

PreSSAD

Presymptomatic synaptic disorders in Alzheimer's disease

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Poster presenter: Chołoniewska Anna

Aims, research questions and working hypothesis

A growing body of evidence suggests that synaptic dysfunction and degradation are critical in both the onset and progression of Alzheimer's disease (AD). As synaptic loss is also considered to be a key predictor of cognitive decline in AD, detected before neuronal degeneration, the main objective of the preSSAD project was to investigate synaptic dysfunction in the context of human AD pathology and as an early presymptomatic diagnostic marker of the disease.

Our aim as a partner in the preSSAD project is to generate human induced pluripotent stem cell (iPSC)-derived neuronal (2D) and cerebral organoid (3D) AD models to study synaptic deficits. Specifically, we investigated which exocytic proteins, including the SNARE complex, may be disrupted in different types of AD. Our other specific aim was to functionally characterise neurons and organoids in terms of changes in calcium ion influx in response to stimulation and electrophysiological parameters.

Means/methods implemented by the consortium

The strategy of the project is to identify common features between presynaptic deficits in human Alzheimer's disease patients at a preclinical stage and those observed in various experimental models of Alzheimer's disease. A major originality of the proposal is in the use of innovative human biological models such as: 1) grafting human neurons with Cre-dependent null alleles for SNARE proteins in newborn mouse neocortex, 2) iPSC-derived cerebral organoids 3) viral-mediated gene targeting in organotypic cortical cultures obtained from human surgical resections.

What are the outcomes of the project?

1. A list of targets related to synaptic dysfunction was revealed by testing CSF samples from AD patients. The list included synaptic markers of degeneration and closely linked to exocytotic markers (SNARE complex and their interaction partners) or AMPA signalling.
2. iPSC-derived neurons were derived from Alzheimer's disease patients diagnosed with: familial AD (FAD) with mutations in PS1 or APP, presymptomatic carriers of PS1 mutation, MCI (mild cognitive impairment) and sporadic (SAD), as well as matched controls were tested for these targets
3. iPSC derived cortical organoids (up to nine months old) were obtained and subjected to analyses (to be accomplished soon).

Significance and impact of the work on the field

The results provide an important basis for further research in the search for pre-symptomatic and early indicators or causal factors of synaptic dysfunction in Alzheimer's disease. We have identified potential candidates: neuronal pentraxins and elements of SNARE - it remains to be seen whether these are symptoms or may underlie Alzheimer's disease.

Next steps and future challenges

We are currently preparing a mass spectrometry study of synaptosomes and RNA sequencing from cerebral organoids. The next step is to establish a genetic model of AMPA receptor and neuronal pentraxin dysfunction to isolate potential degenerative effects.