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Meeting abstract

C-terminal splicing reveals intramolecular gating modulation in $Ca_V1.3$ L-type Ca^{2+} channels

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Neuronal excitability and pace-making in the sinoatrial node are controlled by low-voltage activated $Ca_V1.3$ L-type Ca^{2+} channels. We recently found that in related $Ca_V1.4$ channels a highly-structured distal C-terminal motif (CTM) modulates voltage- and Ca^{2+}-dependent gating (CDI). In $Ca_V1.3$, C-terminal splicing leads to a full-length ($Ca_V1.3L$) and at least 1 short ($Ca_V1.3S$) splice form. If a CTM would also modulate $Ca_V1.3$ gating it would be present in $Ca_V1.3L$ but not $Ca_V1.3S$ variants. We therefore compared the biophysical properties of $Ca_V1.3L$ or $Ca_V1.3S$ coexpressed with β3 + α2δ-1 in tsA-201 cells using the whole-cell patch-clamp technique. $Ca_V1.3S$ channels activated at more negative potentials compared to $Ca_V1.3L$ (~ -10 mV, $p < 0.0001$), inactivated faster ($p < 0.01$) and showed more CDI ($p < 0.01$). These changes resulted in a decreased window current shifted to more hyperpolarized potentials likely to cause a reduction in the channels' dynamic range. Removal of the C-terminal 158 ($Ca_V1.3_{\Delta1158}$) or 76 amino acids was sufficient to induce gating properties similar to $Ca_V1.3S$. FRET experiments revealed interaction of the last 158 amino acids (C_{158}) to a proximal C-terminal domain in $Ca_V1.3L$. Coexpression of C_{158} with $Ca_V1.3_{\Delta1158}$ completely restored $Ca_V1.3L$ gating properties confirming this protein interaction. Thus $Ca_V1.3$ channel gating is under control of the distal C-terminus allowing alternative splicing to fine-tune channel activity and adapt channel function to physiological needs.