
Their work advances understanding of molecular and cellular mechanisms pathologies” represent more than 50 human

diseases, including several affecting skeletal muscle contraction, such as the periodic paralyses and nondystrophic myotonia (see “Muscle channelopathies”).

Hypokalemic periodic paralysis

Plasma membrane channels in skeletal muscle are essential for the generation and propagation of action potentials, leading to release of intracellular calcium through the process of excitation-contraction coupling. Ion channel dysfunction can hinder contraction by impairing action potential firing along the membrane. A characteristic symptom of this phenomenon is known as “periodic paralysis,” a form of paroxysmal weakness that occurs in the absence of neuromuscular junction or motor neuron disease. Periodic paralysis is most often thought of as an inherited disease, but certain acquired conditions can produce a similar phenotype. Disturbances in plasma potassium ion concentration often accompany bouts of weakness, and the direction of change has been used to classify the condition as hypokalemic, hyperkalemic, or normokalemic periodic paralysis (6). These conditions are not lethal, because respiratory muscles are spared.

Although the clinical features and inheritance pattern have been known since the first half of the twentieth century, the pathophysiology of periodic paralysis remained mysterious until approximately 30 years ago, when investigators in Germany published their electrophysiological observations on explanted intercostal muscle fibers from subjects with periodic paralysis (7). These studies revealed that resting membrane potential was less nega-
The gene encoding the skeletal muscle sodium channel, SCN4A, caused exclusively by mutations in

but left unanswered key questions about

of the pathogenesis of periodic paralysis

observation occurring in HyperPP fibers but had no effect on HypoPP muscle. These obser-

sodium channels, reversed the depolariza-

electrochemical inexcitable, owing to inactiva-

and insulin treatment rendered the fibers
electrically inexcitable, owing to inactiva-

normal muscle. Further, exposure of the
to low extracellular potassium concent-

centration evoked a further depolarization,

This observation led to the hypothesis that
4 segments generate a proton pore that is

The sodium and calcium channels expressed

Voltage-gated channel structure

The sodium and calcium channels expressed in nerve, heart, and muscle belong to a

formed subunit of an L-type voltage-gated calcium channel (CaV1.1), and less com-
monly by SCN4A mutations (2). Although both syndromes are associated with notable
allelic heterogeneity, CACNA1S and SCN4A mutations associated with HypoPP are
clustered within voltage-sensor domains. A brief digression on the topic of voltage-gat-

current flowing through the voltage-sensor pore (also known as the gating pore) was
termed the “omega” or “gating pore” current (Figure 1B).

Because these S4 segment histidine substitu-
tions created unnatural channels, astute researchers investigating the func-
tional consequences of channelopathy-associated mutations recognized that this
mechanism might explain the pathophysi-
ology of HypoPP. Specifically, sodium channel mutations associated with HypoPP that
replace S4 segment arginine residues create channels that conduct an anom-
alous inward current at resting membrane potentials (15–18). The in vivo relevance
of this mechanism was demonstrated sub-
sequently using a mouse model of the dis-
ease (Na\textsubscript{v}1.4 R669H knock-in), in which an anomalous inward current was detected in

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The sodium and calcium channels expressed in nerve, heart, and muscle belong to a

superfamily of ion channels that are gated
(opened and closed) by changes in mem-
brane potential (9). The main pore-forming
α-subunits have a four-fold symmetry con-
sisting of structurally homologous domains
(D1–D4), each containing four transmem-
brane segments that comprise the voltage-
sensor domain (S1–S4) and a separate pore
domain (S5–S6), important for determining
ion selectivity (Figure 1A). The S4 segment,
which functions as the main voltage-sensing

element, is amphipathic, with basic amino
acids (arginine or lysine) at every third
position surrounded by hydrophobic resi-
dues. Activation of voltage-gated channels is
evoked by a membrane depolarization that
acts to propel the S4 segments in an

outward direction away from the negative

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current rather than ionic current conducted through a known ion channel (20). These findings offered a mechanistic link between calcium channel mutation and attacks of muscle weakness. Anomalous gating pore current creates a precarious balance between the inward and outward currents that maintain the membrane potential. Factors such as hypokalemia that transiently depress potassium currents, which are required to maintain a normal resting membrane potential, can render the muscle severely depolarized and, consequently, inexcitable owing to inactivation of sodium channels.

Now that a common mechanism of evoking gating pore current has been established in HypoPP, several new and intriguing questions emerge. Can aberrant gating pore current be selectively blocked, and would this prevent attacks of paralysis? Do carbonic anhydrase inhibitors such as acetazolamide and dichlorphenamide, which are effective treatments for HypoPP regardless of genotype, affect gating pore current directly or indirectly? Are there triggering factors that act specifically by potentiating gating pore current? Finally, what is the basis for vacuolar myopathy, and why is there a sex-biased penetrance of mutations? These and other important questions can now be addressed using the mouse model developed by Wu and colleagues.

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Figure 1

Voltage-gated sodium and calcium channel structural domains and location of gating pore. (A) Predicted transmembrane topology model of typical voltage-gated sodium or calcium channel. The S4 segments within voltage-sensing domains are indicated by a column of plus (+) signs. The inset illustrates locations of the separate voltage-sensing and pore domains that are repeated four times in the channel protein. (B) A cutaway view showing the pathway through which ionic current or gating pore currents are conducted. The cylinders within the channels represent the S4 segments, and the approximate location of the HypoPP mutation CaV1.1 R528H is indicated. Figure modified from the Journal of General Physiology (23).
Low levels of phosphate can disrupt bone ossification and predispose to fractures. FGF23 is one of the major determinants of phosphate homeostasis, acting to increase urinary phosphate excretion. However, the regulation of FGF23 is incompletely understood. In this issue of the JCI, Smith et al. show that the cleaved form of αKlotho, the membrane-bound form of which is an FGF23 coreceptor, serves as a novel endocrine regulator of phosphate homeostasis, capable of inducing FGF23 production in osteocytes.

Phosphate is a critical component of bone, and it serves numerous biological functions in the synthesis of DNA and membrane lipids, protein modifications, energy metabolism, and second messenger formation. FGF23 and parathyroid hormone (PTH) are the major regulators of phosphate homeostasis (1, 2). Both hormones increase urinary phosphate excretion by reducing proximal tubular expression of the sodium-dependent phosphate cotransporters, NPT2a and NPT2c, thereby lowering serum phosphate levels. However, in contrast to FGF23, which decreases serum levels of 1,25-dihydroxyvitamin D (1,25D) by inhibiting renal 1α-hydroxylase and stimulating 24-hydroxylase, PTH increases renal production of 1,25D, which consequently enhances the absorption of phosphate (and calcium) from the intestinal tract (3).

FGF23 belongs to the subfamily of endocrine FGFs and mediates its phosphate-regulating actions in the kidney through FGF receptors (FGFRs), most prominently FGFR1. These actions require the transmembrane form of αKlotho (mKL), which acts as the coreceptor that enhances the binding affinity of FGF23 to different FGFRs (4, 5). Ablation of αKlotho in mice leads to severe hyperphosphatemia, elevated levels of 1,25D, hypercalcemia, diffuse soft tissue calcifications, accelerated aging, and premature death (6). These findings are largely indistinguishable from those observed in FGF23 loss-of-function models (7, 8).

Osteocytes are the primary cellular source of FGF23 after the fetal period (9), but little is known about their regulation and secretion. Although discovery of the molecular causes of monogenic hypophosphatemic rickets disorders has helped to identify a set of bone-derived proteins that decrease FGF23 production, the mechanisms of how these inhibitors suppress FGF23 remain largely unknown. Furthermore, despite our knowledge that changes in dietary phosphate intake can alter FGF23 levels in healthy individuals (10, 11), how serum phosphate or phosphate balance is sensed and how this signal is conveyed to the osteocyte to alter FGF23 expression remains completely unknown.

A novel regulator of FGF23 synthesis

In this issue of the JCI, Smith et al. provide intriguing new findings about the