Schicker et al. BMC Pharmacology and Toxicology 2012, 13(Suppl 1):A69
http://www.biomedcentral.com/2050-6511/13/S1/A69

BMC Pharmacology & Toxicology

MEETING ABSTRACT Open Access

Biophysical characterization of $Ca_V1.4$ L-type calcium channel mutants causing congenital stationary night blindness type 2 in humans

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From 18th Scientific Symposium of the Austrian Pharmacological Society (APHAR). Joint meeting with the Croatian, Serbian and Slovenian Pharmacological Societies.
Graz, Austria. 20-21 September 2012

Background

$Ca_V1.4$ L-type calcium channels show unique biophysical properties such as slow inactivation due to the lack of calcium-dependent inactivation (CDI). These properties make $Ca_V1.4$ channels appropriate candidates for triggering persistent glutamate release at retinal photoreceptor cell synapses. Mutations in the CACNA1F gene encoding for the $Ca_V1.4$ α1 subunit are described in patients with X-linked congenital stationary night blindness type 2 (CSNB2). Impaired transmission between rod photoreceptor cells and second-order neurons manifests as night blindness and various other visual symptoms in the affected individuals.

Methods

The aim of this study was to investigate the functional properties of $Ca_V1.4$ mutants L849P and R1816stop compared to wild-type (WT) in transiently transfected tsA 201 cells (+β3,+α2δ-1) via whole-cell patch clamp technique using 15 mM Ba^{2+} and Ca^{2+} as charge carrier. For statistics, either Mann-Whitney (two groups) or Kruskal-Wallis test and Dunn's Post hoc test (multiple comparisons) were used.

Results

L849P was mainly characterized by a reduced current density (pA/pF: WT: −16.3 ± 1.6 (n = 38), L849P: −2.5 ± 0.3 (n = 12), $p < 0.0001$; Ca^{2+}), only minor, not significant ($p > 0.05$) changes in the voltage-dependent activation properties were observed. In presence of the dihydropyridin-activator BayK8644 (5 μM) the current density was increased ~10-fold ($p < 0.001$). The fold-increase in current density was comparable to WT. As expected R1816stop, which lacks an intrinsic C-terminal modulator (CTM), exhibited CDI (f-value: WT: 0.11 ± 0.03 (n = 8); R1816stop: 0.63 ± 0.02 (n = 22)) and shifted the voltage-dependence of activation to more negative voltages ($V0.5_{act}$ in mV: WT: 1.8 ± 0.3 (n = 74), R1816stop: −12.3 ± 0.3 (n = 23)). In presence of the $Ca_V1.4$-CTM; comprising the last 122 C-terminal residues WT conditions were fully restored, e.g. $V0.5_{act}$ 2.2 ± 1.0 mV (n = 14) ($p < 0.0001$).

Conclusions

We assume that the reduced current density observed in mutant L849P derives from decreased channel expression, which might be explained by a folding defect of the $Ca_V1.4$ channel protein rather than a reduced open probability. Moreover, the fact that the functional phenotype of the R1816stop can be rescued bears a potential pharmacotherapeutic concept based to the C-terminal modulatory mechanism present in $Ca_V1.4$ channels.

Acknowledgements
Financial support was given by the Austrian Science Fund (FWF, grant P22526 to A.K.).

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Published: 17 September 2012

doi:10.1186/2050-6511-13-S1-A69
Cite this article as: Schicker *et al.*: Biophysical characterization of $Ca_V1.4$ L-type calcium channel mutants causing congenital stationary night blindness type 2 in humans. *BMC Pharmacology and Toxicology* 2012 **13**(Suppl 1):A69.