The effects of amyloid beta on synapses in the brain

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Country

Netherlands

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The effects of amyloid beta on synapses in the brain

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NWO

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5.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract
Alzheimer?s disease (AD) manifests itself by a decreased ability to store memories. A prime suspect to cause AD is a peptide fragment called amyloid beta (Abeta). Oligomeric clusters of Abeta perturb the connections through which neurons communicate (i.e. synapses). However, the mechanisms by which Abeta causes synaptic perturbations remain largely unknown. Neurons communicate through synapses by releasing glutamate at the pre-synaptic site, which

activates AMPA-type glutamate receptors (AMPARs) at the post-synaptic site. Different types of AMPARs exist, dependent on subunit composition. I found that neurons that lack AMPAR-subunit GluR3 are fully resistant to Ab-mediated synaptic depression. This finding offers the unique opportunity to assess which factors make synapses susceptible to Abeta. We use state-of-the-art electrophysiology and imaging techniques to analyze Abeta-induced synaptic deficits. The consequences of increased neuronal Abeta-production on memory formation and brain network activity are tested in mouse model systems.
The selectivity of Abeta for synapses that contain GluR3 has implications for both excitatory signaling and inhibitory signaling in the brain. Excitatory synapses are strengthened after learning new experiences by the synaptic insertion of AMPARs that contain subunit GluR1. Synapses that remain non-potentiated mostly contain subunit GluR3. I therefore hypothesize that learning new experiences increases the number of synapses that are Abeta-resistant. Our proposed experiments may provide a biological explanation for the observation that people who frequently engage in intellectual activities show a delayed onset of AD.
The group of inhibitory neurons that control network activity expresses high levels of GluR3. I hypothesize that Abeta selectively suppresses the synaptic input onto these inhibitory interneurons, leading to an increase in network activity. This study may provide a potential mechanistic explanation for the increased risk for seizure activity observed in AD-patients.

Lay Summary
Further information available at:

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