Summary: Molecular dynamics of the neuronal Ca^{2+} -binding proteins Caldendrin and Calneurons

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The calcium sensor protein Caldendrin is an EF-hand protein with a high homology of Calmodulin (CaM). Calneurons are two novel calcium binding proteins that apart from CaM represent the closest homologues of Caldendrin in brain. Caldendrin and Calneuron-1 and -2 are abundantly expressed in neurons and retinal cells. Caldendrin is highly abundant in the postsynaptic density (PSD) of a subset of excitatory synapses in brain whereas the cellular localization of Calneurons is more resticted to the Golgi complex.

Previously it was shown that Caldendrin is a binding partner of Jacob. Strictly depending upon activation of N-methyl-D-aspartat-type glutamate receptors (NMDARs) Jacob is recruited to neuronal nuclei, resulting in a rapid stripping of synaptic contacts and in a drastically altered morphology of the dendritic tree. The nuclear trafficking of Jacob from distal dendrites crucially requires the classical Importin pathway. In this thesis it was shown that Caldendrin controls the extra-nuclear localization of Jacob by calcium (Ca^{2+})-dependently competing with the binding of Importin-α to the nuclear localization signal (NLS) of Jacob. The NLS of Jacob partially overlaps with an incomplete IQ-motif – an interaction domain for Caldendrin. Interaction of Caldendrin with Jacob is specific and cannot be substituted by CaM. The Caldendrin-Jacob interaction requires sustained synapto-dendritic Ca^{2+}-levels, which presumably cannot be achieved by activation of extrasynaptic NMDARs, but are confined to Ca^{2+}-microdomains such as postsynaptic spines. Extrasynaptic NMDARs as opposed to their synaptic counterparts trigger the CREB shut-off pathway and cell death. We found that nuclear knock down of Jacob prevents CREB shut-off after extrasynaptic NMDARs activation while its nuclear overexpression induces CREB shut-off without NMDAR stimulation. This defines a novel mechanism of synapse-to-nucleus communication via a synaptic Ca^{2+}-sensor protein, which links the activity of NMDARs to nuclear signaling events involved in modelling synapto-dendritic input and NMDAR induced cellular degeneration.

In the second part of the thesis the characterization of a new subfamily of neuronal calcium sensor (NCS) proteins – the Calneurons was provided. By virtue of their biophysical properterties Calneurons are high affinity Ca^{2+} sensors that exhibit a relatively narrow dynamic range of Ca^{2+}-binding with respect to the resting Ca^{2+}-levels in neurons. In this study we show that Calneuron-1 and -2 physically associate with Phosphatidylinositol 4-OH kinase IIIß (PI-4Kβ), an enzyme involved in the regulated local synthesis of phospholipids that are crucial for trans-Golgi network to plasma membrane trafficking. This interaction causes the inhibition of the enzyme at resting and low Ca^{2+} levels, and negatively interfere with Golgi-to-plasma membrane trafficking. At high Ca^{2+} levels this inhibition is released via a preferential association of PI-4Kβ with NCS-1 that competes for the binding site with Calneurons. The opposing roles of Calneurons and NCS-1 provide a molecular switch to decode local Ca^{2+} transients at the Golgi and impose a Ca^{2+} threshold for PI-4Kβ activity and vesicle trafficking.