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 S4 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 S4 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 S4 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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