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Summary

The function of Neurobeachin in the central nervous system

The smell of freshly mown grass, the memory of a sweet melody, the pain of a rotting tooth - these are all experiences made possible by about 1.4 kg of tissue in our heads, i.e. the brain. The latter is composed of a multitude of nerve cells (neurons), which communicate with each other through specialized connections called synapses. At synapses chemicals (neurotransmitters) are released from one neuron and move to the next neuron, where they get accepted at specialized sites called receptors. This process is highly regulated and can be disturbed by a variety of abnormalities, e.g. deficiencies in neurotransmitter release, receptor functioning, decrease in receptor numbers at the postsynaptic site etc.

Neurotransmitter receptors travel through various cellular compartments (organelles) before they are delivered to the cell surface, where they are inserted into the plasma membrane. After receptors get synthesized in the endoplasmic reticulum, they proceed through the Golgi apparatus, where they undergo extensive modification. In the trans-Golgi network, which is a unique compartment located at the exit face of the Golgi, they are sorted and packaged into membrane carriers, which are then sent to distinct domains of the plasma membrane.

The main topic of this thesis is a protein called Neurobeachin (Nbea) that regulates the delivery of receptors to the postsynaptic site. It is a very large (327 kDa) protein, which is abundant in the brain and has been shown to bind a specific enzyme (protein kinase A, PKA) that plays an important role in cell signaling pathways. Mice that lack Nbea die shortly after birth, because they cannot initiate respiration. Electrophysiological examination revealed a complete absence of evoked neurotransmitter release at the site where neurons connect to muscle fibers, while spontaneous release was intact.

This thesis tries to elucidate the function of Nbea in neurons in the central ner-

vous system. Nbea is found throughout the somatic cytoplasm and dendrites. In the soma it concentrates near the ERGIC (intermediate compartment between the ER and the Golgi) and the Golgi complex and shows highest colocalization with a protein called Vti1A that has also been associated with the Golgi complex. Nbeas localization suggests an involvement in neuronal post-Golgi membrane traffic, where it might function in recruiting protein kinase A to discrete intracellular locations.

In line with this, we show that neurons lacking Nbea have less neurotransmitter receptors expressed at the cell surface, which leads to strongly reduced synaptic responses. While the receptors do not reach the synapse (some of them accumulate early in the secretory pathway), surface expression of other membrane proteins, synapse formation, and presynaptic function are unaffected.

So far, only few binding partners of Nbea have been found and the precise mechanism of their trafficking remains unclear. We use mass spectrometry to identify SAP102, a protein implicated in trafficking of the ionotropic glutamate AMPA- and NMDA-type receptors during synaptogenesis, as a novel Nbea interacting protein in mouse brain. Experiments in heterologous cells confirm this interaction and reveal that SAP102 binds to the C-terminal part of Nbea that contains the DUF, PH, BEACH and WD40 domains. Introducing a mutation in Nbeas PH domain, which disrupts its interaction with the BEACH domain, abolishes this binding, thereby creating an excellent starting point to further investigate Nbea-SAP102 function in the CNS.

Taken together, it seems likely that Nbea plays a dual role in the secretory pathway. Its earliest action is at the level of the ER exit, where it seems to be involved in a quality control mechanism ensuring that only properly assembled multimeric protein complexes leave the ER. Additional experiments are needed to determine whether Nbeas binding to SAP102 is important for this action. In addition, our results suggest that Nbea also functions later in the secretory pathway, i.e. in the transport of receptors from the Golgi to the plasma membrane. However, the site of action and the precise mechanism remain to be determined.