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# Identification of a new C-terminal splice variant of $Ca_V1.3$ L-type calcium channels with unique functional properties

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## Background

In L-type voltage-gated calcium channels (VGCCs) the long C-terminal tail contains several sites for modulation by protein-protein interaction. $Ca_V1.3$ VGCCs ($Ca_V1.3_L$) activate at negative voltages and support sinoatrial node pacemaking and hearing, and shape neuronal excitability. In $Ca_V1.3_L$ an intermolecular automodulatory C-terminal interaction (CTM) has been described which affects channel gating. CTM is characterized by interaction of a distal C-terminal regulatory domain (DCRD) with a more proximal regulatory domain (PCRD). If this CTM is absent as in previously described short $Ca_V1.3_{42A}$, calcium-dependent inactivation (CDI) increases and the channel activation range shifts to more negative voltages (i.e. "short" gating properties). Here we show that alternative splicing in exon 43 creates a new short splice variant $Ca_V1.3_{43S}$ found in human and mouse brain. It lacks CTM, but still contains the PCRD motif, in contrast to previously described $Ca_V1.3_{42A}$. Semiquantitative PCR experiments showed that in mouse brain 39% of $Ca_V1.3$ channels contain exon 43S contrary to heart (6% 43S).

## Methods and results

Biophysical analysis showed "short" gating properties for $Ca_V1.3_{43S}$ in both 15 mM and 2 mM external $Ca^{2+}$ when co-expressed with β3 and α2δ-1 subunits in tsA-201 cells. In 2 mM $Ca^{2+}$ the inactivation rate of $Ca_V1.3_{43S}$ was faster for $Ca_V1.3_L$, but slower for $Ca_V1.3_{42A}$ (% inactivation after 100 ms at $V_{max}$: $Ca_V1.3_{42A}$: 64.5 ± 3.5%; $Ca_V1.3_{43S}$: 52 ± 4.5%, $Ca_V1.3_L$: 37.4 ± 3%, $p < 0.001$) by affecting the extent of CDI. Due to a presence of PCRD, DCRD-containing C-terminal fragments from $Ca_V1.3$ or $Ca_V1.2$ channels could restore $Ca_V1.3_L$ gating behaviour. Indeed, co-expression of GFP-$Ca_V1.2_{C349}$ fully restored long channel gating properties in $Ca_V1.3_{43S}$ ($V_{0.5}$: $Ca_V1.3_{43S}$+GFP-$Ca_V1.2_{C349}$: 1.37 ± 1.3 mV; $Ca_V1.3_L$: −2.4 ± 0.6 mV). C-terminal splicing also changed $I_{Ca}$ kinetics during stimuli mimicking trains of action potential waveforms, revealing a lower total $I_{Ca}$ during AP bursts in short splice variants.

## Conclusions

Taken together, our data indicate that $Ca_V1.3$ C-terminal splicing can serve as an important mechanism to fine-tune the dynamics of calcium entry in neurons in an activity dependent manner.

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