Synaptic mechanisms implicated in Alzheimer´s disease

https://www.neurodegenerationresearch.eu/survey/synaptic-mechanisms-implicated-in-alzheimers-disease/

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Sweden

Title of project or programme

Synaptic mechanisms implicated in Alzheimer´s disease

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Swedish Research Council

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€ 261,153

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01/01/2013

Total duration of award in years

4

Keywords
Research Abstract
This project aims to improve our understanding of the synaptic pathology in Alzheimer´s disease (AD) and to identify presynaptic drug targets through which the toxicity of amyloid precursor protein (APP) products can be relieved. To target synaptic APP processing we will take advantage of the recent discovery that the mode of synaptic vesicle recycling is controlled by Rab GTPase signaling. Synaptic vesicles can recycle via a single endocytic step, or via an endosomal pathway, the latter being linked to AD pathogenesis by the endosomal enrichment of APP and gamma-secretase. In Drosophila, synaptic vesicle recycling via the endosomal pathway is massively enhanced by mutation in a Rab GTPase activating protein (*inhibitor*, GAP), Skywalker. We aim to identify, in mammalian synapses, *enhancers*, i.e. GDP-GTP

exchange factors (GEFs) by taking advantage of automated high throughput technology. Second, induced pluripotent stem cell (iPSC) technology will be used to generate model neurons from AD patients. Identified GEFs will be knocked down in such patient-derived neurons to examine effects on APP processing, tau and synaptic survival. Rab GEFs of which functional suppression relieves synaptic pathology will be of key interest for small molecule screening. In view of the strong synaptic phenotype in AD, synapse-directed therapeutic strategies are likely to be beneficial and may give rise to less side-effects than currently tested pharmaceuticals.

Further information available at:

Types:
Investments < €500k

Member States:
Sweden

Diseases:
N/A

Years:
2016

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