

MEETING ABSTRACT

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# Biophysical characterization of Ca<sub>v</sub>1.4 L-type calcium channel mutants causing congenital stationary night blindness type 2 in humans

Klaus W Schicker<sup>1†</sup>, Verena Burtscher<sup>1†</sup>, Dagmar Knoflach<sup>1</sup>, Anamika Singh<sup>2</sup>, Thomas Stockner<sup>1</sup>, Alexandra Koschak<sup>1\*</sup>

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## Background

Ca<sub>v</sub>1.4 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<sub>v</sub>1.4 channels appropriate candidates for triggering persistent glutamate release at retinal photoreceptor cell synapses. Mutations in the CACNA1F gene encoding for the Ca<sub>v</sub>1.4  $\alpha$ 1 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<sub>v</sub>1.4 mutants L849P and R1816stop compared to wild-type (WT) in transiently transfected tsA 201 cells (+ $\beta$ 3,+ $\alpha$ 2 $\delta$ -1) via whole-cell patch clamp technique using 15 mM Ba<sup>2+</sup> and Ca<sup>2+</sup> 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:  $-16.3 \pm 1.6$  (n = 38), L849P:  $-2.5 \pm 0.3$

(n = 12),  $p < 0.0001$ ; Ca<sup>2+</sup>), only minor, not significant ( $p > 0.05$ ) changes in the voltage-dependent activation properties were observed. In presence of the dihydropyridin-activator BayK8644 (5  $\mu$ M) 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:  $0.11 \pm 0.03$  (n = 8); R1816stop:  $0.63 \pm 0.02$  (n = 22)) and shifted the voltage-dependence of activation to more negative voltages ( $V_{0.5act}$  in mV: WT:  $1.8 \pm 0.3$  (n = 74), R1816stop:  $-12.3 \pm 0.3$  (n = 23)). In presence of the Ca<sub>v</sub>1.4-CTM; comprising the last 122 C-terminal residues WT conditions were fully restored, e.g.  $V_{0.5act}$   $2.2 \pm 1.0$  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<sub>v</sub>1.4 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<sub>v</sub>1.4 channels.

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## Author details

<sup>1</sup>Department of Neurophysiology and Neuropharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria

\* Correspondence: alexandra.koschak@meduniwien.ac.at

† Contributed equally

<sup>1</sup>Department of Neurophysiology and Neuropharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria

Full list of author information is available at the end of the article

Austria. <sup>2</sup>Department of Pharmacology and Toxicology, Institute of Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria.

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