Periodic Paralysis: Understanding Channelopathies

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Familial periodic paralyses are typical channelopathies (*ie*, caused by functional disturbances of ion channel proteins). The episodes of flaccid muscle weakness observed in these disorders are due to underexcitability of sarcolemma leading to a silent electromyogram and the lack of action potentials even upon electrical stimulation. Interictally, ion channel malfunction is well compensated, so that special exogenous or endogenous triggers are required to produce symptoms in the patients. An especially obvious trigger is the level of serum potassium (K^+), the ion responsible for resting membrane potential and degree of excitability. The clinical symptoms can be caused by mutations in genes coding for ion channels that mediate different functions for maintaining the resting potential or propagating the action potential, the basis of excitability. The phenotype is determined by the type of functional defect brought about by the mutations, rather than the channel effected, because the contrary phenotypes hyperkalemic periodic paralysis (HyperPP) and hypokalemic periodic paralysis (HypoPP) may be caused by point mutations in the same gene. Still, the common mechanism for inexcitability in all known episodic-weakness phenotypes is a long-lasting depolarization that inactivates sodium ion (Na^+) channels, initiating the action potential.

Introduction

Membrane excitability, an elementary property for muscle function, is mediated by voltage-gated ion channels. It is, therefore, not surprising that ion channels can be involved in the pathogenesis of diseases of skeletal muscle. Pioneer work on excised intact myofibers from patients with hereditary periodic paralysis demonstrated that the underlying defect was a persistent sodium ion (Na^+) inward current that depolarized the membrane and thus caused inexcitability and weakness [1]. Cloning and analysis of the gene encoding the voltage-gated Na^+ channel of skeletal muscle led to the detection of the first mutations that cause impaired ion channel function [2]. This made hyperkalemic periodic paralysis the first channel disorder to be identified. Since then, more than 20 such diseases, now termed channelopathies, have been described showing basic recurring patterns of mutations, functional disturbances, mechanisms of pathogenesis, and therapeutic strategies [3••].

Function and Significance of Voltage-gated Cation Channels

The upstroke of the action potential is generated by the opening of voltage-gated Na^+ channels generating an inward Na^+ current that renders the cells positive inside (depolarization). Rapid recharging (repolarization rendering the cells more negative back to the resting potential of -90 millivolts [mV]) of the membrane is enabled by the closing of the Na^+ channels and additionally supported by the opening of potassium ion (K^+) channels that conduct an outward K^+ current. The signal spreads along the transverse tubular system, activating the voltage-gated dihydropyridine-sensitive calcium ion (Ca^{2+}) channels that initiate intracellular Ca^{2+} release and muscle contraction by a direct protein-protein interaction with the Ca^{2+}-release apparatus. It can easily be deduced that mutations in exactly these channels may lead to either hyperexcitability or inexcitability depending on the type of functional defect (*ie*, gain or loss of function). Likewise, depending on the resulting excitability of muscle fiber membrane, symptoms of paralysis (inexcitability) or myotonia (involuntary muscle contraction due to hyperexcitability) will be the consequence.

Voltage-sensitive cation channels can assume at least one open and two closed states. From one of the closed states (the resting state), the channel can be directly opened (be activated); from the other one (the inactivated state), it can not. This implies that there are at least two gates regulating the opening of the pore (an activation and an inactivation gate), both of which are part of the α subunit. Activation is a voltage-dependent process; inactivation and the recovery from the inactivated state are also time-dependent (Fig. 1). In the periodic paralyses, the inactivation of the cation channels is disturbed, causing malclosure or reopenings

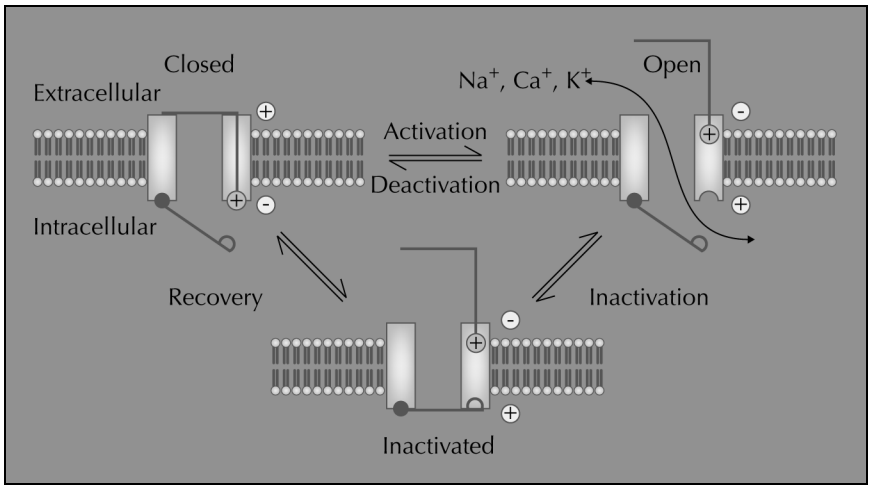


Figure 1. Three states of a voltage-gated cation channel that opens rapidly upon depolarization and then closes to an inactivated state from which it cannot reopen immediately. Repolarization of the membrane leads to recovery from inactivation, from which activation is again possible (*ie*, the resting state). Outward movement of the positively charged voltage sensor upon depolarization results in both opening of the pore and exposure of a docking site for the inactivation gate.

of the channels in one case, whereas in the other case the inactivated-state channels can barely open at all.

Hyperkalemic and Hypokalemic Periodic Paralysis: Contrasting Clinical Features

Two hereditary muscle diseases, each dominantly transmitted with a prevalence of about one per 100,000 people, are characterized by episodes of flaccid muscle weakness of variable duration, severity, and frequency (*ie*, hyperkalemic periodic paralysis [HyperPP] and hypokalemic periodic paralysis [HypoPP]). The attacks usually occur during rest after strenuous physical work. Sustained mild exercise may postpone or prevent an attack. Muscle strength usually begins to wear off in the proximal leg muscles, and the weakness then spreads distally and to the arms. This pattern is completely reversed after one (in HyperPP) to several hours (in HypoPP), together with a normalization of serum K^+. A cold environment, emotional stress, and pregnancy provoke or worsen the attacks. In either disease, the age of onset of attacks is the first or second decade of life. A progressive muscle weakness may develop, independently of the number of attacks, starting in most cases after the age of 40 years, an age at which the attacks of weakness ease up. This myopathy is characterized histologically by central vacuoles in the myofibers and ultrastructurally by a dilation and proliferation of the sarcoplasmic reticulum [4].

Hyperkalemic periodic paralysis and hypokalemic periodic paralysis are not only distinguished by the name-giving direction in which serum K^+ changes during an attack (in the attack-free interval, patients with either disease have normal values), but also by the response to certain provocative tests. Oral administration of K^+ triggers attacks and glucose is a remedy in HyperPP, whereas glucose (and insulin) provokes attacks in HypoPP, which are relieved by K^+ intake. In addition to episodic weakness, HyperPP may present with two different types of muscle stiffness. The first, termed myotonia, ameliorates by exercise and can be associated with transient weakness during quick movements lasting only for seconds. The second, termed paradoxical myotonia or paramyotonia, worsens with exercise or cold and is followed by long spells of limb weakness lasting from hours to days. In contrast, no myotonia of any type occurs in HypoPP [4].

Hyperkalemic and Hypokalemic Periodic Paralysis: Contrasting Mutation Patterns

Hyperkalemic periodic paralysis and hypokalemic periodic paralysis are caused by point mutations in the α subunit of voltage-gated cation channels, leading to exchange of a single amino acid residue in the resulting protein. Basic motif of α subunits is a tetrameric association (I–IV) of a series of six transmembrane α-helical segments, numbered S1–S6. These are connected by both intracellular and extracellular loops (the interlinkers) (Fig. 2). The α subunit contains the ion-conducting pore and, therefore, determines the main characteristics of the channel (*eg*, its ion selectivity, voltage sensitivity, pharmacologic properties, and its binding characteristics for endogenous and exogenous ligands). The voltage sensitivity of cation channels is mediated by the S4 segments, which, on single channel proteins, are thought to move outward and to rotate upon depolarization, thus opening the channel [5,6••]. During channel closing, not all voltage sensors move back at once. This generates a variety of closed states and explains why several voltage-sensor mutations exist that lead to various phenotypic disorders. The ion-conducting pore is thought to be lined by the four S5–S6 interlinkers. They also probably form the ion-selectivity filter. The activation gate is most likely located within the pore, whereas the inactivation gate may be located in different regions in the various Na^+ and K^+ channels (*eg*, the III–IV interlinker) [7,8].

Hypokalemic periodic paralysis type 1, which accounts for approximately 35% of all cases of periodic paralysis, is caused by one of three voltage-sensor mutations in domains II and IV of the Ca^{2+}-channel α subunit (Fig. 2b) [9–11]. HypoPP type 2, found in 5% of the patients, is caused by mutations located in domain IIS4 of the Na^+-

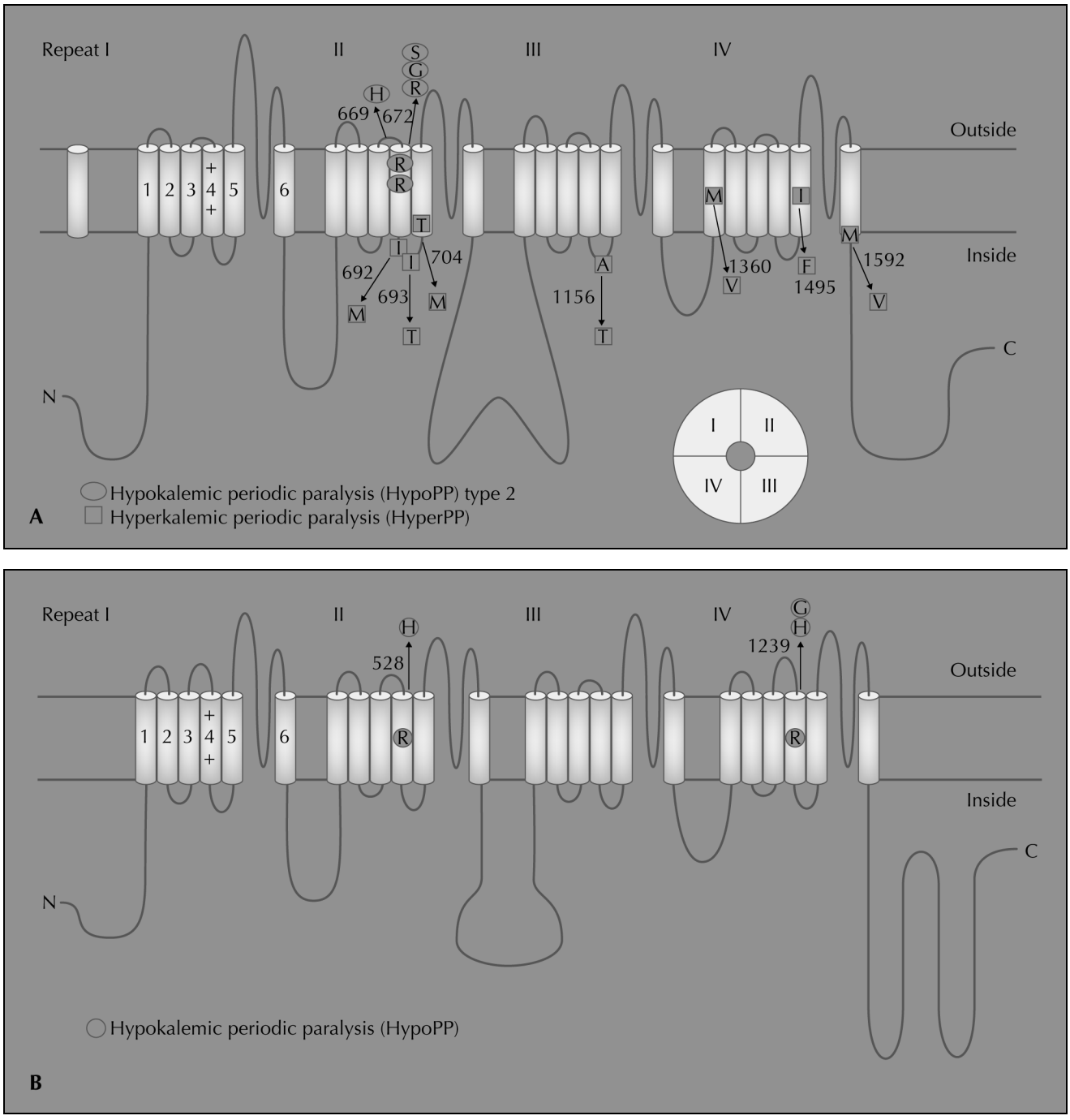
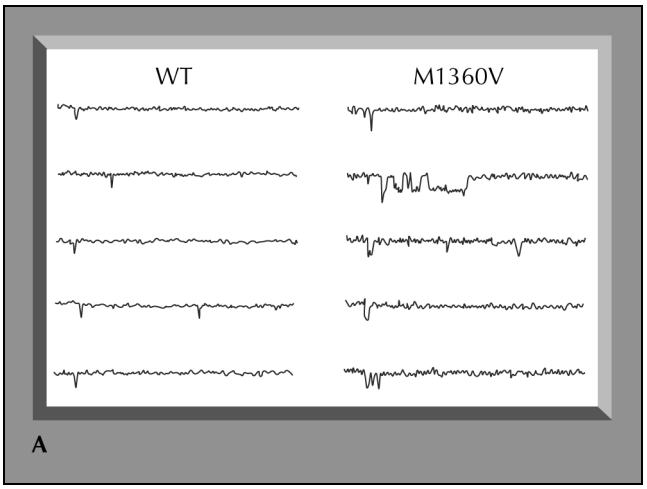
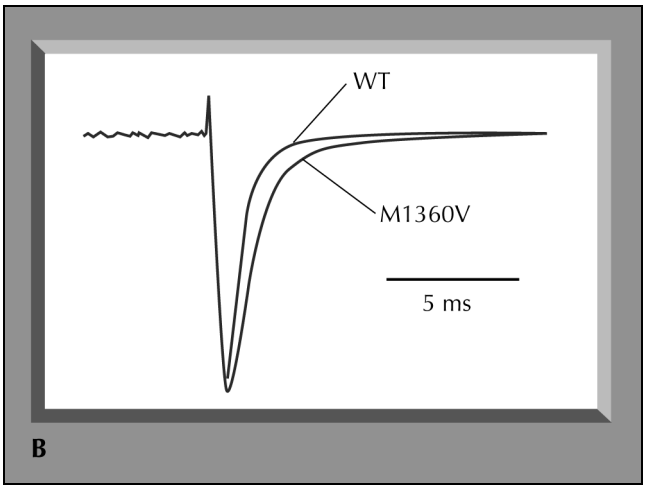


Figure 2. The α subunits of the voltage-gated Na^+ and voltage-gated L-type Ca^{2+} channels of skeletal muscle. Both subunits consist of four highly homologous domains (repeats I–IV) containing six transmembrane segments each (S1–S6). The S5–S6 loops and the transmembrane segments S6 form the ion-selective pore. The S4 segments contain positively charged residues conferring voltage dependence to the protein function. The repeats are connected by intracellular loops. When inserted in the membrane, the four repeats of each protein fold to generate a central pore (inset in bottom of **A**). **A**, Mutations in the supposed docking site for the inactivation particle (*squares*) cause hyperkalemic periodic paralysis; mutations in the voltage sensor of repeat II (*ovals*) cause hypokalemic periodic paralysis type 2. **B**, Mutations in the voltage sensors of repeats II and IV cause hypokalemic periodic paralysis type 1. (Conventional one-letter abbreviations are used for replacing and replaced amino acids.)

channel α subunit (Fig. 2a) [12,13•,14•,15]. The clinical differences between the two types are marginal. Some type 2 patients cannot tolerate the standard drug acetazolamide [14], or may have massive tubular aggregates in muscle biopsy [15], but these findings are valid for only a few patients. HyperPP, on the other hand, is caused by seven different mutations near the interior membrane surface of the Na^+-channel α subunit. The mutations detected thus far account for over half of all effected individuals (Fig. 2a) [16–19,20•].





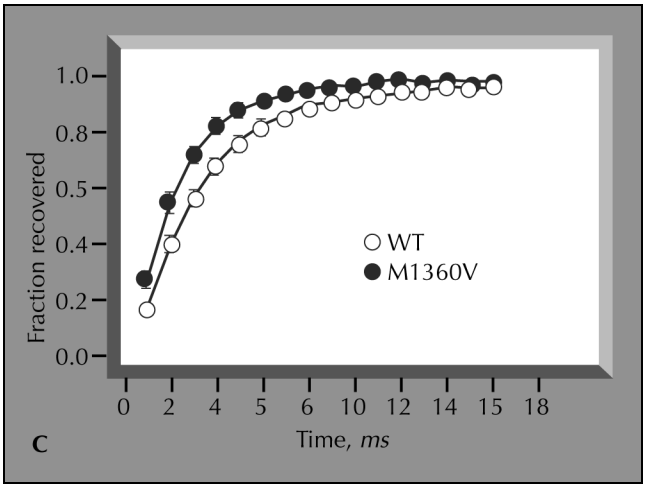


Figure 3. **A**, Single-channel recordings and **B**, whole-cell recordings of Na^+ currents conducted by normal (WT) or mutant (M1360V) Na^+ channels expressed in human embryonic kidney cells. M1360V is a mutation causing hyperkalemic periodic paralysis. The single-channel traces illustrate the flickering of the mutant channel, contrasting the single events in WT. This leads to a slowing of inactivation (slower current decay) of the whole-cell current. **C**, The refractory period is shortened in the mutant channel as illustrated by their faster recovery from inactivation. (*Adapted from* Sternberg *et al*. [15].)

From the evidence presented thus far, the attentive reader may guess that HypoPP mutations will affect the voltage dependence of inactivation, which additionally suggests that the voltage sensor of domain IV has a different significance in Na^+ and in Ca^{2+} channels. Additionally, the reader may assume that the residues mutated in HyperPP will not directly represent the inactivation gate, but perhaps its binding sites instead (acceptor of the inactivation gate).

Hyperkalemic and Hypokalemic Periodic Paralysis: Contrasting Pathomechanisms

For HyperPP (and two related myotonic disorders), the underlying pathomechanism is a gating defect of the Na^+ channel that destabilizes the inactivated state. This inactivation defect is caused by mutations that are thought to participate in the docking site for the inactivation particle, and any malformation may reduce the affinity between the "latch bar and the catch." As a consequence, the mutant channels avoid the inactivated state and, in contrast to normal Na^+ channels, reopen or flicker between the inactivated and the open state (Fig. 3) [19,20•,21,22]. The pathologically increased Na^+ influx into the myofibers generates bursts of action potentials (*ie*, myotonia). If the Na^+ influx is permanently increased, the associated sustained-membrane depolarization may become large enough to inactivate the nonmutant Na^+ channels (in a dominant disorder, both the mutant and wild-type alleles are present). This causes muscle inexcitability and, thus, weakness. That is to say, the same pathogenetic mechanism is able to produce both overexcitability (myotonia) and inexcitability (paralysis), depending on whether the degree of depolarization generated by the defect is small (a few millivolts) or large (≥10 mV). Depolarizing triggers, such as increased extracellular K^+ levels, may cause an additional effect. Also, defects of refractoriness after long-lasting depolarizations (so called slow inactivation) may explain why episodes may sometimes last up to several hours [23, 24•,25].

Although the inactivated state of the Na^+ channel is destabilized in HyperPP, it is stabilized in the Na^+ channel variant of HypoPP type 2. Functional expression of the mutants revealed reduced current amplitudes, reduced voltage thresholds for the inactivation curve, and a slowed recovery from the fast-inactivated state [13•,14•,26]. All changes lead to a reduced number of Na^+ channels available for the generation and propagation of action potentials (*ie*, the excitability of the myofibers is generally reduced) (Fig. 4). In

agreement with these findings, smaller and more slowly conducted action potentials were recorded in myofibers from biopsies of patients carrying a Na^+ channel mutation [13•]. These abnormal channel properties reduce the availability of Na^+ channels when HypoPP fibers are already depolarized (*eg*, following infusion of triggering agents such as insulin and glucose), but do not explain the development of the depolarization itself. It is speculated that because the triggering agents reduce the K^+ conductance and stimulate the Na^+/K^+ pump, they cause depolarization that then leads to inactivated Na^+ channels, which in turn causes weakness [27–29,30•].

The mutations causing the more frequent Ca^{2+} channel variant, HypoPP type 1, show functional consequences such as a reduction of current amplitudes, slight lowering of the voltage threshold for inactivation, and slowing of the rate of activation, the significance of which is still unclear [31–34,35•]. How the alterations of the determined Ca^{2+} current are related to hypokalemia-induced attacks of muscle weakness can only be speculated upon. Because electrical muscle activity, evoked by nerve stimulation, is reduced or even absent during attacks [36], a failure of excitation is more likely than a failure of excitation-contraction coupling. Nevertheless, the hypokalemia-induced, large-membrane depolarization observed in excised muscle fibers [37] might also reduce Ca^{2+} release by inactivating sarcolemmal and T-tubular Na^+ channels, and would explain why repolarization of the membrane by activation of adenosine triphosphate (ATP)-sensitive K^+ channels restores force.

Periodic Paralysis: a K^+ Channel Variant

Functional voltage-gated K^+ channels consist of four α subunits (and accessory β subunits). In other words, the α subunits in K^+ channels contain only one set of six transmembane segments, corresponding to only one domain of the α subunits of voltage-gated Na^+ or Ca^{2+} channels. The gene responsible for an unclassified periodic paralysis variant, *KCNE3*, encodes minK-related peptide 2 (MiRP2), the accessory β subunit to a classic voltage-gated delayed rectifier, the Kv3.4 K^+-channel α subunit [38••]. MiRP2 consists of a single transmembrane segment, and the described mutation, R83H, is predicted within the intracellular C-term of this protein (Fig. 5). Two small unrelated families have been found with this mutation. Afflicted members present with episodic weakness that is not triggered by, but is ameliorated by, carbohydrate intake. The weakness was not regularly provoked by insulin/glucose infusion. The K^+ level seemed normal during episodes, and oral K^+ administration did not improve the state of the patients. Even though this phenotype was first described as more closely related to HypoPP than HyperPP, the correct classification is still a matter of debate.

First functional tests in a murine skeletal-muscle cell line demonstrated that the properties of the Kv3.4 K^+-channel α subunit were completely altered when MiRP2 was coexpressed, so that this accessory β subunit seems essential for correct channel function. The mutant R83H caused the current density to be reduced, and this may account for a slight membrane depolarization because the channel contributes to repolarizing the membrane following an action potential and to sustaining a high resting membrane potential [38••]. As in HyperPP, the underlying defect is, therefore, compatible with the theory of depolarization-induced weakness.

Andersen's Syndrome: Dyskalemia Induces Episodic Paralysis and Arrhythmia

Andersen's syndrome (not to be confused with Andersen disease, type IV glycogen storage disease) is defined as a clinical triad consisting of K^+-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features [39,40]. The dysmorphic features may be variable and include small stature, low-set ears, hypoplastic mandible, clinodactyly, and scoliosis. Cardiac disturbances may also show a variety of phenotypes, such as prolongation of the QT interval, ventricular bigeminy, and short runs of bidirectional ventricular tachycardia. Sudden death in this syndrome, probably due to cardiac arrest, has been reported. Similarly to HypoPP, myotonia is not a feature of this syndrome. In contrast to HyperPP and HypoPP patients, the response to oral K^+ is unpredictable: it improves weakness in patients with low serum K^+, however, in some families it improves arrhythmia but exacerbates episodic paralysis. During an attack, serum K^+ may be high, low, or normal.

Several mutations in a voltage-insensitive α subunit of a K^+ channel expressed in both skeletal and cardiac muscle have been described (Fig. 5) [41••]. These subunits are protein tetramers each consisting of only two membrane-spanning segments (M1 and M2) and an interlinker forming the ion-conducting pore. They function as inward-going rectifiers (*ie*, they are decisive for maintaining the resting potential by conducting K^+ into the cell). This increases the concentration gradient across the cell membrane and hyperpolarizes the cell. The mutations causing Andersen's syndrome reduce this K^+ current, and a mutant monomer is capable of exerting a dominant-negative effect on a whole tetramer corresponding to the dominant mode of transmission of the disorder [41••].

Conclusions

The pathophysiology of HyperPP has been well elucidated by studying the effects of disease-causing mutations in molecular detail. Not entirely clear is why the clinical symptoms are aggravated by oral intake of K^+. Initial electrophysiologic experiments that showed a direct effect of K^+ on mutant channels [21] could not be reproduced [19,42]. Therefore, the effect of K^+ is most likely explained by a membrane-depolarizing effect of this ion. An

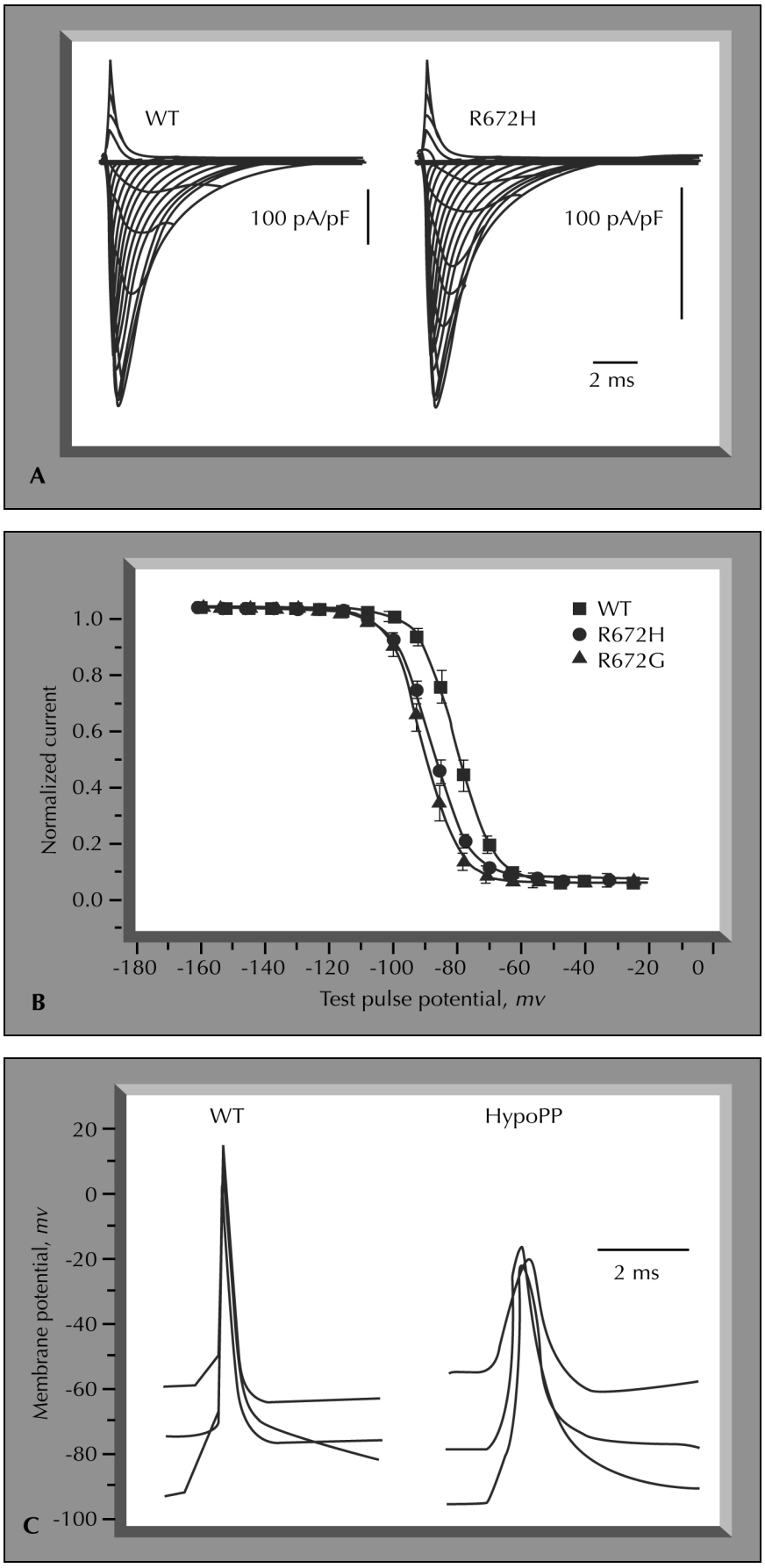


Figure 4. Na^+ currents in **A**, steady-state fast inactivation curves **B**, in action potentials **C**, in normal (WT) skeletal muscle Na^+ channels and of mutant (R672H) channels. R672H causes hypokalemic periodic paralysis (HypoPP) in man. **A**, Whole-cell currents were elicited in tsA-201 cells by a family of 10-ms lasting depolarizations from a -140 mV holding potential to voltages ranging from -80 to +70 mV. **B**, Steady-state inactivation was determined from a holding potential of -160 mV using a series of 300-ms prepulses from -190 to -55 mV in 7.5-mV increments prior to the test pulse to -20 mV. Note the shift of the mutants to lower threshold voltages for inactivation. **C**, Representative action potentials from a native muscle-fiber segment of a HypoPP patient compared with those of a normal control patient. They were elicited from various holding potentia ls by a short depolarizing pulse. Note the slower rise and fall for HypoPP. (*Adapted from* Jurkat-Rott *et al*. [13•]).

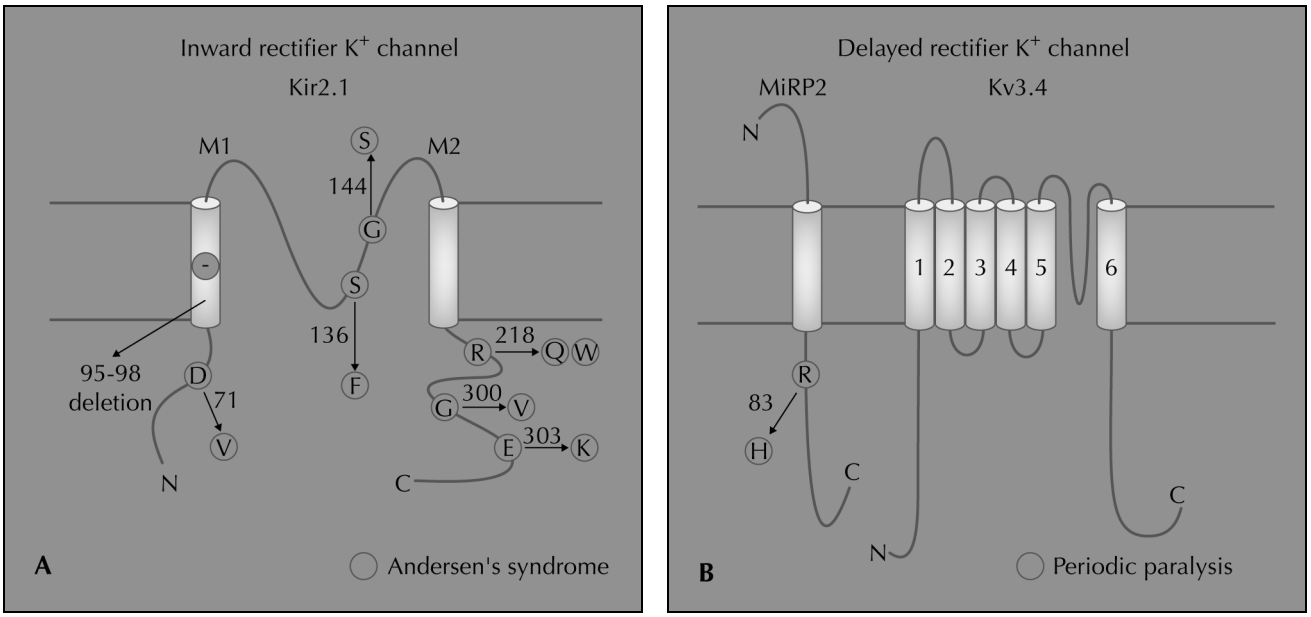


Figure 5. Paralysis-causing mutations in two K^+ channels of skeletal muscle. **A**, Several mutations of the voltage-insensitive inward-going rectifier, Kir2.1, cause Andersen's syndrome. **B**, Mutation R83H in MiRP2, the β subunit of the Kv3.4 K^+ channel, has been suggested to be responsible for a yet unclassified form of familial periodic paralysis.

additional unsolved problem is the occurrence of a progressive vacuolar myopathy with proximal leg weakness in HyperPP patients with the T704M mutation.

In contrast to HyperPP, the pathophysiologic mechanism linking a Ca^{2+} channel mutation to membrane depolarization and paralysis in HypoPP is entirely unresolved. It seems likely that other structures are involved, perhaps interacting with the channel and/or reacting to hypokalemia [27]. The Na^+ channel mutations in HypoPP contribute to underexcitability and weakness of skeletal muscle membrane without explaining the long-lasting depolarization during attacks or the provocative effects of reduced extracellular K^+ levels. The third variant, caused by *KCNE3* mutations, suggests a contribution of K^+ channels to the pathogenesis, but a link to the Na^+ and Ca^{2+} channels is by no means given. The mechanism of the progressive myopathy that HypoPP patients develop is not understood, especially because it does not respond to therapy in the same way as the attacks.

In Andersen's syndrome, it is unclear why the K^+ level during the attack and the reaction to K^+ intake are so unpredictable. From the knowledge of the channels, a phenotype of HypoPP would be expected. Additionally surprising is that ion channels contribute to embryogenesis, as indicated by the dysmorphic features. With time, additional distinct entities among the periodic paralyses will emerge, such as an X-linked variant that was recently described, the phenotype of which resembles myasthenia in several features [43]. It is expected that there will be many nonchannelopathies among them.

Localization and functional consequences of the underlying mutations in the channels correlate well with, and are transferable to, disorders of other excitable tissues, such as heart and brain.

Acknowledgements

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