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Activity Pattern-Dependent LTP in the Hippocampus and Neocortex of Wild-Type and GluR-A Subunit Deficient Mice

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The AMPA receptor subunit GluR-A is a major target for biochemical signaling cascades that initiate expression of long term potentiation. The protein structure of the GluR-A receptor thereby provides multiple domains for protein-protein interactions and phosphorylation sites, which can modify AMPA receptor kinetics and connect the receptor to activity dependent AMPA receptor trafficking pathways. However the role of GluR-A dependent signalling during expression of long term potentiation is not exclusive. Electrophysiological analysis of GluR-$A^{-/-}$ mice showed, that GluR-A independent forms of long term potentiation in the hippocampus remained intact in the absence of GluR-A. Behavioural testing of GluR-$A^{-/-}$ mice revealed furthermore, that a deficit in GluR-A does not result in a global hippocampal spatial memory deficit, but rather in a focal deficit in hippocampal spatial working memory.
The aim of this thesis was first to characterize associative pairing induction requirements for GluR-A dependent and independent long term potentiation in the hippocampus. A second aim of this thesis was to test for GluR-A dependent and independent long term potentiation expression mechanisms in the somatosensory cortex. Finally it was the aim of this study to investigate whether GluR-A dependent AMPA receptor trafficking also applies to the present findings as mechanism for the expression of long term potentiation.
Whole-cell patch clamp recordings were performed in CA1 pyramids and in layer 2/3 pyramids of the somatosensory cortex. CA3 to CA1 synapses and layer 2/3 to layer 2/3 connections were stimulated with extracellular field stimulation. Three different associative pairing paradigms were used for the induction long term potentiation. These protocols were in descending order of postsynaptic depolarization intensity: postsynaptic depolarization pairing, theta burst pairing and spike timing dependent pairing.
Results presented here indicate that at CA3 to CA1 synapses postsynaptic depolarization pairing triggers a completely GluR-A dependent form of long term potentiation, whereas theta burst pairing initiated both GluR-A dependent and GluR-A independent long term potentiation at the same synapse. A spike timing dependent pairing protocol when applied to the CA3 to CA1 synapse elicited a completely GluR-A independent form of LTP. These results show that biochemical expression and induction mechanisms of GluR-A dependent versus GluR-A independent long term potentiation are independent.
In a second set of experiments presented here it is shown, that theta burst pairing and spike timing dependent pairing triggers only GluR-A independent long term potentiation in layer 2/3 pyramids of the somatosensory cortex, as opposed to coincident induction of GluR-A dependent and independent long term potentiation with theta burst pairing in CA1 pyramids. These results show that low expression levels of GluR-A correlate well with a predominantly GluR-A independent mechanism for the expression of long term potentiation.
All forms of long term potentiation tested here across brain regions, required postsynaptic NMDA receptor activation and Calcium influx. Furthermore GluR-A dependent postsynaptic

depolarization induced long term potentiation was blocked by postsynaptic application of an exocytosis inhibitor as well as GluR-A dependent pairing induced long term potentiation, which suggests that both GluR-A dependent and independent long term potentiation require insertion of postsynaptic AMPA receptors.

It is concluded that two biochemical pathways for GluR-A dependent and independent long term potentiation co-exist independent from each other. Specific associative pairing conditions exist that can trigger either one or the other pathway or both at the same time. GluR-A dependent spatial working memory and GluR-A independent spatial reference memory functions can therefore be theoretically separated temporally during behavioural testing, because they rely on independent biochemical mechanisms. Furthermore it is concluded that GluR-A dependent long term potentiation is not required for the induction of long term potentiation in the somatosensory cortex. The contribution of GluR-A subunits to the expression of LTP is therefore probably dependent on the abundance of GluR-A subunits in a particular brain region.