Synaptojanin 1, a key Down syndrome protein, is upregulated and is associated with Alzheimer lesions in Alzheimer disease brains

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Summary:

The scientists of the teams of Dr. Marie-Claude Potier (Institut du cerveau, at Paris, France) and Dr. Jean-Pierre Brion (Université Libre de Bruxelles, Belgium) have reported that lipid phosphatase Synaptojanin 1 (SYNJ1) is significantly upregulated in Alzheimer brains and is associated with Alzheimer key lesions such as Amyloid plaques, Neurofibrillary tangles and Hirano bodies [1].

Background:

Individuals with Down syndrome are more likely to develop Alzheimer's disease. Previous studies have suggested that SYNJ1, whose gene maps to chromosome 21, should be a key link between Down syndrome and Alzheimer's disease. SYNJ1 has been implicated in learning deficits in mouse model of Down syndrome [6] and in endosomal abnormalities in peripheral and neuronal cells of the individuals with Down syndrome [3-5].

Central issue:

Although SYNJ1 is a key mediator of amyloid-induced toxicity [2], its localisation and protein levels remained unknown. In this study, we aimed to elucidate the protein localization, the protein levels, the protein solubility and the mRNA levels of SYNJ1 in Alzheimer brains compared to non-demented control brains [1].

Main results:

SYNJ1 has a significant association with Alzheimer lesions in *post-mortem* brain tissues of Alzheimer patients and an individual with DS with Alzheimer lesions. SYNJ1 protein was detected around amyloid plaques and was partially colocalized with the synaptic marker Synaptophysin. SYNJ1 was detected in some Neurofibrillary tangles in association with hyperphosphorylated tau proteins. SYNJ1 was also accumulated with actin in Hirano bodies of Alzheimer brains. The *SYNJ1* mRNA was significantly upregulated in Alzheimer brains. SYNJ1 protein undergoes solubility change and was detected in the most insoluble fractions of Alzheimer brain lysates.

Implications for people with DS:

SYNJ1 could be a very important therapeutic target not only for Alzheimer's disease, but also for DS. Rescuing pathological alterations of SYNJ1 or finding pharmaceutical inhibitors of this lipid phosphatase may improve learning and cognitive abilities of DS individuals and of Alzheimer's disease patients.

Conclusions:

SYNJ1 undergoes upregulation, protein solubility change and becomes associated with Alzheimer brain lesions. Since SYNJ1 may be a key link between DS and AD, modulating SYNJ1 expression and/or activity could be one of the strategies to prevent DS individuals from developing Alzheimer disease.

Take home messages:

SYNJ1 is a link between Down syndrome and Alzheimer's disease
SYNJ1 mRNA is upregulated and SYNJ1 protein is associated with Alzheimer brain lesions.
Modulating SYNJ1 could be a therapeutic strategy not only for Alzheimer patients but also for individuals with Down syndrome.

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Links to articles to read further:
Lott IT, Head E (2019) Dementia in Down syndrome: unique insights for Alzheimer disease research. Nat Rev Neurol 15: 135-147