Division of Neurophysiology

Translational Research on Channelopathies

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Channelopathies are diseases caused by dysfunction of ion channels, which are expressed in many cell types, tissues and organs, hence explaining the wide phenotypic diversity of their clinical manifestations. In voltage-gated cation channels, a recurrent pattern for mutations is the neutralization of positively charged residues in the voltage-sensing S_4 transmembrane segments. These mutations cause dominant ion channelopathies affecting many tissues such as brain, heart and skeletal muscle (Groome et al. 2011). Recent studies suggest that the pathogenesis of associated phenotypes is not limited to alterations in the gating of the ion-conducting alpha pore. Instead, aberrant so-called omega currents facilitated by the movement of the mutated S_4 segments during activation and during recovery contribute to symptoms (Fig. 1A). Surprisingly, these omega currents display uni- or bi-directionality and conduct cations with varying ion selectivity. Additionally, the voltage sensitivity enables the channels to conduct omega currents that are activated in either a hyperpolarized or a depolarized voltage range (Jurkat-Rott et al. 2012).

One of these channelopathies with mutant voltage sensors, hypokalemic periodic paralysis (HypoPP), is clinically characterized by paroxysmal episodes and late-onset muscle dystrophy. The weakness spells are triggered by hypokalemia. The disease is caused by neutral replacements of the first arginine of S_4 segments of calcium and sodium channel of skeletal muscle. The mutations form an omega pore conducting an inward Na^+ omega current at normal resting membrane potential and at hyperpolarization (Fig. 1B). The omega current shows an above-linear increase with hyperpolarization (Fig. 1C) although the electrical field is focused to a single amino acid (Ohm resistor) and not constantly increasing within the membrane (constant field theory). The non-linearity of the omega current reflects the stochastic process of a voltage-dependent open probability and follows a Boltzmann distribution.

In addition, we have shown that the resting membrane potential of excitable cells is distributed around two electrically stable values and the membrane is therefore electrically bistable (Fig. 2A, Jurkat-Rott et al. 2009). In weak HypoPP patients, the fraction of fibers in the depolarized state (P2) is large (Fig. 2B, right panel). Due to the sustained depolarization, the sodium channels are inactivated (Fig. 2C). Therefore, the fibers cannot generate an action potential (Fig. 2D) and are paralyzed. Substances such as carbonic anhydrase and aldosterone inhibitors can shift the fibers in the P2 state in the normal P1 state (Fig. 2B, left panel).

Lowering extracellular K^+ aggravates the omega-induced depolarization, which is in contrast to the predictions of the Goldman equation (Fig. 2E). Due to the permanent Na^+ influx, HypoPP muscle fibers accumulate intracellular Na^+ and water. The edema is cytotoxic and causes muscle degeneration in the periodic paralysis (Amarteifio et al. 2012) and also in the more frequent Duchenne muscle dystrophy (Weber et al. 2011, Lehmann-Horn et al. 2012).

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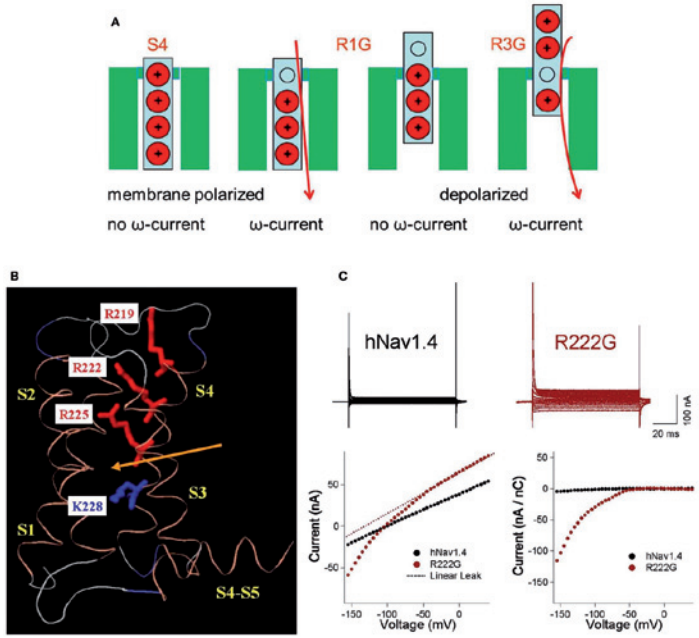

Fig. 1: Omega pores and currents dependent on the position within the S4 segment, the voltage sensor. A. Replacement of the outermost arginine (red) by a neutral amino acid (grey) such as glycine (R1G) opens a conductive pathway through the polarized membrane, resulting in an omega current (red). At depolarized potentials at which the S4 segment moves outward, the conductive pathway is closed by a deeper arginine and the omega current ceases. In contrast, the replacement of a deeper arginine (R3G) only opens the omega pore if the membrane is depolarized. B. Homology model of domain I in hNav1.4 based on crystal structure of NavAb (activated-closed; crystal structure at 0 mV), using Modeller. The positions of arginine and lysine residues of S4 are shown, relative to the putative gating pore constriction (arrow). C. Comparison of current-voltage (I/V) traces for wild type hNav1.4 and R222G, with plots of raw I/V, linear leak, and normalized current (linear leak subtracted from IV and normalized to gating current at 40 mV). The mutation R222G causes HypoPP type 2. External solution contained 120 mM K^+ and 1 µM TTX.

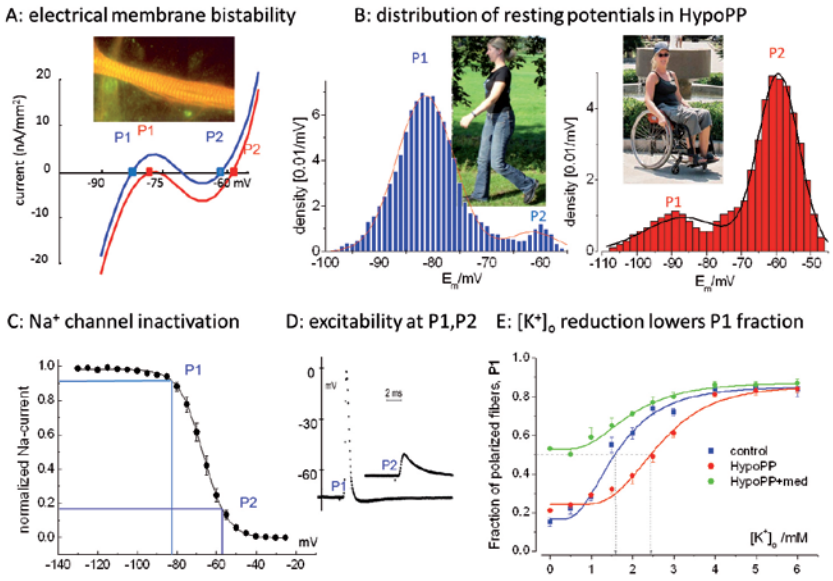

Fig. 2: A. the membrane of muscle fibers (insert) is electrically bistable. B. the fraction of fibers in the depolarized state (P2) is large in weak HypoPP patients before (right panel) and after treatment (left panel). C. the inactivation curve of voltage-gated sodium channels shows highly negative P1 values and less negative P2 values. D. in contrast to fibers in the P1 state, fibers in P2 state cannot generate an action potential and are paralyzed. E. at lowered extracellular K^+, HypoPP fibers (red) are shifted to the right compared to control fibers (blue); medication shifts the HypoPP curve to the left (green).

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Selected Publications:

- *Groome J, Lehmann-Horn F, Holzherr B (2011): Open- and closed-state fast inactivation in sodium channels: Differential effects of a site-3 anemone toxin. Channels 5, 65-78.*
- *Jurkat-Rott K, Weber MA, Fauler M, Guo XH, Holzherr BD, Paczulla A, Nordsborg N, Joechle W, Lehmann-Horn F (2009): K+-dependent paradoxical membrane depolarization and Na+ overload, major and reversible contributors to weakness by ion channel leaks. Proc Natl Acad Sci USA 106, 4036-41.*
- *Amarteifio E, Nagel AM, Weber MA, Jurkat-Rott K, Lehmann-Horn F (2012): Hyperkalemic Periodic Paralysis and Permanent Weakness: 3-T MR Imaging Depicts Intracellular ^{23}Na Overload. Radiology 264, 154-63.*
- *Weber MA, Nagel AM, Jurkat-Rott K, Lehmann-Horn F (2011): Sodium (^{23}Na) MRI detects elevated muscular sodium concentration in Duchenne muscular dystrophy. Neurology 77, 2017-24.*
- *Lehmann-Horn F, Weber MA, Nagel AM, Meinck HM, Breitenbach S, Scharrer J, Jurkat-Rott K (2012): Rationale for treating oedema in Duchenne muscular dystrophy with eplerenone. Acta Myol 31, 31-9.*
- *Jurkat-Rott K, Groome J, Lehmann-Horn F (2012): Pathophysiological role of omega pore current in channelopathies. Front Pharmacol 3, 112.*