Inherited disorders of voltage-gated sodium channels

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A variety of inherited human disorders affecting skeletal muscle contraction, heart rhythm, and nervous system function have been traced to mutations in genes encoding voltage-gated sodium channels. Clinical severity among these conditions ranges from mild or even latent disease to life-threatening or incapacitating conditions. The sodium channelopathies were among the first recognized ion channel diseases and continue to attract widespread clinical and scientific interest. An expanding knowledge base has substantially advanced our understanding of structure-function and genotype-phenotype relationships for voltage-gated sodium channels and provided new insights into the pathophysiological basis for common diseases such as cardiac arrhythmias and epilepsy.

Introduction

Voltage-gated sodium channels (Na_VChs) are important for the generation and propagation of signals in electrically excitable tissues like muscle, the heart, and nerve. Activation of Na_VChs in these tissues causes the initial upstroke of the compound action potential, which in turn triggers other physiological events leading to muscular contraction and neuronal firing. Na_VChs are also important targets for local anesthetics, anticonvulsants, and antiarrhythmic agents.

The essential nature of Na_VChs is emphasized by the existence of inherited disorders (sodium "channelopathies") caused by mutations in genes that encode these vital proteins. Nearly 20 disorders affecting skeletal muscle contraction, cardiac rhythm, or neuronal function and ranging in severity from mild or latent disease to life-threatening or incapacitating conditions have been linked to mutations in human Na_VCh genes (Table 1). Most sodium channelopathies are dominantly inherited, but some are transmitted by recessive inheritance or appear sporadic. Additionally, certain pharmacogenetic syndromes have been traced to variants in Na_VCh genes. The clinical manifestations of these disorders depend primarily on the expression pattern of the mutant gene at the tissue level and the biophysical character of Na_VCh dysfunction at the molecular level.

This review will cover the current state of knowledge of human sodium channelopathies and illustrate important links among clinical, genetic, and pathophysiological features of the major syndromes with the corresponding biophysical properties of mutant Na_VChs. An initial brief overview of the structure and function of Na_VChs will provide essential background information needed to understand the nuances of these relationships. This will be followed by a review of the major syndromes, organized by affected tissue. Emphasis will be placed on relating clinical phenotypes to patterns of channel dysfunction that underlie pathophysiology of these conditions.

Structure and function of Na_VChs

Sodium channels are heteromultimeric, integral membrane proteins belonging to a superfamily of ion channels that are gated (opened and closed) by changes in membrane potential (1, 2). Sodium channel proteins from mammalian brain, muscle, and myocardium consist of a single large (approximately 260 kDa) pore-forming α subunit complexed with 1 or 2 smaller accessory β subunits (Figure 1). Nine genes (*SCN1A*, *SCN2A*, etc.) encoding distinct α subunit isoforms and 4 β subunit genes (*SCN1B*, *SCN2B*, etc.) have been identified in the human genome. Many isoforms are expressed in the central and peripheral nervous system (3), while skeletal muscle and cardiac muscle express more restricted Na_VCh repertoires (4–9). The α subunits are constructed with a 4-fold symmetry consisting of structurally homologous domains (D1–D4) each containing 6 membrane-spanning segments (S1–S6) and a region (S5–S6 pore loop) controlling ion selectivity and permeation (Figure 1). The S4 segment, which functions as a voltage sensor (10, 11), is amphipathic with multiple basic amino acids (arginine or lysine) at every third position surrounded by hydrophobic residues. Each domain resembles an entire voltage-gated potassium channel subunit as well as a primitive bacterial Na_VCh (12).

Na_VChs switch between 3 functional states depending on the membrane potential (Figure 2) (13). In excitable membranes, a sudden membrane depolarization causes a rapid rise in local Na^+ permeability due to the opening (*activation*) of Na_VChs from their resting closed state. For this to occur, voltage sensors (the 4 S4 segments) within the Na_VCh protein must move in an outward direction, propelled by the change in membrane potential, and then translate this conformational energy to other structures (most likely S6 segments) that swing out of the way of incoming Na^+ ions. This increase in Na^+ permeability causes the sudden membrane depolarization that characterizes the initial phase of an action potential. Normally, activation of Na_VChs is transient owing to *inactivation*, another gating process mediated by structures located on the cytoplasmic face of the channel protein (mainly the D3–D4 linker). Na_VChs cannot reopen until the membrane is repolarized and they undergo *recovery from inactivation*. Membrane repolarization is achieved by fast inactivation of Na_VChs and is augmented by activation of voltage-gated potassium channels. During recovery from inactivation, Na_VChs may undergo *deactivation*, the transition from the open to the closed state (14). Activation, inactivation, and recovery from inactivation occur within a few milliseconds. In

Table 1

Inherited disorders of Na$_V$Chs

Muscle sodium channelopathies (*SCN4A*)
    Hyperkalemic periodic paralysis
    Paramyotonia congenita
    Potassium-aggravated myotonia
    Painful congenital myotonia
    Myasthenic syndrome
    Hypokalemic periodic paralysis type 2
    Malignant hyperthermia susceptibility
Cardiac sodium channelopathies (*SCN5A*)
    Congenital long QT syndrome (Romano-Ward)
    Idiopathic ventricular fibrillation (Brugada syndrome)
    Isolated cardiac conduction system disease
    Atrial standstill
    Congenital sick sinus syndrome
    Sudden infant death syndrome
    Dilated cardiomyopathy, conduction disorder, arrhythmia
Brain sodium channelopathies (*SCN1A, SCN2A, SCN1B*)
    Generalized epilepsy with febrile seizures plus
    Severe myoclonic epilepsy of infancy (Dravet syndrome)
    Intractable childhood epilepsy with frequent generalized tonic-clonic seizures
    Benign familial neonatal-infantile seizures
Peripheral nerve sodium channelopathies (*SCN9A*)
    Familial primary erythermalgia

addition to these rapid gating transitions, Na$_V$Chs are also susceptible to closing by slower inactivating processes (*slow inactivation*) if the membrane remains depolarized for a longer time (15). These slower events may contribute to determining the availability of active channels under various physiological conditions.

Muscle sodium channelopathies

Disturbances in the function of muscle Na$_V$Chs can affect the ability of skeletal muscle to contract or relax. Two symptoms are characteristic of muscle membrane (sarcolemma) Na$_V$Ch dysfunction, myotonia and periodic paralysis (16). Myotonia is characterized by delayed relaxation of muscle following a sudden forceful contraction and is associated with repetitive action potential generation, a manifestation of sarcolemmal hyperexcitability. By contrast, periodic paralysis represents a transient state of hypoexcitability or inexcitability in which action potentials cannot be generated or propagated.

Periodic paralysis and myotonia. Periodic paralysis is characterized by episodic weakness or paralysis of voluntary muscles occurring with normal neuromuscular transmission and in the absence of motor neuron disease. Patients with familial periodic paralysis present typically in childhood (17). Attacks of weakness are often associated with changes in the serum potassium (K$^+$) concentration as a result of abrupt redistribution of intracellular and extracellular K$^+$. This clinical epiphenomenon forms the basis for classifying periodic paralysis as hypokalemic, hyperkalemic, or normokalemic. In paramyotonia congenita, the dominant symptom is cold-induced muscle stiffness and weakness (17, 18). Potassium-aggravated myotonia is characterized by myotonia without weakness and worsening symptoms following K$^+$ ingestion (19). In general, these disorders are not associated with disabling muscular dystrophy, although chronic weakness may develop in some individuals with long-standing hyperkalemic periodic paralysis (20).

In vitro electrophysiological studies determined that both myotonia and periodic paralysis are associated with abnormal muscle cell membrane sodium conductance (21), and these findings pointed to *SCN4A* as the most plausible candidate gene. Genetic linkage studies confirmed this hypothesis (22–24). Hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia are all associated with missense mutations in *SCN4A*. There are 2 predominant mutations associated with hyperkalemic periodic paralysis (T704M and M1592V), and these occur independently in unrelated kindreds (20, 25). Allelic diversity is greater for paramyotonia congenita and potassium-aggravated myotonia (26–32). In addition, approximately 15% of patients with genotype-defined hypokalemic periodic paralysis carry *SCN4A* mutations (33). Patients with *SCN4A* mutations may present rarely with life-threatening myotonic reactions upon exposure to succinylcholine resembling the syndrome of malignant hyperthermia susceptibility (34, 35). In 1 report, congenital myasthenia has been linked to *SCN4A* mutations (36).

Characterization of SCN4A mutations and pathophysiology. Using heterologously expressed recombinant Na$_V$Chs, several laboratories have characterized the biophysical properties of many mutations associated with either periodic paralysis or various myotonic disorders. These studies demonstrated that variable defects in the rate or extent of inactivation occur in virtually all cases. Mutations associated with hyperkalemic periodic paralysis exhibit incomplete inactivation leading to a small level (1–2% of peak current) of persistent Na$^+$ current that is predicted to cause sustained muscle fiber depolarization (Figure 3) (37, 38). Sustained depolarization will cause the majority of Na$_V$Chs (mutant and wild type) to become inactivated, and this explains conduction failure and electrical inexcitability observed in skeletal muscle during an attack of periodic paralysis (39, 40). By this mechanism, mutant Na$_V$Chs exert an indirect dominant-negative effect on normal channels. In addition, some, but not all, mutations associated with hyperkalemic periodic paralysis have impaired slow inactivation (41), and this may contribute to sustaining the effect of persistent Na$^+$ current (42).

SCN4A mutations in the myotonic disorders slow the rate of inactivation, speed recovery from inactivation, and slow deactivation (30, 43–47). These biophysical defects are predicted to lengthen the duration of muscle action potentials (48). Prolongation of action potentials along T-tubule membranes will exaggerate the local rise in extracellular K$^+$ concentration by efflux through persistently activated potassium channels. Extracellular K$^+$ in T-tubules exerts a depolarizing effect on the resting membrane potential, increasing the probability of an aberrant afterdepolarization. A large afterdepolarization can trigger spontaneous action potentials in adjacent surface membranes, which in turn cause persistent muscle contraction and delayed relaxation, the physiological hallmarks of myotonia (Figure 4) (49).

Treatment strategies for muscle sodium channelopathies. Pharmacological treatment for periodic paralysis with carbonic anhydrase inhibitors is often successful, but the mechanism of action is poorly understood (50, 51). Certain local anesthetic/antiarrhythmic agents have antimyotonic activity and are sometimes useful treatments for nondystrophic myotonias (52, 53). These drugs are effective because of their ability to interrupt rapidly conducted
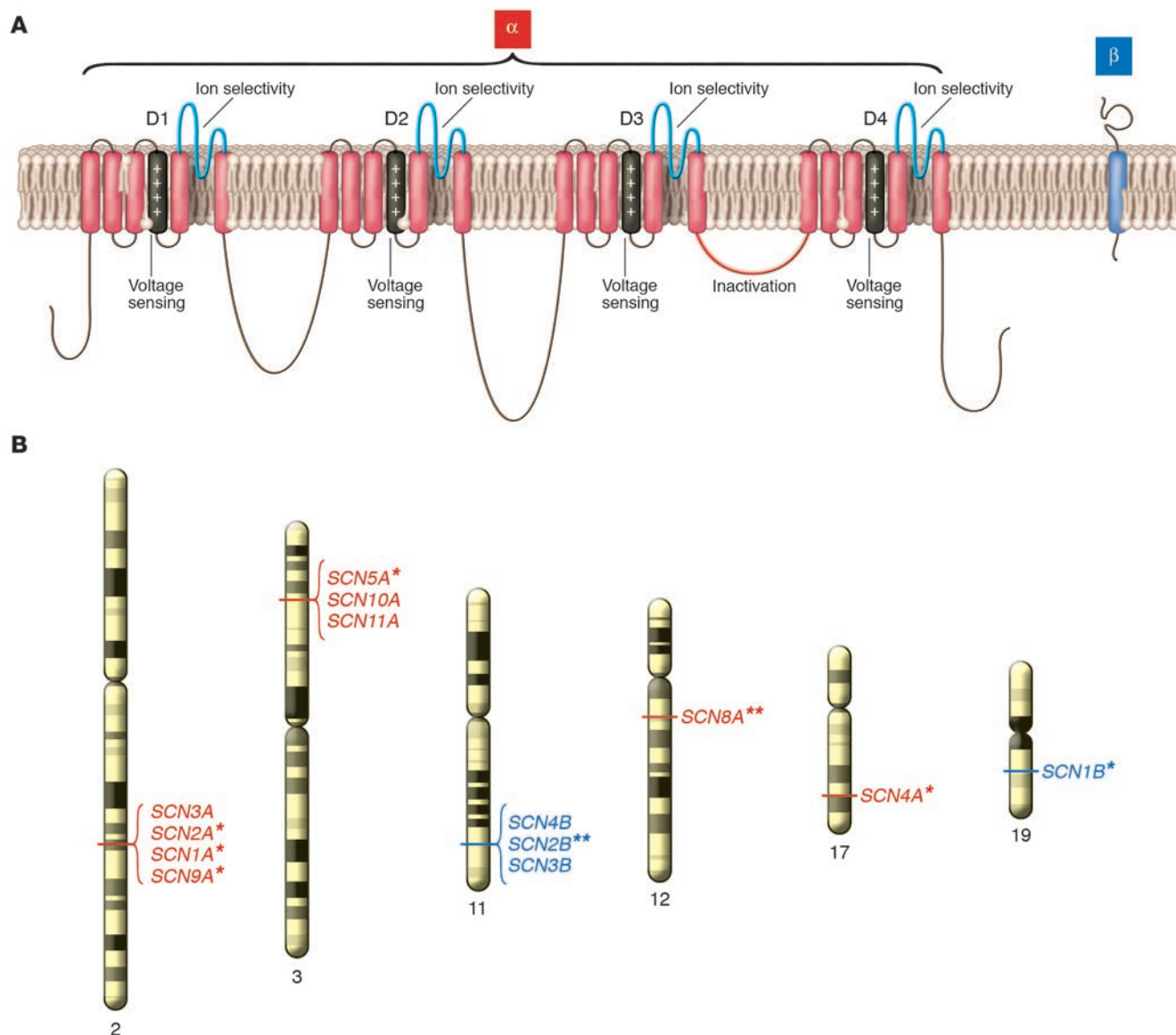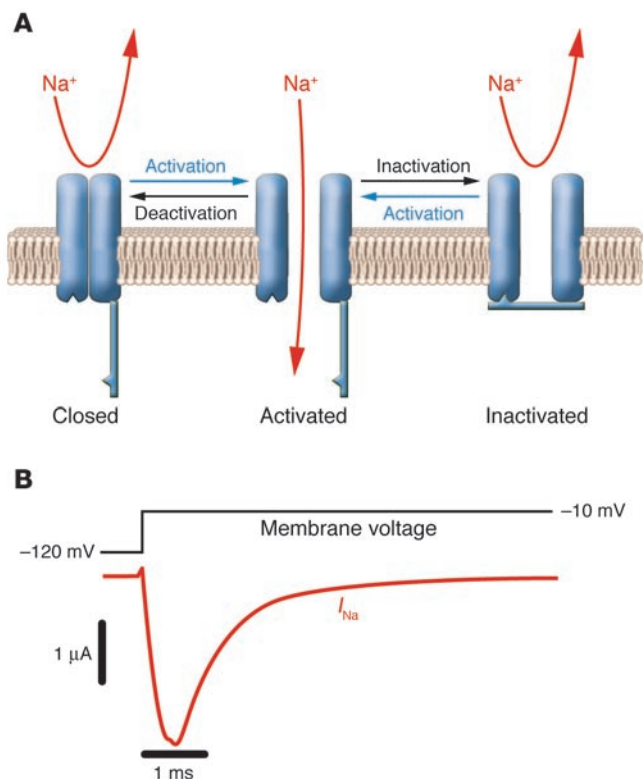
Figure 1
Structure and genomic location of human Na$_V$Chs. (**A**) Simple model representing transmembrane topology of α and β Na$_V$Ch subunits. Structural domains mediating key functional properties are labeled. (**B**) Chromosomal location of human genes encoding α (red) and β (blue) subunits across the genome. An asterisk next to the gene name indicates association with an inherited human disease. A double asterisk indicates association with murine phenotypes.

trains of action potentials through their use-dependent Na$_V$Ch-blocking action. Mexiletine is the most commonly used antimyotonic agent, and there have been in vitro studies demonstrating its effectiveness (54), but there have been no clinical trials comparing this agent with either placebo or other treatments. A more potent Na$_V$Ch blocker, flecainide, may also have utility in severe forms of myotonia that are resistant to mexiletine (55). The efficacy of flecainide for treating myotonia associated with certain *SCN4A* mutations may be greatest when there is a depolarizing shift of the steady-state fast inactivation curve for the mutant channel, whereas mutations that induce hyperpolarizing shifts in this curve are predicted to have greater sensitivity to mexiletine (56). Long-term treatment of myotonia with Na$_V$Ch blockers is often limited by drug side effects.

Cardiac sodium channelopathies
In the heart, Na$_V$Chs are essential for the orderly progression of action potentials from the sinoatrial node, through the atria, across the atrioventricular node, along the specialized conduction system of the ventricles (His-Purkinje system), and ultimately throughout the myocardium to stimulate rhythmic contraction. Mutations in *SCN5A*, the gene encoding the principal Na$_V$Ch α subunit expressed in the human heart, cause inherited susceptibility to ventricular arrhythmia (congenital long QT syndrome, idiopathic ventricular fibrillation) (57–59), impaired cardiac conduction (60), or both (61–65). *SCN5A* mutations may also manifest as drug-induced arrhythmias (66), sudden infant death syndrome (SIDS) (67, 68), and other forms of arrhythmia susceptibility (69).

Figure 2
Functional properties of Na$_V$Chs. (**A**) Schematic representation of an Na$_V$Ch undergoing the major gating transitions. (**B**) Voltage-clamp recording of Na$_V$Ch activity in response to membrane depolarization. Downward deflection of the current trace (red) corresponds to inward movement of Na$^+$.

predominance. A family history of unexplained sudden death is typical. SUDS is a very similar syndrome that causes sudden death, typically during sleep, in young and middle-aged males in Southeast Asian countries (81–83).

Disorders of cardiac conduction. Mutations in *SCN5A* are also associated with heterogeneous familial disorders of cardiac conduction manifest as impaired atrioventricular conduction (heart block), slowed intramyocardial conduction velocity, or atrial inexcitability (atrial standstill) (60, 62, 84, 85). The degree of impaired cardiac conduction may progress with advancing age and is generally not associated with prolongation of the QT interval or ECG changes consistent with Brugada syndrome. Heart block in these disorders is usually the result of conduction slowing in the His-Purkinje system. In most cases, inheritance of the phenotype is autosomal dominant. By contrast, atrial standstill has been reported to occur either as a recessive disorder of *SCN5A* (congenital sick sinus syndrome) (85) or by digenic inheritance of a heterozygous *SCN5A* mutation with a promoter variant in the connexin-40 gene (84).

Mutations in *SCN5A* may also cause more complex phenotypes representing combinations of LQTS, Brugada syndrome, and conduction system disease. There have been documented examples of LQTS combined with Brugada syndrome (63) or congenital heart block (86, 87), and cases of Brugada syndrome with impaired conduction (88). In 1 unique family, all 3 clinical phenotypes occur together (65). *SCN5A* mutations have also been discovered in families segregating impaired cardiac conduction, supraventricular arrhythmia, and dilated cardiomyopathy (64, 89). Certain mutations may manifest different phenotypes in different families.

Characterization of SCN5A mutations and arrhythmogenesis. The clinical heterogeneity associated with *SCN5A* mutations is partly explained by corresponding differences in the degree and characteristics of channel dysfunction. In congenital LQTS, *SCN5A* mutations have a dominant gain-of-function phenotype at the molecu-
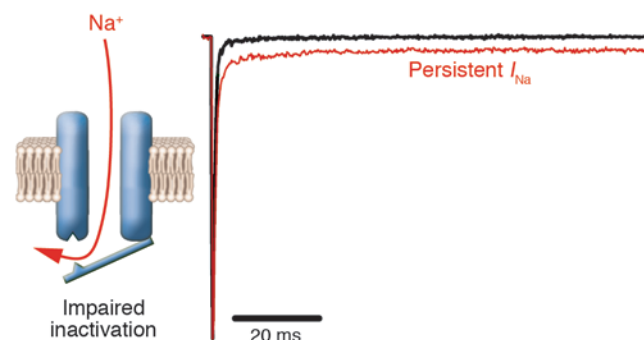
Inherited arrhythmia syndromes: long QT and Brugada. Congenital long QT syndrome (LQTS), an inherited condition of abnormal myocardial repolarization, is characterized clinically by an increased risk of potentially fatal ventricular arrhythmias, especially torsade de pointes (70, 71). The syndrome is transmitted most often in families as an autosomal dominant trait (Romano-Ward syndrome) and less commonly as an autosomal recessive disease combined with congenital deafness (Jervell and Lange-Nielsen syndrome). The syndrome derives its name from the characteristic prolongation of the QT interval on surface ECGs of affected individuals, a surrogate marker of an increased ventricular action potential duration and abnormal myocardial repolarization. Approximately 10% of LQTS cases are caused by *SCN5A* mutations, whereas the majority of Romano-Ward subjects harbor mutations in 2 cardiac potassium channel genes (*KCNQ1* and *HERG*) (72, 73). Triggering factors associated with arrhythmic events are different among genetic subsets of LQTS. *SCN5A* mutations often produce distinct clinical features including bradycardia, and a tendency for cardiac events to occur during sleep or rest (74, 75).

Mutations in *SCN5A* have also been associated with idiopathic ventricular fibrillation, including Brugada syndrome (59, 76) and sudden unexplained death syndrome (SUDS) (77, 78). Individuals with Brugada syndrome have an increased risk for potentially lethal ventricular arrhythmias (polymorphic ventricular tachycardia or fibrillation) without concomitant ischemia, electrolyte abnormalities, or structural heart disease. Individuals with the disease often exhibit a characteristic ECG pattern consisting of ST elevation in the right precordial leads, apparent right bundle branch block, but normal QT intervals (79). Administration of Na$_V$Ch-blocking agents (i.e., procainamide, flecainide, ajmaline) may expose this ECG pattern in latent cases (80). Inheritance is autosomal dominant with incomplete penetrance and a male

Figure 3
A common form of defective inactivation exhibited by mutant Na$_V$Chs associated with hyperkalemic periodic paralysis, long QT syndrome, and inherited epilepsy. The defect is caused by incomplete closure of the inactivation gate (left panel) resulting in an increased level of persistent current (right panel, red trace) as compared with Na$_V$Chs with normal inactivation (black trace).
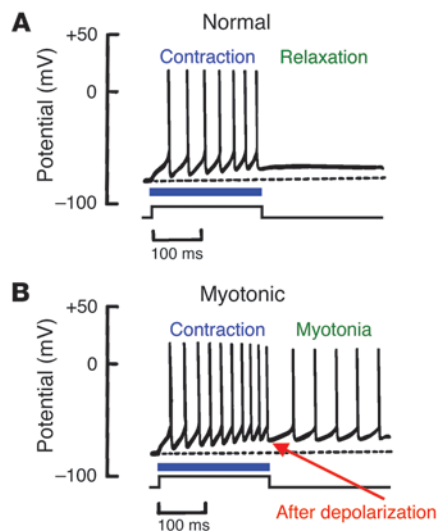
Figure 4
Differences between normal and myotonic muscle action potentials. (**A**) Generation of action potential spikes during electrical stimulation (horizontal blue line and square wave) of a normal muscle fiber. Contraction occurs during action potential firing, followed by muscle relaxation when stimulation ceases. (**B**) Action potentials in myotonic muscle during and immediately after electrical stimulation. An afterdepolarization triggers spontaneous action potentials that fire after termination of the electrical stimulus (myotonic activity).

lar level. Specifically, most mutant cardiac Na$_V$Chs associated with LQTS exhibit a characteristic impairment of inactivation, leading to persistent inward Na$^+$ current during prolonged membrane depolarizations (Figure 3) (90–92). A general slowing of inactivation may be present in mutations associated with severe LQTS (93), while some mutations alter voltage-dependence of activation and inactivation but do not have measurable non-inactivating current (94). Persistent Na$^+$ current during the cardiac action potential explains abnormal myocardial repolarization in LQTS (95). By contrast with nerve and muscle, cardiac action potentials last several hundred milliseconds because of a prolonged depolarization phase (plateau), the result of opposing inward (mainly Na$^+$ and Ca^{2+}) and outward (K$^+$) ionic currents. Repolarization occurs when net outward current exceeds net inward current. Non-inactivating behavior of mutant cardiac Na$_V$Chs will shift this balance toward inward current and delay onset of repolarization, thus lengthening the action potential duration and the corresponding QT interval (Figure 5). Delayed repolarization predisposes to ventricular arrhythmias by exaggerating the dispersion of refractoriness throughout the myocardium and increasing the probability of early afterdepolarization, a phenomenon caused largely by reactivation of calcium channels during the action potential plateau (96). Both of these phenomena create conditions that allow electrical signals from depolarized regions of the heart to prematurely re-excite adjacent myocardium that has already repolarized, the basis for a reentrant arrhythmia. Additional proof of the role of cardiac Na$_V$Ch mutations in LQTS has come from studies of mice heterozygous for a prototypic LQTS *SCN5A* mutation (delKPQ). These mice have spontaneous life-threatening ventricular arrhythmias and a persistent Na$^+$ current

in cardiac myocytes (97). *SCN5A* mutations associated with SIDS also exhibit this biophysical phenotype; this suggests a pathophysiological relationship with LQTS (67, 68).

The proposed cellular basis of Brugada syndrome involves a primary reduction in myocardial sodium current that exaggerates differences in action potential duration between the inner (endocardium) and outer (epicardium) layers of ventricular muscle (96, 98, 99). These differences exist initially because of an unequal distribution of potassium channels responsible for the transient outward current (I_{TO}), a repolarizing current more prominent in the epicardial layer that contributes to the characteristic spike and dome shape of the cardiac action potential. Reduced myocardial Na$^+$ current will cause disproportionate shortening of epicardial action potentials because of unopposed I_{TO}, leading to an exaggerated transmural voltage gradient, dispersion of repolarization, and a substrate promoting reentrant arrhythmias (Figure 6). This hypothesis has been validated using animal models and computational methods. The theory helps explain the characteristic ECG pattern observed in Brugada syndrome and the effects of Na$_V$Ch-blocking agents to aggravate the phenotype.

Consistent with reduced sodium current as the primary pathophysiological event in Brugada syndrome, many *SCN5A* mutations associated with this disease cause frameshift errors, splice site defects, or premature stop codons (59, 100) that are predicted to produce nonfunctional channels. Furthermore, some missense mutations have also been demonstrated to be nonfunctional because of either impaired protein trafficking to the cell membrane or presumed disruption of Na$^+$ conductance through the channel (101–104). However, other missense mutations associated with Brugada syndrome are functional but have biophysical defects predicted to reduce channel availability, such as altered voltage-dependence of activation, more rapid fast inactivation, and enhanced slow inactivation (105–107).

Pathophysiology of SCN5A dysfunction in cardiac conduction disorders. Defects in cardiac Na$_V$Ch function due to mutations associated

Figure 5
Electrophysiological basis for LQTS. (**A**) Relationship of surface ECG (top) with a representative cardiac action potential (bottom). The QT interval approximates the action potential duration. Individual ionic currents responsible for different phases of the action potential are labeled. (**B**) Prolongation of the QT interval and corresponding abnormal cardiac action potential (blue) resulting from persistent sodium current. I_{Ca}, calcium current; I_{K1}, inward rectifier current; I_{Kr}, rapid component of delayed rectifier current; I_{Ks}, slow component of delayed rectifier current; I_{Na}, sodium current; I_{TO}, transient outward current.
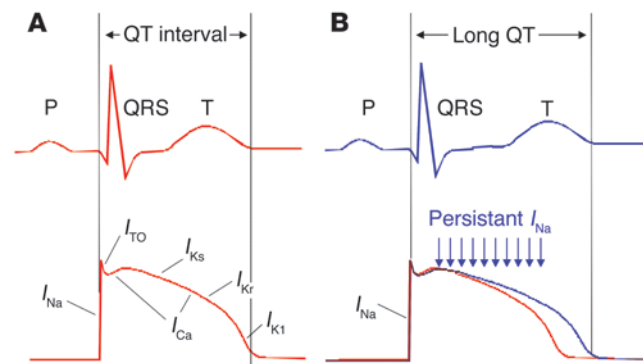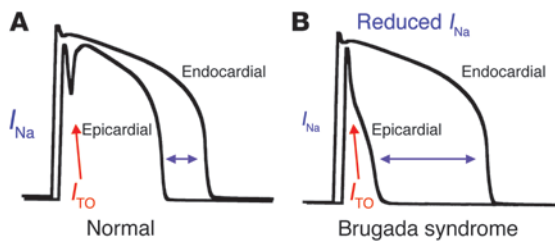
Figure 6
Electrophysiological basis for Brugada syndrome. (**A**) Comparison of endocardial and epicardial action potentials in normal heart. The epicardial action potential is shorter because of large transient outward current. (**B**) Endocardial and epicardial action potentials in Brugada syndrome. Reduced sodium current causes disproportionate shortening of epicardial action potentials with resulting exaggeration of the transmural voltage gradient (horizontal double arrow).

with disorders of cardiac conduction exhibit more complex biophysical properties (61, 62). Mutations causing isolated conduction defects have generally been observed to cause reduced Na_VCh availability as a consequence of mixed gating disturbances. In the case of a Dutch family segregating a specific missense allele (G514C), the mutation causes unequal depolarizing shifts in the voltage-dependence of activation and inactivation such that a smaller number of channels are activated at typical threshold voltages (61). Computational modeling of these changes supports reduced conduction velocity, but the level of predicted Na_VCh loss is insufficient to cause shortened epicardial action potentials, which explains why these individuals do not manifest Brugada syndrome. Two other *SCN5A* mutations causing isolated conduction disturbances (G298S and D1595N) are also predicted to reduce channel availability by enhancing the tendency of channels to undergo slow inactivation in combination with a complex mix of gain- and loss-of-function defects (62). However, other alleles exhibiting complete loss of function have also been associated with isolated cardiac conduction disease (108, 109) without the Brugada syndrome. These observations suggest that additional host factors may contribute to determining whether a mutation will manifest as arrhythmia susceptibility or impaired conduction. This idea is supported by the observation that a single *SCN5A* mutation causes either Brugada syndrome or isolated conduction defects in different members of a large French family (88).

Biophysical properties of mutant cardiac Na_VChs associated with combined phenotypes are also more complex. An in-frame insertion mutation (1795insD) has been identified in a family segregating both LQTS and Brugada syndrome (63). This mutation causes an inactivation defect resulting in persistent Na^+ current characteristic of most other *SCN5A* mutations associated with LQTS, but it also confers enhanced slow inactivation with reduced channel availability that is more characteristic of Brugada syndrome (63). The 2 biophysical abnormalities are predicted to predispose to ventricular arrhythmia at extremes of heart rate by different mechanisms (110). Whereas persistent current will prolong the QT interval to a greater degree at slow heart rates, enhanced slow inactivation predisposes myocardial cells to activity-dependent loss of Na_VCh availability at fast rates. In another unusual case, deletion of lysine-1500 in *SCN5A* was associated with the unique combination of LQTS, Brugada syndrome, and impaired conduction in the same family (65). The mutation impairs inactivation, resulting in

a persistent Na^+ current, and reduces Na_VCh availability by opposing shifts in voltage-dependence of inactivation and activation.

Unlike LQTS, Brugada syndrome, and isolated cardiac conduction disease, in which affected individuals are heterozygous for single Na_VCh mutations, there are cases in which individuals with severe impairments in cardiac conduction have inherited mutations from both parents. Lupoglazoff et al. described a child homozygous for a missense *SCN5A* allele (V1777M) who exhibited LQTS with rate-dependent atrioventricular conduction block (86). In a separate report, probands from 3 families exhibited perinatal sinus bradycardia progressing to atrial standstill (congenital sick sinus syndrome) and were found to have compound heterozygosity for mutations in *SCN5A* (85). Compound heterozygosity in *SCN5A* has also been observed in 2 infants with neonatal wide complex tachycardia and a generalized cardiac conduction defect (111). In each case of compound heterozygosity, individuals inherited 1 nonfunctional or severely dysfunctional mutation from 1 parent and a second allele with mild biophysical defects from the other parent. Interestingly, the parents who were carriers of single mutations were asymptomatic, which suggests that they had subclinical disease or other host factors affording protection. These unusually severe examples of *SCN5A*-linked cardiac conduction disorders illustrate the clinical consequence of nearly complete loss of Na_VCh function. Complete absence of the murine *Scn5a* locus results in embryonic lethality (112), and it is likely that homozygous deletion or inactivation of human *SCN5A* is also not compatible with life.

Treatment strategies for cardiac sodium channelopathies. Specific therapeutic options for *SCN5A*-linked disorders are limited. β-Adrenergic blockers remain the first line of therapy in LQTS albeit this treatment strategy may be less efficacious in the setting of *SCN5A* mutations (113). Clinical and in vitro evidence suggests that mexiletine may counteract the aberrant persistent Na^+ current and shorten the QT interval (114, 115) in *SCN5A* mutation carriers, although there are no data indicating an improvement in mortality. Mexiletine has also been demonstrated to rescue trafficking defective *SCN5A* mutants in vitro (116). Flecainide has also been observed to shorten QT intervals in the setting of certain *SCN5A* mutations (117, 118), but some have raised concern over the safety of this therapeutic strategy (119). Class III–type antiarrhythmic agents (quinidine, sotalol) may be beneficial in Brugada syndrome (120, 121). Device therapy (implantable defibrillator for LQTS and Brugada syndrome; pacemaker for conduction disorders) is also an important treatment option.

Neuronal sodium channelopathies

Neuronal Na_VChs are critical for the generation and propagation of action potentials in the central and peripheral nervous system. Most of the 13 genes encoding Na_VCh α or β subunits are expressed in the brain, peripheral nerves, or both (1). In addition to their critical physiological function, neuronal Na_VChs serve as important pharmacological targets for anticonvulsants and local anesthetic agents (122, 123). Their roles in genetic disorders including a variety of inherited epilepsy syndromes and a rare painful neuropathy have been revealed during the past 7 years.

Sodium channels and inherited epilepsies. Genetic defects in genes encoding 2 pore-forming α subunits (*SCN1A* and *SCN2A*) and the accessory β$_1$ subunit (*SCN1B*) are responsible for a group of epilepsy syndromes with overlapping clinical characteristics but divergent clinical severity (124–129). Generalized epilepsy with febrile

seizures plus (GEFS+) is usually a benign disorder characterized by the frequent occurrence of febrile seizures in early childhood that persist beyond age 6 years, and epilepsy later in life associated with afebrile seizures with multiple clinical phenotypes (absence, myoclonic, atonic, myoclonic-astatic). Mutations in 3 neuronal Na$_V$Ch genes (*SCN1A*, *SCN1B*, and *SCN2A*) and a GABA receptor subunit (*GABRG2*) may independently cause GEFS+ or very similar disorders (130, 131). Mutations in *SCN2A* have also been associated with benign familial neonatal-infantile seizures (BFNIS), a seizure disorder of infancy that remits by age 12 months with no long-term neurological sequelae (129, 132). Interestingly, despite expression of *SCN1A* and *SCN1B* in the heart (9), there are no apparent cardiac manifestations associated with these disorders.

By contrast, severe myoclonic epilepsy of infancy (SMEI) and related syndromes have severe neurological sequelae. The diagnosis of SMEI is based on several clinical features, including (a) appearance of seizures, typically generalized tonic-clonic, during the first year of life, (b) impaired psychomotor development following onset of seizures, (c) occurrence of myoclonic seizures, (d) ataxia, and (e) poor response to antiepileptic drugs (133). Two designations, borderline SMEI (SMEB) (133, 134) and intractable childhood epilepsy with frequent generalized tonic-clonic seizures (ICEGTC) (128), have been assigned to patients with a condition resembling SMEI but in whom myoclonic seizures are absent and less severe psychomotor impairment is evident. *SCN1A* mutations have been identified in probands affected by all of these conditions.

More than 100 *SCN1A* mutations have been identified, with missense mutations being most common in GEFS+ (125, 135–139) and more deleterious alleles (nonsense, frameshift) representing the majority of SMEI mutations (126, 140, 141). Only missense mutations in *SCN1A* have been reported for patients diagnosed with either ICEGTC or SMEB. There are rare reports of families segregating both GEFS+ and either SMEI or ICEGTC (128). The overlapping phenotypes and molecular genetic etiologies among the *SCN1A*-linked epilepsies suggest that they represent a continuum of clinical disorders (142).

Sodium channel dysfunction and epileptogenesis. The first human Na$_V$Ch mutation associated with an inherited epilepsy (GEFS+) was discovered in *SCN1B* encoding the β$_1$ accessory subunit (124). However, mutations in this gene have very rarely been associated with inherited epilepsy. Only 2 *SCN1B* mutations have been described to date, including a missense allele (C121W) and a 5–amino acid deletion (del70–74) (124, 143). Both mutations occur in an extracellular Ig-fold domain of the β$_1$ subunit that is important for functional modulation of Na$_V$Ch α subunits (144, 145) and mediates protein-protein interactions critical for Na$_V$Ch subcellular localization in neurons (146). The C121W mutation disrupts a conserved disulfide bridge in this domain, and functional expression studies demonstrated a failure of the mutant to normally modulate the functional properties of recombinant brain Na$_V$Chs (124, 147). These findings and the observed seizure disorder in mice with targeted deletion of murine β$_1$ subunit indicate that *SCN1B* loss of function explains the epilepsy phenotype (148). Functional characterization of the *SCN1B* deletion allele has not been reported.

Expression studies of α subunit mutations have demonstrated a wide range of functional disturbances. Early findings indicated that *SCN1A* mutations causing GEFS+ promote a gain of function, while mutations associated with SMEI are predicted to disable channel function. Two studies have demonstrated that increased persistent Na$^+$ current is caused by several GEFS+ mutations (149, 150). This behavior is reminiscent of the channel dysfunction associated with 2 other human sodium channelopathies discussed above, hyperkalemic periodic paralysis and LQTS (Figure 3). Non-inactivating Na$^+$ current may facilitate neuronal hyperexcitability by reducing the threshold for action potential firing. However, not all GEFS+ mutations exhibit increased persistent current. For example, a shift in the voltage-dependence of inactivation to more depolarized potentials has been observed for 2 other GEFS+ mutations (T875M and D1866Y). This functional change is predicted to increase channel availability at voltages near the resting membrane potential and is sufficient to enhance excitability in a simple computational model of a neuronal action potential (150). This may be an oversimplification, as T875M also exhibits enhanced slow inactivation, which is predicted to decrease channel availability. For D1866Y, the changed voltage-dependence of inactivation was attributed to decreased modulation by the β$_1$ subunit, a novel epilepsy-associated mechanism. Other GEFS+ mutations have been described that are nonfunctional (V1353L, A1685V) or exhibit depolarizing shifts in voltage-dependence of activation (I1656M, R1657C) predicted to reduce channel activity (151). These findings indicate that more than 1 biophysical mechanism accounts for seizure susceptibility in GEFS+.

Most *SCN1A* mutations associated with SMEI are predicted to produce nonfunctional channels by introducing premature termination or frameshifts into the coding sequence. This observation led to the notion that SMEI stems from *SCN1A* haploinsufficiency. Consistent with this idea was the finding that some missense mutations associated with SMEI are nonfunctional (151, 152). However, a simple dichotomy of gain versus loss of function to explain clinical differences between GEFS+ and SMEI is not consistent with recent observations. As mentioned above, some GEFS+ mutations exhibit loss-of-function characteristics. More recently, 2 SMEI missense alleles (R1648C and F1661S) were demonstrated to encode functional channels that exhibit a mixed pattern of biophysical defects consistent with either gain (persistent Na$^+$ current) or loss (reduced channel density, altered voltage-dependence of activation and inactivation) of function (152). The precise cellular mechanism by which this constellation of biophysical disturbances leads to epilepsy is uncertain and motivates further experiments in animal models to help determine the impact of Na$_V$Ch mutations.

SCN9A and painful inherited neuropathy. Mutations in another neuronal Na$_V$Ch gene, *SCN9A*, encoding an α subunit isoform expressed in sensory and sympathetic neurons, have been discovered in patients with familial primary erythermalgia, a rare autosomal dominant disorder characterized by recurrent episodes of severe pain, redness, and warmth in the distal extremities. Two missense *SCN9A* mutations were recently identified in Chinese patients (153). Both mutations cause a hyperpolarizing shift in the voltage-dependence of channel activation and slow the rate of deactivation (154). This combination of biophysical defects is predicted to confer hyperexcitability on peripheral sensory and sympathetic neurons, accounting for the episodic pain and vasomotor symptoms characteristic of the disease. Consistent with overactive Na$_V$Chs are anecdotal reports of improved symptoms during treatment with local anesthetic agents (i.e., lidocaine, bupivacaine) or mexiletine (155–157).

Summary and future challenges

Na$_V$Chs are important from many perspectives. Their recognized importance in the physiology and pharmacology of nerve, muscle,

and heart is now further emphasized by their role in inherited disorders affecting these tissues. The sodium channelopathies provide outstanding illustrations of the delicate balances that maintain normal operation of critical physiological events such as muscle contraction and conduction of electrical signals.

Despite the extensive array of disorders listed in Table 1, it is likely that other inherited or pharmacogenetic disorders are caused by mutations or polymorphisms in Na_VCh genes. Only 6 of the 13 known genes encoding Na_VCh subunits have been linked to human disease. However, spontaneous or engineered disruption of 2 other genes (*Scn8a* and *Scn2b*) causes neurological phenotypes in mice (158–160), suggesting that other human sodium channelopathies might exist. Establishing new geno-type-phenotype relationships, exploring pathophysiology, and developing new treatment strategies remain exciting challenges for the future.

Acknowledgments

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