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Modulation of neuronal membrane expression of C-terminal splice-variants of the human L-type calcium channel CaV1.3 by PDZ-domain scaffold proteins

L-type Cav1.3 Ca^{2+} channels critically contribute to neuronal excitability, pacemaking, the formation of dendritic spines and have been implicated in the etiology of Parkinson's disease. Alternative splicing gives rise to a long ($Cav1.3_L$) and two short ($Cav1.3_{42A}$, $Cav1.3_{43S}$) C-terminal variants, which differ in their voltage-dependence of activation and Ca^{2+} conductance.

Neuronal membrane expression of the short splice variants $Cav1.3_{42A}$ and $Cav1.3_{43S}$ was significantly reduced when compared to $Cav1.3_L$. Coexpression of the auxiliary β_{4b} subunit resulted in remarkable increased surface expression of the full length $Cav1.3_L$ and only slight increase in expression of $Cav1.3_{42A}$ and $Cav1.343_S$.

The long variant $Cav1.3_L$ contains a C-terminal PDZ ligand (ITTL). Consistent with a role of PDZ-domain proteins, deletion of the ITTL motif reduced $Cav1.3_L$ surface expression to the levels of the short splice variants.

Our data indicates an decreased membrane expression of $Cav1.3_L$ upon coexpression with densin-180 or erbin. This effect is strongly redused in short splice variants ant ITTL mutant.

Together our results demonstrate the importance of C-terminal splicing for membrane expression.