DEVELOPMENTAL PLASTICITY OF THE GLUTAMATE SYNAPSE: ROLES OF LOW FREQUENCY STIMULATION, HEBBIAN INDUCTION AND THE NMDA RECEPTOR

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal 2119, Hus 2, Hälsovetarbacken Göteborg, fredagen den 12 februari 2010 kl 09.00

av
Joakim Strandberg

Fakultetsopponent:
Professor Martin Garwicz
Institutionen för experimentell medicinsk vetenskap
Lunds universitet

Avhandlingen baseras på följande delarbeten:

I. Strandberg J., Wasling P. and Gustafsson B.
Modulation of low frequency induced synaptic depression in the developing CA3-CA1 hippocampal synapses by NMDA and metabotropic glutamate receptor activation.
Journal of Neurophysiology (2009) 101:2252-2262

II. Strandberg J. and Gustafsson B.
Lasting activity-induced depression of previously non-stimulated CA3-CA1 synapses in the developing hippocampus; critical and complex role of NMDA receptors.
In manuscript

III. Strandberg J. and Gustafsson B.
Hebbian activity does not stabilize synaptic transmission at CA3-CA1 synapses in the developing hippocampus.
In manuscript

Göteborg 2010

UNIVERSITY OF GOTHENBURG

DEVELOPMENTAL PLASTICITY OF THE GLUTAMATE SYNAPSE: ROLES OF LOW FREQUENCY STIMULATION, HEBBIAN INDUCTION AND THE NMDA RECEPTOR

Joakim Strandberg
Department of Physiology, Institute of Neuroscience and Physiology, Univeristy of Gothenburg, Sweden, 2010

Abstract
The glutamate synapse is by far the most common synapse in the brain and acts via postsynaptic AMPA, NMDA and mGlu receptors. During brain development there is a continuous production of these synapses where those partaking in activity resulting in neuronal activity are subsequently selected to establish an appropriate functional pattern of synaptic connectivity while those that do not are elimimated. Activity dependent synaptic plasticities, such as Hebbian induced long-term potentiation (LTP) and low frequency (1 Hz) induced long-term depression (LTD) have been considered to be of critical importance for this selection. However, in the neonatal brain the glutamate synapse displays a seemingly distinct plasticity in that even very low frequency stimulation (0.05-0.2 Hz) results in depression of the AMPA receptor mediated signaling and hence to possible synaptic elimination. The aim of this thesis was to investigate the relationship and interaction between this very low frequency induced plasticity and the more conventional forms of synaptic plasticity, such as mGlu receptor dependent LTD and NMDA receptor dependent LTP and LTD, using the neonatal rat hippocampal CA3-CA1 synapse as a model synapse.

This thesis shows that very low frequency induced depression is related to NMDA receptor dependent LTD. While elicited even during NMDA receptor blockade, this plasticity is facilitated and stabilized by NMDA receptor activity and largely occludes NMDA receptor dependent LTD. Surprisingly, considering their role in conventionally induced LTD, mGlu receptors were not found to participate in either the very low frequency induced depression or in low frequency induced long-lasting depression. A preceding LTP-inducing Hebbian stimulation was found to only partially stabilize against the very low frequency induced depression, and possibly also only in a temporary manner.

In conclusion; during brain development glutamate activated AMPA receptors are very easily lost upon activation rendering these synapses AMPA silent, and Hebbian activity will only temporarily rescue them from AMPA silence. Thus, synapses in the developing brain will maintain their AMPA signaling only by more or less continuous participation in cooperative neuronal activity, synaptic activity outside this context leading to AMPA silencing and possible elimination.

Keywords: AMPA receptor, development, glutamate, hippocampus, long-term depression, long-term potentiation, NMDA receptor, synaptic depression

ISBN: 978-91-628-7882-5