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International Union of Pharmacology. XLVII. Nomenclature and Structure-Function Relationships of Voltage-Gated Sodium Channels

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***Abstract*——The family of voltage-gated sodium channels initiates action potentials in all types of excitable cells. Nine members of the voltage-gated sodium channel family have been characterized in mammals, and a 10th member has been recognized as a related protein. These distinct sodium channels have similar structural and functional properties, but they initiate action potentials in different cell types and have distinct regulatory and pharmacological properties. This article presents the molecular relationships and physiological roles of these sodium channel proteins and provides comprehensive information on their molecular, genetic, physiological, and pharmacological properties.**

Introduction

Voltage-gated sodium channels are responsible for action potential initiation and propagation in excitable cells, including nerve, muscle, and neuroendocrine cell types. They are also expressed at low levels in nonexcitable cells, where their physiological role is unclear. Sodium channels are the founding members of the ion channel superfamily in terms of their discovery as a protein and determination of their amino acid sequence. This article presents an introduction to their biochemical, molecular, and genetic properties, physiological roles, and pharmacological significance.

Sodium Channel Subunits

Sodium channels consist of a highly processed α subunit, which is approximately 260 kDa, associated with auxiliary β subunits (Catterall, 2000). Sodium channels in the adult central nervous system and heart contain β_1 through β_4 subunits, whereas sodium channels in adult skeletal muscle have only the β_1 subunit (Isom, 2001). The pore-forming α subunit is sufficient for functional expression, but the kinetics and voltage dependence of channel gating are modified by the β subunits, and these auxiliary subunits are involved in channel localization and interaction with cell adhesion molecules, extracellular matrix, and intracellular cytoskeleton. The α subunits are organized in four homologous domains (I–IV), each of which contain six transmembrane α helices (S1–S6) and an additional pore loop located between the S5 and S6 segments (Fig. 1). The pore loops line the outer, narrow entry to the pore, whereas the S5 and S6 segments line the inner, wider exit from the pore. The S4 segments in each domain contain positively charged amino acid residues at every third position. These residues serve as gating charges and move across the membrane to initiate channel activation in response to depolarization of the membrane. The short intracellular loop connecting homologous domains III and IV serves as the inactivation gate, folding into the channel structure and blocking the pore from the inside during sustained depolarization of the membrane.

Sodium Channel Classification and Nomenclature

A variety of different sodium channels has been identified by electrophysiological recording, biochemical purification, and cloning (Goldin, 2001). The sodium channels are members of the superfamily of ion channels that includes voltage-gated potassium and calcium channels (Yu and Catterall, 2004); however, unlike the different classes of potassium and calcium channels, the functional properties of the known sodium channels are relatively similar. Despite their similarity of function, the sodium channels were originally named in many different ways, with no consistent nomenclature for the various isoforms. To eliminate confusion resulting from the multiplicity of names, a standardized nomenclature was

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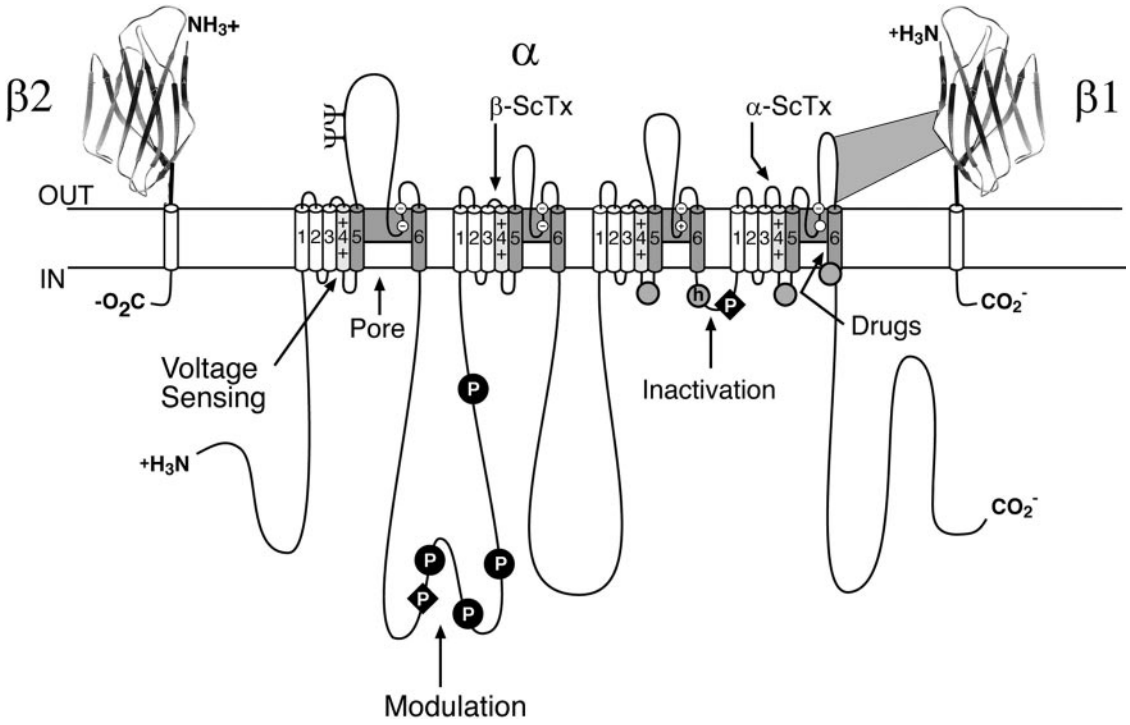

FIG. 1. Transmembrane organization of sodium channel subunits. The primary structures of the subunits of the voltage-gated ion channels are illustrated as transmembrane-folding diagrams. Cylinders represent probable α-helical segments. Bold lines represent the polypeptide chains of each subunit, with length approximately proportional to the number of amino acid residues in the brain sodium channel subtypes. The extracellular domains of the β1 and β2 subunits are shown as immunoglobulin-like folds. Ψ, sites of probable N-linked glycosylation; P, sites of demonstrated protein phosphorylation by protein kinase A (circles) and protein kinase C (diamonds); shaded, pore-lining S5-P-S6 segments; white circles, the outer (EEDD) and inner (DEKA) rings of amino residues that form the ion selectivity filter and tetrodotoxin binding site; ++, S4 voltage sensors; h in shaded circle, inactivation particle in the inactivation gate loop; open shaded circles, sites implicated in forming the inactivation gate receptor. Sites of binding of α- and β-scorpion toxins and a site of interaction between α and β1 subunits are also shown.

developed for voltage-gated sodium channels (Goldin et al., 2000). This nomenclature is based on that for voltage-gated potassium channels (Chandy and Gutman, 1993). It uses a numerical system to define subfamilies and subtypes based on similarities between the amino acid sequences of the channels. A comparable nomenclature has also been adopted for voltage-gated calcium channels (Ertel et al., 2000; Catterall et al., 2005). In this nomenclature system, the name of an individual channel consists of the chemical symbol of the principal permeating ion (Na) with the principal physiological regulator (voltage) indicated as a subscript (Na_V). The number following the subscript indicates the gene subfamily (currently only Na_V1), and the number following the full point identifies the specific channel isoform (e.g., $Na_V1.1$). This last number has been assigned according to the approximate order in which each gene was identified. Splice variants of each family member are identified by lowercase letters following the numbers (e.g., $Na_V1.1a$).

The nine mammalian sodium channel isoforms that have been identified and functionally expressed are all greater than 50% identical in amino acid sequence in the transmembrane and extracellular domains, where the amino acid sequence is similar enough for clear alignment (Fig. 2A). For potassium channels and calcium channels, all members of distinct subfamilies are less than 50% identical to those of other families, and there is much closer sequence similarity within families (Chandy and Gutman, 1993; Ertel et al., 2000). The sodium channel sequences vary more continuously, without defining separate families. By this criterion, all of the nine sodium channel isoforms may be considered members of one family.

Sodium Channel Genes

To test this hypothesis more critically, the nine sodium channel amino acid sequences were aligned and compared for relatedness using a maximum parsimony procedure that measured their evolutionary distance by calculating the number of nucleotide changes required for the change in codon at each position (Fig. 2B). The resulting phylogenetic tree is consistent with designation of these sodium channels as a single family. $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, and $Na_V1.7$ are the most closely related group by this analysis. All four of these sodium channels are highly tetrodotoxin-sensitive and are broadly expressed in neurones. Their genes are all located on human chromosome 2q23-24, consistent with a common evolutionary origin. $Na_V1.5$, $Na_V1.8$, and $Na_V1.9$ are also closely related (Fig. 2B), and their amino acid sequences are greater than 64% identical to those of the four sodium channels encoded on chromosome 2. These sodium channels are tetrodotoxin-resistant to varying degrees due to changes in amino acid sequence at a

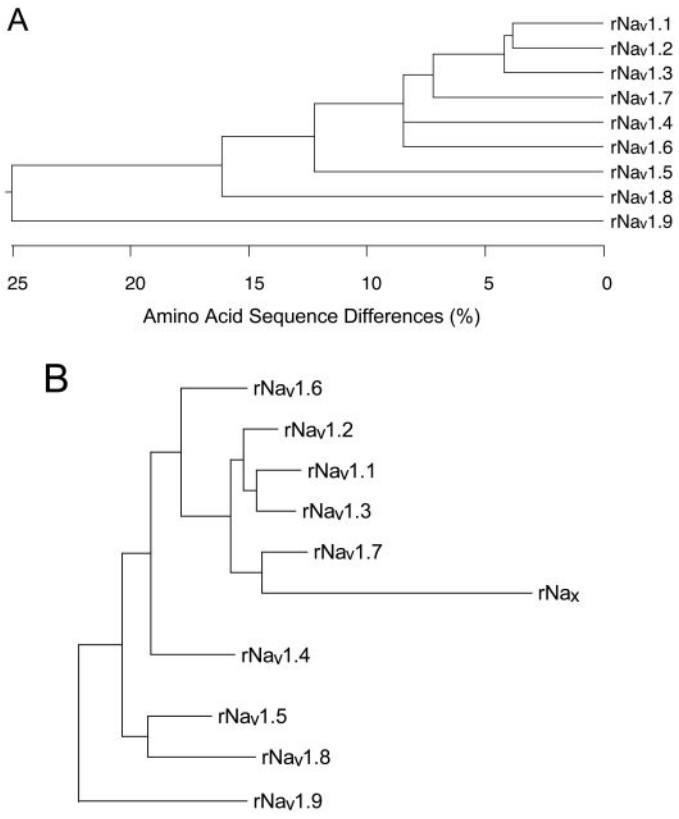

FIG. 2. Amino acid sequence similarity and phylogenetic relationships of voltage-gated sodium channel α subunits. Phylogenetic relationships by maximum parsimony analysis of rat sodium channel sequences $Na_v1.1$–$Na_v1.9$ and Na_x. To perform the analysis, the amino acid sequences for all isoforms were aligned using Clustal W. The amino acid sequences in the alignments were then replaced with the published nucleotide sequences, and the nucleotide sequence alignments were subjected to analysis using the program PAUP*. Divergent portions of the terminal regions and the cytoplasmic loops between domains I–II and II–III were excluded from the PAUP* analysis. The tree was rooted by including the invertebrate sodium channel sequences during the generation of the tree, although these sequences are not shown in the figure.

single position in domain I, and they are highly expressed in heart and dorsal root ganglion neurons (Fozzard and Hanck, 1996; Catterall, 2000). Their genes are located on human chromosome 3p21-24, consistent with a common evolutionary origin. The isoforms $Na_V1.4$, expressed primarily in skeletal muscle, and $Na_V1.6$, expressed primarily in the central nervous system, are set apart from these other two closely related groups of sodium channel genes (Fig. 2B). Although their amino acid sequences are greater than 84% identical to the group of sodium channels whose genes are located on chromosome 2 (Fig. 2A), their phylogenetic relationship is much more distant when analyzed by parsimony comparison (Fig. 2B). This distant evolutionary relationship is consistent with the location of the genes encoding these two sodium channels on chromosomes 17q23-25 and 12q13, respectively. The chromosome segments carrying the sodium channel genes are paralogous segments that contain many sets of related genes, including the homeobox gene clusters. These segments were generated by whole genome duplication events during early vertebrate evolution (Plummer and Meisler, 1999). The comparisons of amino acid sequence identity and phylogenetic and chromosomal relationships lead to the conclusion that all nine members of the sodium channel family that have been functionally expressed are members of a single family of proteins and have arisen from gene duplications and chromosomal rearrangements relatively recently in evolution. These results contrast with those for potassium channels and calcium channels, for which distinct gene families have arisen earlier in evolution and have been maintained as separate families to the present (Chandy and Gutman, 1993; Ertel et al., 2000).

In addition to these nine sodium channels that have been functionally expressed, closely related sodium channel-like proteins have been cloned from mouse, rat, and human but have not yet been functionally expressed (Na_x). They are approximately 50% identical to the Na_V1 subfamily of channels but more than 80% identical to each other. They have significant amino acid sequence differences in the voltage sensors, inactivation gate, and pore region that are critical for channel function and have previously been proposed as a distinct subfamily (George et al., 1992). These atypical sodium channel-like proteins are expressed in heart, uterus, smooth muscle, astrocytes, and neurones in the hypothalamus and peripheral nervous system. Because of their sequence differences, it is possible that these channels are not highly sodium-selective or voltage-gated. Although these proteins have striking differences in amino acid sequence in highly conserved regions of sodium channels, their amino acid sequence is greater than 50% identical to other sodium channels. They are closely related phylogenetically to the group of sodium channels on human chromosome 2q23-24, where their gene is also located (Goldin et al., 2000). Successful functional expression of these atypical sodium channel-like proteins and identification of additionally related sodium channels may provide evidence for a second sodium channel subfamily.

Four auxiliary subunits of sodium channels have been defined thus far: $Na_V\beta_1$, $Na_V\beta_2$, $Na_V\beta_3$, and $Na_V\beta_4$ (Cat-

TABLE 1
Receptor sites on sodium channels

Receptor Site	Toxin or Drug	Domains
Neurotoxin receptor site 1	Tetrodotoxin Saxitoxin μ-Conotoxin	IS2–S6, IIS2–S6 IIIS2–S6, IVS2–S6
Neurotoxin receptor site 2	Veratridine Batrachotoxin Grayanotoxin	IS6, IVS6
Neurotoxin receptor site 3	α-Scorpion toxins Sea anemone toxins	IS5–IS6, IVS3–S4 IVS5–S6
Neurotoxin receptor site 4	β-Scorpion toxins	IIS1–S2, IIS3–S4
Neurotoxin receptor site 5	Brevetoxins Ciguatoxins	IS6, IVS5
Neurotoxin receptor site 6	δ-Conotoxins	IVS3–S4
Local anesthetic receptor site	Local anesthetic drugs Antiarrhythmic drugs Antiepileptic drugs	IS6, IIIS6, IVS6

terall, 2000; Isom, 2001; Yu et al., 2004). In the event that additional subunits are identified, we propose that the nomenclature should be comparable to that for the auxiliary subunits of calcium channels (Ertel et al., 2000).

Sodium Channel Molecular Pharmacology

All of the pharmacological agents that act on sodium channels have receptor sites on the α subunits. At least six distinct receptor sites for neurotoxins and one receptor site for local anesthetics and related drugs have been identified (Cestèle and Catterall, 2000; Table 1). Neurotoxin receptor site 1 binds the nonpeptide pore blockers tetrodotoxin and saxitoxin and the peptide pore blocker μ-conotoxin (Fozzard and Hanck, 1996; Terlau and Stühmer, 1998; Catterall, 2000). The receptor sites for these toxins are formed by amino acid residues in the pore loops and immediately on the extracellular side of the pore loops at the outer end of the pore. Neurotoxin receptor site 2 binds a family of lipid-soluble toxins, including batrachotoxin, veratridine, aconitine, and grayanotoxin, which enhance activation of sodium channels. Photoaffinity labeling and mutagenesis studies implicate transmembrane segments IS6 and IVS6 in the receptor site for batrachotoxin (Cestèle and Catterall, 2000). Neurotoxin receptor site 3 binds the α-scorpion toxins and sea anemone toxins, which slow the coupling of sodium channel activation to inactivation. These peptide toxins bind to a complex receptor site that includes the S3-S4 loop at the outer end of the S4 segment in domain IV (Cestèle and Catterall, 2000). Neurotoxin receptor site 4 binds the β-scorpion toxins, which enhance activation of the channels. The receptor site for the β-scorpion toxins includes the S3-S4 loop at the extracellular end of the voltage-sensing S4 segments in domain II (Cestèle and Catterall, 2000). Neurotoxin receptor site 5 binds the complex polyether toxins brevetoxin and ciguatoxin, which are made by dinoflagellates and cause toxic red tides in warm ocean waters (Cestèle and Catterall, 2000). Transmembrane segments IS6 and IVS5 are implicated in brevetoxin binding from photoaffinity labeling studies (Cestèle and Catterall, 2000). Neurotoxin receptor site 6 binds δ-conotoxins, which slow the rate of inactivation like the α-scorpion toxins. The location of neurotoxin receptor site 6 is unknown. Finally, the local anesthetics and related antiepileptic and antiarrhythmic drugs bind to overlapping receptor sites located in the inner cavity of the pore of the sodium channel (Catterall, 2000). Amino acid residues in the S6 segments from at least three of the four domains contribute to this complex drug receptor site, with the IVS6 segment playing the dominant role.

Tables 2 through 10 summarize the major molecular, physiological, and pharmacological properties for each of the nine sodium channels that have been functionally expressed. Quantitative data are included for voltage dependence of activation and inactivation, single-channel conductance, and binding of drugs and neurotoxins, focusing on those agents that are widely used and diagnostic of channel identity and function.

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TABLE 2
$Na_V1.1$ channels

Channel name	$Na_V1.1$
Description	Voltage-gated sodium channel α subunit
Other names	Brain type I, rat 1, R-I
Molecular information	Human: 2009aa, P35498, X65362, chr. 2q24.3, *SCN1A* Rat: 2009aa, P04775 NM_03975, chr. 3q21 Mouse: 2048aa, Q68V28, XM_61957, chr. 2
Associated subunits	β_1, β_2, β_3, β_4
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	Not established
Ion selectivity	$Na^+ > K^+ > Ca^{2+}$
Activation	$V_a = -33$ mV[1]
Inactivation	$V_h = -72$ mV, $t_h = 0.7$ ms at -10 mV[1]
Activators	Veratridine, batrachotoxin, aconitine, grayanotoxin, and related natural organic toxins; β-scorpion toxins
Gating modifiers	α-Scorpion toxins, sea anemone toxins, and δ-conotoxins, which all slow inactivation
Blockers	Tetrodotoxin (EC_{50} = 6 nM)[1], saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs
Radioligands	[^{3}H]saxitoxin, [^{3}H]batrachotoxin, [^{125}I]scorpion toxins
Channel distribution	Central neurons: primarily localized to cell bodies[2]; cardiac myocytes[3]
Physiological functions	Action potential initiation and repetitive firing in neurons; excitation-contraction coupling in cardiac myocytes
Mutations and pathophysiology	Point mutations and deletions cause inherited febrile seizures, GEFS+, and severe myoclonic epilepsy of infancy[4–6]
Pharmacological significance	Site of action of antiepileptic drugs; potential site of side effects of local anesthetics that enter the general circulation or cerebrospinal fluid

aa, amino acids; chr., chromosome; GEFS+, generalized epilepsy with febrile seizures plus.

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TABLE 3
$Na_V1.2$ channels

Channel name	$Na_V1.2$
Description	Voltage-gated sodium channel α subunit
Other names	Brain type II, rat II, R-II
Molecular information	Human: 2005aa, Q99250, X65361, M94055, NM_021007, chr. 2q22-23, *SCN2A* Rat: 2006aa, P04775, X03630, X61149, NM_012647, 3q24 Mouse: Q68V27, fragment only, chr. 2
Associated subunits	β_1, β_2, β_3, β_4
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	Not established
Ion selectivity	$Na^+ > K^+ > Ca^{2+}$
Activation	$V_a = -24$ mV, $\tau_a < 0.4$ ms at V_a [1,2] (see "Comments")
Inactivation	$V_h = -53$ mV, $\tau_h = 8$ ms at V_a, $t_h = 0.8$ ms at 0 mV[1,2]
Activators	Veratridine, batrachotoxin, aconitine, grayanotoxin, and related organic toxins; β-scorpion toxins
Gating modifiers	α-Scorpion toxins, sea anemone toxins, and δ-conotoxins, which all slow inactivation
Blockers	Tetrodotoxin (EC_{50} = 12 nM),[3] saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs (EC_{50} = 11 mM for lidocaine in inactivated state)
Radioligands	[^{3}H]saxitoxin (K_d = 1 nM),[5] [^{3}H]batrachotoxin, [^{125}I]α-scorpion toxin (K_d = 2 nM),[6] [^{125}I]β-scorpion toxin (K_d = 0.2 nM)[7]
Channel distribution	Central neurones: primarily localized to unmyelinated and premyelinated axons[8–10]
Physiological functions	Action potential initiation and conduction, repetitive firing
Mutations and pathophysiology	A point mutation has been reported to cause inherited febrile seizures and epilepsy[11]
Pharmacological significance	Site of action of antiepileptic drugs; probable site of side effects of local anesthetics that reach the general circulation or the cerebrospinal fluid
Comments	Values given for activation and inactivation parameters are for α subunits expressed alone in mammalian cells and measured with an intracellular solution containing aspartate or chloride[2] as the primary anion; coexpression of different β subunits gives positive or negative shifts in voltage dependence

aa, amino acids; chr., chromosome.

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TABLE 4
$Na_V1.3$ channels

Channel name	$Na_V1.3$
Description	Voltage-gated sodium channel α subunit
Other names	Brain type 3, rat 3, R-III
Molecular information	Human: 1951aa, Q9NY46, XP0336775, NP008853, chr. 2q23-24, *SCN3A* Rat: 1951aa, P08104, Y00766, NM_012647, chr. 3q24 Mouse: 2071aa, Q68V26, XM_355332, chr. 2
Associated subunits	β_1 and β_3 modulate inactivation; time course of expression parallels β_3[1,2]
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	Not established
Ion selectivity	$Na^+ > K^+ > Ca^{2+}$
Activation	$V_a = -23$ to -26 mV[3,4]
Inactivation	$V_h = -65$ to -69 mV, $\tau_h = 0.8$ to 1.5 ms at -10 mV[3,4]
Activators	Veratridine, batrachotoxin, aconitine, grayanotoxin, and related natural organic toxins; β-scorpion toxins
Gating modifiers	α-Scorpion toxins, sea anemone toxins, and δ-conotoxins, which all slow inactivation
Blockers	Tetrodotoxin ($EC_{50} = 4$ nM),[1] saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs
Radioligands	[^{3}H]saxitoxin, [^{3}H]batrachotoxin, [^{125}I]scorpion toxins
Channel distribution	Central neurones: primarily expressed in embryonic and early prenatal life; preferentially localized in cell bodies in adult rat brain[2,5,6]; cardiac myocytes[7]
Physiological functions	Action potential initiation and conduction; repetitive firing
Mutations and pathophysiology	Not fully established; up-regulated in dorsal root ganglion neurons and dorsal horn neurons in axotomy and other nerve injuries[7,8]; rapid recovery from inactivation contributes to hyperexcitability following nerve injury[10]
Pharmacological significance	Site of action of antiepileptic drugs; potential site of side effects of local anesthetics that enter the general circulation or the cerebrospinal fluid

aa, amino acids; chr., chromosome.

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TABLE 5
$Na_V1.4$ channels

Channel name	$Na_v1.4$
Description	Voltage-gated sodium channel α subunit
Other names	SkM1, $\mu1$[1]
Molecular information	Human: 1836aa, M81758, O60217, Q9H3L9,[2,3] chr. 17q23-25,[3] *SCN4A* Rat: 1840aa, M26643, O70611[1] Mouse: 1841aa, AJ278787, Q9ER60,[4] chr. 11[64],[5] Scn4A
Associated subunits	β_1
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	24.9pS human[6] 19.8pS rat[7]
Ion selectivity	$Na^+ > K^+ > Rb^+ > Cs$ (channels reconstituted from rat skeletal muscle sarcolemma)[8]
Activation	$V_a = -30$ mV (rat α subunit in *Xenopus* oocytes)[9] $V_a = -26$ mV (human α subunit in CHO cells)[10]
Inactivation	$V_h = -50.1$ mV, $\tau_h = 0.8$ and ~8 ms at -30 mV, $\tau_h = \sim0.3$ and ~3.5 ms at 10 mV (human α subunit in *Xenopus* oocytes with 200-ms depolarizations using macropatch voltage-clamp)[6] $V_h = -56$ mV, $\tau_h = 1.1$ ms at -20 mV (human α subunit in CHO cells with 500-ms depolarizations)[10]
Activators	Protein: β-scorpion toxins[11] Alkaloids: veratridine,[12] batrachotoxin,[12] grayanotoxin[13]
Gating Modifiers	α-Scorpion toxins and sea anemone toxins, which all slow inactivation[14]
Blockers	Selective: μ-conotoxin GIIIA (EC_{50} = 19–54 nM in rat,[15,16] 1.2 μM in human[6]), μ-conotoxin PIIIA (EC_{50} = 41 nM in rat[16]) Nonselective: tetrodotoxin (EC_{50} = 5 nM in rat,[1] 25 nM in human[6]), saxitoxin (EC_{50} = 4.1 nM in rat[17]) Drugs: local anesthetic, antiepileptic, and antiarrhythmic drugs (lidocaine EC_{50} = 2128 μM in resting state at -130 mV in rat α subunit, 176 μM in rat $\alpha\beta_1$ subunits, 4.4 μM for inactivated state in rat α subunit, 0.9 μM in rat $\alpha\beta_1$ subunits[18]; mexiletine EC_{50} = 431 μM in resting state at -120 mV in rat $\alpha\beta_1$ subunits, 68 μM for inactivated state in rat $\alpha\beta_1$ subunits[19])
Radioligands	[^{125}I]α scorpion toxin, [^{3}H]batrachotoxin, [^{3}H]saxitoxin, [^{3}H]tetrodotoxin
Channel distribution	High levels in adult skeletal muscle and low levels in neonatal skeletal muscle[20]
Physiological functions	Action potential initiation and transmission in skeletal muscle
Mutations and pathophysiology	Point mutations in many locations cause hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonias[21]
Pharmacological significance	Target of local anesthetics used to treat myotonia

aa, amino acids; chr., chromosome; CHO, Chinese hamster ovary.

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TABLE 6
$Na_V1.5$ channels

Channel name	$Na_V1.5$
Description	Voltage-gated sodium channel α subunit
Other names	h1, skm II, cardiac sodium channel
Molecular information	Human: 2016aa, Q14524, M77235, NM_198056 chr. 2q24, *SCN5a* Rat: 1951aa, P15389, A33996, NM_013125 Mouse: 2019aa, Q9JJV9, AJ271477, NP067510, chr. 2
Associated subunits	β_1, β_2, β_3, β_4
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	19–22pS[1]
Ion selectivity	$Na^+ > K^+ > Ca^{2+}$
Activation	$V_a = -47$ mV, -56 mV with F as the major anion in the intracellular solution[2,3] $V_a = -27$ mV with aspartate as the major anion in the intracellular solution[4] $\tau_a = 2.8$ ms, 1.6 ms at V_a[2,4]
Inactivation	$V_h = -84$ mV, -100 mV with F as the major anion in the intracellular solution[2,3] $V_h = -61$ mV with aspartate as the major anion in the intracellular solution, $\tau_h = 1$ ms at 0 mV[4]
Activators	Veratridine, batrachotoxin, aconitine, and related natural organic toxins
Gating modifiers	β-Scorpion toxins, sea anemone toxins, and δ-conotoxins, which all slow inactivation (see "Comments")
Blockers	Tetrodotoxin (TTX-insensitive, K_d = 1–2 mM),[5] saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs (EC_{50} = 16 mM for lidocaine block of inactivated channels[6])
Radioligands	[^{3}H]batrachotoxin (K_d = 25 nM in the presence of α-scorpion toxin)[7,8]
Channel distribution	Cardiac myocytes,[9] immature and denervated skeletal muscle,[10] certain brain neurons[11]
Physiological functions	Action potential initiation and conduction
Mutations and pathophysiology	Point mutations and deletions cause long QT syndrome and idiopathic ventricular fibrillation due to slow and incomplete inactivation of the cardiac sodium current and resulting prolongation of the action potential[12]
Pharmacological significance	Site of action of antiarrhythmic drugs; site of toxic side effects of local anesthetics that reach the general circulation
Comments	$Na_V1.5$ has lower affinity for α- and β-scorpion toxins than neuronal sodium channels[13]

aa, amino acids; chr., chromosome; TTX, tetrodotoxin.

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TABLE 7
$Na_V1.6$ channels

Channel name	$Na_v1.6$
Description	Voltage-gated sodium channel α subunit
Other names	NaCh6,[1] PN4,[2] CerIII[3]
Molecular information	Human: 1980aa, O95788, Q9NYX2, A9UQD0, AF050736, AF225988, chr. 12q13,[4] *SCN8A* Rat: 1976aa, L39018, AF049239, AF049240[1,2] Mouse: 1976aa, Q60858, AF050736, AF225988,[5,6] chr. 15[64],[5] *Scn8A*
Associated subunits	β_1, β_2
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	Not established
Ion selectivity	Na^+
Activation	$V_a = -8.8$ mV (mouse α subunit in *Xenopus* oocytes with cut-open oocyte voltage-clamp)[6] $V_a = -17$ mV (mouse α subunit with β_1 and β_2 in *Xenopus* oocytes with cut-open oocyte voltage-clamp)[6] $V_a = -26$ mV, $\tau_a = 0.51$ ms and 4.65 ms at -10 mV (mouse α subunit with inactivation removed and β_1 and β_2 in *Xenopus* oocytes with cut-open oocyte voltage-clamp)[7] $V_a = -37.7$ mV, τ_a not determined (rat α subunit in *Xenopus* oocytes with macropatch voltage-clamp)[2,7]
Inactivation	$V_h = -55$ mV, $\tau_h = 1.2$ and 2.1 ms at -10 mV, $\tau_h = 0.98$ and 11.6 ms at 10 mV (mouse α subunit in *Xenopus* oocytes with 500-ms depolarizations using two-electrode voltage-clamp)[6] $V_h = -51$ mV, $\tau_h = 7.1$ ms at -20 mV, $\tau_h = 0.78$ and 8.1 ms at 10 mV (mouse α subunit with β_1 and β_2 in *Xenopus* oocytes with 500-ms depolarizations using two-electrode voltage-clamp)[6] $V_h = -97.6$ mV, $\tau_h = 1$ ms at -30 mV (rat α subunit in *Xenopus* oocytes with 5-s depolarizations using macropatch voltage-clamp)[2]
Activators	Veratridine, batrachotoxin (based on studies with rat brain sodium channels)
Gating modifiers	α-Scorpion toxins and sea anemone toxins, which all slow inactivation[8]
Blockers	Nonselective: tetrodotoxin (EC_{50} = 1 nM in rat,[2] 6 nM in mouse[6]), saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs
Radioligands	[^{125}I]α-scorpion toxin, [^{3}H]batrachotoxin, [^{3}H]saxitoxin [^{3}H]tetrodotoxin (based on studies with rat brain sodium channels)
Channel distribution	Somatodendritic distribution in output neurons of the cerebellum, cerebral cortex, and hippocampus; Purkinje cells in the cerebellar granule cell layer; brainstem and spinal cord, astrocytes, and Schwann cells; DRG; nodes of Ranvier of sensory and motor axons in the PNS; nodes of Ranvier in the CNS[1,9–11]
Physiological functions	Action potential initiation and transmission in central neurons and their myelinated axons; partially responsible for the resurgent and persistent current in cerebellar Purkinje cells[12]
Mutations and pathophysiology	Point mutation in II S4-S5 causes cerebellar ataxia in *jolting* mice[13]; gene disruption causes *motor endplate disease* in mice[5]
Pharmacological significance	Potential target for antiepileptic and analgesic drugs

aa, amino acids; chr., chromosome; DRG, dorsal root ganglion; PNS, peripheral nerve system; CNS, central nervous system.

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12. Raman IM, Sprunger LK, Meisler MH, and Bean BP (1997) Altered subthreshold sodium currents and disrupted firing patterns in Purkinje neurons of *Scn8a* mutant mice. *Neuron* **19:**881–891.

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TABLE 8
$Na_V1.7$ channels

Channel name	$Na_v1.7$
Description	Voltage-gated sodium channel α subunit
Other names	PN1,[1,2] hNE-Na,[3] Nas[4]
Molecular information	Human: 1977aa, X82835,[3] chr. 2q24, *SCN9A* Rat: 1984aa, AF000368, U79568[1,2] Mouse: chr. 2[36],[5,6] *Scn9A*
Associated subunits	β_1, β_2
Functional assays	Voltage-clamp, neurotoxin-activated ion flux, voltage-sensitive dyes
Current	I_{Na}
Conductance	19.5pS (for TTX-sensitive current in DRG neurons)[7]
Ion selectivity	Na^+
Activation	$V_a = -31$ mV (rat α subunit in *Xenopus* oocytes with macropatch)[2] $V_a = -45$ mV (TTX-sensitive current in DRG neurons)[7]
Inactivation	$V_h = -78$ mV, $\tau_h = 0.46$ and 20 ms at -30 mV, $\tau_h = 0.1$ and 1.8 ms at 10 mV (rat α subunit in *Xenopus* oocytes with 10-s depolarizations using two-electrode voltage-clamp)[2] $V_h = -60.5$ mV (human α subunit in HEK cells with 2-s depolarizations using whole-cell patch clamp)[3] $V_h = -39.6$ mV (human α subunit with β_1 subunit in HEK cells with 2-s depolarizations using whole-cell patch clamp)[3] $V_h = -65$ mV (TTX-sensitive current in DRG neurons with 50-ms to 1-s depolarizations using whole-cell patch clamp)[7]
Activators	Veratridine, batrachotoxin (based on studies with rat brain sodium channels)
Gating modifiers	α-Scorpion toxins and sea anemone toxins, which probably slow inactivation based on studies with peripheral nerves and $Na_v1.2$[8,9]
Blockers	Nonselective: tetrodotoxin (EC_{50} = 4 nM in rat,[2] 25 nM in human[3]), saxitoxin; local anesthetic, antiepileptic, and antiarrhythmic drugs (lidocaine EC_{50} = 450 μM in resting state at -100 mV[10])
Radioligands	[^{125}I]α-scorpion toxin, [^{3}H]batrachotoxin, [^{3}H]saxitoxin [^{3}H]tetrodotoxin (based on studies with rat brain sodium channels)
Channel distribution	All types of DRG neurons, sympathetic neurons, Schwann cells, and neuroendocrine cells[2,3,11]
Physiological functions	Action potential initiation and transmission in peripheral neurons; slow closed-state inactivation facilitates response to slow, small depolarizations[12]
Mutations and pathophysiology	Mutations (I848T and I858H), observed in inherited erythromelalgia, negatively shift activation, slow deactivation, and enhance response to small depolarizations[13,14]
Pharmacological significance	Probable target of local anesthetics in the peripheral nervous system

aa, amino acids; chr., chromosome; TTX, tetrodotoxin; DRG, dorsal root ganglion; HEK, human embryonic kidney.

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13. Yang Y, Wang Y, Li S, Xu Z, Li H, Ma I, Fan J, Bu D, Liu B, Fan Z, et al. (2004) Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genetics* **41:**171–174.

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TABLE 9
$Na_V1.8$ channels

Channel name	$Na_V1.8$
Description	Voltage-gated sodium channel α subunit
Other names	SNS, PN3
Molecular information	Human: 1957aa, Q9Y5Y9, NM_006514, chr. 3P21-3P24, *SCN10A* Rat: Q63554, Q62968, NM_017247, U53833 Mouse: P70276, NM_009134, chr. 9
Associated subunits	Not established
Functional assays	Voltage-clamp, voltage-sensitive dyes
Current	$I_{TTX\text{-}Rslow}$
Conductance	Not established
Ion selectivity	Na^+
Activation	Threshold = −40 to −30 mV (rat DRG)[1,2] V_a = −16 to −21 mV (rat DRG)[1,2] τ_a = 0.54 ms at −20 mV, 0.36 ms at −10 mV
Inactivation	V_h = ~−30 mV (rat DRG), τ_h = 13.5 ms at −20mV, 5.6 ms at −10 mV
Activators	Not established
Gating modifiers	Not established
Blockers	Tetrodotoxin (TTX-resistant, EC_{50} = 60 mM), lidocaine (and probably other local anesthetics) at high concentrations[3]
Radioligands	None
Channel distribution	Small and medium-sized DRG neurones and their axons[4]
Physiological functions	Contributes substantially to the inward current underlying the action potential in DRG neurones[5]; adds a slowly inactivating sodium current component
Mutations and pathophysiology	Point mutation of Ser356 to an aromatic residue removes TTX resistance[6]; $Na_V1.8$-null mice exhibit reduced pain responses to noxious mechanical stimuli, delayed development of inflammatory hyperalgesia, and small deficits in noxious thermoreception,[7]suggesting a role of $Na_v1.8$ in nociception and in chronic pain; $Na_v1.8$ is up-regulated in some models of inflammatory pain[8]
Pharmacological significance	Potential target for analgesic drugs
Comments	Rapid recovery from inactivation is conferred by a three-amino acid insert in IVS3–S4[9]; expression is regulated by NGF and GDNF[10]; insertion of functional $Na_v1.8$ channels in cell membrane is facilitated by annexin II/p11[11]

aa, amino acids; chr., chromosome; TTX, tetrodotoxin; DRG, dorsal root ganglion; NGF, nerve growth factor; GDNF, glial cell-derived growth factor.

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TABLE 10
$Na_V1.9$ channels

Channel name	$Na_V1.9$
Description	Voltage-gated sodium channel α subunit
Other names	NaN, SNS-2
Molecular information	human: 1792aa, Q9UHE0, AF188679, chr. 3p21-3p24, *SCN11A* Rat: 1765aa, 088457, NM_019265, AJ237852, Mouse: 1765aa, Q9R053, NM_011887, chr. 9
Associated subunits	Not established
Functional assays	Voltage clamp
Current	$I_{NaTTX\text{-}RP}$
Conductance	Not established
Ion selectivity	Na^+
Activation	Threshold = −70 to −60 mV (rat DRG), −80mV (human) V_a = −47 to −54 mV (rat DRG)[1,2,3]; τ_a = 2.93 ms at −60 mV, 4.1 ms at −50 mV, 3.5 ms at −20 mV, and 2.5 ms at −10 mV[3]
Inactivation	V_h = −44 to −54 mV[1,3]; τ_h = 843 ms at −60 mV, 460 ms at −50 mV, 43 ms at −20 mV, and 16 ms at −10 mV[3]
Activators	Not established
Gating modifiers	Not established
Blockers	Tetrodotoxin (TTX-resistant, EC_{50} = 40 mM)
Radioligands	None
Channel distribution	c-type DRG neurones, trigeminal neurones and their axons; preferentially expressed in nociceptive DRG neurons[4]
Physiological functions	Contributes a depolarizing influence to resting potential, amplifies slow subthreshold depolarizations[1,3] and modulates excitability of cell membrane[5]
Mutations and pathophysiology	Preferential expression in c-type dorsal root ganglion neurons suggests a role in nociception
Pharmacological significance	Potential target for analgesic drugs
Comments	Expression is regulated by GDNF[6]; $Na_V1.9$ current is increased by inflammatory mediators such as PGE_2[7]

aa, amino acids; chr., chromosome; DRG, dorsal root ganglion; TTX, tetrodotoxin; GDNF, glial cell-derived growth factor; PG, prostaglandin.

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