

News and Views to: Domain III S4 in closed-state fast inactivation: Insights from a periodic paralysis mutation. James R Groome, Karin Jurkat-Rott, Frank Lehmann-Horn. Channels. Vol. 8, Iss. 5, 2014

### **Hypokalemic periodic paralysis: an omega pore mutation affects inactivation**

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Among the human diseases caused by ion channel mutations hypokalemic periodic paralysis (HypoPP) has thrown up more than its fair share of puzzles. Patients have attacks of skeletal muscle paralysis associated with low serum potassium, and harbor dominant mutations affecting the muscle calcium (CaV1.1) or sodium (NaV1.4) channels respectively. Why do mutations in either channel converge on a common phenotype, while other mutations in NaV1.4 lead to a quite different form of periodic paralysis associated with high or normal serum potassium, or muscle hyperexcitability manifesting as myotonia?

A breakthrough in understanding the disease mechanisms came from the realization that the mutations affect arginine residues in the fourth transmembrane helix (S4) of the voltage-sensing domains (VSDs) of either channel<sup>1</sup>. These mutations affect channel function by two distinct mechanisms. They can cause a loss-of-function of the channel by interfering with voltage-dependent activation and inactivation, which does not explain the phenotype, but they also open up an aberrant gating or 'omega' pore through the mutated VSD<sup>2</sup>. The cation-mediated leak current through the gating pore is now thought to depolarize muscle fibers, inactivating sodium channels and reducing cell excitability, eventually leading to muscle paralysis.

Both CaV1.1 and NaV1.4 channels contain four homologous domains (DI-DIV), each of which has a VSD consisting of four alpha helices (S1-S4). Each S4 contains three or more regularly spaced arginines which normally occlude a potential aqueous pore through the VSD. Charge neutralizing mutations of these

arginines allow ions to leak through the gating pore. The HypoPP mutations tend to affect the most extracellular arginines (R1 or R2) of S4. Gating pore currents caused by these mutations are active in the hyperpolarized resting state of the VSD, when it is in the 'down' state.

But what about arginine residues deeper in the S4? Groome and coworkers recently characterized the functional properties of the first two mutations, R1135H and R1135C, affecting the third arginine (R3) of DIII S4 associated with HypoPP<sup>3</sup>. One of the mutations (R1135C) occurred in the homozygous state, which has not previously been reported for HypoPP. Biophysical analysis of these mutations brings new insights into the molecular rearrangements and roles of this domain in channel gating.

Typical for HypoPP channels the R1135H and R1135C mutations cause loss-of-function of sodium currents and introduce gating pore currents<sup>3</sup>. Atypical for HypoPP channels, these gating pore currents are activated by depolarization. A likely explanation is that the DIIIR3 normally occludes the gating pore in the 'up' state of the VSD. A mutation affecting another R3, DIIR3, similarly uncovers a gating pore activated by depolarization<sup>4</sup>, but the R3 gating pore currents show important differences between domains II and III. In response to prolonged depolarization the DIIR3 gating pore is locked in an active state<sup>4</sup> while the DIIIR3 gating pore seems to enter another state with reduced conductance<sup>3</sup>. Repolarization eventually closes the DIIR3 gating pore, but re-activates the DIIIR3 gating pore. The significance of the unusual DIIIR3 gating pore currents for pathogenesis is unclear. However, the resting membrane potential of the R1135H muscle fibers is depolarized<sup>3</sup>.

Groome and co-workers now turn to the loss-of-function effects of DIIIR3, accounted for by a substantial enhancement of closed state inactivation<sup>3</sup>. Groome et al. show that a fraction of the S4 gating charges of R1135C channels activate at more hyperpolarized voltages than the wild-type S4s<sup>5</sup>. In addition, the sodium channel and the gating charge availabilities at sub-threshold voltages are both reduced in the mutant channel. Assuming that the R1135C mutation affects mainly the gating charge movement locally in DIII, the data would suggest that the enhanced activation of the DIII VSD is associated with enhanced closed-state inactivation. Enhanced mobility of the DIII VSD may provide a docking site for the inactivation particle.

The altered mobility of DIII R3 mutants in Nav1.4 enhances inactivation and is likely to contribute to reduced action potential amplitude in the muscle. The gating pore currents are likely to underlie the periodic paralysis of the homozygous R1135C patient, and the role of loss of Nav1.4 function for the pathology remains to be elucidated. Thus far, there is only one report of loss-of-function mutation of Nav1.4 without gating pore currents causing a myasthenic syndrome<sup>6</sup>. HypoPP still keeps some puzzles in store.

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