. The complex regulation that controls extra- and intra-cellular A? peptide levels suggests that this peptide widely seen as only toxic in the disease may have a normal physiological function. There is a remarkably complexity in APP processing, degradation and feedback regulation. APP and its various metabolites also include the APP intracellular domain AICD, which has a role in nuclear signaling. For example AICD regulates the transcription of the protease that is best at degrading A?, neprilysin. Remarkably, with aging levels of neprilysin decline at specifically synapses. This promotes A? accumulation at synapses with age, which is most pronounced in AD. Current experimental treatment strategies focus on getting rid of A? and therefore, knowledge about its potential normal function could be critical. We plan to determine the potential normal role of A? at synapses, while continuing to focus on the mechanisms by which this peptide leads to synapse dysfunction. Prior work supports that A? acts via tau to cause damage of nerve cell processes, followed by degeneration of nerve cells. Of note, tau is the main component of the other hallmark brain lesion of AD, the neurofibrillary tangles, although mutations in tau are linked with familial forms of a distinct disease, frontotemporal dementia. The pathological steps between A? and tau remain unclear. The more upstream one can intervene therapeutically in this pathological cascade should be the most effective. We will use nerve cells in culture and mouse models of AD to dissect and therapeutically modulate molecular pathways causing A?-induced synapse dysfunction. Genetics of neurodegenerative diseases are pointing to the involvement also to components of the internalization and degradation pathway in cells, the endosome-lysosome system. Increasing evidence supports that impaired function of this major cellular degradation system leads to aberrant accumulation of aggregation prone peptides with aging. Given that A? normally localizes to a component of this pathway, the late endosome, wherein it accumulates in mouse models of AD, we are working to define and therapeutically modulate the biology of endosomes, which are also important in regulating the biology of synapses and interact closely with two interconnected degradation pathways, autophagy and the proteasome. Cellular degradation is regulated by the signaling pathway that is most implicated in the biology of aging, the extended insulin/PI3K/Akt/GSK3/mTOR/TFEB pathway. This central signaling pathway supports many central cellular functions such as cell growth and synaptic plasticity when active, while boosting endosome-lysosome mediated protein degradation when inhibited. How A? aggregation modulates and is modulated in endosomes by this central signaling pathway - particularly at synapses- needs to be better understood to therapeutically target the molecular mechanisms underlying AD and related diseases.

Further information available at:

Types:
Investments < €500k

Member States:
Sweden

Diseases:
N/A

Years:
2016

Database Categories:

N/A

Database Tags:
N/A