

NEUROLOGY

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Neurology 2009;72;1540-1541; originally published online Feb 25, 2009;

DOI: 10.1212/01.wnl.0000345878.82061.cb

This information is current as of May 4, 2009

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<http://www.neurology.org/cgi/content/full/72/18/1540>

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Getting a charge out of periodic paralysis?



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Neurology® 2009;72:1540–1541

Hypokalemic periodic paralysis (HypoPP) is the most prevalent form of familial periodic paralysis and classically presents with recurrent attacks of moderate to severe generalized weakness in association with hypokalemia (often <3.0 meq/L). As with all forms of periodic paralysis, the defect in force generation in HypoPP stems from a reduction or complete loss of muscle excitability. Affected fibers are persistently depolarized, which inactivates muscle sodium channels and thereby prevents the fibers from generating a propagated action potential. The molecular basis for this electrical catastrophe originates in mutations of genes encoding ion channels of skeletal muscle.¹ Remarkably, mutations of either the voltage-gated sodium channel or the voltage-gated calcium channel can cause clinically indistinguishable HypoPP. In this issue of *Neurology*®, Matthews et al.² provide compelling evidence that missense mutations of arginine residues in specialized voltage-sensing regions of the two different ion channels are a common theme in HypoPP.

Over the past 2 decades, it has been firmly established that the many variants of familial periodic paralysis and nondystrophic myotonia are all channelopathies that arise from mutations of genes encoding voltage-sensitive ion channels expressed in skeletal muscle. For many of these disorders, it has been possible to construct a mechanistic link directly from the functional derangement of a mutant ion channel to the defect of muscle excitability that results in myotonia (enhanced) or periodic paralysis (reduced). HypoPP has been a glaring exception. The discovery in 1994 that all three mutations in the calcium channel gene (*CACNA1S*) that cause HypoPP are missense substitutions for arginine residues (which have a fixed charge of +1) in domains that give the channel its voltage sensitivity^{3,4} was predicted to be a physiologic certainty. The expectation was that the voltage sensitivity of mutant Ca channels would be altered in some way that would provide insight to the pathogenesis of HypoPP. Functional expression studies of Ca-HypoPP mutants showed a slowed rate of activa-

tion by depolarization or reduced expression level, but these changes did not readily account for the depolarization or hypokalemia during attacks.

In 1999, it was reported that a missense mutation of an arginine in the skeletal muscle sodium channel (SCN4A) could also cause HypoPP.⁵ Subsequently, a dozen mutations of SCN4A were identified in families with HypoPP. Calcium channel mutations still accounted for the majority of HypoPP cases (~60% of families vs ~20% for SCN4A). Meanwhile, ion channel biophysicists studying the fundamental mechanisms by which the sensors move in voltage-sensitive ion channels discovered that mutations at the critical arginines may disrupt the molecular fit and thereby introduce an aberrant pathway for ions to move through the channel and produce a “gating-pore” current.⁶ Those studying channelopathies subsequently showed that arginine mutations in HypoPP had a similar effect. To date, five HypoPP mutations at two different arginines (R669, R672) in SCN4A have been studied, and all showed anomalous gating-pore currents.^{7–9} Moreover, substitution of arginine by histidine always results in a proton-selective current, whereas the other mutations (cysteine, serine, glycine) do not discriminate among monovalent cations. This difference may be clinically important for influencing the efficacy of carbonic anhydrase inhibitors as the prophylactic treatment of choice for HypoPP. It is important to recognize that these anomalous gating-pore currents are very small in amplitude, on the order of 1/5,000th of the Na current through the conventional pore that elicits the action potential. Nevertheless, computer simulations demonstrate that these small currents may tip the balance at the resting potential to produce an anomalous depolarization in response to hypokalemia.¹⁰

The report by Matthews et al.² strengthens the notion that mutation at any one of several arginine residues in the voltage sensor domains is the critical common theme among mutations of Ca or Na channels that produce susceptibility to attacks of HypoPP.

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e-Pub ahead of print on February 25, 2009, at www.neurology.org.

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Disclosure: The author reports no disclosures.

Statistically, the data are now becoming overwhelming. Including the three new mutation sites reported by Matthews et al., there are three arginine sites in CACNA1S and 7 sites in SCN4A that all result in HypoPP. There are no exceptions wherein a different class of channel mutation produces HypoPP. From a different perspective, the large survey of 83 HypoPP families by Matthews et al. would predict that 90% will have a known mutation at an arginine in the voltage sensor of CACNA1S or SCN4A. Much work remains to be done, however. Because of technical challenges, none of the Ca channel mutations have been adequately screened for the presence of an anomalous gating pore current, and four Na channel sites remain to be studied. Further studies in intact muscle fibers are also needed to prove the gating-pore current is sufficient to cause the paradoxical depolarization during an attack of HypoPP. And what of the remaining 10% of HypoPP families with no identified mutation? Odds are these also will be channelopathies, but perhaps from a new class of molecular defect or in a different channel. The rapid pace of discoveries in this field will likely yield some answers.

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