Mobility and Turnover of Presynaptic Calcium Channels

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Synaptic plasticity is one major variable to modulate information processing in neuronal networks. Fast changes in synaptic function are due to changes in the composition and function of pre- and postsynaptic components, which can be influenced by ongoing neuronal activity. At the presynaptic compartment the opening of voltage gated calcium channels (VGCC) is essential for neurotransmitter release, which depend on molecular composition, number and position of individual calcium channels.

Using single molecule tracking approach of endogenous $Ca_V2.1$ channels revealed that $Ca_V2.1$ channels are highly mobile within the presynaptic membrane and visit transient individual release sites within the presynaptic membrane. This suggests that the reliability of synapses is not only dependent on the number of releasable vesicles but also on the availability of VGCC. Optogenetic immobilisation of $Ca_V2.1$ altered the reliability of synapses and reduced the response to frequent stimulation >10 Hz. These experiments indicate that mobile channels increase the frequency range of a synapse and participate in short term plasticity.

Mechanisms that immobilise or confine VGCC in the synapse are mainly dependent on interactions with scaffold proteins on the presynaptic membrane. Identified protein-protein interactions are manyfold and often of low affinity. Despite scaffold proteins as Bassoon have been shown to indirectly stabilize $Ca_V2.1$-channels in synapses, the mechanism behind remains enigmatic. Manipulating the phosphorylation state of Bassoon lead to a huge decrease of synaptic release probability and alters channel dynamics and local density. These experiments support the idea that coupling of VGCC and synaptic vesicles is a very dynamic process and activity dependent variable to finetune channel position and number within the synapse in parallel to docking and priming of releasable vesicles. The immobilisation of calcium channel induced reduction in reliability of the synapse let argue that at high release frequencies channel mobility facilitate the usage of multiple release sides within the presynaptic membrane. Our study suggests that not only changes in the kinetic properties of VGCC but tuning the dynamics within the presynaptic membrane provide a fast mechanisms to regulate the release probability of synapses.