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Novel Insights into the Pathomechanisms of Skeletal Muscle Channelopathies

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Abstract The nondystrophic myotonias and primary periodic paralyses are an important group of genetic muscle diseases characterized by dysfunction of ion channels that regulate membrane excitability. Clinical manifestations vary and include myotonia, hyperkalemic and hypokalemic periodic paralysis, progressive myopathy, and cardiac arrhythmias. The severity of myotonia ranges from severe neonatal presentation causing respiratory compromise through to mild later-onset disease. It remains unclear why the frequency of attacks of paralysis varies greatly or why many patients develop a severe permanent fixed myopathy. Recent detailed characterizations of human genetic mutations in voltage-gated muscle sodium (gene: *SCN4A*), chloride (gene: *CLCN1*), calcium (gene: *CACNA1S*), and inward rectifier potassium (genes: *KCNJ2, KCNJ18*) channels have resulted in new insights into disease mechanisms, clinical phenotypic variation, and therapeutic options

Keywords Channel · Channelopathy · Muscle · Myotonia · Periodic paralysis · Hyperkalemic · Hypokalemic · Andersen-Tawil · Chloride · Potassium · Sodium · Bistability · Electrophysiology · Skeletal

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Introduction

This review focuses on recent developments in our understanding of disease mechanisms in nondystrophic myotonia and primary periodic paralysis, hereditary syndromes caused by ion channel defects in the skeletal muscle sarcolemma and T-tubule system. The nondystrophic myotonias are characterized by often disabling muscle stiffness (myotonia), and in addition some patients experience attacks of weakness. The electrophysiologic correlate of clinical myotonia is a burst of autonomous muscle action potentials that last a few seconds after the cessation of motor neuron activity and delay relaxation. The primary periodic paralyses are autosomal-dominant disorders characterized by episodic weakness, and some patients additionally experience myotonia. Attacks of weakness occur when a proportion of muscle fibers become electrically inexcitable. Triggers to attacks include serum potassium change, cooling, rest after strenuous exercise, carbohydrate-rich meals, and emotional stress. Andersen-Tawil syndrome (ATS) is a form of periodic paralysis in which patients have dysmorphic features and cardiac arrhythmias in addition to periodic paralysis.

Electric Current Flow in Skeletal Muscle: Physiology and Pathophysiology

Normal Electrical Flows

Channelopathies of skeletal muscle alter the behavior of transmembrane currents (which control the cellular potential) and can disturb the normal one-to-one relationship between an action potential in the muscle fiber and its innervating motor neuron. Normally, a given region of the sarcolemma changes potential with respect to the extracellular milieu at a rate

proportional to the rate of charge deposition/removal at its intracellular surface by transmembrane current in that region and axial current to and from more distant regions. At rest, the whole sarcolemma maintains constant voltage, no axial current flows (no potential differences to drive it along the cell), and inward and outward transmembrane currents in any particular region are balanced (all charges entering the cell exit again, so none accumulate on the membrane, thus constant voltage). The action potential is triggered by an influx of cations through acetylcholine receptors that depolarizes the end-plate region above the threshold at which sufficient numbers of sodium channels open to initiate a regenerative cycle of inward sodium flux, triggering further depolarization and opening of more sodium channels. Axial and radial currents propagate the action potential bidirectionally along the surface sarcolemma and deep into the interior of fibers via the T-tubule system. Although sodium channels open in response to depolarization, they quickly close again (fast inactivation) and can only re-open after repolarization (recovery from inactivation). Fast inactivation initiates repolarization by curtailing the depolarizing inward sodium current, uncoupling the cell from the sodium equilibrium potential. The process is completed by potassium efflux through delayed rectifier potassium channels.

Disturbed Electrical Flows in Muscle Channelopathies

Abnormal membrane depolarization is important in both myotonia and periodic paralysis. Normally potassium accumulation in the T-system causes a small, transient after-depolarization at the end of muscle contraction. When exaggerated and/or when the sarcolemma is hyperexcitable this potassium accumulation can drive autonomous muscle fiber action potentials after the normal contraction should finish (myotonia) [1, 2]. Longer-duration depolarization may inactivate sodium channels and render the sarcolemma inexcitable, and muscle strength (force generation) declines as more myofibers become depolarized. The clinical consequences depend upon the time course and magnitude of the depolarization and the excitability of the sarcolemma and -system. Myotonia or weakness can occur in isolation. Myotonia can predominate but can be accompanied by transient weakness. Alternatively, periods of weakness can predominate with occasional, sometimes subclinical, myotonia.

In hyperkalemic periodic paralysis (HyperPP) incomplete fast inactivation leads to persistent inward sodium flow that tends to depolarize muscle fibers, driving potassium out into the extracellular space [3]. Attacks of weakness are the predominant feature, but mild (often subclinical) myotonia is frequently present interictally. Attacks are triggered by rest after exercise but can be aborted or ameliorated by continued gentle exercise. The beneficial effect of exercise may result from stimulation of the sodium potassium ATPase by calcitonin gene-related peptide released from intramuscular nerve terminals [4].

In hypokalemic periodic paralysis (HypoPP) myotonia is not observed [5] and muscle fibers are abnormally sensitive to low extracellular potassium concentrations, which (paradoxically) also lead to muscle fiber depolarization [6••]. The last few years have seen exciting advances in our understanding of HypoPP pathomechanisms [6••, 7•, 8], although the origin of the very marked hypokalemia that develops during attacks remains unclear. In normal muscle fibers the resting potential of about −90 mV closely follows the potassium equilibrium potential, but when external potassium falls below a certain critical value, rather than hyperpolarizing the cell (as predicted by the Nernst equation), it causes paradoxical depolarization (Fig. 1). Low extracellular potassium reduces the conductance of the inward rectifier potassium (Kir) channels responsible for setting the normal resting potential [9]. The fall in potassium conductance uncouples the resting potential from

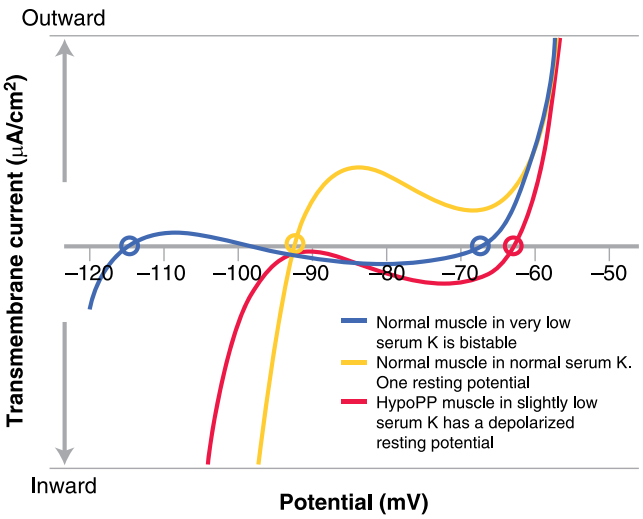

Fig. 1 Current–voltage relationships in normal and hypokalemic periodic paralysis (HypoPP) muscle. Each curve represents the net current at steady state resulting from inward rectifier, delayed rectifier, and leak currents (after the model by Struyk and Cannon [10] with parameters adjusted for purposes of the illustration). At zero net current (intersection with voltage axis) the cell rests at constant potential. Stable resting potentials are *circled*. Through its effect on inward rectifier (Kir) channels, low serum potassium hyperpolarizes the normal membrane potential and leads to the appearance of a second stable resting potential at a more depolarized voltage (*blue curve* – bistability). When the IV curve is already moved down toward the x-axis by an abnormal inward leak current (HypoPP), a small reduction in external potassium is sufficient to flip the resting potential to the depolarized state. In this state inactivation of sodium channels prevents the cell from firing action potentials

the potassium equilibrium potential, and allows depolarizing inward currents more influence. Inward rectification means that the outward potassium current through Kir channels is also reduced by depolarization, leading to a cycle of reduced potassium current and further depolarization that rapidly flips the cell to a new resting potential around −60 to −50 mV. In normal muscle, paradoxical depolarization occurs at extremely low potassium concentrations (~1 mM). The critical concentration at which fibers return to the normal resting potential as external potassium is increased again is higher than the concentration at which they entered the depolarized state on reducing external potassium (a phenomenon known as hysteresis in the language of dynamical systems theory) [3, 9]. Consequently, there is a range between the two critical potassium concentrations where muscle cells are bistable and can rest at either of the two potentials. When inward current is abnormally large (as in HypoPP caused by *CACNA1S* and *SCN4A* mutations) or the Kir conductance is impaired (as in Andersen-Tawil syndrome), paradoxical depolarization occurs with only slight reduction of extracellular potassium [10]. In these conditions, triggers to attacks increase the proportion of fibers at the more depolarized potential, causing muscle weakness through inactivation of sodium channels. Abnormal inward current may also explain the accumulation of sodium within muscle, which may in turn play an important role in the long-term structural damage and persistent weakness that develops in many patients with periodic paralysis [6••].

Ion Channels and Their Associated Diseases (Table 1)

SCN4A Mutations Associated with Myotonia and HyperPP

The α (pore-forming) subunit of the skeletal muscle sodium channel, $Na_v1.4$, is encoded by *SCN4A*. Four identical domains (DI to DIV), each with six transmembrane α helices (S1–S6), surround a single pore. Depolarization opens the channel (activation) by causing movement of the S4 segment in each domain, but also causes a separate (but not entirely independent) mechanism to occlude the pore shortly afterward (fast inactivation). Fast inactivation keeps the action potential brief. Slow inactivation operates on a much longer time scale.

Mutations in *SCN4A* are associated with a spectrum of overlapping myotonic/periodic paralysis syndromes including potassium-aggravated myotonia, paramyotonia congenita (PMC), HyperPP, and HypoPP. More recently a new, potentially lethal myotonia phenotype known as severe neonatal episodic laryngospasm (SNEL) has been described [11, 12].

Myotonia and HyperPP mutations cause gain of channel function (increased sodium current) in a variety of ways that include slowing fast inactivation, impairing slow inactivation, hastening recovery from inactivation, slowing deactivation (closure of the channel upon re-polarization), and shifting the voltage dependence of activation to more negative potentials. A single mutation often affects several of these processes. For example, the A799S mutation responsible for SNEL shifts the steady-state activation curve to more hyperpolarized potentials, slows deactivation, and also slows fast inactivation [13]. Until 2011, all the known *SCN4A* mutations associated with disease were in exons. Mutations in introns, for example at splice sites of other channels (eg, *ClC1*, discussed later), tend to cause loss of function or reduced expression. Kubota et al. [14] described the first gain-of-function mutation in *SCN4A* that occurs in an intron. The resultant splicing defect produces one mRNA isoform that encodes a functional $Na_v1.4$ α subunit that displays aberrant fast inactivation owing to an elongated loop between domains III and IV [14].

A new mechanism for sodium channel myotonia was recently proposed by Jarecki et al. [15•]. In certain tissues, such as dorsal root ganglia, native sodium channels re-open and conduct a so-called "resurgent" current during the repolarization phase itself, whereas in heterologous expression systems (eg, *Xenopus* oocytes) the same channels remain in the inactivated state during repolarization. Theoretically, abnormal enhancement of resurgent sodium current in skeletal muscle could produce autonomous muscle fiber action potentials, but owing to its brevity (it only lasts a few tens of milliseconds) should not produce the persistent depolarization associated with periodic paralysis. However, it is not yet known whether skeletal muscle actually supports this type of current [16]. Interestingly, the skeletal muscle sodium channel $Na_v1.4$ can behave in this way when it is expressed in cultured dorsal root ganglion cells, and in this unnatural cellular environment, mutations associated with myotonia not only resulted in slowed inactivation, but also exaggerated the resurgent current [15•].

The syndromes associated with *SCN4A* mutations are classified as autosomal dominant based on their occurrence in heterozygotes. In 2010, the first non-lethal cases of homozygosity for any *SCN4A* mutation were reported. Homozygous mutations of *SCN4A* were previously thought to be lethal owing to its critical role in the muscle action potential. Interestingly, homozygosity for I1393T (which causes PMC) and R1132Q (HypoPP) causes a more severe phenotype than heterozygosity. The same is true for the *CLCN1* mutation I556N (autosomal-dominant myotonia congenita [MC]) [17]. Strictly speaking, an allele is dominant when it determines the phenotype of a heterozygote, and a single copy of a truly dominant allele produces the same phenotype as two copies. When homozygotes are more severely affected inheritance is semidominant. The extreme rarity (or lethality) of homozygotes for dominant mutations

Table 1 Summary of molecular and cell membrane defects in nondystrophic myotonia and PP

Syndrome	HypoPP		HyperPP	PMC	PAM	SNEL	MC
Duration of depolarization	Persistent abnormal resting potential		Intermediate duration	Intermediate duration	Transient	?Transient	Transient
Mechanism of depolarization	Paradoxical response to low external K		Nernstian response to raised external K (including K accumulated in T-system)				
Consequence of depolarization	Sodium channel inactivation prevents action potentials		Mix of autonomous action potentials and sodium channel inactivation			Autonomous action potentials	
Primary abnormal membrane current	Kir current reduced	Inward leak current increased		Sodium current increased			Chloride current reduced
Channel (gene)	Kir2.1 (*KCNJ2*)	$Ca_v1.1$ (*CACNA1S*)		$Na_v1.4$ (*SCN4A*)			CIC1 (*CLCN1*)
	-ATS	-HypoPP I					
	Kir2.6 (*KCNJ18*)	$Na_v1.4$ (*SCN4A*)					
	-Thyrotoxic PP	-HypoPP II					
Molecular defects	Loss of function (dominant negative)	Gain of function (dominant)		Gain of function (dominant)			Loss of function (some dominant negative)
	Effects include impaired trafficking to membrane and reduced interaction with PIP	Gating pore current (proven for $Na_v1.4$, presumed for $Ca_v1.1$)		Effects include slowed inactivation; reduced extent of inactivation; shifted voltage dependence; ?resurgent current (see text)			Effects include reduced expression; shifted voltage dependence; altered ion selectivity; slowed activation kinetics

ATS Andersen-Tawil syndrome; *HyperPP* hyperkalemic periodic paralysis; *HypoPP* hypokalemic periodic paralysis; *MC* myotonia congenita; *PAM* potassium-aggravated myotonia; *PMC* paramyotonia congenita; *PP* periodic paralysis; *SNEL* severe neonatal episodic laryngospasm.

means many diseases traditionally classified as dominant on the basis of their occurrence in heterozygotes are actually semidominant [18, 19].

CACNA1S and *SCN4A* Mutations Associated with HypoPP

HypoPP is most commonly associated with mutation of *CACNA1S* (type I HypoPP), which encodes the α subunit of the voltage-gated calcium channel, $Ca_v1.1$ (also known as the skeletal muscle L-type calcium channel, and the dihydropyridine receptor). $Ca_v1.1$ in the T-tubular membrane is attached to the ryanodine receptor of sarcoplasmic reticulum, for which it acts as a voltage sensor. About 10% of HypoPP is associated with mutations in *SCN4A* (type 2 HypoPP), which encodes the skeletal muscle sodium channel. In contrast to HyperPP, the pathomechanisms that link mutations in both *CACNA1S* and *SCN4A* to the HypoPP phenotype have been unclear. However, recent work has shed light on a brand new potential disease mechanism.

$Na_v1.4$ and $Ca_v1.1$ α subunits are structurally homologous, and recent observations indicate that almost all HypoPP mutations in both channels are substitutions of arginine residues in S4 segments [7•, 20•]. In $Na_v1.4$ defects, the fundamental effect of the mutations that cause HypoPP appears to be the introduction of an accessory ion conduction pathway past the S4 segment, independent of the normal conduction pathway. The accessory pathway, known as a gating pore, has been demonstrated in all six of the HypoPP $Na_v1.4$ mutants that have been tested so far (R669H, R672H/G/S/C in the domain II voltage sensor, and most recently R1132Q in the domain III voltage sensor) [20•]. Although almost all HypoPP is associated with substitution of S4 arginines, not all S4 arginine substitutions cause HypoPP. The fact that R1448C in the domain IV S4 segment of $Na_v1.4$ does not cause a gating pore and is associated with PMC not HypoPP lends further support to the gating pore hypothesis [7•, 20•]. For technical reasons it has not yet been possible to record the gating pore current directly from mutant $Ca_v1.1$ in heterologous expression systems, but a nonselective cation leak consistent with a gating pore current has been recorded from muscle cells biopsied from patients with $Ca_v1.1$ HypoPP mutations [6••]. The small inward current that leaks through the gating pore makes muscle cells more sensitive to the paradoxically depolarizing effect of low extracellular potassium and is thought to be critical to the pathogenesis of HypoPP.

Ruff [21] pointed out that both types I and II HypoPP cause abnormalities over and above the gating pore. Reduced sodium conductance, possibly owing to reduced numbers of sodium channels [22•], and reduced outward component of the Kir conductance occur in HypoPP I. Reduced sodium conductance also occurs in HypoPP II secondary to enhanced inactivation of mutant sodium channels. These additional abnormalities may well contribute to the phenotype caused by the gating pore.

KCNJ2 and *KCNJ18* and Periodic Paralysis

KCNJ2 and *KCNJ18* encode Kir-type potassium channels and have been linked with different forms of periodic paralysis. For both *KCNJ2* and *KCNJ18* genes, four gene products (four Kir proteins) assemble into a channel with a single central pore. *KCNJ2* encodes Kir2.1, which can form a homotetramer or co-assemble with other related proteins including Kir2.2, Kir2.3, and Kir2.6. Kir2.1 has no intrinsic voltage sensor, but conducts a strongly voltage-dependent (inwardly rectified) current owing to block of the pore by intracellular magnesium and polyamines at depolarized potentials. Mutations in *KCNJ2* cause ATS, an autosomal-dominant triad of periodic paralysis, skeletal deformity, and long QT syndrome [23]. *KCNJ2* is the only gene currently associated with ATS, but in about 40% of clinically defined ATS patients, no mutation is found [23]. Not every patient exhibits all three aspects of the syndrome, and there is no consistent genotype–phenotype relationship. The ATS phenotype has been reported to involve the central nervous system, where Kir2.1 is also expressed. Chan et al. [24] recently described a patient in whom genetically confirmed ATS is associated with depression, diffuse intracranial white matter lesions, and pyramidal tracts signs.

Most *KCNJ2* mutations cause dominant-negative impairment of Kir2.1 channel function, and many alter the sensitivity to PIP2, which normally activates the channel [23]. New mutations continue to be identified [25–28]. The recently described S369X mutation causes a loss of the endoplasmic reticulum export motif and impaired trafficking of the channel to the plasma membrane [28].

KCNJ18 was identified in 2010 in a search for genes associated with thyrotoxic periodic paralysis [29••]. It encodes Kir2.6 and is expressed primarily in skeletal muscle. Kir2.6 is more than 98% identical with Kir2.2. Sensitivity to thyroid hormone is thought to be mediated by the thyroid hormone response element that sits upstream of *KCNJ18* and regulates the gene's expression. Some mutations associated with thyrotoxic periodic paralysis lead to loss of function by producing truncated proteins that cannot form functional channels. Other mutations lead to gain of channel function by altering phosphorylation. Kir2.6 can co-assemble with Kir2.1 and Kir2.2 and may limit their expression owing to the inefficiency with which Kir2.6 is exported from the endoplasmic reticulum [30]. Two Kir2.1 mutations have recently been identified in the heterozygous state in sporadic (non-thyrotoxic) HypoPP [31]; one patient was heterozygous for R43P and the other for A200P. Both mutations reduce the

function and surface expression of Kir2.6 in HEK293 cells, and cause dominant-negative suppression of co-expressed wild-type Kir2.6 and Kir2.1.

CLCN1 and Myotonia Congenita

CLCN1 encodes the voltage-gated chloride channel ClC1, which is responsible for the very large resting chloride conductance of skeletal muscle. ClC1 limits the after-depolarization caused by T-tubule potassium accumulation, and loss-of-function mutations cause MC. Regulation of ClC1 expression at transcriptional and post-transcriptional levels helps to match the properties of a muscle cell to the demands of its motor neuron [32]. Fast muscle expresses more ClC1 than slow muscle and is more prone to myotonia when its chloride conductance is impaired [33].

Debate over the location of ClC1 (sarcolemma, T-tubules, or both) was reignited in 2010. DiFranco et al. [34] used a potentiometric dye to measure the T-tubular potential in a region of a dissociated mouse flexor digitorum brevis (FDB) muscle fiber under two electrode voltage clamps. In a mathematical model, the only distribution of ClC1 that could explain their data was an equal density of chloride channels in the T-tubules as in the sarcolemma [34]. Lueck et al. [35] recorded chloride currents from the same dissociated mouse FDB muscle fibers before and after disconnection of the T-tubules by osmotic shock. In spite of a convincing alteration of cell capacitance (indicating successful detubulation), there was no reduction in chloride current suggesting a purely sarcolemmal chloride conductance [35]. In the T-system a large chloride conductance could prevent transmission of tubular depolarization to the sarcolemma by shortening the length constant of the tubular membrane (ie, promoting current across the tubular membrane rather than along the length of the tubule). It would also enable chloride ions rather than potassium ions to carry some of the depolarizing current after tubular action potentials, limiting potassium efflux [36]. Conversely, in the small spaces of the T-system, flow through ClC1 could easily shift the chloride equilibrium potential toward the tubular potential compromising its ability to maintain the normal resting potential [37]. In small mammalian muscle fibers (FDB fibers from mouse), changes in sarcolemmal potential are transmitted to the T-tubule almost instantaneously [38, 39]. A purely sarcolemmal chloride conductance could therefore stabilize the tubular membrane by "remote control."

ClC1 is a homodimer, each subunit with its own pore and gate ("protopore" or "fast" gate). A separate common gate opens and closes both pores simultaneously. The fact that inheritance can be autosomal recessive (heterozygotes are unaffected even for complete loss of function of one allele) supports physiologic evidence that myotonia does not occur until the chloride conductance is reduced well below 50% of normal [40]. Dominant CLCN1 mutations cluster at the dimer interface, enabling the mutant allele to impair the normal one by damaging the common gate in wild-type mutant heteromers [41]. Over 100 mutations are known, occurring throughout the gene's exons and flanking intronic regions. The majority show recessive inheritance, and many of these are predicted to reduce channel expression (eg, nonsense-mediated decay of mRNA from alleles with frameshifts or substitutions that introduce premature stop codons). Abnormalities of channel function including shifts of voltage dependence or ion selectivity also occur [42]. A novel way to impair function has been proposed for the dominant P480T mutation, which only causes a minor alteration of voltage dependence, but slows channel activation in mutant wild-type heteromers. The mean current during a 50-Hz train of depolarizing stimuli (mimicking tetanic muscle contraction) was significantly smaller than for wild-type channels owing to the slower activation kinetics of the mutant [43]. The investigators comment that the common gate may be responsible, although this hypothesis was not tested [43].

Variable severity in MC is only partially explained by differences in mutation; therefore, other genes may well modify the phenotype [40]. The myostatin gene seems a reasonable candidate for contributing to variable muscle hypertrophy, but this could not be demonstrated in the family examined by Muniz et al. [44]. Variants within *CLCN1* itself might also modify the phenotype of a co-existing MC mutation without being frankly pathogenic. A variant that reduces chloride conductance by 20% in heterozygotes and 40% in homozygotes could not on its own produce myotonia and might be classified as benign if identified in controls. But a 20% reduction could exacerbate the myotonia caused by a bona fide pathogenic MC genotype. Furthermore, such modifiers may test normal in heterologous functional expression systems if they exert their effect not by altering channel function but by muscle-specific mechanisms that reduce channel abundance. Interestingly, *CLCN1* can modify the severity of low chloride conductance myotonia that occurs in type II myotonic dystrophy (DM2, caused by expansion in the *ZNF9* gene) [45]. In the Finnish population, *CLCN1* mutations are over-represented in DM2 patients compared with controls owing to exacerbation of the DM2 phenotype that makes those patients with co-existing MC mutations more likely to be diagnosed (selection bias) [46].

In severe disease, myotonic stiffness may be accompanied by transient weakness that, like stiffness, disappears with repeated contraction (the warm-up phenomenon). The mechanism of the warm-up phenomenon remains uncertain. *In vitro*, rat diaphragm and extensor digitorum longus muscle made myotonic by pharmacologic block of ClC1 warms up on a much shorter time scale (within a minute)

than fatigue (loss of force) develops [33], so fatigue and warm-up appear to be quite separate. This fits with the clinical observation that in patients with transient weakness, warm-up causes increased strength—quite the opposite of fatigue. Interestingly, investigations into the mechanisms of muscle fatigue by Pedersen et al. [47, 48] showed that normal muscle can alter its membrane conductances on a time scale of seconds during trains of action potentials. Perhaps this type of phenomenon could be involved in warm-up of myotonic muscle.

Conclusions

There have been exciting developments in the field of skeletal muscle channelopathies, particularly with respect to periodic paralysis, but a number of questions remain. The primary sarcolemmal abnormality in both HypoPP and HyperPP is an inward, depolarizing current, but HyperPP attacks occur in the context of raised serum potassium whereas HypoPP is associated with low serum potassium. Alterations in serum potassium most likely reflect shifts between myoplasm and the extracellular space but details remain to be clarified, particularly the origin of hypokalemia in HypoPP. Secondary changes in muscle biology, such as the abnormal inward rectifier current that occurs in HypoPP, may well be important. The precise relationship between abnormal ionic currents and the significant structural muscle damage that often occurs also needs to be elucidated so that better treatments may be developed. Recent evidence suggests that intracellular sodium accumulation is important and may be preventable by carbonic anhydrase inhibitors [6••]. Knowledge of interacting skeletal muscle pathways and ion currents will hopefully be translated into new and better drug therapies. For example, HypoPP could potentially be treated by drugs that open potassium channels to balance the abnormal inward leak [49]. Alternatively, it might be possible to block the accessory conduction pathway past a mutant S4 segment. For example, Sokolov et al. [50•] found that 1-(2,4-xylyl) guanidinium can block gating pore current at millimolar concentrations and suggest that guanidine-based gating pore blockers could be therapeutically useful.

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