

MEETING ABSTRACT

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Structural determinants of $\text{Ca}_V1.3$ L-type calcium channel gating

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Background

$\text{Ca}_V1.3$ channels, which belong to the family of voltage-gated L-type calcium channels (LTCCs), are involved in important physiological (e.g. hearing, hormone release and cardiac and neuronal pace making) and pathophysiological functions (e.g. Parkinson's disease). We have recently discovered that an intramolecular protein interaction within the C-terminus of $\text{Ca}_V1.3 \alpha 1$ subunits fine-tunes $\text{Ca}_V1.3$ channel function. This C-terminal modulatory mechanism (CTM) is present in the long ($\text{Ca}_V1.3_l$) but is absent in the short ($\text{Ca}_V1.3_{42A}$) splice variant. Its absence induces activation at a more negative voltage range and increases Ca^{2+} -dependent inactivation (CDI). Interestingly a functional CTM is present in the human [1] and rat $\text{Ca}_V1.3 \alpha 1$ subunit isolated from pancreatic islets (D38101, r $\text{Ca}_V1.3_{\text{pan}}$) but not in a rat $\text{Ca}_V1.3 \alpha 1$ subunit cDNA clone isolated from superior cervical ganglion (scg) (AF370010; r $\text{Ca}_V1.3_{\text{scg}}$). This causes substantial differences in the voltage- and Ca^{2+} -dependent gating of scg and pan.

Methods

We systematically compared scg and pan $\text{Ca}_V1.3 \alpha 1$ subunits by expression in tsA201 cells and analysis of their functional properties using the whole-cell patch-clamp technique, to determine the structural basis for this difference.

Results

r $\text{Ca}_V1.3_{\text{scg}}$ differs from r $\text{Ca}_V1.3_{\text{pan}}$ at three amino acid positions (S244G, V1104A, A2073V) and one alternatively

spliced locus (absence of exon 31). Alternative splicing did not explain the functional differences between the two r $\text{Ca}_V1.3 \alpha 1$ subunits. The amino acid difference A2073V is located within the recently identified distal part (DCRD) of a C-terminal modulatory domain. Mutation of A2073 in r $\text{Ca}_V1.3_{\text{scg}}$ to the corresponding valine (A2073V) in r $\text{Ca}_V1.3_{\text{pan}}$ fully restores the slower CDI of r $\text{Ca}_V1.3_{\text{pan}}$. In contrast, A2073V only weakly affected the activation voltage range (rescue of only 5.3 mV of the 17.2 mV difference in the half-maximal voltage activation range (V_h)). Additional mutation of S244 to G in the r $\text{Ca}_V1.3_{\text{scg}}$ S4-S5 linker of domain I caused a further shift to a more positive voltage close to the V_h of r $\text{Ca}_V1.3_{\text{pan}}$.

Conclusions

Our data identify residues at proposed interfaces between voltage sensors and the intracellular channel gate controlling the voltage-dependence of $\text{Ca}_V1.3$ activation. We also show that the DCRD domain can moderate CDI independently of its effect on V_h , suggesting that these processes occur through different DCRD-dependent mechanisms.

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Reference

1. Singh A, Gebhart M, Fritsch R, Sinnecker-Brauns MJ, Poggiani C, Hoda JC, Engel J, Romanin C, Striessnig J, Koschak A: Modulation of voltage- and Ca^{2+} -dependent gating of $\text{Ca}_V1.3$ L-type calcium channels by alternative splicing of a C-terminal regulatory domain. *J Biol Chem* 2008, 283:20733-20744.

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