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Meeting abstract

RIM modulates $Ca_V1.3$ Ca^{2+} channels

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Calcium channel β subunits (Ca_Vβs) are essential cytoplasmic components of voltage-gated calcium channels (VGCCs) affecting their gating and targeting. Ca_Vβs bind with high affinity to the cytoplasmic loop between transmembrane segments I and II of the α1 subunit (loop-I-II). To identify new proteins that modulate VGCCs by interaction with Ca_Vβs we performed a yeast two-hybrid screen using Ca_Vβ2a as bait. Screening of a human fetal brain cDNA library identified a C-terminal fragment of RIM1α (Rab3-interacting molecule) which contains a highly conserved C2B domain as potential interaction partner. To proof the interaction between RIM and Ca_Vβs we developed a protein targeting assay in tsA-201 cells heterologously expressing the loop-I-II of $Ca_V1.3$ channels with diverse Ca_Vβ subunits. The $Ca_V1.3$-loop-I-II was transported to the plasma membrane and co-targeted all Ca_Vβ subunits indicating that the $Ca_V1.3$-loop-I-II and the Ca_Vβ subunits formed a functional complex. The C-terminal fragment of RIM1α or the full-length form of RIM2β exhibited a cytoplasmic distribution but when co-expressed with Ca_Vβs in presence of the $Ca_V1.3$-loop-I-II both were co-localized at the plasma membrane. Using qualitative RT-PCR analysis we detected various RIM isoforms in the total organ of Corti and RIM2α in cochlea inner hair cells (IHCs) at an early developmental stage, before the onset of hearing. As RIM is a presynaptic active zone protein involved in Ca^{2+}-induced neurotransmitter release, we asked the question whether the association of RIM with $Ca_V1.3$ could account for the slow $Ca_V1.3$ current inactivation seen in IHCs. In whole-cell patch-clamp analysis of tsA-201 cells using 15 mM Ca^{2+} as charge carrier the C2B domain containing fragments of RIM1α and RIM2α caused a significant depolarizing shift of the activation-curve of $Ca_V1.3$ (7–12 mV) and slowed the inactivation of both Ca^{2+} and Ba^{2+} currents ($p < 0.05$) albeit to a lesser extent as found in native IHCs. To investigate if a slowly inactivating $Ca_V1.3$ spliceform (1b) could contribute to this effect we examined its expression with RT-PCR analysis. However, we did not detect $Ca_V1.3$(1b) transcripts in the total organ of Corti at the same developmental stage as we found RIM. Taken together these data showed that indeed RIM modulated $Ca_V1.3$ Ca^{2+} channels. However, we assume that a mixture of diverse proteins and/or $Ca_V1.3$ splice variants probably accounts for the slow current inactivation of these channels in native IHCs.

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