

Spectrum of sodium channel disturbances in the nondystrophic myotonias and periodic paralyses

STEPHEN C. CANNON

Department of Neurobiology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA

Spectrum of sodium channel disturbances in the nondystrophic myotonias and periodic paralyses. Several heritable forms of myotonia and periodic paralysis are caused by missense mutations in the voltage-gated sodium channel of skeletal muscle. Mutations produce gain-of-function defects, either disrupted inactivation or enhanced activation. Both defects result in too much inward Na current which may either initiate pathologic bursts of action potentials (myotonia) or cause flaccid paralysis by depolarizing fibers to a refractory inexcitable state. Myotonic stiffness and periodic paralysis occur as paroxysmal attacks often triggered by environmental factors such as serum K⁺, cold, or exercise. Many gaps remain in our understanding of the interactions between genetic predisposition and these environmental influences. Targeted gene manipulation in animals may provide the tools to fill in these gaps.

The nondystrophic myotonias and periodic paralyses are rare inherited disorders of skeletal muscle in which the primary defect is an alteration in the electrical excitability of the muscle fiber [reviewed in 1–3]. Excitability of skeletal muscle is needed to propagate action potentials from the neuromuscular junction longitudinally along the fiber and into the transverse tubules, where depolarization triggers Ca²⁺ release from the sarcoplasmic reticulum. The aberrant electrical activity of diseased muscle implicated voltage-gated ion channels as candidate disease genes. In the past eight years, the molecular genetic defect has been identified for each of the nondystrophic myotonias and periodic paralyses. Mutations in the skeletal muscle chloride channel cause myotonia. Missense mutations in the α subunit of the skeletal muscle calcium channel produce periodic paralysis, and missense mutations in the sodium channel α subunit may cause myotonia, periodic paralysis, or both.

Excitability is pathologically enhanced in myotonic muscle. A brief stimulus elicits a burst of myotonic discharges lasting for several seconds, whereas normal muscle becomes quiescent immediately upon removal of the

stimulus. The aberrant excitability resides in the muscle, as nondepolarizing blockers of neuromuscular transmission, such as curare, do not abolish myotonia [4]. The afterdischarges in myotonia produce an activity-dependent defect in the relaxation of muscle force that patients usually describe as stiffness. Myotonic stiffness fluctuates from moment to moment and is dependent on past activity and environmental factors (for example, temperature, serum K⁺). Stiffness is usually greatest with forceful movement after inactivity for 15 minutes or longer and diminishes with exercise, the so-called warm-up phenomenon. Some Na channel mutations, but none of the Cl channel mutations, give rise to paramyotonia, a distinct form of myotonia that paradoxically becomes worse with repeated contractions and is also usually aggravated by cooling. The nondystrophic myotonias are unisystem disorders, affecting skeletal muscle only. In contrast, myotonic dystrophy is a multisystem disorder affecting brain, eye, heart, hair, and gonads, as well as skeletal muscle in which dystrophy usually predominates over mild myotonia, and the genetic defect is an expanded trinucleotide repeat in the untranslated region of myotonin kinase.

Muscle excitability is reduced during attacks of periodic paralysis. Affected muscles are flaccid and electrically inexcitable. The resting membrane potential is depolarized at -50 to -40 mV from a normal value of -95 mV [5]. Weakness is usually generalized and lasts for tens of minutes to hours, and full strength may not return for days. The frequency varies from a few attacks in a lifetime to several episodes per week. Patients are unable to stand or raise a limb against gravity during an episode of paralysis. The diaphragm and bulbar muscles are spared, and respiratory failure does not occur.

MISSENSE MUTATIONS IN SKM1 MAY CAUSE MYOTONIA, PERIODIC PARALYSIS, OR BOTH

Several clinically delineated disorders with dominantly inherited myotonia, episodic weakness, or both are associated with mutations in the α subunit of the adult skeletal muscle sodium channel (SkM1). The Na channel was

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Table 1. Clinical classification of Na channel disorders of skeletal muscle

Disorder	Potassium aggravated myotonia	Paramyotonia congenita	Hyperkalemic periodic paralysis
Inheritance	AD	AD	AD
Weakness	Never	Sometimes	Moderate to severe, K ⁺ aggravated
Myotonia	Mild to severe, K ⁺ aggravated	Moderate, paramyotonic features, cold-aggravated	None or mild

initially implicated by electrophysiological studies [5, 6] on fibers biopsied from patients with hyperkalemic periodic paralysis (HyperPP) and paramyotonia congenita (PMC). Affected fibers had an anomalous inward persistent current and excessive depolarization of the resting potential, both of which were abolished by tetrodotoxin, a potent and specific blocker of sodium channels. In skeletal muscle, the Na channel is a heterodimer consisting of the pore-forming α subunit (SkM1) and a non-covalently associated β_1 subunit [1]. No mutations in the β_1 subunit have been identified in the nondystrophic myotonias and periodic paralyses. Genetic linkage showed that HyperPP and PMC were allelic disorders that mapped to 17q23-25, in the vicinity of *SCNA4*, the gene coding for SkM1 [7, 8]. To date, 23 missense mutations have been identified in coding regions of *SCNA4* from families with HyperPP, PMC, and in families with myotonia that is worsened by K⁺ administration but who never have weakness, termed potassium-aggravated myotonia (PAM). The distinguishing clinical features for HyperPP, PMC, and PAM are listed in Table 1, and the location of the missense mutations in the primary sequence of SkM1 is shown in Figure 1.

FUNCTIONAL DEFECTS IN MUTANT SODIUM CHANNELS

Fast-gating behavior

The functional consequences of missense mutations in SkM1 associated with HyperPP, PMC, and PAM have been studied with patch-clamp techniques in primary cultures of diseased myotubes and in heterologously expressed channels. The alterations in channel behavior produced by this diverse collection of mutations share several common features. Every mutation produces a “gain of function” in that mutant channels pass more inward Na current than wild-type (WT) channels. The anomalously augmented Na current results from alterations in the gating of mutant channels; conduction through the open pore is not affected. The most common

gating defect is an impairment of fast inactivation that has been observed for every mutation tested to date. In a subset of mutants, channel opening is enhanced by a leftward (hyperpolarized) shift in the voltage dependence of activation. In addition to these defects in fast-gating behavior (that is, millisecond time scale), a subset of mutations disrupt a form of slow inactivation that occurs on the scale of seconds to minutes. These mutation-specific differences in aberrant gating behavior probably underlie the genotype–phenotype correlations observed between the sodium channel disorders delineated in Table 1 and Figure 1. In particular, defects in slow inactivation predispose to attacks of periodic paralysis.

The range of fast inactivation defects observed for mutant Na channels is illustrated in Figure 2. The anomalous persistent Na current was the first recognized gating defect and is detected most easily in single-channel recordings [9]. Figure 2A shows unitary Na currents recorded from cell-attached patches on normal (left) and HyperPP (right) human myotubes in culture. In response to depolarization, Na channels open after a brief latency and then shut within a millisecond to the fast-inactivated state from which further openings are normally exceedingly rare. Channels must be reprimed for subsequent opening by hyperpolarizing the membrane to allow recovery from fast inactivation. Mutant channels often exhibit bursts of openings and closings, as shown for the unitary Na currents recorded from HyperPP myotubes (Fig. 2A, right). In addition, individual open durations are often prolonged. Both defects are indicative of an impairment of fast inactivation. Ensemble averaged responses (bottom traces in Fig. 2A) show that the persistent current is only a small fraction of the peak Na current, typically 0.5 to 5.0% for mutant channels compared with approximately 0.1% for WT channels.

Once missense mutations were identified, the behavior of mutants could be studied by heterologous expression of channels in mammalian (HEK) cells. This expression system is more amenable to recording macroscopic whole-cell Na currents from which additional features of fast inactivation can be measured more easily [10–13]. The voltage dependence of fast inactivation is shifted to more depolarized potentials for some mutants, as shown in Figure 2B for G1306E, which causes a severe form of PAM. This shift represents a destabilization of fast inactivation because a larger depolarization is required to fast inactivate mutant channels (that is, reduce availability) to the same extent as WT ones. The persistent current and depolarized shift in availability are both steady-state features of fast inactivation. The kinetics of fast inactivation may also be altered by missense mutations. The rate of inactivation is often slowed by mutations associated with myotonic phenotypes, as illustrated for G1306E in Figure 2C. This defect is particularly prominent for a cluster of PMC mutations [12, 14] that

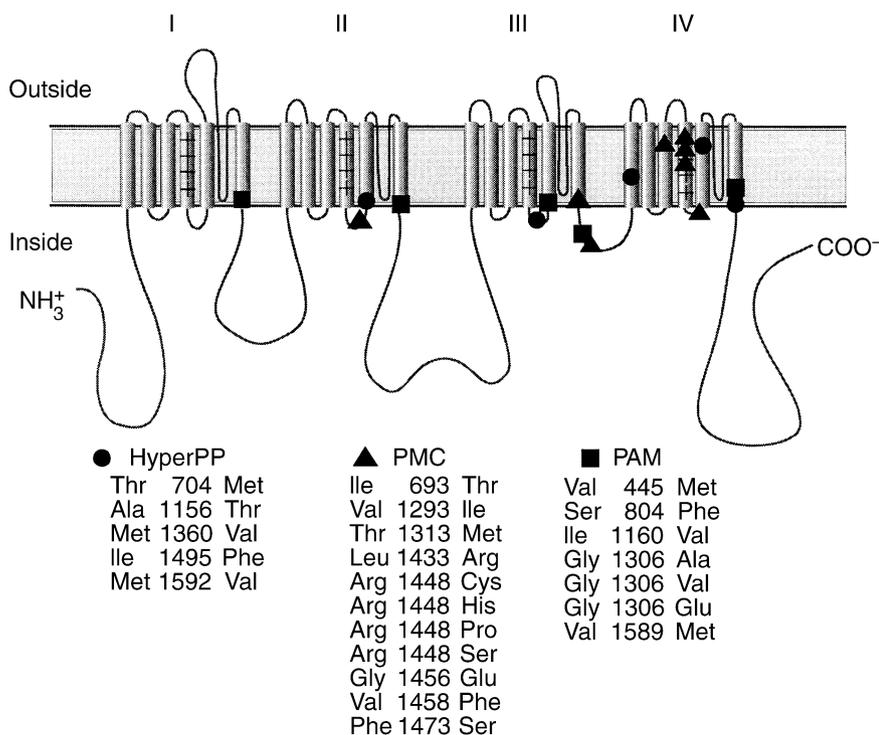


Fig. 1. Membrane-folding model of the Na channel α subunit and locations of missense mutations associated with hyperkalemic periodic paralysis (HyperPP; ●), paramyotonia congenita (PMC; ▲), and potassium-aggravated myotonia (PAM; ■).

lie in a proposed voltage sensor of the channel, the fourth membrane-spanning segment of domain IV (Fig. 1). A reciprocal change may be observed in the rate of recovery from fast inactivation. Some mutant channels recover twofold to fivefold faster than WT as shown in Figure 2D for T1313M, a commonly occurring mutation in PMC.

Each mutation listed in Figure 1 has been evaluated by heterologous expression, and in every case, at least one, and often more than one, of the defects of fast inactivation illustrated in Figure 2 have been detected. These alterations in gating are consistent with contemporary structure–function models of voltage-gated Na channels [1, 15]. The primary sequence of SkM1 schematized in Figure 1 has four homologous domains (I through IV). Each domain contains six predicted transmembrane segments (S1 through S6), the fourth of which has a cluster of charged amino acids thought to form the voltage-sensor of the channel. The short segments between S5 and S6 in each domain form the selectivity filter of the pore. The cytoplasmic loop linking domains III and IV is critical for fast inactivation and is thought to act as a hinged lid to occlude inner vestibule of the pore [16]. Four of the 23 mutations are in this inactivation gate. Ten mutations are located at the cytoplasmic end of S5 or S6 segments, which are thought to form a docking site for the inactivation gate at the inner vestibule of the pore. Finally, eight mutations are clustered in and around the S4 segment of domain IV, which is critical for coupling activation to fast inactivation. Taken to-

gether, 22 of the 23 missense mutations are in regions of the channel known to be important for fast inactivation.

Activation of the Na channel is also altered by a subset of mutations [11, 17, 18]. The voltage dependence of the peak Na conductance is shifted to hyperpolarized potentials, as shown in Figure 2B for T704M, the most commonly occurring mutation in HyperPP. This shift in voltage dependence reflects the fact that mutant channels open more readily, that is, with less depolarization, than WT ones. From a functional standpoint, the impairment of fast inactivation and the augmentation of activation both result in a “gain-of-function,” wherein mutant channels have a higher probability of being open and conducting Na current.

Slow-gating behavior

The gating behaviors described thus far, fast inactivation and activation, occur on a millisecond time scale or faster. A slower form of inactivation occurs in all voltage-gated Na channels and operates on a time scale of seconds to minutes. Slow inactivation is particularly relevant for periodic paralysis, which results from a persistent Na current that induces prolonged episodes of depolarization-induced inexcitability. The slow-gating process could attenuate the anomalous persistent Na current resulting from impaired fast inactivation and thereby prevent attacks of weakness [19]. Sodium channels become slow inactivated at depolarized potentials, and the slow-inactivated state is detected as an inability to rapidly

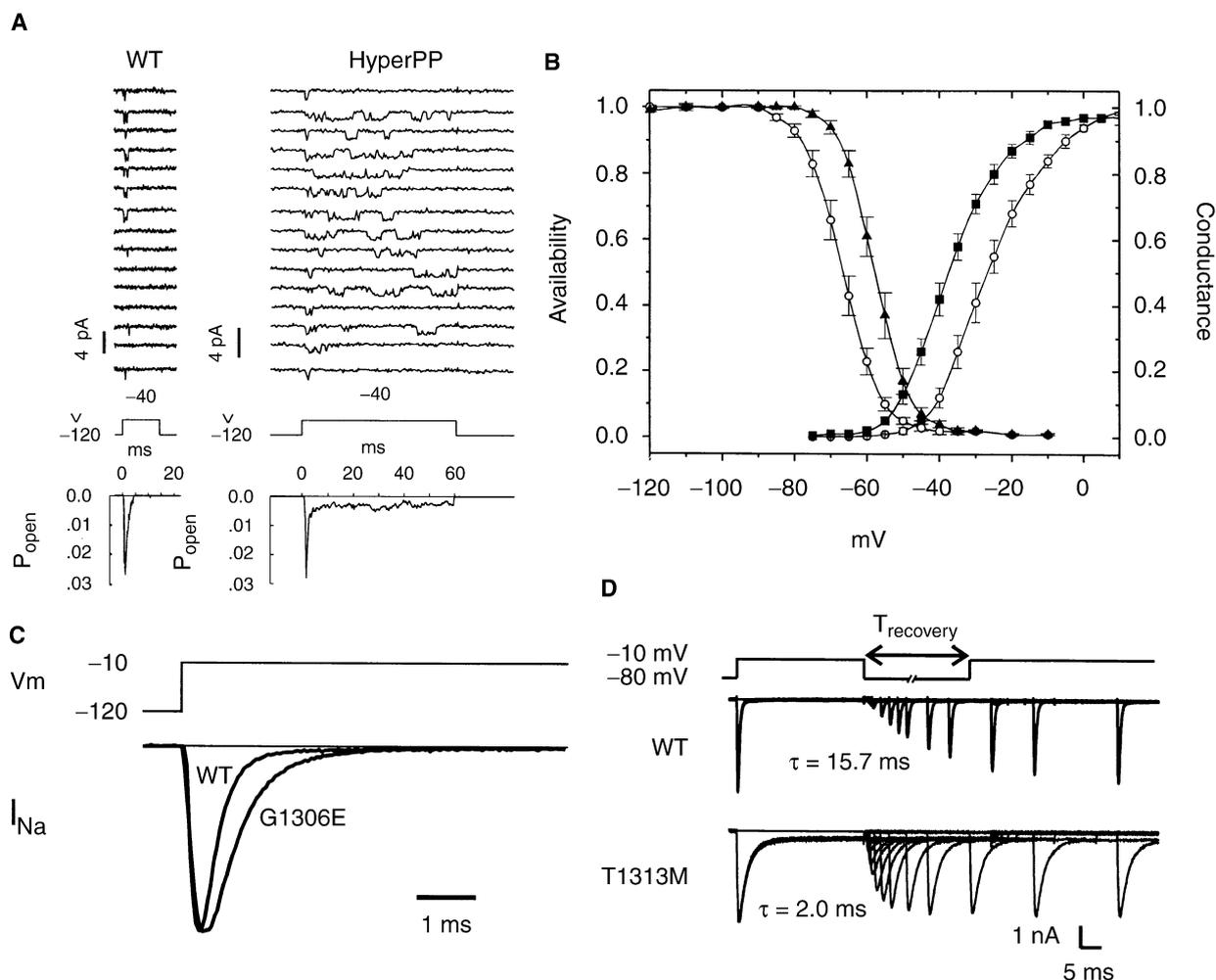


Fig. 2. Alterations in fast-gating behavior of mutant Na channels. (A) Cell-attached patch recordings from cultured human myotubes show disrupted fast inactivation with bursts of openings (downward deflections) in a HyperPP mutant channel (M1592V). The rapid decline in open probability (P_{open}) in the ensemble averaged responses demonstrate that mutant channels inactivate for the majority of trials but intermittent bursts cause a small persistent Na current. Adapted with permission from Cannon, Brown, and Corey, and *Neuron* [9]. Whole-cell recordings of macroscopic Na currents conducted by heterologously expressed rat SkM1 channels in HEK cells reveal additional defects in gating (B–D). Adapted with permission from Hayward, Brown, and Cannon, and the *Journal of General Physiology* [13]. (B) Destabilization of fast inactivation produces a depolarized shift in the voltage dependence of channel availability (left curves). Availability was measured as the relative peak current elicited at -10 mV, after a 300 msec conditioning pulse at potentials ranging from -120 to -10 mV. Activation gating may also be enhanced by missense mutations. T704M channels (HyperPP) activate at milder depolarizations, as shown by the hyperpolarized shift in the relative peak conductance (right curves). Symbols are: (○) WT; (▲) G1306E; (■) T704M. (C) A superposition of amplitude-normalized Na currents show a slowed rate of fast inactivation for the PAM mutation G1306E. (D) Recovery from fast inactivation is accelerated by the PMC mutation T1313M. The initial 30 msec pulse to -10 mV elicits a control Na current and fast inactivates the channels. Recovery is measured as the relative current available after a brief return to -80 mV (multiple trials are superimposed).

recover the total available Na current upon repolarization. The fraction of channels that are slow inactivated is measured using a two-pulse protocol, as the reduction in the peak Na current that is able to recover quickly (for example, within 20 milliseconds at -100 mV) after a prolonged depolarized conditioning pulse. Slow inactivation is impaired for a subset of mutations in which paralysis is the predominant symptom [20–22]. Figure 3A shows that after a 30-second conditioning pulse to -10 mV, only about 10% of WT channels recover within

20 milliseconds at -100 mV. In other words, 90% of the WT channels are slow inactivated. For T704M, the most common mutation in HyperPP, however, 50% of the mutant channels recover within 20 milliseconds, indicating that half of the mutant channels failed to undergo slow inactivation. The voltage dependence of slow inactivation is compared for WT and five mutant channels Figure 3B. The extent of slow inactivation is reduced (that is, larger available relative current) at voltages greater than -50 mV for I693T, T704M, and M1592V

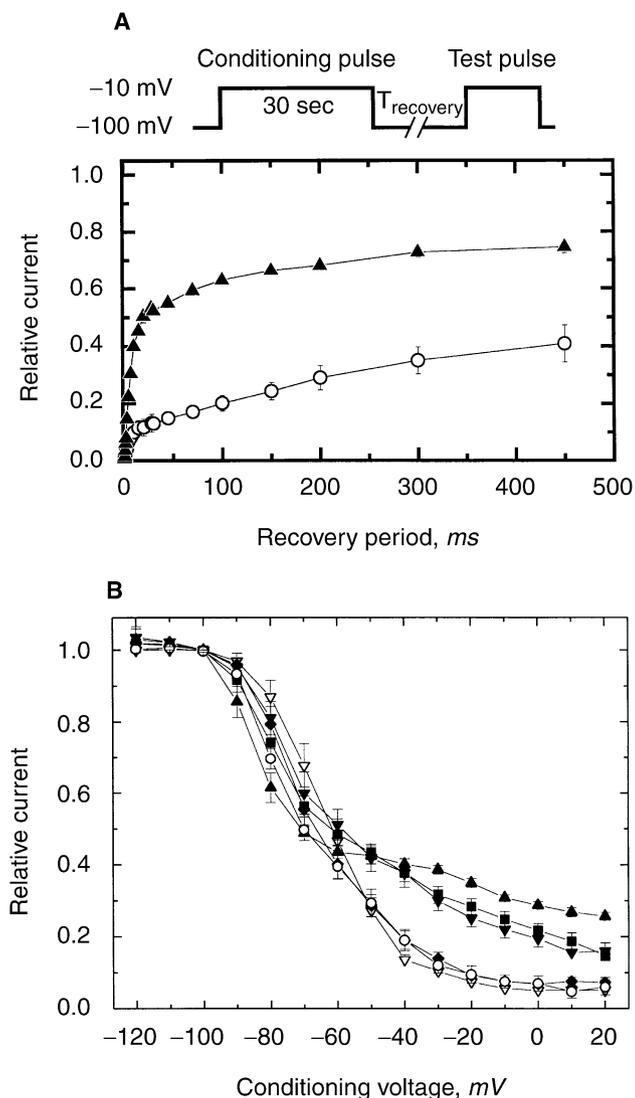


Fig. 3. Slow inactivation defects in paralysis-associated mutant Na channels. Sodium currents were recorded from channels transiently expressed in HEK cells. (A) A defect of slow inactivation is demonstrated by the rapid recovery of Na current for rat T698M (\blacktriangle ; ortholog of human T704M) after a 30-second conditioning pulse to -10 mV, which slow inactivates approximately 90% of WT (\circ) channels. Adapted with permission from Hayward, Brown, and Cannon, and *Biophysical Journal* [21]. (B) Slow inactivation is less complete at depolarized potentials for several paralysis-associated mutations (I693T, T704M, M1592V). Symbols are: (\blacksquare) I693T; (\blacktriangle) T704M; (\blacklozenge) A1156T; (∇) V1589M; (\blacktriangledown) M1592V; (\circ) WT. The relative current shows the fraction of heterologously expressed human SkM1 channels that were not slow inactivated by a 60-second conditioning pulse to the indicated voltage. Adapted with permission from Hayward, Sandoval, and Cannon, and *Neurology* [22].

mutants, each of which causes periodic paralysis as the predominant symptom. On the other hand, not all paralysis-associated mutations produce a defect. Slow inactivation is normal for M1360V (a rare form of HyperPP with incomplete penetrance) and for several PMC mutants (T1313M, R1448C, which cause significant weakness). Four PAM-associated mutant Na channels have

been tested, and slow inactivation was intact for each. Thus, a defect of slow inactivation predisposes to episodes of periodic paralysis, but not all mutations associated with periodic paralysis have a disruption of slow inactivation.

PATHOPHYSIOLOGIC BASIS FOR MYOTONIA AND PERIODIC PARALYSIS

Animal models and computer simulations have been used to explore the pathophysiologic mechanisms by which defects in mutant Na channel gating give rise to myotonia and periodic paralysis. To mimic the fast inactivation defect of mutant channels, a toxin from sea anemone (ATXII) was applied to rat fast twitch muscle in vitro [23]. Micromolar concentrations of ATXII partially disrupted inactivation such that in depolarized muscle, a persistent Na current, about 2% of the transient peak, was observed in patch-clamp recordings. In ATXII-exposed muscle, the relaxation in twitch force was slowed an order of magnitude, and a brief current pulse elicited a burst of myotonic discharges that continued after the stimulus. This proves experimentally that even a small persistent Na current is sufficient to generate myotonia. The Na channel-based myotonia shares a mechanistic feature in common with myotonia produced by a severe reduction in the resting chloride conductance, as occurs in myotonia congenita [24]. In both instances, the afterdischarges are dependent on the integrity of the transverse tubules. Disrupting the transverse tubules by osmotic shock with glycerol abolishes the afterdischarges. Transverse tubules are long, narrow invaginations of the sarcolemma that effectively propagate depolarization to the core of a fiber, but also produce a barrier to the diffusion of K^+ . The activity-dependent accumulation of K^+ in the transverse tubules (an extracellular space) tends to depolarize the fiber. Normally, chloride currents oppose this depolarization. With a loss of the chloride conductance, the accumulated K^+ causes a larger depolarizing shift in the resting potential and triggers an afterdischarge. With inactivation-deficient Na channels, even a small potassium-induced depolarization is sufficient to activate a substantial Na current, which further depolarizes the fiber and triggers myotonic discharges.

A second technique has been to use computer simulations of a model muscle fiber to explore quantitatively the consequences of persistent Na currents [25]. The model is based on Hodgkin-Huxley simulations of ionic currents and includes both surface and transverse tubular compartments to simulate the effects of extracellular K^+ accumulation. With normal values for the model parameters, a suprathreshold current pulse elicits a single action potential, as shown in Figure 4A. The aberrant persistent Na current was simulated by disrupting fast inactivation for a small fraction, f , of the channels. In

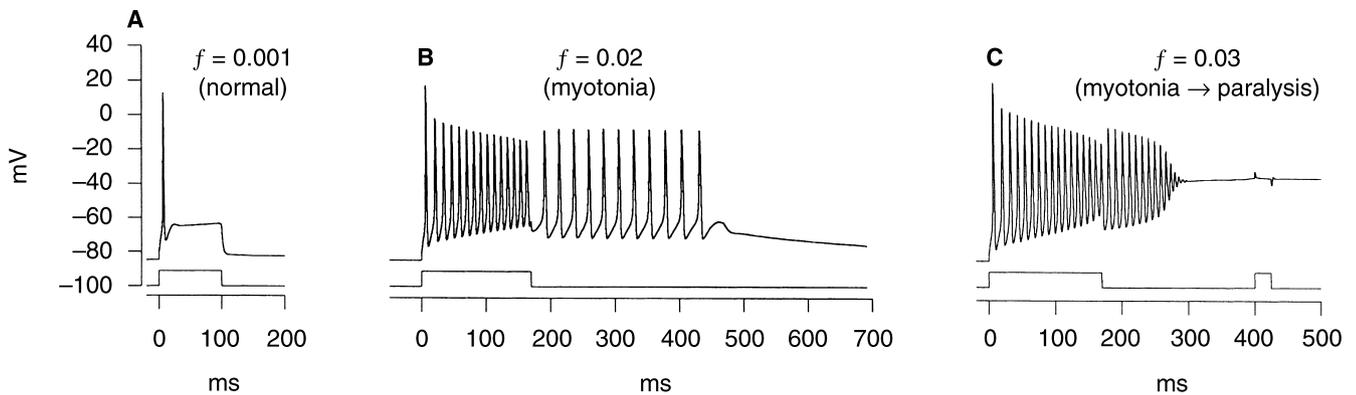


Fig. 4. Simulated responses of a model muscle cell demonstrate that a small persistent Na current is sufficient to generate myotonia and depolarization-induced paralysis. Computer simulations were performed with a two-compartment model that simulates the sarcolemma and transverse tubular membranes of skeletal muscle, and the fraction of Na channels, f , that failed to fast inactivate was varied. (A) With normal values of the parameters ($f = 0.001$), a suprathreshold current pulse elicits a single action potential, and the cell repolarizes after the stimulus. (B) When 2% of the Na channels fail to inactivate ($f = 0.02$), an identical current pulses elicits a burst of myotonic discharges that continues beyond the end of the stimulus, followed by repolarization to the normal resting potential. (C) Any further disruption of fast inactivation (for example, $f = 0.03$) causes a failure of repolarization after the myotonic discharges. From this anomalously depolarized resting potential, the majority of the Na conductance is inactivated, and no additional action potentials can be elicited. Adapted with permission from Cannon, Brown, and Corey, and *Biophysical Journal* [25].

agreement with the ATXII experiments on rat muscle, when 0.8% to 2.0% of model Na channels fails to inactivate, a brief stimulus triggers a burst of myotonic discharges (Fig. 4B). A slightly larger defect of inactivation ($f = 0.03$ or larger) results in a train of afterdischarges that settles to an anomalously depolarized resting potential of about -40 mV. From this stably depolarized state, the majority of Na channels (97% in this example) is fast inactivated, and the system is refractory from firing additional action potentials in response to subsequent current injection (Fig. 4C). This mechanism explains the basis for dominant expression of weakness in HyperPP. Roughly half the Na channels in heterozygotes are expected to be mutant, and mutant channels fail to inactivate only rarely. The persistent inward Na current conducted by this small fraction of noninactivating mutant channels is sufficient to depolarize the membrane and inactivate the majority of the remaining Na channels, which renders the membrane inexcitable. This behavior is the model equivalent of the depolarization-induced weakness observed in patients with periodic paralysis.

If the simulated Na current is modified to include slow inactivation, then in fibers aberrantly depolarized by fast inactivation defects, the persistent Na current will be attenuated over a period of seconds, and the fiber may repolarize. Slow inactivation is too sluggish, however, to impact simulations over a time scale of hundreds of milliseconds, as shown in Figure 4. The exact behavior depends on the relative sizes of the persistent Na current (a fast-inactivation defect) and the severity of the disruption of slow inactivation. Model simulations show that that the experimentally observed defects of slow inactivation

are sufficient to increase greatly the propensity for periodic paralysis and suggest that slow inactivation may normally protect against episodes of depolarization-induced weakness [20, 21].

Computer simulations also provide a mechanism to test the consequences of specific types of gating defects, as shown in Figure 2. One goal is to understand why some mutations cause periodic paralysis (HyperPP; Fig. 1), whereas others cause myotonia without weakness (for example, PAM). Although all of the Na channel mutations in Figure 1 result in a gain of function, differences in the severity or type of gating defect presumably determines the clinical phenotype [26]. Experimental data and model simulations support this hypothesis, although there is a great deal of overlap in the gating defects. As detailed previously in this article, if slow inactivation is disrupted, then periodic paralysis will be the predominant phenotype. Any gating defect that increases the steady-state open probability of a mutant Na channel could, in principle, produce the depolarization-induced inexcitable state shown in Figure 4C. Model simulations show that the system is most sensitive to increased persistent currents (Fig. 2A) and to hyperpolarized shifts in activation (Fig. 2B, right hand curves). In contrast, a depolarized shift of fast inactivation (Fig. 2B, left hand curves) must be very large (>20 mV) to produce a pathologically depolarized resting potential. In heterologous expression studies, mutations associated with HyperPP usually cause some combination of (1) increased persistent current ($>1.5\%$ of peak), (2) hyperpolarized shift of activation (>5 mV), or (3) disrupted slow inactivation. On the other hand, mutations associ-

ated with myotonia only have smaller persistent Na currents (<1% of peak), only small shifts in activation (<5 mV), and never disrupt slow inactivation. For many myotonic mutations, the major alteration of gating is a slowed rate of inactivation (Fig. 4C) or an accelerated rate of recovery (Fig. 4D). Because the resting potential is an equilibrium property of the system, alterations in the rate of inactivation alone (without a change in the extent) cannot produce a new aberrantly depolarized resting potential. On the other hand, altered rates of inactivation do influence the dynamic behavior of the model. Model simulations suggest that a major consequence of a slowed rate of inactivation is to increase the duration of the action potential, which in turn, results in a much greater load of K⁺ to the transverse tubules per discharge and thereby promotes repetitive firing.

The pathomechanisms by which environmental factors such as cold or serum K⁺ trigger attacks of weakness or myotonia remain to be elucidated. Computer simulations demonstrate that raised extracellular K⁺ acts synergistically with Na channel-gating defects to produce myotonic discharges [13, 18] or anomalous depolarization of the resting potential [21]. These simulations do not explain, however, why attacks are precipitated by K challenge for some (HyperPP and PAM) but not other (PMC) Na channel mutations. Channel gating is strongly temperature dependent, and the rate of inactivation changes threefold to fourfold with a 10°C shift in temperature. The temperature dependence of inactivation for mutations associated with cold-aggravated myotonia (PMC) is not, however, different from WT channels [12–14]. The temperature sensitivity of PMC may arise from a threshold effect. Because even at 37°C, inactivation is slower for PMC mutants than WT channels, then upon cooling, a threshold level of acceptable slowing would be exceeded for PMC before WT channels. Further insights on this interaction between genetic predisposition and environmental triggers of myotonia and periodic paralysis will require studies in fully differentiated muscle fibers or even whole animals and will likely await the development of targeted gene manipulation in animal models. Despite these gaps in our knowledge, the Na channel disorders of skeletal muscle represent one of the greatest successes in tracing the pathophysiologic basis of a human disease, from gene defect to altered protein function to symptoms of myotonia and periodic paralysis.

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Reprint requests to Stephen C. Cannon, M.D., Ph.D., Department of Neurobiology, Harvard Medical School, EDR 413, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
E-mail: cannon@helix.mgh.harvard.edu

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