Learning to resist Alzheimer’s disease: Novel molecular mechanisms that protect neurons against amyloid-beta

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Learning to resist Alzheimer’s disease: Novel molecular mechanisms that protect neurons against amyloid-beta

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ZonMw

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The project/programme is most relevant to:

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Research Abstract

During the early stages of Alzheimer’s disease (AD) an excess of amyloid-beta (Abeta) impairs memory formation by corrupting synaptic function. However, not all people are equally affected

by the presence of Abeta in the brain. In particular an active, learning brain is capable of building a ‘cognitive reserve’ that protects against Abeta-mediated memory deficits. A biological explanation for this protective cognitive reserve is still lacking. We are taking a unique and original approach by studying the molecular mechanisms that occur in a learning brain to provide protection against the detrimental effects of Abeta. This program builds on two mechanisms that we recently discovered and that show that neurons can defend themselves against Abeta-induced synapse dysfunction and loss.

First, we will perform a detailed analysis of the changes in the molecular composition of the synapse that occur after Egr1-4 induction. These studies aim to elucidate the Egr-driven molecular signaling that protects synapses against Abeta.

Second, By using proteomics technologies, we aim to identify the AMPAR-associated factors that render synapses resistant or susceptible to Abeta.

This research program aims to fully decipher these key plasticity pathways, which are induced by learning behavior and are critically involved in protecting neurons against Abeta. We hypothesize that in an active, learning brain neurons become less susceptible to the detrimental effects of Abeta due to elevated expression levels of Egr1-4. We propose that this protection is achieved by an increase of GluA1-containing AMPARs in synapses. To test this hypothesis, we will apply advanced techniques in electrophysiology, live-imaging and proteomics of amyloidosis-based AD mouse-models. Importantly, our findings will be verified in human AD-brain samples and brain samples from people who, despite their old age, were not affected by dementia. The results of our studies will have important implications for the design of novel pharmacological, gene therapy-based, and behavioral therapeutic strategies that effectively protect against AD.

Lay Summary
Further information available at:

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Alzheimer's disease & other dementias

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