Commentary

Skeletal muscle sodium current is reduced in hypokalemic periodic paralysis

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Hypokalemic periodic paralysis (HypoPP), described a recent issue of PNAS by Jurkat-Rott and colleagues (1), has great scientific and clinical interest because its pathophysiology touches on several important properties of skeletal muscle. Besides providing the force for movement, skeletal muscle is an electrically excitable tissue and an important endocrine target organ as the largest protein store for humans (2). Jurkat-Rott *et al.* (1) defined some of the abnormalities in surface membrane ionic currents that are responsible for the phenotype of HypoPP. HypoPP is an autosomal dominant disease characterized by episodic attacks of muscle paralysis usually associated with hypokalemia. Paralysis is caused by membrane depolarization triggering sodium channel inactivation, which renders the membrane inexcitable (3–5). Membrane hyperexcitability, such as myotonia, is never associated with HypoPP. Insulin administration may trigger a paralytic attack without appreciable hypokalemia (3–5). The first recognized linkage of HypoPP was to chromosome 1Q31–32 (6–8). The defective gene (*CACNA1S*) encodes a skeletal muscle dihydropyridine-sensitive or L-type calcium channel. Two mutations have been described in segment 4 of domain 2 (D2/S4, Arg-528→His) and D4/S4 (Arg-1239→His) of the α-subunit of the skeletal muscle L-type calcium channel. A third less common mutation also involves D4/S4 (Arg-1239→Gly) (5, 7, 9, 10). Two recent studies demonstrated that point mutations in the SCN4A gene affecting D2/S4 of the α-subunit of the mature innervated and tetrodotoxin-sensitive isoform of the skeletal muscle sodium channel can produce the phenotype of HypoPP. Bulman *et al.* (11) described one family with an Arg-669→His mutation. In this issue, Jurkat-Rott *et al.* (1) described five families, each of which had one of two mutations Arg-672→His or Arg-672→Gly.

HypoPP Patients with Sodium or Calcium Channel Mutations Have Similar Phenotypes. Jurkat-Rott *et al.* (1) demonstrated that HypoPP patients with sodium channel mutations shared the salient clinical features found in patients with calcium channel mutations (Table 1). Subjects with sodium channel mutations had episodes of paralysis associated with hypokalemia. Muscle fibers were depolarized and inexcitable during paralysis. Hypokalemia triggered depolarization, and insulin potentiated the depolarization and paralysis. Studies performed before the channel mutations were recognized demonstrated that muscle fiber conduction velocities were slowed in patients with HypoPP. Studies performed before HypoPP mutations were recognized may have included subjects with sodium or calcium mutations. These early studies demonstrated a universal reduction in muscle fiber conduction velocity among HypoPP subjects (12, 13). HypoPP patients with the Arg-528→His (14) or Arg-1239→His (15) calcium channel mutations had reduced muscle fiber conduction velocities, which suggested attenuated membrane sodium current.

How Do the Calcium and Sodium Channel Mutations Relate to the Membrane Abnormalities in HypoPP? Understanding how channel mutations produce the membrane abnormalities that lead to the clinical phenotype in HypoPP is a challenge. The Table lists four important features of HypoPP. The calcium channel mutations do not directly explain any of the four cardinal features of HypoPP, hence the calcium channel mutations represent an indirect channelopathy (16–18). Some of the properties of HypoPP muscle are directly understood from the sodium channel mutations. Episodic hypoglycemia results from excessive cellular uptake of potassium, which may be stimulated by glucose intake and insulin release (3–5). Our current understanding of muscle physiology does not suggest how the sodium or calcium channel mutations associated with HypoPP lead to exaggerated cellular potassium uptake by skeletal muscle.

Paradoxical membrane depolarization in response to hypokalemia occurs in HypoPP patients with sodium or calcium channel mutations. In people with HypoPP caused by calcium channel mutations, membrane depolarization resulted from hypokalemia activating a pathological depolarizing cationic current and from reduced inward rectifier K^+ channel conductance (16, 18, 19). The pathological depolarizing current was not blocked by tetrodotoxin or by the dihydropyridine class of calcium channel blockers (16, 18). The abnormal inward rectifier K^+ conductance was in part because of reduced density of ATP-sensitive K^+ channels (20). Jurkat-Rott *et al.* (1) demonstrated that HypoPP patients with sodium channel mutations had attenuated sodium current because of excess inactivation of mutant sodium channels and reduced density of sodium channels. However, the reduced sodium current does not explain why the membrane paradoxically depolarized in response to hypokalemia.

Insulin potentiates depolarization in patients with the Arg-528→His calcium channel mutation by reducing the outward component of the inward rectifier K^+ conductance (16, 18). How insulin depolarizes HypoPP fibers with sodium channel mutations is not yet known.

Skeletal muscle membrane excitability is impaired in HypoPP. HypoPP muscle fibers are very susceptible to depolarization-induced inexcitability (3–5). The conduction velocities of HypoPP skeletal muscle fibers are slow (12, 14, 15). Susceptibility to depolarization-induced paralysis and slow muscle fiber conduction velocities both suggest impaired sodium channel function in HypoPP. Some studies of muscle fiber conduction velocity were performed before the channel mutations were recognized and likely

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Table 1. Characteristics of HypoPP because of sodium or calcium channel mutations

Characteristic of HypoPP	Present with calcium channel mutations	Present with sodium channel mutations	Explained by calcium channel mutations	Explained by sodium channel mutations
Episodic hypokalemia	Yes (6–8, 21)	Yes (1, 11)	No (16, 17, 22–24)	No (1)
Muscle membrane depolarizes in response to reduced extracellular K^+	Yes (16, 19)	Yes (1)	No (16, 17, 22–24)	No (1)
Insulin potentiates depolarization	Yes (16, 19, 20, 25)	Yes (1)	Indirectly via altered impact of insulin on potassium conductance (16, 25, 26)	No (1)
Reduced interictal skeletal muscle membrane excitability	Yes (14, 15)	Probably studies performed before mutations recognized (12, 13)	Indirectly via reduced sodium channel density (18)	Yes (1)

included patients with sodium and calcium channel mutations (12, 13). HypoPP patients with the Arg-528→His (14) and Arg-1239→His (15) calcium channel mutations have slow skeletal muscle fiber conduction velocities. Jurkat-Rott *et al.* (1) explained the slow skeletal muscle fiber conduction velocities for HypoPP with sodium channel mutations patients by demonstrating reduced action potentialrates of rise because of lower sodium current density on isolated muscle fibers. The low sodium current amplitude resulted from a high susceptibility to inactivation of the mutant sodium channels and reduced total density of sodium channels. The production and insertion of normal sodium channels into the surface membranes of HypoPP fibers did not compensate for the reduced sodium current passing through the mutant sodium channels. The inability of the HypoPP muscle fibers to compensate for the reduced sodium current through mutant channels raises questions about how skeletal muscle fibers regulate sodium channel production and membrane insertion to control the excitability of the surface membrane. Interestingly, the reduced excitability of muscle fibers from patients with HypoPP because of the Arg-528→His calcium channel mutation was also associated with reduced sodium current amplitude (18). Reduced sodium current amplitudes resulted from a lower density of sodium channels with no alteration in the voltage dependence of sodium channel activation, fast inactivation or slow inactivation. Consequently, the Arg-528→His calcium channel mutation reduced the expression or membrane trafficking of normal sodium channels via an undetermined mechanism. The commonality of reduced sodium current amplitude in both forms of HypoPP suggests that reduced sodium current may be an important pathophysiological change needed to produce the phenotype of HypoPP.

In summary, Jurkat-Rott *et al.* (1) were able to relate several of the pathophysiological characteristics of HypoPP to membrane changes that directly resulted from the sodium channel mutations. The mutant channels inactivated at hyperpolarized membrane potentials compared with normal channels, and the sodium current amplitude was reduced in HypoPP fibers. The reduced sodium current resulted from the susceptibility of mutant channels to inactivation and a reduced density of sodium channels. Given that the HypoPP fibers heterogeneously expressed normal and mutant sodium channels, the reduced fiber sodium current suggests that HypoPP fibers cannot compensate for the reduced sodium current by enhancing the production of normal sodium channels. The diminished sodium current directly explains the reduced excitability of HypoPP fibers. The sodium channel mutations do not explain why patients with HypoPP caused by sodium channel mutations in D2/S4 develop episodic hypokalemia, why the HypoPP fibers depolarize in response to hypokalemia, and why insulin potentiates fiber depolarization and paralysis.

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