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Das Thema der Dissertation lautet: „ Jacob – an activity-regulated morphogenetic factor for synapto-dendritic cytoarchitecture“

Summary

N-methyl-D-aspartate (NMDA) receptor-mediated calcium signaling plays an essential role in many processes in neurons such as nuclear gene transcription and synaptic plasticity. Calcium-dependent signaling from the synapses to the nucleus can result in long-lasting changes of synaptic input and dendritic cytoarchitecture. Moreover, the site of calcium entry can determine the biological outcome of the signal and therefore calcium channel-associated signaling complexes might have a key role in mediating the selective activation on gene transcription programs in response to calcium influx.
The neuronal calcium-sensor protein Caldendrin is highly enriched in dendrites including dendritic spines and tightly associated with the postsynaptic density (PSD). At elevated calcium levels Caldendrin binds to Jacob – a newly identified brain-specific protein. Jacob displays a distribution similar to that of Caldendrin in the PSD and dendritic spines but, in contrast to Caldendrin, is also found in neuronal nuclei. Jacob harbors a bipartite nuclear localization signal (NLS) in its central α-helical region and translocates to the nucleus in response to NMDA receptor activation. Immunofluorescence studies in primary hippocampal neurons demonstrate that the presence of the NLS sequence is essential for Jacob’s nuclear transport. Moreover, after enhanced synaptic activation Caldendrin binds Jacob and masks Jacob’s NLS, and thereby interferes with Jacob’s nuclear recruitment. Furthermore, nuclear accumulation of Jacob is mainly initiated by calcium flux through extrasynaptic NMDA receptors, triggers the Ca2+/cAMP-responsive element binding protein (CREB) shut-off pathway and in consequence, negatively regulates CREB target gene expression, which results in cell death. Nuclear knockdown of Jacob prevents CREB shut-off after extrasynaptic NMDA receptor activation. Moreover, overexpression experiments show that nuclear accumulation of Jacob has a drastic negative effect on synapto-dendritic architecture, whereas overexpression of extranuclear Jacob leads to an increased number of dendrites and the formation of PSD-like structures that eventually promote formation of dendritic protrusions with multiple active synaptic contacts. It could be proposed that Jacob in the nucleus either blocks an essential nuclear signaling pathway required to prevent the removal of synaptic input or regulates the expression of genes that will destabilize synapses. On the other hand, overexpression of extranuclear Jacob triggers the formation of huge PSD-like structures in neurons suggesting that the presence of Jacob in synapses could be a stabilizing factor for the synaptic PSD and prevents spine dismantling. Altogether these data suggest that Jacob can be recruited via Caldendrin binding only in the extensively activated synapse and this recruitment leads to stabilization of the existing PSD or recruitment of new PSD-proteins and therefore strengthening of the synapse, whereas less activated synapses could not recruit Jacob and will be removed by a mechanism that involves the nuclear accumulation of Jacob. These findings are discussed in the context of homeostatic plasticity mechanisms that must exist to keep the system functional throughout live.