

MEETING ABSTRACT

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# A mouse model to study the C-terminal regulation of Ca<sub>v</sub>1.3 L-type calcium channels

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## Background

Ca<sub>v</sub>1.3 voltage-gated L-type Ca<sup>2+</sup> channels (LTCCs) play an important role for hearing, cardiac pacemaking and neuronal excitability. The C-terminus of Ca<sub>v</sub>1.3 tightly controls channel gating by an intramolecular protein interaction involving two putative  $\alpha$ -helices (termed PCRD, DCRD), which form a C-terminal modulatory mechanism (CTM) only in full-length Ca<sub>v</sub>1.3 variants. In short (Ca<sub>v</sub>1.3<sub>42A</sub> and Ca<sub>v</sub>1.3<sub>43S</sub>) Ca<sub>v</sub>1.3  $\alpha$ 1 subunit splice variants CTM is absent which leads to profound changes in channel gating: activation occurs at more negative voltages and Ca<sup>2+</sup>-dependent inactivation (CDI) is faster.

## Methods

We quantified Ca<sub>v</sub>1.3 splice variants by qPCR analysis and transcript scanning, using different mouse tissues. To assess the physiological relevance of CTM, we generated a mutant mouse strain in which CTM function is disrupted by an HA-tag (Ca<sub>v</sub>1.3-DCRD<sup>HA/HA</sup> mice). We used anti-HA antibodies to detect the expression of the HA-tagged full length channel by Western blot analysis.

## Results

The short variants Ca<sub>v</sub>1.3<sub>42A</sub> (highest relative abundance in substantia nigra (SN) and ventral tegmental area (VTA)) and Ca<sub>v</sub>1.3<sub>43S</sub> are both less abundant in mouse brain indicating that the full length form Ca<sub>v</sub>1.3<sub>L</sub> comprises the most abundant form (about 50% of all transcripts). In mouse heart short transcripts are rare and Ca<sub>v</sub>1.3<sub>L</sub> represents about 90% of all known transcripts.

Ca<sub>v</sub>1.3-DCRD<sup>HA/HA</sup> mice contain a homozygous interruption of the CTM by disrupting the DCRD helix with an HA-tag. We show that this induces “short” gating properties in this mutant full-length variant. Homozygous mice are viable and display no gross anatomical and functional abnormalities. Expression of the HA-tagged full-length channel could be detected in mouse whole brain membrane preparations. Heterozygous mice show no overt differences in locomotor activity during daytime.

## Conclusions

We have successfully generated a mouse model which will enable us to study the physiological role of CTM function *in vivo*. It mimics the (permanent) pharmacological inhibition of CTM function and will thus allow predictions about its potential as a new drug target. Furthermore, the HA-tagged  $\alpha$ 1 subunit will provide a tool to specifically determine the expression of Ca<sub>v</sub>1.3<sub>L</sub> channels with anti-HA antibodies in mouse tissues.

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