Structural determinants of CaV1.3 L-type calcium channel gating

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Background
CaV1.3 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 CaV1.3 α1 subunits fine-tunes CaV1.3 channel function. This C-terminal modulatory mechanism (CTM) is present in the long (CaV1.3l) but is absent in the short (CaV1.3s2A) splice variant. Its absence induces activation at a more negative voltage range and increases Ca2+-dependent inactivation (CDI). Interestingly a functional CTM is present in the human [1] and rat CaV1.3α1 subunit isolated from pancreatic islets (D38101, rCaV1.3pan) but not in a rat CaV1.3α1 subunit cDNA clone isolated from superior cervical ganglion (scg) (AF370010; rCaV1.3scg). This causes substantial differences in the voltage- and Ca2+-dependent gating of scg and pan.

Methods
We systematically compared scg and pan CaV1.3 α1 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
rCaV1.3scg differs from rCaV1.3pan 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 rCaV1.3 α1 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 rCaV1.3scg to the corresponding valine (A2073V) in rCaV1.3pan fully restores the slower CDI of rCaV1.3pan. 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 (Vh)). Additional mutation of S244 to G in the rCaV1.3scg S4-S5 linker of domain I caused a further shift to a more positive voltage close to the Vh of rCaV1.3pan.

Conclusions
Our data identify residues at proposed interfaces between voltage sensors and the intracellular channel gate controlling the voltage-dependence of CaV1.3 activation. We also show that the DCRD domain can moderate CDI independently of its effect on Vh, suggesting that these processes occur through different DCRD-dependent mechanisms.

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