Extrasynaptic glutamate signalling and synapoptosis in brain development and degeneration

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Sweden

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Research Abstract

Elimination of synapses, or synapoptosis, is one of the most prominent features of brain development, but also of degenerative brain disorders. Yet, very little is known about the initiation, the regulation and the mechanisms underlying synapoptosis. In this research program we propose the hypothesis that the combined activation of synaptic AMPA receptors and extrasynaptic NMDA receptors is the initiating step for synapoptosis of glutamate synapses. We further suggest that the loss of synaptic receptors renders the synapses susceptible for physical

elimination by microglia via activation of the complement system. The proposed research aims to test this hypothesis by using a combination of electrophysiology and two-photon microscopy in living brain tissue. To test specific aspects of the hypothesis we will use transgenic animals, pharmacology, immunohistochemistry and cerebrospinal fluid from patients suffering from neurodegenerative disorders. Synapoptosis is clearly a double-edged sword, decisive for proper development of the brain, but also detrimental in neurodegenerative diseases. To develop new strategies for treating neurodevelopmental and neurodegenerative disorders we need to diminish the large gap in our understanding of the basic mechanisms of synapoptosis. We take here a comparative approach to study developmental and degenerative synapoptosis in parallel, with the aim to diminish this gap.

Further information available at:

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