

MEETING ABSTRACT

Open Access

Identification of a new C-terminal splice variant of $Ca_v1.3$ L-type calcium channels with unique functional properties

Gabriella Juhasz-Vedres, Anja Scharinger, Mathias Gebhart, Perrine Busquet, Chiara Poggiani, Simone B Sartori, Martina J Sinnegger-Brauns, Alexandra Koschak, Jörg Striessnig*

From 17th Scientific Symposium of the Austrian Pharmacological Society (APHAR). Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) Innsbruck, Austria. 29-30 September 2011

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 β_3 and $\alpha_2\delta-1$ 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} : $Ca_v1.3_{42A}$: $64.5 \pm 3.5\%$; $Ca_v1.3_{43S}$: $52 \pm 4.5\%$, $Ca_v1.3_L$: $37.4 \pm 3\%$, $p < 0.001$) 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.

Acknowledgements

Supported by FWF P-20670 JS, P-22528 AK, and SFB F44.

Published: 5 September 2011

doi:10.1186/1471-2210-11-S2-A44

Cite this article as: Juhasz-Vedres et al: Identification of a new C-terminal splice variant of $Ca_v1.3$ L-type calcium channels with unique functional properties. *BMC Pharmacology* 2011 **11**(Suppl 2):A44.

* Correspondence: joerg.striessnig@uibk.ac.at

Department of Pharmacology and Toxicology, Institute of Pharmacy, and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, 6020 Innsbruck, Austria