Quantitative localization and function of Kir3 and $Ca_v2.1$ channels in hippocampal neurons

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The balance between the excitatory and inhibitory synaptic inputs is essential for the normal functioning of the central nervous system. This requires well-regulated detection and release of transmitters as well as appropriate distribution of proteins involved in these processes, such as ion channels and neurotransmitter receptors on somato-dendritic and axonal membranes of the neurons. On the postsynaptic dendritic compartment, the hyperpolarizing G-protein-coupled inwardly rectifying potassium (Kir3) channels, by mediating the effects of various metabotropic receptors including $GABA_B$ receptors ($GABA_BRs$), play a crucial role in the control of neuronal excitation. Presynaptically, the high voltage-activated $Ca_v2.1$ calcium channels, which conduct P/Q-type current, play role in coupling presynaptic action potential to transmitter release and thereby have a major influence on the efficacy of neurotransmission at central synapses. The impact of the activation of proteins on synaptic integration and regulation of transmitter release depends on their distribution relative to synaptic sites and their functional interaction on subcellular compartments of the neurons. Using high-resolution immunoelectron microscopy in combination with quantification of protein densities we, therefore, investigated (i) the distribution and spatial relationship of Kir3 channels and $GABA_BRs$ on postsynaptic dendrites and (ii) the subcellular organization of the $Ca_v2.1$ calcium channels in presynaptic axon terminals of hippocampal neurons. (i) Postsynaptically, we found a high degree of coclustering of Kir3 channels and $GABA_BRs$ around excitatory synapses on dendritic spines of principal cells. These protein complexes counteract excitatory postsynaptic responses by hyperpolarization and by shunting the excitatory synaptic currents as well as they can act as a break on NMDA receptor responses. (ii) Presynaptically, we demonstrated the enrichment and clustered distribution of $Ca_v2.1$ channels in axon terminals of inhibitory and excitatory neurons providing evidence that GABAergic and glutamatergic synapses share a common nanoarchitecture of $Ca_v2.1$ and make extensive use of tight coupling between calcium channels and calcium sensors for fast transmitter release. These qualitative and quantitative data provide insight into the signaling mechanisms mediated by potassium and calcium channels in post- and presynaptic compartments of principal cells and GABAeric interneurons in the hippocampal circuits.