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Channelopathies of skeletal muscle excitability

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Abstract

Familial disorders of skeletal muscle excitability were initially described early in the last century and are now known to be caused by mutations of voltage-gated ion channels. The clinical manifestations are often striking, with an inability to relax after voluntary contraction (myotonia) or transient attacks of severe weakness (periodic paralysis). An essential feature of these disorders is fluctuation of symptoms that are strongly impacted by environmental triggers such as exercise, temperature, or serum K^+ levels. These phenomena have intrigued physiologists for decades, and in the past 25 years the molecular lesions underlying these disorders have been identified and mechanistic studies are providing insights for therapeutic strategies of disease modification. These familial disorders of muscle fiber excitability are “channelopathies” caused by mutations of a chloride channel (ClC-1), sodium channel ($Na_V1.4$), calcium channel ($Ca_V1.1$) and several potassium channels (Kir2.1, Kir2.6, Kir3.4). This review provides a synthesis of the mechanistic connections between functional defects of mutant ion channels, their impact on muscle excitability, how these changes cause clinical phenotypes, and approaches toward therapeutics.

Introduction

The ion channelopathies of skeletal muscle include a wide variety of disorders that degrade the fidelity of neuromuscular transmission, adversely alter the excitability of the sarcolemma, disrupt excitation-contraction coupling, or impair calcium homeostasis of organelles (28, 69, 113, 153). This review is focused on the channelopathies of voltage-gated ion channels expressed at the surface membranes of the sarcolemma and transverse tubules (T-tubules). Mutations of ion channel genes may destroy the coding potential to produce a functional channel or result in modest changes of channel gating (136, 167), but the impact on sarcolemmal excitability can be profound (31). Muscle fiber excitability is usually preserved at baseline, but the channel defects predispose individuals to paroxysmal attacks of muscle stiffness (myotonia from pathologically enhanced excitability) or intermittent failure of excitability resulting in severe weakness (periodic paralysis). These rare disorders have a prevalence of about 1 : 100,000 (106). Most are inherited in a Mendelian pattern as autosomal dominant traits, and most affect only skeletal muscle without defects of heart, peripheral nerve, or the central nervous system. Progress in understanding the pathomechanisms for the channelopathies of skeletal muscle has been rapid in comparison to the pace of discovery for other heritable disorders, which often involves a novel gene product, because the functional properties of the mutant gene product – a voltage-gated ion channel – has been extensively well characterized over the past 60 years (35, 102), the roles of various voltage-gated ion channels in the regulation of muscle

fiber excitability are well known (111), and the requirements of sarcolemma excitability to achieve effective excitation-contraction coupling are known. These concepts are now being tested with knock-in mutant mouse models that have advanced our understanding for the basis of muscle excitability (275, 278) and demonstrated proof-of-principle for therapeutic approaches to alleviate symptoms (277).

Disorders of Skeletal Muscle Excitability

The precise control of skeletal muscle contraction, orchestrated by the timing of impulses arriving at the axon terminals of motor neurons, requires a rapid and reliable signaling cascade that ultimately results in Ca^{2+} release from the sarcoplasmic reticulum (SR). The neuromuscular junction (NMJ) is a high-fidelity synapse wherein the post-synaptic end plate potential (EPP) elicited by a single nerve impulse normally exceeds the threshold for generation of a muscle action potential (274). Coupling of this EPP to the generation and propagation of an action potential throughout the muscle fiber is essential to achieve rapid and spatially uniform contraction. Propagated impulses travel from the NMJ longitudinally along the surface membrane of the muscle fiber (sarcolemma) and radially inward along the transverse tubules (2, 88) where depolarization induces a conformational change of $Ca_V1.1$ calcium channels that activates ryanodine receptors, the Ca^{2+}-release channels of the SR. When muscle excitability is altered, excitation-contraction coupling may be compromised to the extent that generation of force is impaired. As an extreme example, depolarizing neuromuscular blockers such as succinylcholine render the fiber inexcitable and result in flaccid relaxation of skeletal muscle that is desired during surgery. Changes in the electrical excitability of muscle, both acquired and inherited, are established causes of compromised muscle function in humans. A reduction of muscle fiber excitability may cause symptomatic weakness, as experienced commonly with fatigue during strenuous exercise (120). More severe derangements of fiber excitability are the primary cause of several inherited disorders of skeletal muscle and are the focus of this review. Intermittent failure of muscle fiber excitability causes transient attacks of severe weakness, called periodic paralysis. Conversely, anomalously enhanced muscle excitability may lead to sustained bursts of discharges that cause involuntary after-contractions, termed myotonia. Non-dystrophic myotonia and periodic paralysis are the cardinal features of several muscle diseases, all of which are caused by mutations of voltage-gated ion channel genes expressed in muscle (28, 139, 156). The functional defects of excitability in these disorders do not involve the motor neuron and are downstream from the generation of the EPP at the NMJ. Myotonic dystrophy is distinct from this group because of progressive muscle wasting and multiple organ involvement.

The channelopathies of skeletal muscle were the first human diseases shown to be caused by mutations of ion channels. The initial evidence came from a classic series of electrophysiological studies on biopsied muscle from myotonic goats and human myotonia congenita in the late 1960s, in which Shirley Bryant and colleagues discovered a severe loss of the chloride conductance in affected muscle (143, 144). Subsequently, the first identification of mutations in a human channelopathy were established for hyperkalemic periodic paralysis caused by missense substitutions of *SCN4A*, encoding the α subunit of the muscle-specific sodium channel $Na_V1.4$ (188, 205). Mutations of the chloride channel gene,

CLCN1, were established as the cause of myotonia congenita the next year (123), and subsequently there has been an explosive growth in the number of genes and diseases established to be channelopathies. In essence, ion channelopathies have been established for every ion channel gene family and every excitable tissue (muscle, heart, brain, peripheral nerve), epithelial transport system, or secretory endocrine organ. A PubMed search on "channelopathy" yielded 1532 papers since the term first appeared in the literature in 1995 (104). Published reviews of channelopathies are most often organized by affected organ, disease, or ion channel. The first book with a comprehensive overview of channelopathies appeared in 2000 (9). The channelopathies affecting skeletal muscle excitability have been reviewed in the clinical literature (137, 156, 195, 264) as well as in mechanistic reviews on the physiology of disease pathogenesis (27–29, 112, 136, 190, 235). An authoritative account of the historical developments and early electrophysiological studies of myotonia (pre-genomic, circa 1985) is available in the classic review by Rüdel and Lehmann-Horn (207).

Myotonia – enhanced muscle excitability with after-discharges

Signs and Symptoms—Individuals with myotonia complain of "stiffness" or "locking up" caused by an inability of muscles to relax after voluntary effort (99, 139). The after-contractions may persist for many seconds and produce discomfort but not the intense pain of a muscle cramp. The duration and intensity of myotonic after-contractions fluctuate over time, most prominently with a dependency on the level of muscle use (258). Myotonic stiffness is most prominent with the first forceful movements following a period of rest for several minutes. With repeated movements, the intensity of myotonia diminishes over seconds to minutes and may even become asymptomatic, a phenomenon called *warm-up*. Conversely, some affected individuals have paradoxical worsening of myotonic stiffness with repeated effort, or *paramyotonia*, which is also characteristically aggravated by muscle cooling. For example, grip myotonia of the hands or inability to open the eyelids after squinting commonly occurs in cold weather for patients with paramyotonia, whereas proximal muscles at core body temperature are unaffected. Additional triggers have been associated with worsening of myotonia including potassium administration, emotional stress, pregnancy, hypothyroidism, depolarizing general anesthetics, or cold exposure (99).

Examination of a patient with myotonia may be normal (fluctuation over time), have signs of myotonia, or show changes in muscle bulk (258). Testing for *action myotonia* is assessed by examining the ability of muscles to relax after forceful voluntary contraction (hand grip, forced eyelid closure) or stiffness of gait upon rising from a chair or quickly climbing a flight of stairs. *Percussion myotonia* (Figure 1) is detected as a persistent dimpling of the muscle in response to a tap with a reflex hammer (207). Myotonia does not cause spontaneous muscle activity or increased resistance to passive movement (increased tone). Maximal voluntary contractile force is usually normal, although some patients may have a very brief transient weakness (5 – 20 seconds, Figure 2) at the onset of forceful contraction (58, 199). Like myotonic stiffness, this transient weakness also diminishes with warm-up (210). Increased muscle bulk and definition with a body-builder appearance occurs in patients with moderate to severe generalized myotonia, secondary to hypertrophy from the involuntary "exercise" of myotonic contractions. The myotonic dystrophies present with

progressive muscle wasting and weakness, associated with myotonia (94). These are multi-system hereditary diseases caused by expanded nucleotide repeats (20, 145) leading to nuclear sequestration of RNA-binding proteins and subsequent defects in post-translational processing of many transcripts (183), including the skeletal muscle chloride channel, ClC-1 (154). This review is focused on primary channelopathies of skeletal muscle excitability caused by mutations of ion channel genes, which are associated only with non-dystrophic forms of myotonia.

Electrodiagnostic features—In myotonia, the needle electromyogram (EMG) shows sustained bursts of muscle after-discharges (99, 208) that persist tens of seconds to minutes after cessation of voluntary contraction or occur in response to provocation by moving the needle (Figure 3). The amplitude and frequency of discharges wax and wane (20 to 80 Hz) which often produces a characteristic “dive bomber” discharge on an audio monitor (99). *Latent myotonia* may be detected electromyographically in asymptomatic patients. The intensity of myotonic discharges (number of active motor units, firing frequency, prevalence on separate needle insertions) and the duration of the bursts correlate with the magnitude and duration of the involuntary after-contraction. Experimental evidence that myotonia originates from the muscle fiber, independent of neuronal input, was first demonstrated in 1939 in goats with congenital myotonia (21). The myotonic discharge and after-contraction, elicited mechanical percussion, were unchanged after complete block of neuromuscular transmission with curare, motor neuron transection, or chronic denervation. The same result was subsequently verified in human myotonia by application of curare during anesthesia (132).

Taken together, these observations provide convincing evidence that myotonic after-contractions are caused by prolonged bursts of action potentials that are generated by the muscle fiber, independent of neuronal activity. The myotonic discharges vary in amplitude and frequency, and may result in SR Ca^{2+} release sufficient to produce sustained contraction.

Overview of mechanisms: reduced Cl conductance or $Na_V1.4$ gain-of-function —All forms of myotonia, whether acquired or inherited, are caused by one or a combination of two possible mechanisms: a reduction of the resting chloride conductance or gain-of-function changes to the voltage-dependent gating of $Na_V1.4$ sodium channels. The initial discovery of a membrane defect underlying susceptibility to myotonia was from microelectrode studies of muscle fibers isolated from goats with hereditary myotonia (Figure 4) (143). The input resistance of fibers from myotonic goats was elevated, with a commensurate decrease in current threshold to elicit an action potential, and ion flux measurements revealed greater than a two-fold decrease in chloride permeability. Similar changes were confirmed in fibers from humans with myotonia congenita (144). Moreover as a proof of principle for the chloride hypothesis, replacement of external Cl^- with an impermeant anion, such as SO_4-, caused normal muscle to develop myotonia (1). Details on the role of the chloride conductance (G_{Cl}) in stabilizing the resting potential and suppressing after-discharges are presented below, under **Chloride Channel Myotonias**. Molecular genetic confirmation of these insights provided by electrophysiological studies was shown

20 years later with the identification of mutations in CLCN1 encoding the ClC-1 chloride channel in myotonic adr mice (236), humans (123), dogs (197), and goats (14). A review in 2002 listed more than 60 mutations of *CLCN1* in patients with non-dystrophic myotonia, most of which had loss-of-function changes confirmed in expression studies (190).

The ability of an altered sodium current to cause myotonia was initially demonstrated by application of the toxin veratridine, which stabilizes the open state and results in bursts of muscle action potentials (261). As further evidence for involvement of sodium channels in myotonia, an anomalous persistent TTX-sensitive current was identified in muscle from patients with myotonia plus periodic paralysis (138, 140). Mutations of *SCN4A* encoding $Na_V1.4$ were subsequently identified in association with hyperkalemic periodic paralysis (188, 205), paramyotonia congenita (187), and sodium channel myotonia (141). Functional expression studies of mutant channels have revealed a variety of gain-of-function defects with impaired inactivation (30, 281) or enhanced activation (48).

Model simulations of muscle excitability show that either reduced G_{Cl} (1) or modest gain-of-function changes for $Na_V1.4$ (31) are sufficient to produce myotonic responses. The two effects act synergistically to increase the likelihood of myotonic discharges. For example, the minimum reduction of G_{Cl} required to produce myotonia is less, as the voltage-dependence of $Na_V1.4$ activation is shifted to more negative potentials (228).

Periodic Paralysis – transient loss of excitability

Symptoms and triggers—The hallmark of familial periodic paralysis is recurrent episodes of weakness, lasting minutes to hours, with spontaneous full recovery (73, 134, 264). Weakness may be regional or generalized, and the severity varies from mild to flaccid paralysis with inability to sit, stand, or walk. Attacks occur at irregular intervals, daily in some to only a few in a lifetime for others, with no regular periodicity despite the name. Patients often notice weakness upon awakening in the morning. Episodes may also start while awake, in which case the onset is gradual, without sudden drop attacks. The muscles of respiration, swallowing, and extraocular movements are relatively spared, such that respiratory failure rarely occurs. Provocation of attacks by environmental stresses is a characteristic feature of periodic paralysis. Rest, after a period of vigorous exercise, is a common trigger. Other exacerbating factors include carbohydrate-rich meals, shifts of serum potassium (high or low), exposure to cold, emotional stress, or pregnancy. Over time, some patients develop a slowly progressive permanent weakness with onset in the fourth or fifth decade that usually affects the proximal leg muscles and is associated with vacuolar myopathy (179).

Electrodiagnostic features—Between episodes of paralysis, the EMG is normal. In a severe attack, muscle excitability is profoundly depressed with a loss of the normal transient activity from needle insertion, and voluntary effort recruits few to no motor units (68, 226). Motor nerve stimulation may fail to elicit a detectable compound muscle action potential (CMAP), and similarly, no electrical activity is seen in response to direct field stimulation of muscle. When permanent muscle weakness is present, the EMG may have myopathic motor unit potentials (small amplitude, polyphasic).

The CMAP exercise test combines the provocative effect of muscle exertion with a quantitative assessment of muscle fiber excitability to screen for periodic paralysis (76, 163, 246). A baseline CMAP response is established at a low stimulation frequency of 3 Hz, and then the patient exerts maximum voluntary effort in either the short-exercise (10–12 sec) or long-exercise (5 min, with brief rest every 30 sec) protocol. The patient then relaxes and the CMAP is monitored over 3 to 60 min. Normally the CMAP amplitude is stable, but in periodic paralysis there will often be a profound decrement (> 50%) as muscle excitability becomes compromised. The CMAP exercise test is more sensitive for detecting periodic paralysis than monitoring maximal voluntary force after exercise.

Final Common Pathway – failure to maintain V_{rest}—In all forms of periodic paralysis, both familial and sporadic, the transient loss of muscle excitability during an attack of weakness is caused by depolarization of the resting membrane potential, V_{rest} (46, 209). Depolarization inactivates $Na_V1.4$ channels, which renders the fiber chronically refractory, unable to generate an action potential. Three different mechanisms have been identified by which mutant channels cause susceptibility to depolarization and loss of excitability in periodic paralysis. The first to be elucidated was a persistent Na^+ current (138) caused by a defect of inactivation wherein 1% to 2% of channels remained open even at strongly depolarized potentials (30). Subsequently, additional gain-of-function changes in gating were identified for mutant $Na_V1.4$ channels, with other defects of inactivation (47, 281) or a hyperpolarized shift of activation (48). All of these changes result in anomalously increased inward Na^+ current and depolarization. The second mechanism is loss-of-function changes for inward rectifier potassium channels, Kir2.1 (185), Kir2.6 (218), and possibly Kir3.4 (124). The K^+ permeability of muscle is a major determinant of V_{rest}, and at this hyperpolarized voltage range (−80 to −90 mV) the K^+ current is carried predominantly by Kir channels. A reduction in the resting K^+ conductance destabilizes V_{rest} and favors depolarization. The newest mechanism to be established is an inward cation current created by missense mutations at arginine residues in the S4 segments of the voltage-sensor domains of $Na_V1.4$ (229, 243) or $Ca_V1.1$ (278). The anomalous current is not conducted through the channel pore, but instead ions traverse the interface between the helical S4 segment and the “gating pore” of the channel through which the S4 segment translocates (232, 233, 252). This so-called gating pore current is voltage-dependent and active at hyperpolarized potentials where the S4 is biased toward inward displacement. The gating pore current amplitude at V_{rest} is small, ~0.5 $\mu A/cm^2$, and therefore causes only a few mV of depolarization. More importantly, the gating pore current increases the susceptibility to paradoxical depolarization in low $[K^+]_o$ and thereby results in K-sensitive periodic paralysis (29, 242).

The Myotonia – Periodic Paralysis Spectrum of Disorders in Muscle Excitability

The ion channelopathies of skeletal muscle give rise to a spectrum of clinically delineated muscle disorders (Figure 5) that span a continuum of altered membrane excitability (28, 74). At one extreme are disorders with enhanced excitability that cause only myotonia, while the opposite end includes forms of periodic paralysis with intermittent failure of excitability and no myotonia. Several disorders straddle these extremes (paramyotonia congenita or hyperkalemic periodic paralysis) such that an affected individual may have fluctuating

episodes of myotonia or periodic paralysis. Collectively, the non-dystrophic myotonias and periodic paralyses are all caused by mutations in genes coding for voltage-gated ion channels (28, 136). The tissue expression of these genes is skeletal-muscle specific for chloride (ClC-1), sodium ($Na_V1.4$), and calcium ($Ca_V1.1$) channels, and consequently patients have symptoms limited to skeletal muscle function. The inward rectifier potassium channels associated with periodic paralysis (Kir2.1, Kir3.4) are expressed in both skeletal muscle and non-muscle cells and thereby cause multi-system disorders with arrhythmia, cranio-facial features, dental anomalies, short stature, and malformed digits (185, 256). The inheritance pattern is autosomal dominant for all the channelopathies of skeletal muscle, with the important exception of ClC-1 mutations in myotonia congenita, which is most often recessive but may be dominant or semi-dominant (190, 235).

Chloride Channel Myotonias

Clinical Features of Myotonia Congenita

Congenital myotonia with an autosomal dominant inheritance pattern was first published in the late 19th century by the Danish physician, Thomsen, who described the disorder in family members and was affected himself (250). Almost 100 years later, a recessive pattern was reported by Becker (15). Recessive generalized myotonia congenita is the more common form, and most patients are compound heterozygotes (176, 190), in other words two different CLCN1 mutations transmitted from each parent. Patients with myotonia congenita (MC) develop symptomatic muscle stiffness in childhood, with muscles of the legs being most commonly affected and handgrip myotonia detectable on examination for three quarters of patients (258). Myotonia is more severe in recessive MC, and in response to the involuntary after-contractions many patients develop muscle hypertrophy with a body-builder appearance (Figure 1A). The intensity of myotonic stiffness varies with activity and is most pronounced with sudden forceful movements after rest, which may also trigger a brief episode of weakness lasting 5 to 20 seconds (58, 199). Relief from muscle stiffness occurs with repeated low-level muscular activity (warm-up) in the majority of patients with MC (258).

Role of the Chloride Channel, ClC-1, in Muscle Excitability

Skeletal muscle has a remarkably high conductance to Cl^- of about 1 mS/cm^2 and constitutes 80% of the total resting membrane conductance (103, 174). In resting fibers the Cl^- current is small since the equilibrium potential is near V_{rest}. The Cl^- current is a major contributor, however, to repolarization from an action potential (1). Skeletal muscle is thereby unique amongst excitable tissues in that the contribution from Cl^- rivals that of K^+ during repolarization. In essence, the large chloride conductance acts as an electrical buffer to stabilize the membrane potential at its resting value. The equilibrium potential for Cl^-, E_{Cl}, is depolarized ~ 3 mV from V_{rest} (5) due to Cl^- influx via the Na^+-K^+-$2Cl^-$ cotransporter (NKCC) which maintains the internal [Cl^-] slightly higher than predicted for passive electrochemical equilibrium (263, 273).

The high chloride conductance of skeletal muscle is a consequence of the robust expression of ClC-1, which is undetectable in other tissues except for trace amounts in heart (238). In

muscle from neonatal mice, ClC-1 mRNA and Cl^- current density are low and increase over the first 20 days of life (122, 150). The ClC-1 channel is a homodimer (62, 70) with a "double-barrel" pore created by a pair of 1.5 pS protopores from each subunit that gate independently and a common gate that regulates both (192, 223). The open probability is about 20% in resting muscle, and ClC-1 is activated by depolarization. The voltage-dependence of gating is less steep than for most voltage-gated cation channels (e-fold per ~25 mV versus e-fold per ~5 mV, respectively) and external Cl^- facilitates opening (191), suggesting the permeant anion contributes to the voltage-sensing machinery. In addition to the effects of voltage and external Cl^-, the gating of ClC-1 is also modified by pH (219) and ATP (17).

ClC-1 Mutations Produce a Variety of Loss-of-Function Defects

A plethora of mutations in CLCN1 have been identified in patients with myotonia congenita. A review from 2008 cataloged more than 130 mutations associated with MC (149). In recessive MC, missense and nonsense mutations of CLCN1 that destroy the potential to code for a functional ClC-1 channel are often identified. Voltage-clamp studies of mutant ClC-1 constructs expressed in oocytes or HEK cells have provided insights on the mechanism for the inheritance pattern. Missense or truncation mutations in recessive MC express poorly at the surface membrane (175) and result in small or undetectable Cl^- currents, and when co-expressed with WT constructs do not impede the assembly of functional channels (127, 148). Other recessive mutations have caused unusual changes, for example an inverted voltage-dependence of activation for D136G, such that the mutant channel opens only at voltages negative to E_{Cl} (71). A depolarized shift of activation is commonly observed for missense mutations of ClC-1 associated with recessive or dominant MC (Figure 6) (193). Mutations with smaller shifts of +10 to +20 mV or those with shifts that are compensated by co-expression of WT ClC-1 occur in recessive MC. Conversely, MC mutations with dominant inheritance produce large positive shifts for activation, even when co-expressed with WT ClC-1, and thereby dramatically reduce the open probability at the muscle resting potential of −85 mV. The dominant MC mutation P280L was identified in descents of Thomsen (237) and when co-expressed with WT caused a +90 mV shift of activation (193). One relatively common mutation, R894x, has been associated with recessive (165) or dominant (86) inheritance of MC. Expression studies in oocytes showed a reduced Cl^- current density, but no voltage shift of activation. Co-injection of WT/R894x resulted in current amplitudes about 30% of normal, which is on the borderline for causing myotonia and thereby may explain why the inheritance may be dominant or recessive (165). Taken together, a multitude of studies have demonstrated that mutations of CLCN1 associated with MC cause loss-of-function changes, with dominant-negative effects from protein-protein interaction of the dimeric ClC-1 resulting in susceptibility to myotonia, whereas haploinsufficiency from a recessive allele is subclinical (43).

Pathophysiologic Mechanisms for Myotonia with low G_{Cl}

The vital role of the Cl^- conductance in skeletal muscle to stabilize V_{rest} and promote repolarization at the end of the action potential was initially surprising in a cation-centric view of cellular excitability, where Na^+ and K^+ were the dominant players. Convincing evidence was provided by demonstrating that normal mammalian muscle develops myotonia

if the extracellular Cl^- is replaced with an impermeant anion such as SO_4^- (Figure 4) (1). The large reduction of the total resting conductance in Cl^- - free saline also caused a decrease in the current threshold required to elicit an action potential (rheobase) and prolonged the time course of the electronic depolarization toward threshold, just as occurred in fibers from myotonic goats. Pharmacologic studies with a series of aromatic carboxylic acids that inhibit G_{Cl} produced myotonia in rat muscle (80). Moreover, the concentration required to produce myotonia was closely correlated to the G_{Cl} inhibition constant for each compound. In general, a reduction of G_{Cl} by about 80% was required to cause myotonia, but this value was not absolute. Higher Ca^{2+} (2.0 mM vs 0.5 mM) and cooler temperature (22 °C vs 30 °C) diminished the myotonic responses. Subsequently, it was shown that over a range of 0.3 to 2.0 mM elevated Ca^{2+} or Mg^{2+} substantially reduce myotonic after contractions in a 9-anthracene carboxylic acid model of in rat muscle (228). The mechanism remains to be established, but in higher Mg^{2+} the authors observed an increase of 4–6 mV for the threshold to elicit an action potential and suggested the reduced excitability may suppress myotonia from a depolarized shift of sodium channel activation by external divalent. Even with the variability of myotonic responses from these environmental modifiers, the requirement for a reduction of G_{Cl} by more than 50% to produce myotonia is clearly established experimentally (80) and supported by computational models (3). This observation explains why a single null allele for ClC-1 is not sufficient to cause symptomatic myotonia in recessive MC.

A distinctive feature of myotonia is the sustained bursts of after-discharges that persist for many seconds after the cessation of stimulation to the muscle fiber. Fibers are not spontaneously active, and so the question is what drives the activity-dependent burst? Adrian and Bryant postulated that activity-dependent accumulation of extracellular K^+ was the source of the depolarization that sustained bursting behavior (1). Potassium efflux from the myoplasm contributes to the repolarizing phase of an action potential and occurs across both the surface membrane (sarcolemma) and the transverse tubule system (T-tubules). The long narrow geometry of the T-tubules (c.a. 40 nm diameter reticular network extending across a 30 μm fiber radius (178)) severely limits equilibration with the interstitial fluid by passive diffusion. Moreover, the high surface area to volume ratio for cylindrical T-tubules (2/radius = 0.1 per nm, equivalent to 10^6 cm^2 / ml) results in a substantial increase in T-tubular $[K^+]$ of about 0.4 mM from the outward K^+ current associated with repolarization after a single action potential (3, 31, 267). Normally an influx of Cl^- also contributes to repolarization, thereby reducing the requirement for K^+ efflux. Moreover, the high Cl^- conductance opposes the depolarization of V_{rest} induced by T-tubular K^+ accumulation. In fibers from myotonic goats or in Cl^- - free conditions, K^+ accumulation in the T-tubules produces an after-depolarization of V_{rest} lasting hundreds of msec (1). The effect is cumulative, such that high frequency stimulation produces additive K^+ accumulation and a progressive after-depolarization of V_{rest} by ~1 mv / spike (Figure 4 E and F). After a few stimulus-evoked spikes, the depolarized shift of V_{rest} may be sufficient to create a myotonic run with self-sustained bursts of action potentials. This proposed mechanism is supported by the effects of “de-tubulation” on myotonia. T-tubules may be physically decoupled from the sarcolemma using transient hyperosmolar shock. The shrinking and then re-swelling of the fiber disrupts the T-system such that the sarcolemma remains intact and excitable but

depolarization is not transmitted to the T-tubules (60). Fiber de-tubulation prevents the after-depolarization of V_{rest} and abolishes myotonic after discharges (1, 32).

The localization of ClC-1 channels to the sarcolemma alone or to both the sarcolemma and the T-tubules remains an unresolved area of investigation. Measurement of G_{Cl} changes with detubulation suggested the chloride conductance is primarily sarcolemmal in frog (64), whereas studies in rat fibers implied a substantial Cl^- conductance in the T-tubules (59, 174). Complementary studies on mechanically skinned fibers demonstrated a large T-tubular G_{Cl} in mammalian fibers and a smaller but significant T-tubular contribution in amphibian muscle (45, 61). Optical studies of T-tubular voltage transients in mouse muscle also supported the notion of a large G_{Cl} in the T-tubules (55). Subsequent to the cloning of ClC-1, immunohisotchemical staining and expression of GFP-tagged channels suggest ClC-1 is localized exclusively to the sarcolemma in adult mouse skeletal muscle (93, 151). This controversy raises the question of whether the membrane compartment localization of ClC-1 is predicted to have an important influence on the susceptibility to myotonia. While the impression may be that to prevent myotonia ClC-1 must be localized to the compartment where K^+ accumulation occurs (235), the first simulation to account for T-tubule effects showed that the sarcolemmal G_{Cl} was sufficient to suppress myotonia (3). The impact of G_{Cl} localization on fiber response to K^+ accumulation depends on the magnitude of the access resistance at the entry zone of the T-tubules (31). With higher access resistance, e.g. 150 Ω-cm^2 estimated for amphibian muscle (2), localization of G_{Cl} to the T-tubules has increased importance in suppressing myotonia. Optical measurements of T-tubule voltage transients in mouse muscle (54) have revealed much greater coupling between sarcolemmal and T-tubular voltages than was predicted for models of amphibian muscle (4). In the extreme case of perfect electrical coupling between sarcolemmal and T-tubular membranes, only the total G_{Cl} would be relevant, and not the membrane localization, to prevention of myotonia.

The mechanisms for the “warm-up” reduction of myotonia with continued muscle activation and for the initial transient weakness (Figure 3) remain unknown. Proposed mechanisms for warm-up include Na/K-ATPase up-regulation, decreasing intracellular pH, or K^+ shift into the T-tubules. Experimental support for K^+ and pH effects have been obtained in model systems (18), whereas ouabain inhibition of the Na/K-ATPase was without effect in humans (262). One hypothesis for warm-up is that the progressive increase in T-tubular [K^+] during sustained activity produces a sufficiently large depolarization of the membrane voltage between spikes such that post-spike recovery from inactivation by sodium channels is impeded. The reduced sodium channel availability will decrease fiber excitability and may prevent myotonic discharges. If this were the case, then warm-up should be dependent on basal extracellular [K^+] at rest. In a mouse model of myotonia created with low Cl^- or ClC-1 block by 9-AC, warm-up was faster and myotonic after-contractions were less forceful with higher external [K^+] (18). It has also been proposed that warm-up results from an activity-dependent reduction in intracellular pH. For this same mouse model, lowering pH by increasing the CO_2 bubbled into a bicarbonate bath greatly reduced myotonia at pH 7.0 or lower (18). Another possible mechanism to produce warm-up is use-dependent changes in G_{Cl}, for MC patients with residual ClC-1 function. Repetitive high-frequency stimulation for seconds produces a PKC-dependent decrease in G_{Gl}, perhaps to augment excitability and

thereby limit fatigue, followed by a large sustained increase (181, 182). These changes could conceivably increase, and then decrease, the likelihood of myotonic discharges.

Therapeutic Management of Myotonia Congenita

The mainstay for symptomatic management in MC is avoidance of activities that trigger myotonic responses (139). Sudden forceful contractions are to be avoided, and instead, a gradual increase of muscular exertion is used to promote warm-up before developing symptomatic muscle stiffness. About 60% of MC patients with genetically confirmed CLCN1 mutations reported worsening of myotonia with muscle cooling (258), while the older literature states cold-sensitivity is prominent only for paramyotonia congenita (200), a disorder caused by $Na_V1.4$ mutations. Therefore avoidance of cold environments may also be beneficial. Use-dependent blockers of voltage-gated sodium channels (tocainide (206), mexitetine (53, 234, 258), flecainide (52)) are effective at reducing the severity of myotonia, regardless of whether the underlying defect is loss-of-function for ClC-1 or gain-of-function for $Na_V1.4$. This observation demonstrates the principle that effective drug therapy for ion channelopathies may be achieved through modulation normal channels, rather than targeting the drug to correct the altered behavior of the causative mutant ion channel. In principle, augmentation of G_{Cl} would be the most direct therapeutic approach for MC patients with some residual ClC-1 function. Despite screening efforts, potent and selective activators of ClC-1 have not been identified. The carbonic anhydrase inhibitor acetazolamide produced a dose-dependent left shift of activation for ClC-1 expressed in HEK cells (63), but this effect has yet to be confirmed in muscle. Moreover while lower pH increases opening for recombinant ClC-1 (219), acidosis reduces opening in muscle (174, 180), and this difference may result from coupling to an intracellular ATP-dependent mechanism (259). The activity of ClC-1 is inhibited by PKC, but attempts to augment G_{Cl} with the PKC inhibitor staurosporine were unable to cause improvement for fibers from myotonic goats (22).

Sodium Channelopathies of Muscle

Clinical Spectrum of Sodium Channel Disorders

Several distinct clinical syndromes have been associated with mutations of SCN4A that produce missense amino acid substitutions in $Na_V1.4$. The phenotypes include myotonia, periodic paralysis, and in rare cases myasthenia (Figure 5, Table 1). Involvement of the sodium channel was initially established from microelectrode studies of biopsied fibers from patients with hyperkalemic periodic paralysis (HyperPP) and a closely related disorder, paramyotonia congenita (PMC). Affected fibers had a small persistent TTX-sensitive current activated around −70 mV that was not observed in control muscle (138, 140). In HyperPP the predominant symptom is recurrent episodes weakness, often occurring in association with elevated blood K^+ levels (5 to 6.5 mM) (114, 139). Inheritance is dominant with high penetrance. Attacks usually begin in childhood and are triggered by ingestion of K^+-rich foods or rest after vigorous exercise. An episode typically lasts for 30 to 120 minutes, and strength between attacks is normal, although patients may report being less than 100% for days. Permanent proximal weakness of the legs, associated with vacuolar myopathy, develops around age 50 for a subset of HyperPP patients, especially those with the common T704M mutation (114). Myotonia may be present symptomatically or by EMG in patients

with HyperPP, particularly with the onset of an attack of weakness. For PMC, the major symptom is myotonic stiffness that often has a striking temperature sensitivity with worsening in a cold environment. The eyelids, face, and hands are most often effected, likely because these muscle groups are more susceptible to cooling. Myotonia paradoxically worsens with repeated effort (paramyotonia) as contrasted with the warm-up improvement in myotonia congenita. With pronounced cooling or after strenuous exercise, patients with PMC may experience an attack of weakness typical of HyperPP. In some families, either HyperPP or PMC features occur in different affected individuals having the same mutation (161), which is further evidence for the overlap of these syndromes. The anomalous TTX-sensitive currents observed in HyperPP and PMC muscle led to initial genetic screens based on a targeted disease-gene approach (75), in which mutations coding for missense substitutions of $Na_V1.4$ were identified (188, 205).

A second group of $Na_V1.4$ disorders presents with dominantly inherited myotonia, but no periodic paralysis. The myotonic stiffness may be mild (myotonia fluctuans (201, 202)) or sufficiently severe to interfere with respiration and swallowing (myotonia permanens (52, 82, 141)). Still others have K^+-sensitive myotonia (potassium-aggravated myotonia (100)). The clinical presentation for these patients is difficult to distinguish from those with dominant myotonia congenita caused by ClC-1 mutations (Thomsen's disease), although the CMAP changes after exercise may provide some discrimination (76). Collectively, this group of disorders is given the name sodium channel myotonia (SCM) (137).

Hypokalemic periodic paralysis (HypoPP) is most frequently caused by mutations in $Ca_V1.1$ (60% of families), but in 20% of families the causative mutation is in $Na_V1.4$ (23, 116, 239). The clinical presentation is very similar for either gene defect, with the primary symptom being recurrent attacks of weakness in the setting of hypokalemia ($K^+ < 3.5$ mM). Weakness is triggered by carbohydrate rich meals, which in response to rising glucose and insulin promotes K^+ uptake into muscle, or by rest after vigorous exercise. Patients often awaken with an episode of weakness. With either gene defect, late-onset permanent myopathy may occur. Myotonia does not occur in HypoPP, including those patients with $Na_V1.4$ mutations. While genetic testing is required to establish whether the causative mutation is in $Na_V1.4$ or $Ca_V1.1$, several features of the clinical presentation provide guidelines for which gene is more likely to be affected (239). Some women with $Ca_V1.1$ mutations do not experience transient attacks weakness, whereas the penetrance is very high for patients with $Na_V1.4$ mutations. Acetazolamide is beneficial for about 50% of HypoPP patients with $Ca_V1.1$ mutations but is ineffective or even deleterious in HypoPP from $Na_V1.4$ mutations (159). The long-exercise CMAP test may show an initial post-exercise increase for $Na_V1.4$ – HypoPP, followed by the diagnostic late decrease which also occurs in $Ca_V1.1$ – HypoPP (76). Finally, the histological changes are predominantly T-tubular aggregates for $Na_V1.4$ – HypoPP, whereas $Ca_V1.1$ mutations most commonly cause vacuolar myopathy.

Two families have been described for which de novo mutations of $Na_V1.4$ caused a myasthenic pattern of weakness (8, 260). Patients had generalized weakness during brief exercise, attacks of weakness involving the face and soft palate, and a decremental CMAP response during repetitive stimulation at 10 Hz and 50 Hz. These features are typical of disorders with a reduced safety factor for synaptic transmission, as occurs with diseases of

the neuromuscular junction. Electrophysiological studies, however, revealed intact synaptic function with a normal amplitude endplate potential (EPP). The defect was in the conversion of the EPP into a propagated muscle action potential because of missense mutations in $Na_V1.4$.

The Na^+ Channel in Skeletal Muscle

Voltage-gated sodium channels are integral membrane protein complexes comprised of a single pore-forming α subunit and one or more associated β subunits (34, 84). Expression of the α subunit alone is sufficient to produce a voltage-activated conductance that is selective for Na^+ and blocked by tetrodotoxin (TTX). The α subunit contains 4 homologous domains (I–IV), each with 6 transmembrane segments (S1–S6) with the S4 segment serving as a voltage sensor with positive residues (arginine or lysine) at each third position on the transmembrane α helix (245). The β subunits influence membrane localization through interactions with the extracellular matrix and intracellular cytoskeleton (25). These accessory subunits also modify the voltage-dependence and kinetics of channel gating (37, 107, 270). In the human genome, 9 distinct genes code for α subunit isoforms and 4 genes code for β subunits. The sodium channel complex in skeletal muscle is a non-covalent heterodimer $\alpha\beta_1$ (12). The skeletal muscle α subunit is predominantly $Na_V1.4$ encoded by SCN4A (85), with a minor contribution of about 10% (79) by the TTX-insensitive isoform $Na_V1.5$ (SCN5A), which is the major α subunit in the heart (83) and is up-regulated in chronically denervated skeletal muscle (280). The β_1 subunit encoded by SCN1B is ubiquitously expressed in all excitable tissues and is non-covalently associated with α subunits. Mutations of β_1 have been associated with epilepsy syndromes (177, 266) and arrhythmia (268, 269), but do not have a skeletal muscle phenotype.

The sodium channel of skeletal muscle activates rapidly (< 1 ms) in response to depolarization and conducts a large inward current (~5 mA/cm^2) that produces the fast depolarizing phase of the action potential (dV/dt ~ 500 mV/ms). The local Na^+ current density is higher at the endplate zone and can reach levels of 100 mA/cm^2, as shown with the loose-patch technique (152, 217). This clustering of sodium channels increases the safety factor of neuromuscular transmission by ensuring a suprathreshold EPP always triggers a local action potential. Fiber type differences in Na^+ current properties have also been reported. Fast-twitch type II fibers have about two-fold higher Na^+ currents and a depolarized shift of inactivation, as compared to currents recorded from slow-twitch type I fibers (213). In addition, the relative clustering of sodium channels at the endplate is higher for type II than type I fibers.

Functional Consequences of $Na_V1.4$ Mutations

Over 50 mutations of SCN4A have been associated with myotonia or periodic paralysis (28, 73, 113), and 2 have been reported in myasthenic syndromes. Aside from one rare exception that alters an intronic splice site in a family with myotonia (129), all SCN4A mutations occur in exons and cause missense mutations. The functional consequences of $Na_V1.4$ mutations identified in patients with myotonia or periodic paralysis have been studied extensively by heterologous expression in non-muscle cells lines, e.g. HEK or tsA201 (16, 33, 48, 95, 96, 168, 281) or frog oocytes (72, 198, 229, 241); whereas relatively few studies

have used primary cell lines established from patient muscle biopsies (30, 170) or recording from acutely dissected fibers (138, 140, 141, 209).

Gain-of-function defects—Mutations associated with HyperPP, PMC or SCM all produce gain-of-function changes for $Na_V1.4$ (Table 1) (26, 28, 136). Most often, this gain-of-function is produced by defects of channel inactivation, but in some cases the anomaly is enhancement of activation. The defects of inactivation that cause gain-of-function changes for mutant channels include (Figure 7): (a) impaired completeness of inactivation, as revealed by small persistent Na^+ currents for maintained step depolarizations (30, 141) or by large inward currents during a slow voltage ramps (33), (b) depolarized shift in the voltage-dependence of steady-state inactivation (95, 168), (c) slower rate of entry to the inactivated state (281), (d) faster rate of recovery from inactivation (95). These changes all affect conventional “fast” inactivation that occurs on a time scale of msec. Sodium channels also undergo slow inactivation over a time scale of seconds. Slow inactivation regulates channel availability in response to shifts of the resting potential (216) or in the setting of sustained trains of action potentials. The two modes of inactivation also involve distinct molecular mechanisms, since abolishing fast inactivation with internal proteases does not disrupt slow inactivation (212). Defects of slow inactivation are found in some mutant $Na_V1.4$ channels associated paralytic phenotypes in HyperPP / PMC but not in SCM, as evidenced by an increased fraction of channels that do not slow inactivate, by a depolarized shift, or by faster recovery (47, 96). The gain-of-function changes caused by altered activation are manifest by a hyperpolarized shift in voltage dependence (48) or slower rates of deactivation when open channels are hyperpolarized (72).

Loss-of-function defects—Mutations of $Na_V1.4$ associated with HypoPP or with myasthenic weakness cause loss-of-function changes. Mutations associated with myasthenia are in the voltage sensor of domain IV and cause enhancement of inactivation resulting from a large −25 to −35 mV hyperpolarized shift in voltage dependence (260). A milder loss-of-function from enhanced inactivation (−10 mV shift and slower recovery) has been observed for several HypoPP mutations in the voltage sensor of domain II (116, 244). Recordings from patient-derived HypoPP muscle fibers also showed a reduced Na^+ current density and action potentials with a slower rate of rise, even after fibers were strongly hyperpolarized with a holding current (116). The failure to restore Na^+ current density by hyperpolarizing the membrane implies that other loss-of-function defects, in addition to the shift in voltage-dependence of inactivation, must be present in mutant channels. Subsequently, a comparison of maximal gating charge displacement to peak Na^+ current revealed decoupling of voltage-sensor displacement to channel opening for HypoPP mutations in domain II (166). This decoupling impairs the efficiency of mutant channel opening in response to membrane depolarization.

Gating pore “leakage” current for R/X mutations of S4 in HypoPP—All 10 HypoPP mutations of $Na_V1.4$ occur at arginine residues in S4 voltage sensors of domains I–III (29, 158). These missense mutations are clustered at the N-terminal ends of S4 segments, toward the extracellular face of the membrane (Figure 8A). At hyperpolarized potentials, mutant channels conduct ionic current through an anomalous pathway in the voltage sensor

domain (229, 241, 243). These so-called gating pore or omega currents are interpreted to be a consequence of ion translocation through an aqueous pathway created by a crevasse between the mutated S4 residue and the protein scaffolding of the voltage sensor domain (Figure 8D). Voltage-dependent inward movement of the S4 segment within the "gating pore" favors the conducting state, whereas outward S4 movement with depolarization is non-conducting because the mutant residue is no longer in the narrow waist of the gating pore. Voltage-dependent gating pore currents for R/X substitutions in S4 were initially discovered K_V channels (232, 252) and have also been detected for homologous mutations in Ca_V channels (278). The conductance of an anomalous gating pore is small, about 1000-fold lower than for Na^+ through the conventional pore (166). In most cases the gating pore conductance is non-selective for monovalent cations, but the two R/H substitutions in S4 of domain II create proton-selective gating pores (243). Homologous mutations in the outer arginines of S4 in domain IV are associated with myotonia, not HypoPP, and expression studies failed to show gating pore current for the PMC mutant in DIV R1448C (78). Eight of the 10 R/X S4 mutations associated with HypoPP have been studied by heterologous expression in oocytes, and all showed gating pore currents activated at hyperpolarized potentials (29). Several families with R/X mutations at the third arginine in S4 of domain II (R675) have a mixed clinical phenotype with features of HypoPP or HyperPP and have therefore been categorized as potassium-sensitive normokalemic periodic paralysis (265). Expression studies in oocytes showed that all three substitution mutations at R675 resulted in gating pore currents activated by depolarization to potentials of −50 mV or greater (230), in sharp contrast to the hyperpolarization activated currents in HypoPP mutants. After prolonged depolarization, the voltage-dependence of gating pore opening was shifted leftward by −50 mV, perhaps because mutation of the third arginine residue in the DIIS4 voltage sensor stabilized the outward conformation. The net effect would be a gating pore current active at the resting potential, thereby transiently producing the equivalent leak that is associated with HypoPP mutant channels.

Pathophysiologic Mechanisms in Sodium Channelopathies

Genotype-phenotype correlations—Among the five allelic disorders caused by mutations of NaV1.4 (Table 1), the consistency of the genotype – phenotype correlation (114, 160, 167) has led to the notion that a mutation-specific alteration in channel function is causally related to the clinical expression of symptoms (26). For example, the T1313M mutation has been identified in several non-related families and affected individuals consistently have a PMC phenotype (160). Similarly, T704M causes HyperPP with late-onset permanent myopathy; whereas mutations at R672 in S4 of DII always produce a HypoPP phenotype (239). As might be anticipated from the overlap of symptoms for HyperPP and PMC, the genotype-phenotype association is not absolute. For example, inheritance of M1592V within a single family has produced HyperPP in some individuals, whereas others had features of PMC (119). The source of this phenotypic variability has not been established experimentally. Modifier genes or alleles have not been established for channelopathies of skeletal muscle. The challenge for understanding this phenotypic variability is illustrated by observations in quarter horses with periodic paralysis. All affected horses have a common Phe → Leu mutation of DIIIS3 in $Na_V1.4$ and can be traced to single sire (172) with a de novo mutation (211). Despite this single mutation being

expressed on a very homogenous genetic background of inbreed horses, the phenotype is variable with regard to severity and frequency of attacks, perhaps due to variability in the expression level of the WT and mutant alleles (285).

The mechanistic link between altered function of mutant $Na_V1.4$ channels and the phenotypic expression of myotonia or periodic paralysis has been explored using animal models and computer simulation. Both pharmacologic models that disrupt inactivation (32) and genetic models with knock-in mutant mice harboring missense mutations of $Na_V1.4$ (97, 275) have established that functional defects of $Na_V1.4$ alone are sufficient to produced myotonia and periodic paralysis. These experimental studies have been complemented by computer simulation of muscle excitability to test the consequence of specific defects in channel function. The sensitivity of the model to changes in simulated channel behavior has provided insights on the types of defects and the magnitude of the changes that are required to create susceptibility to myotonia or periodic paralysis (31, 112, 228).

Myotonia and hyperkalemic periodic paralysis—The model correlate of myotonia is self-sustained trains of action potentials that persist beyond the termination of a stimulus current; whereas periodic paralysis is manifest as a stable depolarized shift of the resting potential that renders the fiber refractory from generating action potentials (Figure 9). This approach has shown that specific types of defects, within the overall gain-of-function category, may cause a predilection for myotonia or paralysis that would account for the spectrum of symptoms in the SCM / PMC / HyperPP group of sodium channelopathies (26). For example, some $Na_V1.4$ mutations associated with SCM alter the kinetics of inactivation (slower entry, sometimes with faster recovery) without a change in voltage-dependence or the completeness of inactivation at depolarized potentials. These changes cause a transiently increased availability just after an action potential because fewer mutant channels inactivated during the spike. The elevated $Na_V1.4$ availability during this repolarizing phase may trigger a subsequent action potential. This effect is also potentiated by the modest depolarization caused K^+ accumulation in the T-tubules. The combined effects produce a train of myotonic after-discharges. In a gain of function model for SCM using anemone toxin to partially disrupt $Na_V1.4$ inactivation in rat muscle, the after-discharges were abolished by detubulation (32) which also abolishes after-discharges in myotonia caused by a reduced chloride conductance (1). The implication is that use-dependent T-tubular K^+ accumulation is an important contributor to the depolarization that drives myotonic discharges in fibers with $Na_V1.4$ or ClC-1 defects. Because this simulated $Na_V1.4$ defect affects only the rate of inactivation, without a persistent Na^+ current in steady-state, the model will never produce a stable depolarization of V_{rest} (Figure 9, *middle*), as occurs in paralysis (90). In contrast, the gain of function change for mutations associated with HyperPP is often an increase in the persistent current resulting from incomplete fast inactivation (30, 33). For WT $Na_V1.4$, the persistent current is barely perceptible, about 0.2% of the transient peak elicited by a step depolarization. Mutations associated with HyperPP disrupt the completeness of fast inactivation, which results in persistent Na^+ currents of 1 to 4%. Although the absolute amplitude of the anomalous persistent current is small, the relative increase is 5 to 20-fold which has a dramatic effect of membrane voltage for a simulated fiber (31). At the normal V_{rest} of −85 mV, mutant channels are closed and

the simulated fiber remains quiescent. In response to a brief stimulus, the inactivation defect is revealed and the fiber may respond with a myotonic burst. The repetitive firing produces a cumulative increase of T-tubular K^+ which in conjunction with the inactivation defect results in a steady inward Na^+ current that keeps the fiber depolarized at about −45 mV (Figure 9, *right*). From this depolarized potential the WT NaV1.4 channels and the majority of the HyperPP mutant ones are inactivated which renders the fiber inexcitable, as occurs in periodic paralysis. Mechanistically, the mutant allele has a dominant-negative effect, acting through voltage-dependent inactivation. The requirement for elevated extracellular K^+ (interstitial or T-tubular) to mildly depolarize the fiber and reveal the inactivation defect explains why attacks may be triggered or aggravated by potassium ingestion in HyperPP. A similar response is predicted for gain-of-function changes produced by a hyperpolarized shift of activation (96). In this case, the increased overlap of steady-state activation and inactivation creates a persistent “window current” in the −60 to −45 mV range.

Slow inactivation of $Na_V1.4$ is predicted to attenuate an anomalous steady-state Na^+ current arising from a disruption of fast inactivation, and thereby may prevent an attack of depolarization-induced paralysis (214). Voltage-clamp studies have demonstrated defects of slow inactivation for the two most common mutations found in HyperPP (T704M and M1592V) and for nearby mutations associated with HyperPP (L689I) or HyperPP/PMC (I693T) (16, 47, 96, 98). Every $Na_V1.4$ mutation for which a disruption of slow inactivation was identified has periodic paralysis as a prominent feature of the clinical phenotype. Conversely, not every HyperPP associated mutation has a detectable defect of slow inactivation. The interpretation is that a defect of slow inactivation dramatically increases the probability of a stable anomalous depolarization, however, because even for WT channels steady-state slow inactivation is only about 70 to 80% complete at −45 mV then a fast inactivation defect alone is also capable producing stable depolarized paralysis.

A conceptual framework for the contribution of various gating defects of mutant $Na_V1.4$ channels to clinically delineated muscle disorders is summarized in the Venn diagram of Figure 10. The overlap of functional defects, especially for the gain-of-function changes caused by altered inactivation, is consistent with continuum of clinical symptoms in these disorders and the occurrence of PMC or HyperPP within the same family (119). The functional defects associated with HypoPP and CMS (see below) are distinctly different, and correspondingly there is no clinical overlap with the SCM-PMC-HyperPP cluster of disorders.

A mouse model for HyperPP was created with a knock-in mutation for M1592V in S6 of domain IV (97). Heterozygous mice have myotonia by EMG and hindlimb stiffness with initial movements after rest. Histological studies showed a fiber type shift to more oxidative type IIa, presumably induced by myotonia leading to chronically increased electrical activity which is known to shift gene expression to an oxidative phenotype (13). Spontaneous attacks of weakness have not been observed, but in vitro challenge with 10 mM K^+ triggered a severe reduction of muscle force. Bath application of the carbonic anhydrase inhibitor acetazolamide protected against K^+-induced loss of force (77). Heterozygous M1592V muscle had an increased dependence on the Na^+/K^+-ATPase to maintain excitability, as shown by loss of force in ouabain. Conversely stimulation of the pump with salbutamol

restored force during high K^+ exposure (42). TTX-sensitive $^{22}Na^+$ influx was increased in resting muscle, thereby demonstrating the gain-of- function defect contributes to a resting internal Na^+ overload (42) as has been observed by MR spectroscopy in human patients (271).

Hypokalemic Periodic Paralysis—The anomalous gating pore leakage current produced by missense mutations at arginines of S4 voltage sensors in domains I–III is the most important contributor to attacks of weakness in HypoPP (29). The task is to understand how mutations of $Na_V1.4$ lead to susceptibility for paradoxical depolarization of V_{rest} in low external K^+. Early data supported the notion of an unusual source for the depolarizing current, since depolarization of HypoPP fibers in low K^+ was not prevented by the pore blocker TTX (116); nor did calcium channel blockers for $Ca_V1.1$ – HypoPP (215). The gating pore hypothesis is also supported by the observation that all 10 HypoPP mutations in $Na_V1.4$ are R/X substitutions in S4 segments (158) and that all 8 tested thus far by functional expression produced gating pore currents (78, 92, 229, 241, 243). At V_{rest}, the gating pore conductance in muscle heterozygous for a HypoPP mutation is estimated to be ~10 μs/cm^2 or about 1% of the total resting membrane conductance (166, 275). Gating pore currents are relatively non-selective for monovalent cations, except for R/H mutations in domain II which are proton selective (241, 243). In either case, the reversal potential for the gating pore current is close to 0 mV. In model simulations with 4.5 mM external K^+, the impact of this gating pore conductance on V_{rest} is small, being about 3 mV depolarization (242). As extracellular K^+ is lowered the fiber initially hyperpolarizes as expected for the negative shift in the Nernst potential for K^+, however, the contribution of the counter-balancing outward K^+ current from the inward rectifier, K_{IR} , diminishes. If external K^+ is low enough, then the K_{IR} current is overwhelmed by the inward currents conducted by the gating pore and ClC-1. This imbalance causes V_{rest} to depolarize until eventually the delayed rectifier K channel, K_{DR}, is activated and re-establishes a net current balance of 0 at about −65 mV (Figure 10). This paradoxical depolarization is the mechanistic basis for loss of excitability in low K^+ during an attack of HypoPP. Because paradoxical depolarization in low K^+ is a consequence of diminishing outward current through K_{IR}, normal muscle will also display this phenomenon, but only for extremely low K^+ values of ~1 mM (227). The presence of the gating pore current in HypoPP fibers causes this depolarization to occur at higher K^+ values of about 2.5 to 3.5 mM. A similar upward shift in the K^+ threshold sufficient to trigger paradoxical depolarization can be created in normal muscle with the ionophore gramicidin, thereby adding credence to the “leak” mechanism for susceptibility to HypoPP (117). This proposed mechanism is also supported by the fact that loss-of-function defects of K_{IR}, either through Ba^{2+} block (81, 242) or disease mutations (185), produce K^+-sensitive periodic paralysis.

The Cl^- gradient is an important modifier for susceptibility to depolarization of HypoPP fibers in low K^+ (87, 277). This effect is a consequence of the high Cl^- conductance of resting muscle. The reversal potential for Cl^- is about 3 mV depolarized from V_{rest} (5) because the influx of Cl^- through the Na^+-K^+-2Cl^- transporter (NKCC) maintains an internal [Cl^-] slightly higher than the concentration predicted for a passively established gradient at V_{rest} (263). Therefore the resting efflux of Cl^- through ClC-1 channels tends to

depolarize the fiber. The paradoxical depolarization of V_{rest} in response to low K^+ has a region of bistability, that is to say two possible values for V_{rest}: normally polarized and depolarized. As K^+ is further reduced, only the depolarized V_{rest} state exists. If K^+ is progressively increased from this state, then repolarization of V_{rest} occurs only after K^+ is at the high end of the bi-stable region. In other words, this nonlinear system has hysteresis for the paradoxical depolarization of V_{rest} in low K^+. The Cl^- gradient biases the bistable region of the response by favoring the hyperpolarized V_{rest} for low internal Cl^- of about 7 mM versus a value of about 15 mM to be permissive for the depolarized state (58). This variation of the Cl^- gradient is the critical "state variable" of the system that enables bi-stability of V_{rest} to exist. This model predicts that reduction of internal Cl^- should be protective against attacks HypoPP whereas increased internal Cl^- would increase the likelihood of an attack (87). Indeed, inhibition of the NKCC transporter with bumetanide prevents the loss of force from a low K^+ challenge in the knock-in mouse model of $Na_V1.4$-HypoPP (Figure 11C) (277). Conversely, stimulation of NKCC by hypertonic challenge can trigger an attack. This osmotic effect operating through NKCC may explain why high salt intake or dehydration can worsen attacks of HypoPP.

Additional mechanisms have been proposed as contributing to the reduced fiber excitability during an attack of weakness in HypoPP. Partial decoupling of voltage sensor movement to channel opening has been observed for R669H and R672G in S4 of domain II, and may be a general feature of R/X mutations in HypoPP (166). This defect reduces the peak Na^+ current and therefore also reduces excitability, independent of a failure to maintain a hyperpolarized V_{rest}. In all five HypoPP mutations tested to date, inactivation was enhanced, either by a leftward shift of voltage-dependence or a slower rate of recovery (92, 116, 244). These changes will also reduce fiber excitability. The cause of late-onset permanent myopathy is unknown.

Myasthenic weakness—Myasthenia attributable to mutations of $Na_V1.4$ is very rare, with only two reported individuals. Both were associated with missense mutations in the S4 of domain IV and resulted in severe loss of function defects from enhanced inactivation. The V1442E mutation shifted the voltage dependence of inactivation leftward by −33 mV (260). At a resting potential of −85 mV, greater than 90% of the mutant channels would be inactivated, thereby effectively causing haploinsufficiency and a 50% reduction of the Na^+ current. In the second reported case, the proband was homozygous for R1457H and heterozygous carriers in the family were asymptomatic (8). Expression studies in HEK cells revealed −15 mV left shift of inactivation and a 10-fold slower rate of recovery from inactivation. While the reduction of sodium channel availability at the resting potential is not as severe for R1457H (~50% available), the homozygous inheritance would produce an equivalent reduction in Na^+ current density. Voltage-clamp protocols using brief pulses at high frequency (> 30 Hz) caused pronounced use-dependent reduction in peak Na^+ current for either mutant channel compared to WT. The proposed mechanism for the fatigable weakness of myasthenia is compromised neuromuscular transmission resulting from a marginally adequate population of available (non-inactivated) Na^+ channels at V_{rest} , that compromises the fidelity with which the (normal) EPP elicits a propagated action potential in the muscle fiber.

Therapeutic Management of Sodium Channelopathies

The first-line approach for management of myotonia and periodic paralysis from $Na_V1.4$ mutations is to avoid provocative maneuvers that trigger attacks (139). For myotonia, this implies avoiding sudden forceful contractions after rest or avoiding cold environments for those with PMC. Attacks of post-exercise weakness in periodic paralysis are minimized by slowly warming up and then warming down after exercise. The frequency and severity for episodes of weakness in HyperPP can be reduced by avoiding K^+-rich foods, eating a carbohydrate snack to truncate an episode, or promoting kaliuresis with diuretics. Conversely, for HypoPP symptoms may be prevented by taking K^+-supplements and avoiding large carbohydrate-rich meals. Even with these measures, many patients still have debilitating symptoms. Use-dependent sodium channel blockers, such as mexiletine, are effective for symptomatic reduction of myotonia (52, 234). Curiously, sodium channel blockers have not been effective in reducing episodes of weakness in HyperPP even though the pathomechanism is clearly from gain-of-function changes in mutant $Na_V1.4$ channels. Carbonic anhydrase inhibitors, such as acetazolamide or dichlorphenamide, are effective as prophylactic agents to reduce attack frequency and severity in HyperPP, but are much less effective or even detrimental for HypoPP from NaV1.4 mutations (222, 239). In contrast about 50% of patients with HypoPP from $Ca_V1.1$ mutations have a favorable response (159, 248). The mechanism by which carbonic anhydrase inhibitors protect against attacks of periodic paralysis remains incompletely understood. The logical suggestion is that inhibition of carbonic anhydrase acts through an effect on pH regulation (157), but a specific mechanism for how that would influence susceptibility to attacks of HypoPP is not clear. Alternatively, the beneficial effect of acetazolamide may be through promoting the opening of Ca-activated K^+ channels (254). In vitro, KATP channel openers such as cromakalin repolarize fibers and restore muscle force in HypoPP (89). The same strategy could improve strength in HyperPP, however, this approach is limited by vasodilation with hypotension and hyperpolarization of pancreatic beta cells which reduces insulin secretion. In the knock-in mouse model of $Na_V1.4$ HypoPP, the NKCC inhibitor bumetanide protects against low K^+ induced weakness and can even restore muscle force during an attack (Figure 11C) (277). As expected, this inhibitor of Cl^- influx does not protect against HyperPP which is not sensitive to the Cl^- gradient. Controlled trials of bumetanide have not yet been performed in patients with HypoPP.

Calcium Channelopathies of Skeletal Muscle

Clinical Syndromes Associated with $Ca_V1.1$ Mutations

Missense mutations of CACNA1S encoding $Ca_V1.1$, the pore-forming α_1 subunit of the skeletal muscle L-type Ca^{2+} channel, have been associated with hypokalemic periodic paralysis (HypoPP) (115, 189), and in rare instances, susceptibility to malignant hyperthermia (MHS) (169, 253). About 60% of families with HypoPP will have a missense mutation of $Ca_V1.1$ (239). Symptoms typically begin at puberty with recurrent episodes of severe weakness in association with serum $K^+ < 3.5$ mM. Myotonia does not occur in HypoPP, but rather is an exclusionary criterion for the diagnosis (137). Attacks are triggered by rest after vigorous exercise or carbohydrate load (109). Late-onset permanent weakness of proximal muscles often occurs in the fifth or sixth decade. The prevalence of transient

attacks is reduced for women, especially those with the $Ca_V1.1$ R528H mutation, while most will still have late-onset permanent weakness (65, 142). This observation implies the pathogenesis for the vacuolar myopathy in permanent weakness is not strongly dependent on cumulative injury from recurrent transient attacks.

Malignant hyperthermia is a pharmacogenomic disorder in which otherwise asymptomatic individuals are susceptible to life-threatening hyperthermia, muscle rigidity, acidosis, rhabdomyolysis, and arrhythmia triggered by volatile anesthetic agents (e.g. halothane) or depolarizing muscle relaxants such as succinyl choline (153). MHS is an autosomal dominant trait mapped to multiple loci and is most commonly associated with mutation of the skeletal muscle ryanodine receptor gene (RyR1) encoding the Ca^{2+} release channel of the SR (204). Five mutations of $Ca_V1.1$ have been identified in patients with MH events, some of which were fulminant with anesthesia-related death (169). These MHS mutations are distinct from those in $Ca_V1.1$ associated with HypoPP, and none of these patients had episodes of periodic paralysis. Conversely, there is a lack of agreement about whether HypoPP carries a slightly increased risk of MHS (24, 135, 155).

Role of $Ca_V1.1$ in Skeletal Muscle

The L-type Ca^{2+} channel of skeletal muscle functions as a voltage-sensor for initiating depolarization-induced Ca^{2+} release from the SR, and as a voltage-gated Ca^{2+} channel (10, 164). Calcium channels are localized to the junctional membrane of the transverse tubules where four $Ca_V1.1$ channels are arranged as tetrads in register with the subunits of every-other RyR1 tetramer (19). Entry of external Ca^{2+} is not required to trigger Ca^{2+} release from the SR (7), because voltage-sensor movement of $Ca_V1.1$ is coupled to activation of RyR1 (203, 247). Voltage-dependent activation of the $Ca_V1.1$ ionophore is slow in comparison to the 3 msec duration of a muscle action potential. Nevertheless, in response to repetitive stimulation or prolonged depolarization, large slow myoplasmic Ca^{2+} transients have been observed in muscle fibers (40). This excitation-coupled Ca^{2+} entry (ECCE) is clearly distinct from store-operated Ca^{2+} entry (SOCE) that is triggered by SR Ca^{2+} depletion, but the physiological relevance to health and disease remains to be established (56).

The skeletal muscle L-type calcium channel is a heteromeric complex of $Ca_V1.1$ with auxiliary $\alpha_2\delta$-1, β_{1a}, and γ_1 subunits (10). The expression of $Ca_V1.1$, β_{1a}, and γ_1 subunits is primarily limited to skeletal muscle. The β_{1a} subunit promotes trafficking to the plasma membrane, facilitates the assembly of tetrads, and is essential formation of a functional channel complex (91, 240). The calcium channelopathies of skeletal muscle in humans are all caused by mutations of $Ca_V1.1$, with no disorders attributed to mutations of auxiliary subunits. The decline is muscle function with aging, however, is associated with an increase in β_{1a} expression, as well as a reduction in $Ca_V1.1$ levels (51).

Altered Function for $Ca_V1.1$ Mutations in HypoPP and MHS

The analysis of $Ca_V1.1$ mutations has lagged behind that of other channelopathies of skeletal muscle because of the need to perform functional testing in a skeletal muscle context rather than heterologous expression cell lines or oocytes.

Seven of the 9 HypoPP mutations in $Ca_V1.1$ are R/X missense substitutions of S4 in the voltage sensors in domains II–IV (29, 158). The others are one residue away from R1 in S4 of domain III (H916Q) or in an adjacent S3 of domain II (V876E). This clustering of HypoPP mutations at arginines in S4 segments led to the hypothesis that an anomalous gating pore current, homologous to those observed for $Na_V1.4$ HypoPP mutant channels, would also occur for HypoPP mutations in $Ca_V1.1$. Indeed, voltage-clamp studies of acutely dissociated fibers from the $Ca_V1.1$ R528H knock-in mouse model for HypoPP revealed a hyperpolarization activated gating pore current (278). Moreover, the magnitude of $Ca_V1.1$ gating pore conductance (14 $\mu S/cm^2$) was comparable to the defect observed for $Na_V1.4$ HypoPP fibers (275). Prior studies in biopsied muscle from HypoPP patients with R528H or R1239H showed anomalous inward currents at hyperpolarized potentials, and these “cation leakage” currents were most likely gating pore currents conducted by mutant CaV1.1 channels (117, 215). Modest loss-of-function changes with reduced current density and slower activation kinetics were reported in voltage-clamp studies of Ca^{2+} currents in R528H fibers from the knock-in mouse , human HypoPP myotubes in culture (R528H) (170), for mutant $Ca_V1.1$ expressed in oocytes (R528H, R1239H/G) (171) or othrologs in $Ca_V1.2$ expressed in HEK cells (131). Studies of excitation – Ca^{2+} release by the SR in R528H mouse fibers showed a modest impairment in heterozygous fibers (analogous to the human disease state) and severe release defects in homozygous mutant fibers (278). In the homozygous state, swollen T-tubules and dilated SR with severe vacuolar changes were present, which was most likely the cause of the Ca^{2+} release defect rather than dysfunction of $Ca_V1.1$ per se. Basal myoplasmic Ca^{2+} levels and SR Ca^{2+} content were normal.

Five mutations of $Ca_V1.1$ have been identified in MHS, and three have been tested functionally by expression in *dysgenic* myotubes that are null for the endogenous $Ca_V1.1$ channel. Surprisingly, SR Ca^{2+} release in response to depolarization was only mildly affected, and the largest changes were observed for L-type Ca^{2+} currents. The R1086H channel had reduced P_{open} (272), while T1345S had accelerated activation (184), and R174W had the most severe defect with no channel opening expect with strong prolonged depolarization or in the presence of agonists (11).

Pathophysiologic Mechanisms for Calcium Channelopathies

Acute attacks of weakness in HypoPP are caused by depolarization of V_{rest} that paradoxically occurs in low external K^+ (209). Susceptibility to this anomalous depolarization appears to be caused by the gating pore leakage current, resulting from the R/X missense mutations in S4 voltage sensors of $Ca_V1.1$. Data in support of this proposal are that hyperpolarization-activated gating pore currents were detected in fibers from R582H knock-in mutant mice (278), and that similar currents have been reported in human R528H and R1339H fibers (117, 215). The other 5 HypoPP mutations from R/X substitutions in S4 of $Ca_V1.1$ have not been tested, but the likelihood of gating pore currents is high, especially for 2 of these which are at the same residues (R528G, R1239H). The HypoPP mutations in S3 or adjacent to R1 in S4 may also result in gating pore currents, as has been observed for similar mutations in K_V channels (251). Further support for the notion that the gating pore current is the critical feature in common with $Na_V1.4$-based and $Ca_V1.1$-based HypoPP is provided by the observation that the Cl^- gradient is a potent modifier for susceptibility to

attacks of weakness for either gene defect. Just as with $Na_V1.4$-HypoPP, in $Ca_V1.1$-R528H mice reduction of internal Cl^- with the NKCC inhibitor bumetanide protects against loss of force, whereas activation of NKCC by hyperosmolality triggers loss of force (276). The histopathology of $Ca_V1.1$ - HypoPP often shows prominent vacuolar changes with dilated T-tubules and SR; whereas $Na_V1.4$-HypoPP has T-tubular aggregates (139, 239). Perhaps this difference occurs because the gating pore leak for $Ca_V1.4$ is localized primarily to the triad, whereas the $Na_V1.4$ gating pore leak is distributed over the sarcolemma and T-tubules. An important hormonal modification of disease expression is demonstrated by the delayed onset until puberty, and the substantially lower incidence of acute paralytic attacks in females compared to males. This sex difference also occurs in the susceptibility to loss of force in low K^+ for the $Ca_V1.1$-R528H mouse model of HypoPP, but the basis for this difference remains unknown (278).

Other mechanisms that may contribute to the acute attacks of weakness in HypoPP have been proposed. A reduction of the inward rectifier K^+ current (215), possibly from a loss of MgADP stimulation of K_{ATP} channels (255), has been reported in fibers from patients with the R528H mutation. The connection between a $Ca_V1.1$ mutation and altered K_{ATP} channel activity is not clear, but reduction of the inward rectifier K^+ current would produce increased susceptibility to paradoxical depolarization. Myoplasmic Na^+ overload and muscle edema have been detected by MRI in resting muscle of HypoPP patients with $Ca_V1.1$ or $Na_V1.4$ mutations (117). Moreover, the chronic loss of muscle strength correlated with the severity of the Na^+ overload, suggesting a myotoxic effect from an inward Na^+ leak.

The $Ca_V1.1$ mutations associated with malignant hyperthermia susceptibility cause marked changes in the L-type Ca^{2+} current and only modest changes in depolarization-induced Ca^{2+} release from the SR (66, 184, 272). Nevertheless, challenge with caffeine or volatile anesthetics for these models systems expressed in *dysgenic* myotubes causes enhanced SR Ca^{2+} release – the hallmark of MHS. Basal Ca^{2+} levels are elevated in *dysgenic* ($Ca_V1.1$ null) myotubes and are corrected by expression of WT $Ca_V1.1$ (67). This observation has led to the proposal that $Ca_V1.1$ inhibits Ca^{2+} leak from basal RyR1 activation, as well as the more widely recognized role as the voltage sensor for excitation-contraction coupling. Indeed, expression of the MHS mutant R147W in dysgenic myotubes does not correct the high basal Ca^{2+} (66). Taken together, these data suggest disrupted inhibition of RyR1 leakiness by $Ca_V1.1$ mutations may cause MHS (10). The potential of a specific pathogenic role for the divergent effects on the L-type Ca^{2+} current remain to be established. Furthermore, MHS from $Ca^V1.1$ mutations can occur without substantial changes in excitation-contraction coupling.

Therapeutic Management of Calcium Channelopathies

The clinical approach to symptom management in HypoPP is a combination of preventive measures and pharmacotherapy (73, 134, 137). Frequency and severity of acute attacks of weakness are minimized by dietary selection of K^+-rich foods, avoiding large carbohydrate meals, and gradually warming up for strenuous exercise and then warming down. Oral K^+ supplementation of 40 to 80 mEq per day is often used by patients. There is a risk of escalating self-administration or of rapid intravenous correction in the emergency

department. While the serum K^+ may be alarmingly low, in the 1.7–2.5 mM range, it is important to recognize that total body K^+ is not depleted. Rather, K^+ has shifted to the intramuscular compartment and will return to the interstitial and vascular spaces as the attack resolves. Carbonic anhydrase inhibitors (acetazolamide or dichlorphenamide) are beneficial in reducing attack frequency and severity in about 60% of HypoPP patients with $Ca_V1.1$ mutations (159, 248). The mechanisms by which carbonic anhydrase inhibitors are beneficial in CaV1.1 – HypoPP are not understood, but include the possibilities discussed above under periodic paralysis in sodium channelopathies. The K_{ATP} channel opener diazoxide reduced the susceptibility to weakness and hypokalemia in response to a glucose challenge (110). Spontaneous attacks of weakness were also decreased, but the benefits waned over a few months and the side effects of hypotension and hyperglycemia have limited the use of this approach. In theory, the therapeutic approach with the greatest specificity would be drugs that block of the gating pore current, but no clinically relevant candidates have been identified. Reduction of myoplasmic Cl^- using the NKCC inhibitor bumetanide completely prevents low-K^+ induced loss of force in the R528H mouse model, and is able to restore about 50% of the loss in force when applied during an established attack (276). A clinical trial of bumetanide in HypoPP has not been done. Because bumetanide is a potent loop diuretic that promotes K^+ loss in the urine, the clinical introduction of this drug for HypoPP must be done judiciously. While chronic therapy would likely require monitoring of serum K^+ and administration of K^+ supplements, bumetanide may be particularly beneficial as intermittent abortive therapy for an established attach. Moreover, reversing the shift of K^+ back out of the intramuscular compartment is likely to have a greater effect on increasing serum K^+ toward the normal range than the reduction from increased kaliuresis.

Malignant hyperthermia is managed as a life-threatening emergency by immediate discontinuation of any potential triggers, administration of dantrolene to inhibit SR Ca^{2+} release, hyperventilation if hypercapnia is present, correction of acidosis, and fluid resuscitation to maintain blood pressure. The treatment protocol is the same for MH caused by $Ca_V1.1$ or RyR1 mutations. Moreover, most instances occur without prior knowledge of the genotype. There are no distinguishing clinical features of an MH episode that would indicate a $Ca_V1.1$ versus an RyR1 defect. Only a few cases of MH are known to be caused by CaV1.1 mutations, which limits a comparative analysis to those from RyR1 mutations, but the available data do show that $Ca_V1.1$-based episodes may result in death and that an abnormal sensitivity to halothane or caffeine is detected by in vitro contraction testing for relatives who have inherited the trait.

Potassium Channelopathies of Skeletal Muscle

Clinical Syndromes Associated with Kir Mutations

The potassium channelopathies of skeletal muscle are all caused by mutations in the Kir superfamily of inward rectifier K^+ channels and present as dominantly inherited periodic paralysis without myotonia. The Andersen-Tawil Syndrome (ATS) is multisystem disorder for which the full spectrum is a triad of K^+-sensitive periodic paralysis, ventricular arrhythmias, and a dysmorphic features (249). The penetrance of the clinical phenotype is

highly variable such that even within the same family affected individuals may have two or only one feature of the full triad. Episodes of periodic paralysis occur in about 65% of individuals with an ATS mutation (257). Sampling of blood K^+ levels during spontaneous episodes of weakness in ATS most often reveals hypokalemia (50) but may also show hyperkalemia, or normokalemia (221). Glucose challenge has triggered attacks and induced hypokalemia in some patients, consistent with HypoPP, whereas K^+ administration has triggered attacks in others, consistent with HyperPP. The long-exercise CMAP test shows an abnormal response with a late decrement of > 40%, similar to other forms of periodic paralysis (246). A variety of arrhythmias have been reported in ATS including long QT interval (LQT7), ventricular tachycardia, bigeminy, and prominent U-waves even with normal K^+ levels (57, 257). The dysmorphic features of ATS are small chin, wide set eyes (hypertelorism), low set ears, curvature of the 5^{th} digit on the hands or feet (clinodactyly), scoliosis, and short stature. An ATS locus was mapped to 17q23, and sequencing of candidate ion channel genes led to the identification of mutations in KCNJ2 encoding the Kir2.1 inward rectifier K^+ channel (185). About 60% of ATS patients have mutations of Kir2.1. In one large ATS family without a Kir2.1 mutation, exon capture resequencing led to the identification of a missense mutation in a G-protein activated inward rectifier K^+ channel, Kir3.4 also called GIRK4 (124).

Thyrotoxic periodic paralysis (TPP) presents with episodes of weakness similar to those in HypoPP, but in the setting of hyperthyroidism and with a striking male predominance (173). The clinical signs of hyperthyroidism may be mild in TPP, and attacks of severe weakness may occur without overt thyrotoxicosis(162). The CMAP exercise test shows a late decline in amplitude, consistent with a post-exercise loss of fiber excitability (6). When patients become euthryoid, the attacks of weakness stop, and the CMAP exercise test normalizes (108). The prevalence of TPP is much higher in Asia (China, Korea, Japan) than in North America or Europe (38, 173). About 2% of this high-prevalence group will have episodes of weakness while hyperthyroid, compared to 0.1–0.2% in other populations. The gender bias is even more dramatic, being about 50:1 male to female. Most cases of TPP are sporadic, but the occurrence of rare familial clusters (130) and the ethnic differences in prevalence rate suggest a genetic component. Screening of candidate ion channel genes identified mutations of KCNJ18 coding for the Kir2.6 inward rectifier K^+ channel (218). While TPP is the most common cause of periodic paralysis, only a minority of patients have an identified mutation in Kir2.6. Moreover, genetic screening of sporadic non-familial HypoPP, and without thyrotoxicosis, has revealed mutations of Kir2.6 (39).

Role of Kir Channels in Skeletal Muscle

The repertoire of K^+ channels in skeletal muscle is highly diverse, with experimental evidence from voltage-clamp, immunocytochemical, and molecular genetic studies supporting the existence of K_V, Kir, K_{Ca}, K_{ATP}, and perhaps two-pore K channels (126). The Ba^{2+}-sensitive Kir current is the major K^+ conductance that is active at V_{rest} and constitutes about 20% of the total resting conductance of the fiber (242). This current is typical of “strong” inward rectifiers formed by homotetramers and heterotetramers of members from the Kir2.x subfamily (101, 286). Rectification refers to the property that inward K^+ current for $V_m < E_K$ is larger than outward current for $V_m > E_K$ due to block by

internal Mg^{2+} or polyamines (147). While the expression of multiple Kir2.x transcripts has been detected in skeletal muscle, Kir2.1 has a central role as demonstrated by transcript abundance, the impact of Kir2.1 mutations in ATS (185), and that knock-out of Kir2.1 is neonatal lethal while Kir2.2 knock-out mice have only a mild phenotype (283). At the protein level, Kir2.1 is enriched in the T-tubule membrane and is also present in the sarcolemma (49, 125).

The Kir conductance is an important contributor for establishing V_{rest} and also promotes the clearance of high K^+ accumulation in the T-tubules. The voltage-dependent K_V and K_{Ca} channels are closed at V_{rest} whereas Kir channels remain active. Normally, V_{rest} in skeletal muscle is depolarized relative to the Nernst potential for K^+, and Kir channels exert a hyperpolarizing influence on V_m through the efflux of K^+ at rest. The strong rectification shuts off the Kir current as the membrane becomes more than about 20 mV depolarized from E_K, which prevents Kir from attenuating the action potential. With high-frequency firing during intensive muscle activity, the K^+ efflux through K_V and K_{Ca} channels produces a K^+ increase in the T-tubules that may reach 10 mM or higher (3, 41). In this scenario, E_K may shift to become depolarized relative to V_{rest} which is held negative by the Cl^- gradient (267). When $E_K > V_{rest}$ a large influx of K^+ will occur through Kir channels, thereby promoting the clearance of use-dependent K^+ accumulation in the T-tubules.

Functional Defects in Kir Mutant Channels Associated with Periodic Paralysis

Expression studies of ATS mutant Kir2.1 channels have revealed loss of function changes that have dominant negative effects when co-expressed with WT Kir2.1 or other Kir2.x subunits (185, 186, 257). All Kir2.x subunits have two transmembrane segments with an intervening pore loop and cytoplasmic N- and C-terminal domains. ATS mutations are clustered in the cytoplasmic ends, and often involve residues that are interaction sites for the membrane-bound phospholipid signaling molecule phosphatidylinositol 4,5-bisphosphate (PIP_2) which stabilizes the open state of Kir2.1 (57, 231). Screening mutagenesis studies have identified 3 PIP_2 binding sites in the C-terminus (231), with one being the PKKR motif (residues 186–189) that are mutated in ATS: P186L, R189I, as well as other neighboring positively charged residues R218W/Q. Mutations at these sites decrease both PIP_2 binding and Kir currents. The characterization of ATS mutations has been extended to a muscle cell context by performing recordings in myotubes cultured from muscle biopsies in ATS patients. The vital role of Kir2.1 was demonstrated by the absence of a Ba^{2+}-sensitive inward rectifier K^+ current and depolarization of the resting potential (220). The G387R variant in the C-terminus of Kir3.4 (GIRK4) has been reported in a family with ATS (124). While no functional evidence of GIRK channels exists in skeletal muscle, expression studies in oocytes showed that WT Kir3.4 negatively regulates the current amplitude of co-expressed Kir2.1. The G387R variant exhibited even greater suppression of Kir currents when Kir2.1 was co-expressed.

The Kir2.6 channel was initially identified as a new member of the Kir superfamily through a candidate gene approach in the search for causes of TPP (218). This channel has highest homology to Kir2.2 (98%), and when expressed in HEK cells produces K^+-selective channel with strong inward rectification. In the original report of Kir2.6 mutations associated with

TPP, one was a frameshift in the pore loop yielding a nonfunctional transcript, one missense mutation resulted in moderately reduced current amplitude, and the remaining four mutations had no discernable effect (218). Subsequent screening of KCNJ18 in patients with TPP or sporadic HypoPP led to the identification of 3 additional missense mutations of Kir2.6, and all had loss-of-function changes with dominant negative inhibition of WT Kir2.6 and Kir2.1 (39). Another proposal is that Kir2.6 regulates the surface expression of Kir2.1 and Kir2.2 (49). In this model, Kir2.6 trafficking to the surface membrane is poor, consistent with small currents observed in expression studies, and most is retained in the endoplasmic reticulum (ER). Association of Kir2.6 with Kir2.1 and Kir2.2 was demonstrated by immunoprecipitation and by co-localization. The mouse genome lacks KCNJ18, and when Kir2.6 was transiently expressed in adult fibers by electroporation, Kir2.1, Kir2.2, and Kir2.6 were retained in the ER.

Pathophysiology of Periodic Paralysis from Kir Mutations

The premise for understanding the mechanism by which Kir mutations cause susceptibility to periodic paralysis is that V_{rest} is depolarized during an acute attack of weakness. In support of this hypothesis, microelectrode recordings in biopsied fibers from patients with TPP showed baseline depolarization of V_{rest} that was worsened by exposure to low K^+ (105, 194). These studies preceded the discovery of Kir2.6 mutations in TPP, and so the status of Kir2.6 was not known. No published reports are available on V_{rest} of fibers in ATS, however, the late decremental response in the CMAP exercise test confirms an abnormal susceptibility to loss of fiber excitability for both TPP and ATS (6, 246). The depolarization of V_{rest} during an attack, in turn, is attributed to loss of function changes observed for Kir2.1 and Kir 2.6. Model simulations show that a reduced Kir conductance produces an equivalent scenario to the abnormal presence of a gating pore current. In the former, the outward current is diminished whereas in the latter the inward current is increased. Either change will cause the paradoxical depolarization of V_{rest} to occur at low $[K^+]$ values in the physiological range (29, 112, 242). In the simulations, the threshold to produce anomalous depolarization of V_{rest} is about a 50% reduction of the Kir conductance (224, 242). The notion that a loss of Kir produces susceptibility to periodic paralysis is also supported by the effects of Ba^{2+} on muscle fibers. Micromolar Ba^{2+} selectively blocks Kir channels, and promotes paradoxical depolarization (242) and loss of contractile force in low K^+ (81).

The multisystem deficits in ATS are consistent with the expression pattern for Kir2.1 and the loss of function caused by mutations. Kir2.1 is expressed predominantly in skeletal muscle, heart, and brain (128). In situ hybridization in embryonic rat also shows Kir2.1 mRNA in bony structures of the head, spine, and limbs (118). The pathomechanism for susceptibility to episodes of periodic paralysis, with the potential for K^+ sensitivity, is attributable to loss of Kir2.1 in skeletal muscle as detailed above. In heart, the I_{K1} inward rectifier current is important for setting the resting potential and shaping repolarization after the plateau phase of the cardiac action potential (225). The I_{K1} channel is a heterotetramer of Kir2.1 and Kir2.2 subunits (286), and Kir2.1 null mice lack a detectable I_{K1} in ventricular myocytes (284). Knock-out of Kir2.1 is neonatal lethal, but the EKG in 1-hr old pups shows bradycardia and microelectrode recordings showed prolongation of the action potential duration. Model simulations of a ventricular myocyte with a 50% reduction of I_{K1} resulted

in prolongation of the action potential duration, early after- depolarizations, and in low external K^+ delayed after-depolarizations (257). Taken together, these studies show the vital role of Kir2.1 in maintaining normal excitability of ventricular myocytes, which when disrupted may cause ventricular arrhythmias observed in ATS. The neonatal demise of Kir2.1 null mice is attributed to a severe cleft palate defect with 100% penetrance (283). This outcome demonstrates a role for Kir2.1 in the formation of bony structures, perhaps through hyperpolarization of the V_{rest} to provide the driving force for signaling through external Ca^{2+} entry.

The emergence of symptoms during hyperthyroidism in TPP may be related directly to changes Kir2.6 gene expression or indirectly through other mechanisms that impact muscle excitability. The KCNJ18 gene encoding Kir2.6 contains thyroid response element (TRE) motifs, and a reporter construct showed that exposure to triiodothyronine (T3) increased expression in C2C12 cells (218). Since Kir2.6 is mostly retained in the ER and is able to co-assemble with Kir2.1 and Kir2.2, the increased expression of Kir2.6 could reduce the total Kir conductance at the membrane (49). This inhibitory regulation by Kir2.6, combined with mutation-related loss of function changes as well, may produce T3-dependent attacks of paralysis. Additional effects of T3 may contribute to reduced fiber excitability with susceptibility to periodic paralysis. Proposed mechanisms include further reduction of Kir current cause by activation of PLC resulting in a reduction of PIP_2 and therefore reduced P_{open} for Kir channels (218), a reduction of the $Na_V1.4$ conductance (194), or increased Na^+/K^+-ATPase activity which may contribute to hypokalemia (36).

Therapeutic management for Kir Channelopathies of Muscle

The definitive therapy for TPP is treating the underlying thyroid disorder. Once a euthryoid state is achieved, the attacks of weakness will cease (196). The prognosis for full resolution of TPP is excellent, regardless of whether hyperthyroidism was autoimmune (Graves' disease) or from some other cause. Patients on thyroid replacement therapy have had recurrences of TPP associated with accidental exogenous hyperthyroidism (133). Management of attacks while waiting for thyroid function to normalize is centered on avoiding triggers (vigorous exercise or heavy carbohydrate load) and oral K^+ supplements as needed (162). Beta-blockers such as propranolol are reported to be beneficial in TPP (44, 282), but have not been studied in a randomized controlled trial. Acetazolamide is not effective in the prevention or management of weakness in TPP.

Therapeutic intervention is limited in ATS because the approach for improving muscle function may be at odds with managing cardiac symptoms (73). In a probable case of ATS in the early literature, acetazolamide was effective for the episodes of weakness, but did not prevent symptomatic ventricular arrhythmia with syncope (146). The ventricular ectopy in ATS is notoriously difficult to treat pharmacologically (256), and some antiarrhythmic agents have caused worsening of skeletal muscle function. The first-line drug of choice for arrhythmia is flecainide, a use-dependent sodium channel blocker, but some patients with life-threatening arrhythmia require an implantable cardioverter defibrillator.

Conclusion

Paroxysmal disorders of skeletal muscle excitability associated with myotonia and periodic paralysis are now firmly established to be caused by mutations of voltage-gated ion channels. The field has matured from a period of clinical fascination, to an era of disease gene discovery, with further advances through functional expression studies in cell-based systems, computer modeling of physiological systems, and now the generation of knock-in mutant mice. This most recent step holds great promise for advancing our understanding of disease mechanism in the high-fidelity context of a model system in mammalian muscle and for providing a platform for proof-of-principle in therapeutic investigation. Although all of these disorders are rare diseases, the insights gained from a mechanistic understanding of altered membrane excitability will have implications for more common diseases of excitable tissues such as epilepsy, arrhythmia, and some forms of migraine headache.

The voltage-gated ion channelopathies of skeletal muscle provide one of the best examples to trace a heritable human disease from gene defect, to altered function of the encoded protein, to disruption of cellular function, altered tissue performance, and clinical symptoms. Along the path of discovery, the study of these channelopathies has refined our understanding of structure-function relations of ion channels (mechanisms of inactivation (30, 95, 168, 281), gating pore current (229, 241)), demonstrated that modest changes in channel function under voltage-clamp may have a profound effect on excitability (small persistent Na^+ current (31)), led to the realization that seemingly esoteric features of gating can have important consequences for cellular homeostasis (slow inactivation and stability of V_{rest} (47, 96)), advanced our knowledge on the regulation of V_{rest} in muscle (paradoxical depolarization in low K^+ (87, 227)) and identified novel therapeutic strategies for symptomatic treatment (inhibition of NKCC (263, 277)).

Of course, much more remains to be accomplished. A causative gene defect remains to be identified in up to one-third of patients (160, 167). The functional studies have focused on the biophysical properties of mutant channels expressed at the surface membrane with much less investigation on the fate of mutant transcripts, post-translational processing, protein-protein interactions and subcellular targeting in muscle. Many questions also remain about the causal basis of robust clinical phenomena such as temperature sensitivity, warm-up from myotonia versus paramyotonia, or the trigger mechanism during rest after exercise. Finally, it is important to recognize that while many therapeutic approaches currently in use are based on sound well-established principles of cellular excitability, many patients continue to have disabling symptoms and more work is need to improve symptomatic treatment options.

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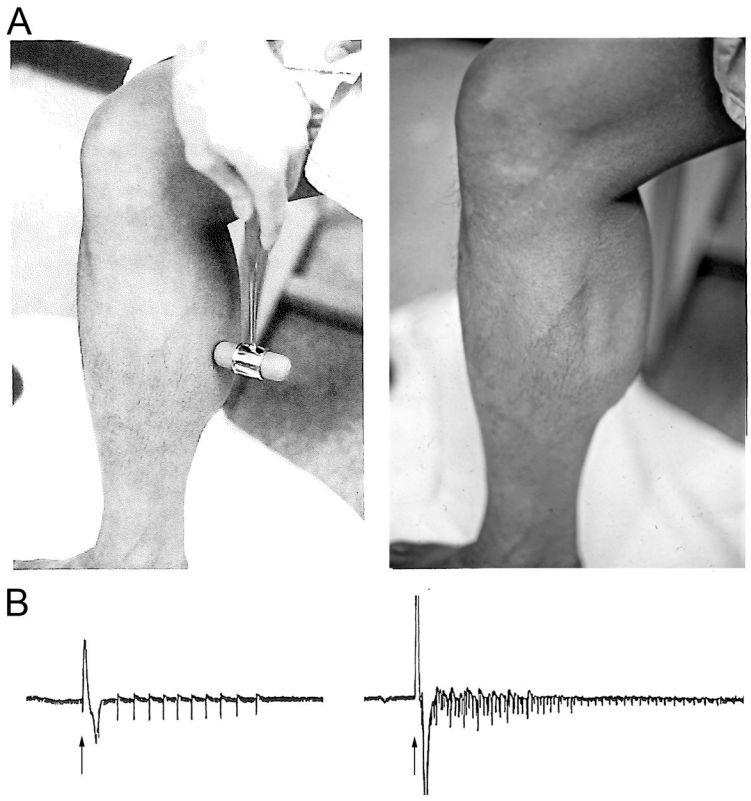

Figure 1.

Percussion myotonia in a patient with myotonia congenita. (A) The calf muscles are hypertrophied, and a direct tap with the reflex hammer elicits a sustained dimpling of the muscle. (B) The needle electromyogram shows myotonic discharges from a single fiber in response to a light tap (left) and from multiple fibers with a stronger tap (right). [Adapted, with permission from reference (99). Originally published in Muscle and Nerve 47:632–648, 2013.]

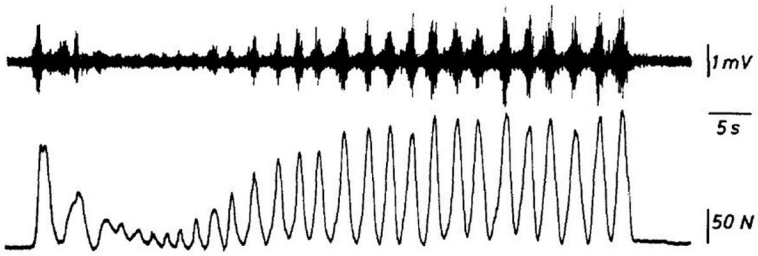

Figure 2.

Transient muscle weakness in severe myotonia congenita. The top trace shows the surface electromyogram and the bottom trace shows grip force recorded with forceful voluntary effort, after a period of rest. The maximum force decreases markedly after the second contraction, and at the same time the force between contractions does not return to baseline. The transient loss of force is accompanied by a marked decrease in muscle electrical activity. [Adapted, with permission, from reference (199). Originally published in J. Neurol. 218:253–262, 1978.]

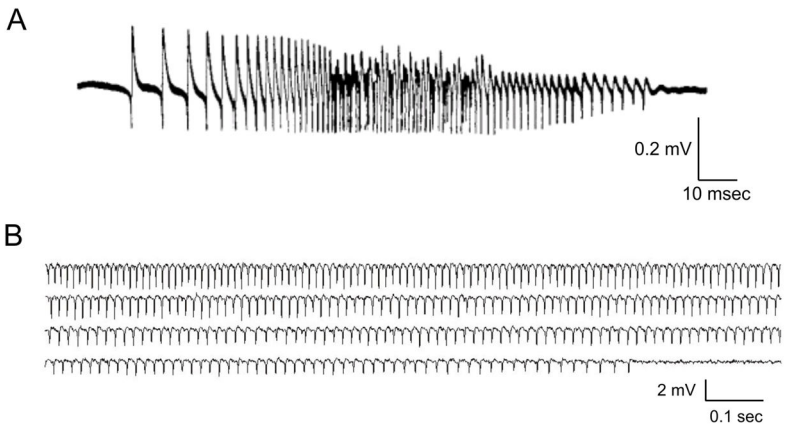

Figure 3.

Electrical myotonia recorded by needle EMG. (A) Burst of myotonic discharges elicited by needle movement shows the waxing and waning of amplitude and frequency. (B) A myotonic burst of discharges may be prolonged, as shown in this continuous EMG recording from the M1592V mouse model of hyperkalemic periodic paralysis. [(A) Reproduced with permission from (121). (b) Adapted with permission from (97). Originally published in J. Clin Invest 4:1437–1449, 2008.]

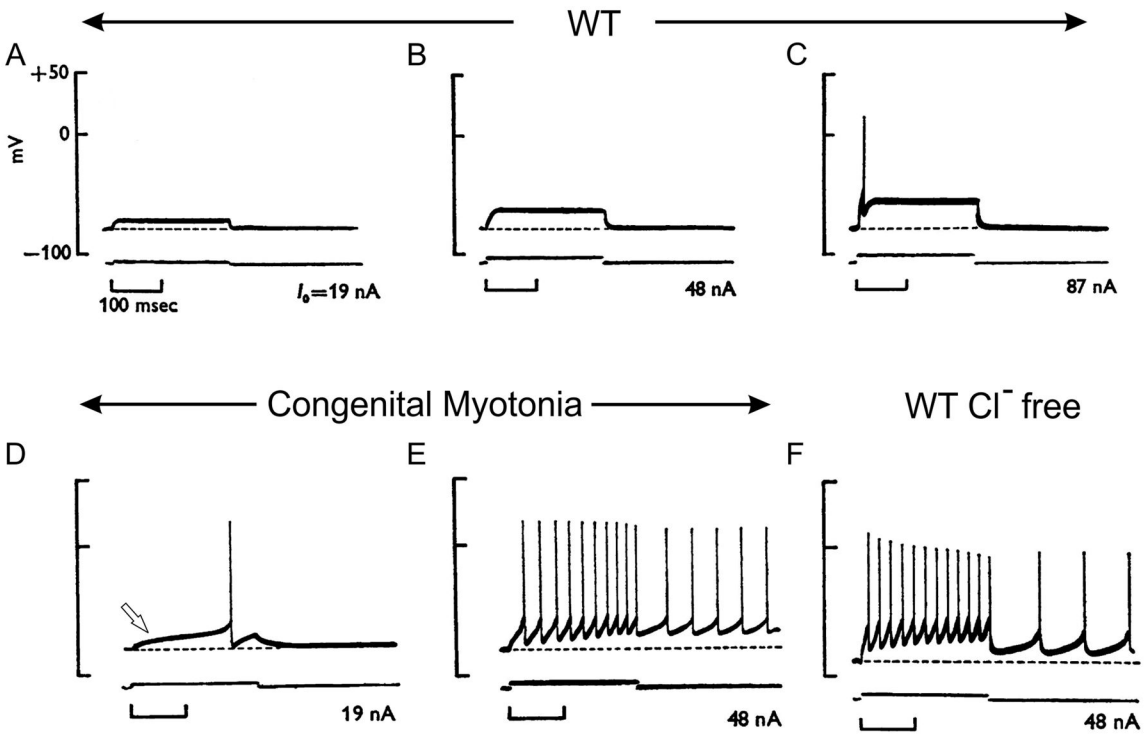

Figure 4.

Action potentials recorded with intracellular microelectrodes from intercostal fibers of wild type (WT) and congenitally myotonic goats. (A–C) Progressively increasing stimulus current in WT fibers elicits passive electrotonic responses until the action potential threshold of 87 nA. (D) Myotonic fibers have a lower threshold of 19 nA and a prolonged electronic approach toward threshold (open arrow). The electronic depolarization is about two-fold larger for myotonic fibers (D) compared to WT fibers with the same current intensity (A), thereby demonstrating an increased input resistance in the former. (E) Stimulus current of 2.5 times threshold elicits multiple spikes and after-discharges that persist beyond the stimulus duration. Notice the progressive depolarized shift in the membrane potential at the end of each spike. This shift reflects cumulative trapping of K^+ in the T-tubules. (F) Myotonic discharges are produced by WT fibers in a Cl^- free bath. [Adapted with permission from (1). Originally published in J. Physiol. 240: 505–515, 1974.]

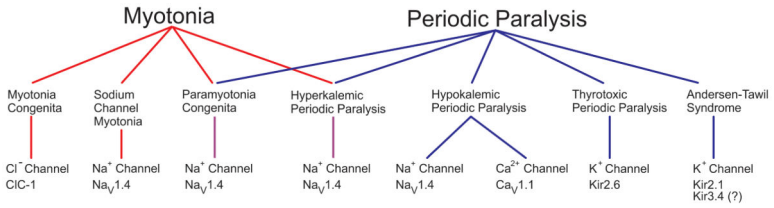

Figure 5.

Spectrum of ion channelopathies of skeletal muscle. The clinical presentation includes myotonia (left), periodic paralysis (right) or a combination of both (middle). The chloride channel disorder myotonia congentia may be dominant or recessive; all others have dominant inheritance. Symptoms are limited to skeletal muscle except for the systemic effects of thyrotoxicosis and Andersen-Tawil Syndrome which also affects heart and bone.

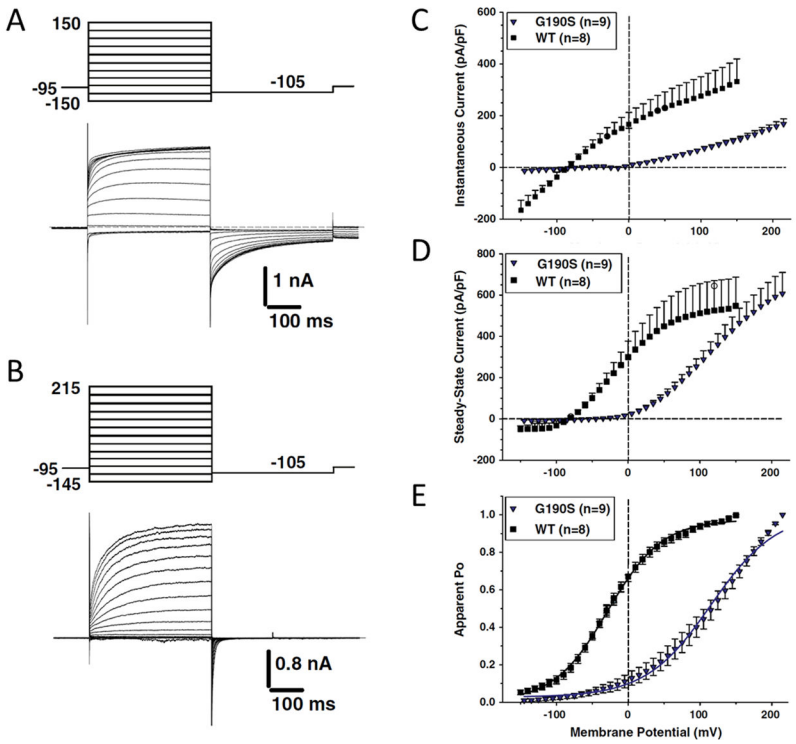

Figure 6.

Loss of function gating defects for ClC-1 G190S associated with dominant myotonia congenita. Chloride currents were recorded from HEK cells transfected with WT ClC-1 (A) or G190S (B). Inward currents were smaller than reported for many other studies of ClC-1 because the pipette (internal) solution contained a normal physiological concentration of 4 mM Cl^- . The instantaneous current elicited by a voltage jump from −95 mV was smaller for G190S (C), and the current deactivated much faster than WT upon hyperpolarization to −105 mV (compare tail currents in panels A and B). (D) The steady-state current –voltage relationship for G190S was shifted to depolarized potentials and had a greatly reduced slope conductance in the voltage range for V_{rest} in muscle. (E) The voltage dependence of the apparent open probability, computed from the initial peak of the tail currents, shows a dramatic right shift for G190S. [Redrawn with permission from (53). Originally published in Exp. Neurol. 248:530–540, 2013.]

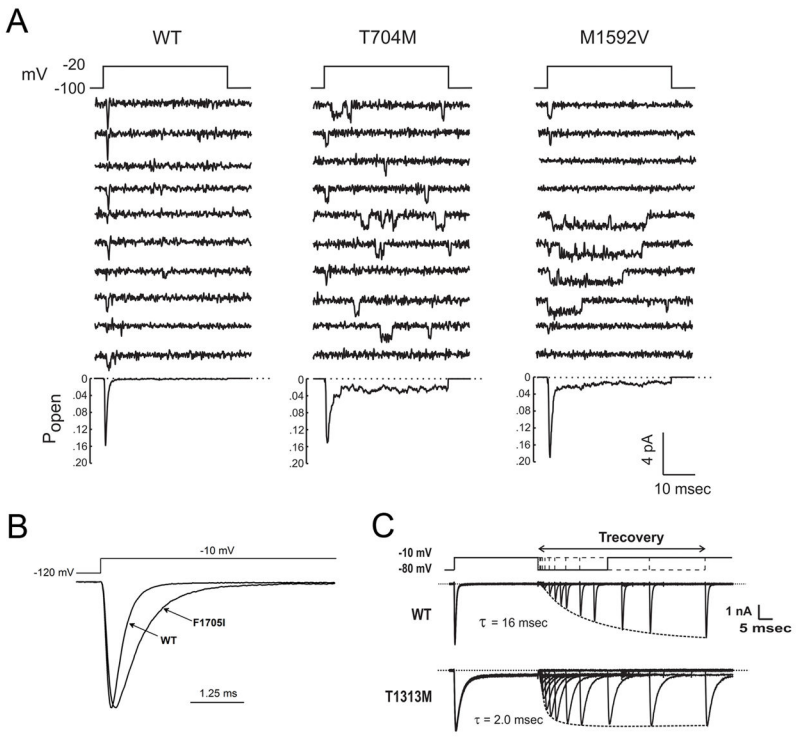

Figure 7.

Fast-inactivation defects for $Na_V1.4$ mutations associated with myotonia and HyperPP. (A) Cell-attached patch recordings from HEK cells expressing WT or HyperPP mutant $Na_V1.4$ (T704M, M1592V) reveal re-openings and prolonged openings (downward deflections) that in the ensemble average produce an abnormal persistent open probability (bottom traces). (B) Whole-cell recordings from HEK cells expressing WT or the SCM mutant $Na_V1.4$ F1705I show two-fold slower rate of inactivation for mutant channels. (C) A two-pulse recovery protocol reveals an accelerated rate of recovery from inactivation for the PMC mutant channel $Na_V1.4$ T1313M. [(A) adapted from (33), originally published in Neuron 2:317–326, 1993. (B) adapted from (279), originally published in J. Physiol. 565:371–380, 2005. (C) adapted from (95), originally published in J. Gen. Physiol. 107:559–576, 1995.]

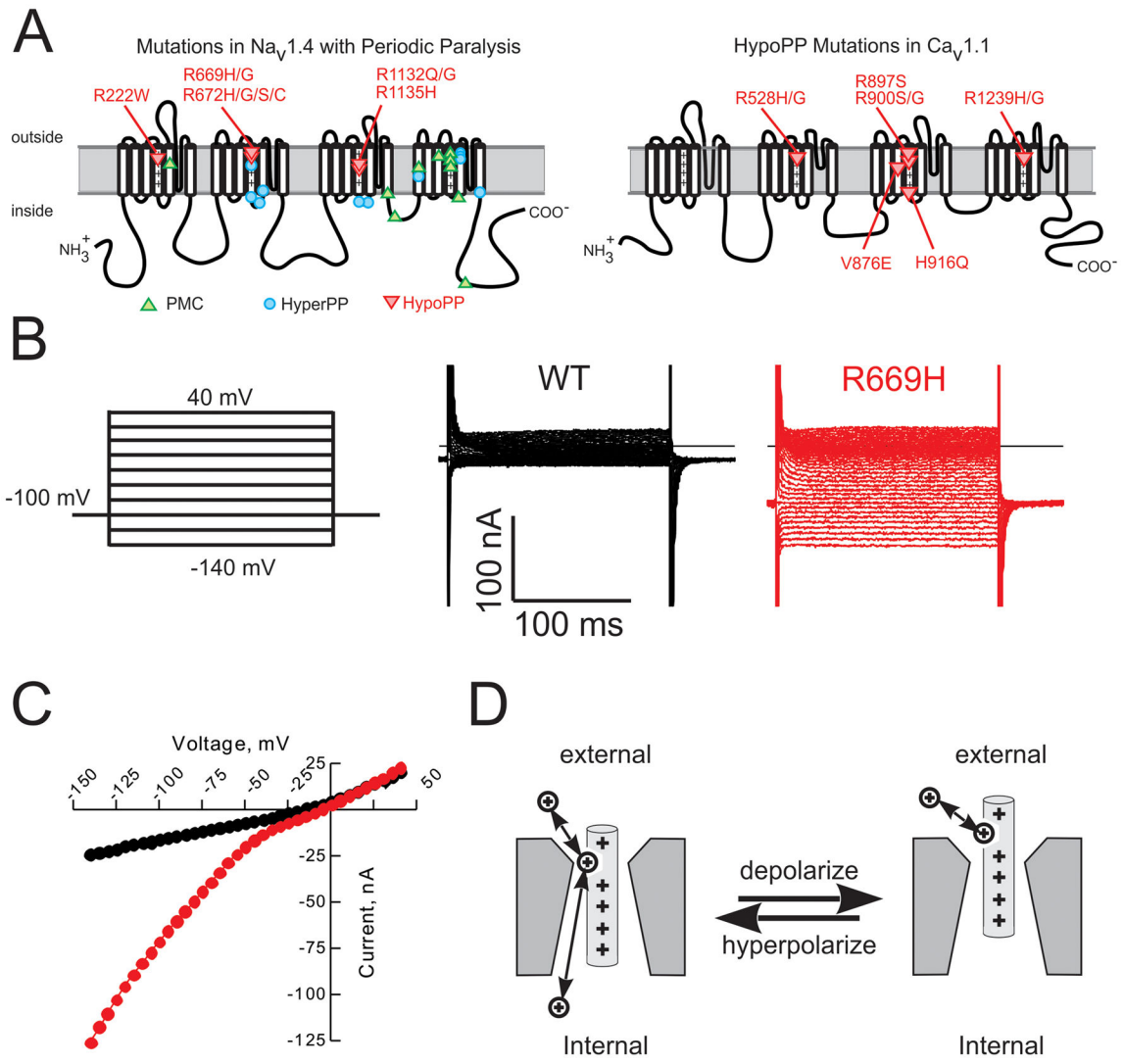

Figure 8.

Gating pore currents resulting from R/X mutations in S4 voltage sensors. (A) Schematic representation for mutations of $Na_V1.4$ associated with periodic paralysis (left) and for mutations of $Ca_V1.1$ associated with HypoPP (right). The mutations linked to HypoPP in either channel are found predominantly at arginine residues at the outer end of S4 voltage sensors. (B) Currents recorded from oocytes expressing the HypoPP mutant R669H $Na_V1.4$ demonstrate inward rectification compared to WT. Recordings performed in 1 μM TTX to block the pore of NaV1.4; no leak subtraction performed. (C) Steady-state current voltage relation shows inward rectification for test potentials < −40 mV. (D) Conceptual model for the voltage-dependence of the gating pore current. Ion conduction occurs at hyperpolarized potentials that bias the S4 sensor to the inward position, which places the mutation at the narrow constriction of the gating pore and allows anomalous conduction. [(B and C) adapted, with permission, from (241). Originally published in J. Gen. Physiol. 130:11–20, 2007.]

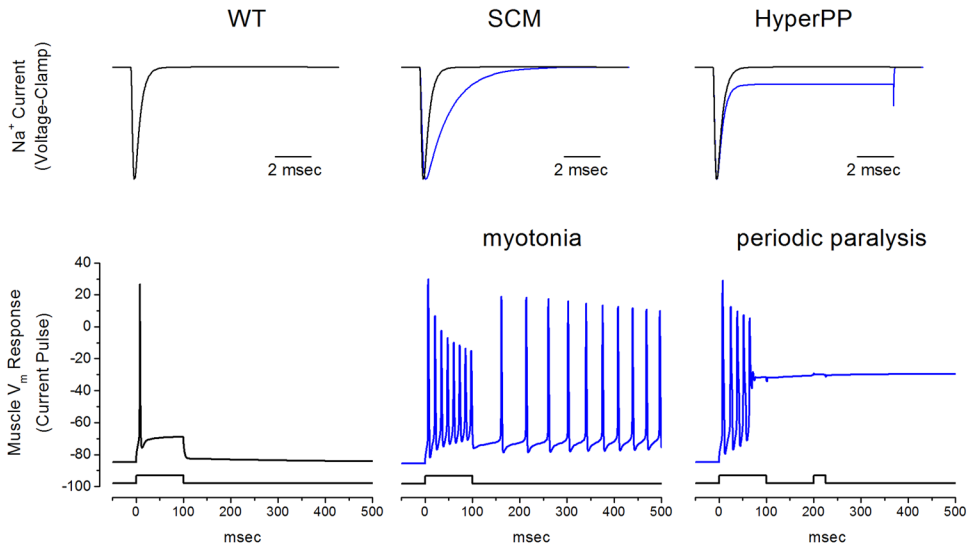

Figure 9.

Model simulation of myotonia and periodic paralysis resulting from $Na_V1.4$ mutations. Simulated $Na_V1.4$ currents using a Hodgkin-Huxley model (31) are illustrated in the top row. The WT response (black) is superimposed on simulations of SCM and HyperPP mutant channels (blue) to emphasize the changes in kinetics and steady-state behavior, respectively. These simulated $Na_V1.4$ currents were used in a model of muscle excitability (31) to compute the voltage response to a 100 msec current pulse (bottom row). Normally, a single action potential is elicited and the fiber accommodates for the remainder of the stimulus (left). The SCM mutation slows inactivation (middle) which results in susceptibility to myotonic bursts of discharges. The progressive depolarized shift between spikes (0–100 msec) is caused by K^+ accumulation in the simulated T-tubule. The persistent current associated with incomplete inactivation for HyperPP mutations (right) produces susceptibility to a stable depolarized potential from which point the fiber is refractory for generating subsequent spikes in response to a current pulse (200 msec).

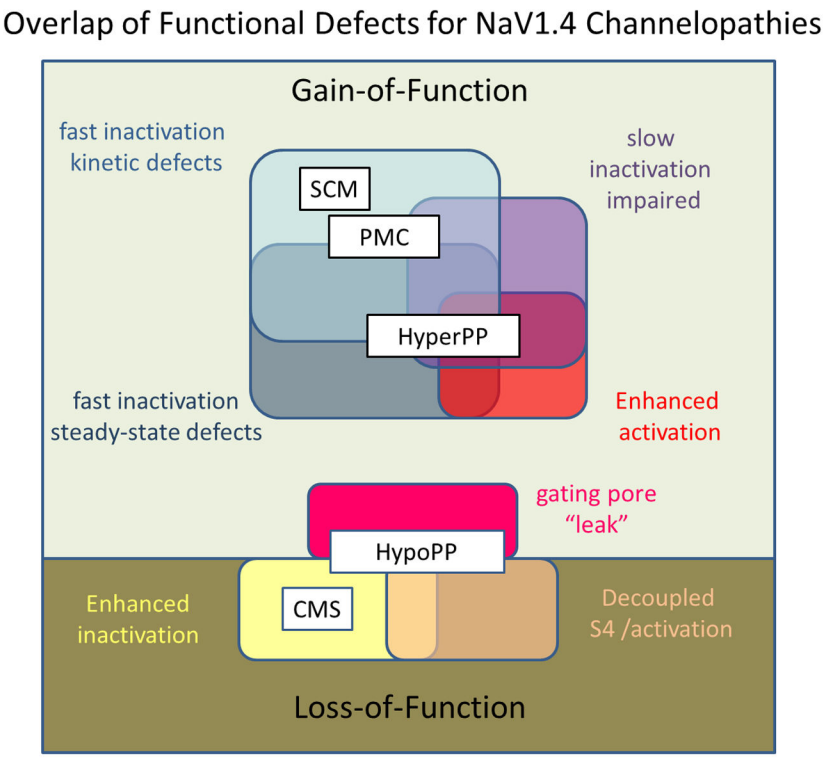

Figure 10.

Overview of $Na_V1.4$ gating defects associated with clinical syndromes for skeletal muscle channelopathies. The Venn diagram illustrates the overlap of functional defects that produce the spectrum of allelic disorders of skeletal muscle caused by missense mutations of $Na_V1.4$. Abbreviations: SCM – sodium channel myotonia, PMC – paramyotonia congenita, HyperPP – hyperkalemic periodic paralysis, HypoPP – hypokalemic periodic paralysis, CMS – congenital myasthenic syndrome.

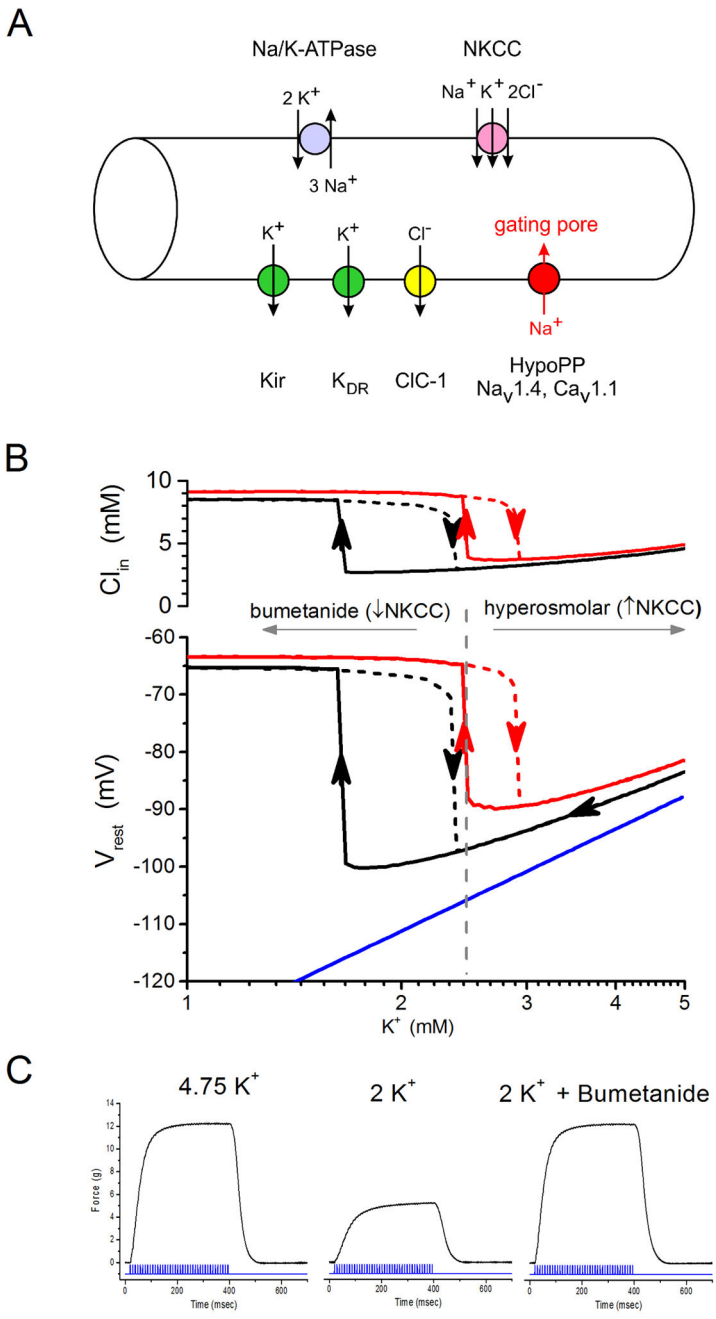

Figure 11.

Mechanistic model for paradoxical depolarization during attacks of HypoPP. (A) Schematic representation of the pumps and transporters (top) and conductances (bottom) that contribute to V_{rest} in skeletal muscle. The arrows indicate the net direction of ion flux at V_{rest}. The gating pore conductance is anomalous and may arise from R/X mutations in S4 of $Na_V1.4$ or $Ca_V1.1$. The diagram illustrates the case for mutations that create a non-selective gating pore and for which the major charge carrier is an influx of Na^+. (B) Simulations of a model fiber containing the elements in (A) show a hysteresis loop for the paradoxical depolarization of V_{rest} as the external K^+ is reduced. For simulated WT fibers (black traces), the paradoxical

depolarization occurs at a K^+ of 1.7 mM, an extremely low value which would not occur under normal physiological conditions. This depolarized shift results from a failure of Kir to maintain V_{rest} in exceptionally low K^+. Consequently, the fiber depolarizes until K_{DR} is sufficiently activated at −65 mV to maintain V_{rest}. At this depolarized potential, internal Cl^- equilibrates at 8.5 mM, two-fold higher than normal. As the K^+ is then increased, the high internal Cl^- state keeps V_{rest} depolarized until K^+ is about 2.4 mM, creating a bistable V_{rest} in the K^+ range from 1.7 – 2.4 mM. In HypoPP fibers (red), the gating pore conductance produces a rightward shift of the K^+ concentration at which paradoxical depolarization may occur, thereby resulting in susceptibility to attacks of depolarization-induced periodic paralysis in the low-normal range of external K^+. Inhibition of the NKCC transporter with bumetanide favors the low internal Cl^- state and thereby shifts the hysteresis loop leftward to lower K^+ values and reduces the likelihood of an attack of weakness in HypoPP. Conversely, up-regulation of NKCC transport by hyperosmolar conditions shifts the hysteresis loop to the right and increases the risk of HypoPP attacks. (C) In vitro tetanic contractions of the soleus muscle from $Na_V1.4$-R669H mice showing the loss of force in a low-K^+ challenge (middle) and the recovery of force by the addition of 1 μM bumetanide while remaining in low K^+. [(B) adapted from (242). Originally published in Muscle & Nerve 37:326–337, 2008. (C) reproduced with permission from (277). Originally published in Neurology 80:1110–1116, 2013.]

Table 1

Sodium Channelopathies of Skeletal Muscle

	Sodium Channel Myotonia	Paramyotonia congenita	Hyperkalemic Periodic Paralysis	Hypokalemic Periodic Paralysis	Congenital Myasthenia
Myotonia	mild to severe	• Paradoxical • cold-aggravated	mild to moderate	none	none
Periodic Paralysis	none	• mild to moderate • cold-aggravated	• moderate to severe • ↑K^+ aggravated	• moderate to severe • ↓K^+ aggravated	none
Fatigable weakness	none	none	none	none	moderate to severe
Permanent Weakness	none	rare	common	common	none
Common Mutations	rare, isolated cases	T1313M R1448C R1448H	I693T T704M M1592V	R672x	rare, isolated cases
Mutation Sites	• S6 cytoplasmic end • III–IV loop	• III–IV loop • DIV S4	S5 or S6 cytoplasmic end (inner pore)	R1 or R2 in S4 segments for domain I, II, III	DIV S3/4 extra-cellular loop
Functional Defect	gain	gain	gain	leak + loss	loss
Gating Defect	• slower rate of entry to inactivation • faster recovery from inactivation	• slower rate of entry to inactivation • persistent current • L shift activation	• persistent current • L shift activation • Impaired slow inactivation	• gating pore “leak” • decoupling S4 movement to activation • enhanced inactivation (modest)	• enhanced inactivation (profound)