0031-6997/05/5704-397–409$7.00
PHARMACOLOGICAL REVIEWS
Vol. 57, No. 4
50402/3070327
Pharmacol Rev 57:397–409, 2005
Printed in U.S.A

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

WILLIAM A. CATTERALL, ALAN L. GOLDIN, AND STEPHEN G. WAXMAN

Department of Pharmacology, University of Washington, Seattle, Washington (W.A.C.); Department of Microbiology and Molecular Genetics, University of California, Irvine, California (A.L.G.); and Department of Neurology, Yale University School of Medicine, New Haven, Connecticut (S.G.W.)

***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

Address correspondence to: Dr. William A. Catterall, Department of Pharmacology, University of Washington, Mailstop 357280, Seattle, WA 98195-7280. E-mail: wcatt@u.washington.edu

The authors serve as the Subcommittee on Sodium Channels of the Nomenclature Committee of the International Union of Pharmacology.

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.57.4.4.

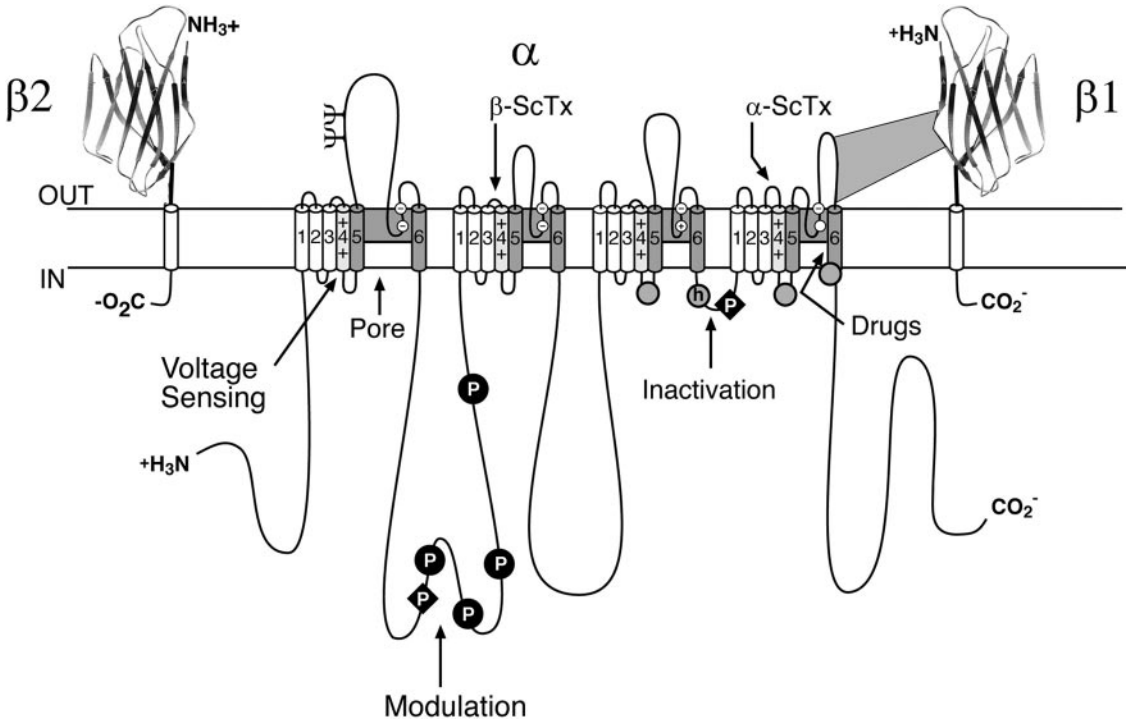

FIG. 1. Transmembrane organization of sodium channel subunits. The primary structures of the subunits of the voltage-gated ion channels are illustrated as transmembrane-folding diagrams. Cylinders represent probable α-helical segments. Bold lines represent the polypeptide chains of each subunit, with 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

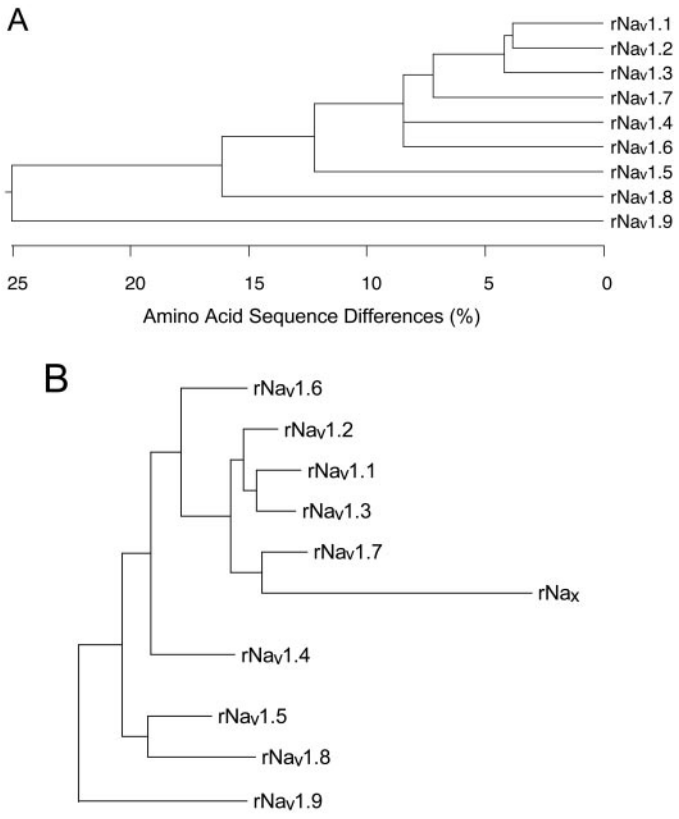

FIG. 2. Amino acid sequence similarity and phylogenetic relationships of voltage-gated sodium channel α subunits. Phylogenetic relationships by maximum parsimony analysis of rat sodium channel sequences $Na_v1.1$–$Na_v1.9$ and Na_x. To perform the analysis, the amino acid sequences for all isoforms were 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.

REFERENCES

Catterall WA (2000) From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* **26:**13–25.

Caterall WA, Perez-Reyes E, Snitch TP, and Striessnig J (2005) International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* **57:**411–425.

Cestèle S and Catterall WA (2000) Molecular mechanisms of neurotoxin action on voltage-gated sodium channels. *Biochimie* **82:**883–892.

Chandy KG and Gutman GA (1993) Nomenclature for mammalian potassium channel genes. *Trends Pharmacol Sci* **14:**434.

Ertel EA, Campbell KP, Harpold MM, Hofmann F, Mori Y, Perez-Reyes E, Schwartz A, Snutch TP, Tanabe T, Birnbaumer L, et al. (2000) Nomenclature of voltage-gated calcium channels. *Neuron* **25:**533–535.

Fozzard HA and Hanck DA (1996) Structure and function of voltage-dependent sodium channels: Comparison of brain II and cardiac isoforms. *Physiol Rev* **76:** 887–926.

George AL Jr, Knittle TJ, and Tamkun MM (1992) Molecular cloning of an atypical voltage-gated sodium channel expressed in human heart and uterus: evidence for a distinct gene family. *Proc Natl Acad Sci USA* **89:**4893–4897.

Goldin AL (2001) Resurgence of sodium channel research. *Annu Rev Physiol* **63:**871–894.

Goldin AL, Barchi RL, Caldwell JH, Hofmann F, Howe JR, Hunter JC, Kallen RG, Mandel G, Meisler MH, Berwald Netter Y, et al. (2000) Nomenclature of voltage-gated sodium channels. *Neuron* **28:**365–368.

Isom LL (2001) Sodium channel beta subunits: anything but auxiliary. *Neuroscientist* **7:**42–54.

Plummer NW and Meisler MH (1999) Evolution and diversity of mammalian sodium channel genes. *Genomics* **57:**323–331.

Terlau H and Stühmer W (1998) Structure and function of voltage-gated ion channels. *Naturwissenschaften* **85:**437–444.

Yu FH, Westenbroek RE, Silos-Santiago I, McCormick KA, Lawson D, Ge P, Ferriera H, Lilly J, DiStefano PS, Catterall WA, et al. (2004) Sodium channel beta4, a new disulfide-linked auxiliary subunit with similarity to beta2. *J Neurosci* **23:**7577–7585.

Yu FH and Catterall WA (2004) The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Science STKE* **253:**re15.

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.

1. Clare JJ, Tate SN, Nobbs M, and Romanos MA (2000) Voltage-gated sodium channels as therapeutic targets. *Drug Discov Today* **5:**506–520.
2. Westenbroek RE, Merrick DK, and Catterall WA (1989) Differential subcellular localization of the R_I and R_{II} Na^+ channel subtypes in central neurons. *Neuron* **3:**695–704.
3. Maier SK, Westenbroek RE, Schenkman KA, Feigl EO, Scheuer T, and Catterall WA (2002) An unexpected role for brain-type sodium channels in coupling of cell surface depolarization to contraction in the heart. *Proc Natl Acad Sci USA* **99:**4073–4078.
4. Escayg A, MacDonald BT, Meisler MH, Baulac S, Huberfeld G, An-Gourfinkel I, Brice A, LeGuern E, Moulard B, Chaigne D, et al. (2000) Mutations ofSCN1A, encoding a neuronal sodium channel, in two families with GEFS + 2. *Nat Genet* **24:**343–345.
5. Spampanato J, Escayg A, Meisler MH, and Goldin AL (2001) Functional effects of two voltage-gated sodium channel mutations that cause generalized epilepsy with febrile seizures plus type 2. *J Neurosci* **21:**7481–7490.
6. Nabbout R, Gennaro E, Dalla Bernardina B, Dulac O, Madia F, Bertini E, Capovilla G, Chiron C, Cristofori G, Elia M, et al. (2003) Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. *Neurology* **60:**1961–1967.

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.

1. Mantegazza M, Yu FH, Catterall WA, and Scheuer T (2001) Role of the C-terminal domain in inactivation of brain and cardiac sodium channels. *Proc Natl Acad Sci USA* **98:**15348–15353.

2. Qu Y, Curtis R, Lawson D, Gilbride K, Ge P, DeStefano PS, Silos-Santiago I, Catterall WA, and Scheuer T (2001) Differential modulation of sodium channel gating and persistent sodium currents by the β1, β2, and β3 subunits. *Mol Cell Neurosci* **18:**570–580.

3. Noda M, Ikeda T, Kayano T, Suzuki H, Takeshima H, Kurasaki M, Takahashi H, and Numa S (1986) Existence of distinct sodium channel messenger RNAs in rat brain. *Nature* **320:**188–192.

4. Ragsdale DR, McPhee JC, Scheuer T, and Catterall WA (1996) Common molecular determinants of local anesthetic, antiarrhythmic, and anticonvulsant block of voltage-gated Na^+ channels. *Proc Natl Acad Sci USA* **93:**9270–9275.

5. West JW, Scheuer T, Maechler L, and Catterall WA (1992) Efficient expression of rat brain type IIA Na^+ channel α subunits in a somatic cell line. *Neuron* **8:**59–70.

6. Rogers JC, Qu Y, Tanada TN, Scheuer T, and Catterall WA (1996) Molecular determinants of high affinity binding of α-scorpion toxin and sea anemone toxin in the S3-S4 extracellular loop in domain IV of the Na^+ channel α subunit. *J Biol Chem* **271:**15950–15962.

7. Cestèle S, Qu Y, Rogers JC, Rochat H, Scheuer T, and Catterall, WA (1998) Voltage sensor-trapping: enhanced activation of sodium channels by β-scorpion toxin bound to the S3-S4 loop in domain II. *Neuron* **21:**919–931.

8. Westenbroek RE, Merrick DK, and Catterall WA (1989) Differential subcellular localization of the R_I and R_{II} Na^+ channel subtypes in central neurons. *Neuron* **3:**695–704.

9. Boiko T, Rasband MN, Levinson SR, Caldwell JH, Mandel G, Trimmer JS. and Matthews G. (2001)Compact myelin dictates the differential targeting of two sodium channel isoforms in the same axon. *Neuron* **30:**91–104.

10. Kaplan MR, Cho MH, Ullian EM, Isom LL, Levinson SR, and Barres BA (2001) Differential control of clustering of the sodium channels $Na_V1.2$ and $Na_V1.6$ at developing CNS nodes of Ranvier. *Neuron* **30:**105–119.

11. Sugawara T, Tsurubuchi Y, Agarwala KL, Ito M, Fukuma G, Mazaki-Miyazaki E, Nagafuji H, Noda M, Imoto K, Wada K, et al. (2001) A missense mutation of the Na^+ channel alpha II subunit gene $Na_V1.2$ in a patient with febrile and afebrile seizures causes channel dysfunction. *Proc Natl Acad Sci USA* **98:**6384–6389.

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.

1. Meadows LS, Chen YH, Powell AJ, Clare JJ, and Ragsdale DS (2002) Functional modulation of human $Na_V1.3$ sodium channels expressed in mammalian cells, by auxiliary β_1, β_2, and β_3 subunits. *Neuroscience* **114:**745–753.

2. Shah BS, Stevens EB, Pinnock RD, Dixon AK, and Lee K (2001) Developmental expression of the novel voltage-gated sodium channel subunit β_3 in rat CNS. *J Physiol (Lond)* **534:**763–776.

3. Chen YH, Dale TJ, Romanos MA, Whitaker WR, Xie XM, and Clare JJ (2000) Cloning, distribution and functional analysis of the type III sodium channel from human brain. *Eur J Neurosci* **12:**4281–4289.

4. Cummins TR, Aglieco F, Renganathan M, Herzog RI, Dib-Hajj SD, and Waxman SG (2001) $Na_V1.3$ sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons. *J Neurosci* **21:**5952–5961.

5. Beckh S, Noda M, Lübbert H, and Numa S (1989) Differential regulation of three sodium channel messenger RNAs in the rat central nervous system during development. *EMBO J* **8:**3611–3616.

6. Westenbroek RE, Noebels JL, and Catterall WA (1992) Elevated expression of type II Na^+ channels in hypomyelinated axons of *shiverer* mouse brain. *J Neurosci* **12:**2259–2267.

7. Maier SK, Westenbroek RE, Schenkman KA, Feigl EO, Scheuer T, and Catterall WA (2002) An unexpected role for brain-type sodium channels in coupling of cell surface depolarization to contraction in the heart. *Proc Natl Acad Sci USA* **99:**4073–4078.

8. Waxman SG, Kocsis JD, and Black JA (1994) Type III sodium channel mRNA is expressed in embryonic but not adult spinal sensory neurons, and is re-expressed following axotomy. *J Neurophysiol* **72:**466–472.

9. Hains BC, Saab CY, Klein JP, Craner MC, and Waxman SG (2004) Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. *J Neurosci* **24:**4832–4840.

10. Cummins TC and Waxman SG (1997) Down-regulation of tetrodotoxin-resistant sodium currents and up-regulation of a rapidly-repriming tetrodotoxin-sensitive sodium current in spinal sensory neurons following nerve injury. *J Neurosci* **17:**3503–3514.

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, $\tau_h =$ ~0.3 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.

1. Trimmer JS, Cooperman SS, Tomiko SA, Zhou J, Crean SM, Boyle MB, Kallen RG, Sheng Z, Barchi RL, Sigworth FJ, et al. (1989) Primary structure and functional expression of a mammalian skeletal muscle sodium channel. *Neuron* **3:**33–49.

2. George AL Jr, Komisarof J, Kallen RG, and Barchi RL (1992) Primary structure of the adult human skeletal muscle voltage-dependent sodium channel. *Ann Neurol* **31:**131–137.

3. Wang J, Rojas CV, Zhou J, Schwartz LS, Nicholas H, and Hoffman EP (1992) Sequence and genomic structure of the human adult skeletal muscle sodium channel alpha subunit gene on 17q. *Biochem Biophys Res Commun* **182:**794–801.

4. Zimmer T, Bollensdorff C, Haufe V, Birch-Hirschfeld E, and Benndorf K (2002) Mouse heart Na^+ channels: primary structure and function of two isoforms and alternatively splice variants. *Am J Physiol Heart Circ Physiol* **282:**H1007–H1017.

5. Ambrose C, Cheng S, Fontaine B, Nadeau JH, MacDonald M, and Gusella JF (1992) The alpha-subunit of the skeletal muscle sodium channel is encoded proximal to Tk-1 on mouse chromosome 11. *Mamm Genome* **3:**151–155.

6. Chahine M, Bennett PB, George AL Jr, and Horn R (1994) Functional expression and properties of the human skeletal muscle sodium channel. *Pflugers Arch Eur J Physiol* **427:**136–142.

7. Zhou J, Potts JF, Trimmer JS, Agnew WS, and Sigworth FJ (1991) Multiple gating modes and the effect of modulating factors on the muI sodium channel. *Neuron* **7:**775–785.

8. Tanaka JC, Eccleston JF, and Barchi RL (1983) Cation selectivity characteristics of the reconstituted voltage-dependent sodium channel purified from rat skeletal muscle sarcolemma. *J Biol Chem* **258:**7519–7526.

9. Cannon SC, McClatchey AI, and Gusella JF (1993) Modification of the Na^+ current conducted by the rat skeletal muscle alpha subunit by co-expression with a human brain beta subunit. *Pflugers Arch Eur J Physiol* **423:**155–157.

10. Bennett ES (2004) Channel activation voltage alone is directly altered in an isoform-specific manner by $Na_v1.4$ and $Na_v1.5$ cytosplasmic linkers. *J Membr Biol* **197:**155–168.

11. Marcotte P, Chen L-Q, Kallen RG, and Chahine M (1997) Effects of Tityus serrulatus scorpion toxin gamma on voltage-gated Na^+ channels. *Circ Res* **80:**363–369.

12. Wang S-Y and Wang GK (1998) Point mutations in segment I-S6 render voltage-gated Na^+ channels resistant to batrachotoxin. *Proc Natl Acad Sci USA* **95**:2653–2658.

13. Kimura T, Yamaoka K, Kinoshita E, Maejima H, Yuki T, Yakehiro M, and Seyama I (2001) Novel site on sodium channel α-subunit responsible for the differential sensitivity of grayanotoxin in skeletal and cardiac muscle. *Mol Pharmacol* **60:**865–872.

14. Chahine M, Plante E, and Kallen RG (1996) Sea anemone toxin (ATX II) modulation of heart and skeletal muscle sodium channel α-subunits expressed in tsA201 cells. *J Membr Biol* **152:**39–48.

15. Chen L-Q, Chahine M, Kallen RG, and Horn R (1992) Chimeric study of sodium channels from rat skeletal and cardiac muscle. *FEBS Lett* **309:**253–257.

16. Safo P, Rosenbaum T, Shcherbatko A, Choi D-Y, Han E, Toledo-Aral J, Olivera BM, Brehm P, and Mandel G (2000) Distinction among neuronal subtypes of voltage-activated sodium channels by μ-conotoxin PIIIA. *J Neurosci* **20:**76–80.

17. Penzotti JL, Lipkind G, Fozzard HA, and Dudley SC Jr (2001) Specific neosaxitoxin interactions with the Na^+ channel outer vestibule determined by mutant cycle analysis. *Biophys J* **80:**698–706.

18. Makielski JC, Limberis J, Fan Z and Kyle JW (1999) Intrinsic lidocaine affinity for Na channels expressed in Xenopus oocytes dependes on α (hH1 vs. rSkM1) and β1 subunits. *Cardiovasc Res* 42:503–509.

19. Wang GK, Russell C, and Wang S-Y (2004) Mexiletine block of wild-type and inactivation-deficient human skeletal muscle hNav1.4 Na^+ channels. *J Physiol (Lond)* **554:**621–633.

20. Trimmer JS, Cooperman SS, Agnew WS, and Mandel G (1990) Regulation of muscle sodium channel transcripts during development and in response to denervation. *Dev Biol* **142:**360–367.

21. Cannon SC (1997) From mutation to myotonia in sodium channel disorders. *Neuromuscul Disord* **7:**241–249.

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.

1. Fozzard HA and Hanck, DA (1996) Structure and function of voltage-dependent sodium channels: Comparison of brain II and cardiac isoforms. *Physiol Rev* **76:**887–926.
2. Sheets MF and Hanck DA (1999) Gating of skeletal and cardiac muscle sodium channels in mammalian cells. *J Physiol* **514:**425–436.
3. Li RA, Ennis IL, Tomaselli GF, and Marban E (2002) Structural basis of differences in isoform-specific gating and lidocaine block between cardiac and skeletal muscle sodium channels. *Mol Pharmacol* **61:**136–141.
4. Mantegazza M, Yu FH, Catterall WA, and Scheuer T (2001) Role of the C-terminal domain in inactivation of brain and cardiac sodium channels. *Proc Natl Acad Sci USA* **98:**15348–15353.
5. Satin J, Kyle JW, Chen M, Bell P, Cribbs LL, Fozzard HA, and Rogart RB (1992) A mutant of TTX-resistant cardiac sodium channels with TTX-sensitive properties *Science* **256:**1202–1205.
6. Nuss HB, Tomaselli GF, and Marbán E (1995) Cardiac sodium channels (hH1) are intrinsically more sensitive to block by lidocaine than are skeletal muscle (μ1) channels. *J Gen Physiol* **106:**1193–1209.
7. Sheldon RS, Cannon NJ, and Duff HJ (1986) Binding of [^{3}H]batrachotoxinin A benzoate to specific sites on rat cardiac sodium channels. *Mol Pharmacol* **30:**617–623.
8. Taouis M, Sheldon RS, Hill RJ, and Duff HJ (1991) Cyclic AMP-dependent regulation of the number of [^{3}H]batrachotoxinin benzoate binding sites on rat cardiac myocytes. *J Biol Chem* **266:**10300–10304.
9. Rogart RB, Cribbs LL, Muglia LK, Kephart DD, and Kaiser MW (1989) Molecular cloning of a putative tetrodotoxin-resistant rat heart Na^+ channel isoform. *Proc Natl Acad Sci USA* **86:**8170–8174.
10. Kallen RG, Sheng ZH, Yang J, Chen LQ, Rogart RB, and Barchi RL (1990) Primary structure and expression of a sodium channel characteristic of denervated and immature rat skeletal muscle. *Neuron* **4:**233–242.
11. Hartmann HA, Colom LV, Sutherland ML, and Noebels JL (1999) Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain. *Nat Neurosci* **2:**593–595.
12. Keating MT and Sanguinetti MC (2001) Molecular and cellular mechanisms of cardiac arrhythmias. *Cell* **104:**569–580.
13. Rogers JC, Qu Y, Tanada TN, Scheuer T, and Catterall WA (1996) Molecular determinants of high affinity binding of α-scorpion toxin and sea anemone toxin in the S3-S4 extracellular loop in domain IV of the Na^+ channel α subunit. *J Biol Chem* **271:**15950–15962.

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.

1. Schaller KL, Krzemien DM, Yarowsky PJ, Krueger BK, and Caldwell JH (1995) A novel, abundant sodium channel expressed in neurons and glia. *J Neurosci* **15:**3231–3242.

2. Dietrich PS, McGivern JG, Delgado SG, Koch BD, Eglen RM, Hunter JC, and Sangameswaran L (1998) Functional analysis of a voltage-gated sodium channel and its splice variant from rat dorsal root ganglion. *J Neurochem* **70:**2262–2272.

3. Vega-Saenz de Miera E, Rudy B, Sugimori M, and Llinas R (1997) Molecular characterization of the sodium channel subunits expressed in mammalian cerebellar Purkinje cells. *Proc Natl Acad Sci USA* **94:**7059–7064.

4. Plummer NW, Galt J, Jones JM, Burgess DL, Sprunger LK, Kohrman DC, and Meisler MH (1998) Exon organization, coding sequence, physical mapping, and polymorphic intragenic markers for the human neuronal sodium channel gene *SCN8A*. *Genomics* **54:**287–296.

5. Burgess DL, Kohrman DC, Galt J, Plummer NW, Jones JM, Spear B, and Meisler MH (1995) Mutation of a new sodium channel gene, *Scn8a*, in the mouse mutant 'motor endplate disease'. *Nat Genet* **10:**461–465.

6. Smith MR, Smith RD, Plummer NW, Meisler MH, and Goldin AL (1998) Functional analysis of the mouse Scn8a sodium channel. *J Neurosci* **18:**6093–6102.

7. Zhou W and Goldin AL (2004) Use-dependent potentiation of the $Na_v1.6$ sodium channel. *Biophys J* **87:**3862–3872.

8. Oliveira JS, Redaelli E, Zaharenko AJ, Cassulini RR, Konno K, Pimenta DC, Freitas JC, Clare JJ, and Wanke E (2004) Binding specificity of sea anemone toxins to Na_v 1.1–1.6 sodium channels. Unexpected contributions from differences in the IV/S3-S4 outer loop. *J Biol Chem* **279:**33323–33335.

9. Whitaker W, Faull R, Waldvogel H, Plumpton C, Burbidge S, Emson P, and Clare J (1999) Localization of the type VI voltage-gated sodium channel protein in human CNS. *Neuroreport* **10:**3703–3709.

10. Tzoumaka E, Tischler AC, Sangameswaran L, Eglen RM, Hunter JC, and Novakovic SD (2000) Differential distribution of the tetrodotoxin-sensitive rPN4/NaCh6/Scn8a sodium channel in the nervous system. *J Neurosci Res* **60:**37–44.

11. Caldwell JH, Schaller KL, Lasher RS, Peles E, and Levinson SR (2000) Sodium channel $Na_v1.6$ is localized at nodes of Ranvier, dendrites, and synapses. *Proc Natl Acad Sci USA* **97:**5616–5620.

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.

13. Kohrman DC, Smith MR, Goldin AL, Harris J, and Meisler MH (1996) A missense mutation in the sodium channel Scn8a is responsible for cerebellar ataxia in the mouse mutant *jolting*. *J Neurosci* **16:**5993–5999.

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.

1. Toledo-Aral JJ, Moss BL, He Z-J, Koszowski G, Whisenand T, Levinson SR, Wolf JJ, Silos-Santiago I, Halegoua S, and Mandel G (1997) Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons. *Proc Natl Acad Sci USA* **94:**1527–1532.

2. Sangameswaran L, Fish LM, Koch BD, Rabert DK, Delgado SG, Ilnikca M, Jakeman LB, Novakovic S, Wong K, Sze P, et al. (1997) A novel tetrodotoxin-sensitive, voltage-gated sodium channel expressed in rat and human dorsal root ganglia. *J Biol Chem* **272:**14805–14809.

3. Klugbauer N, Lacinova L, Flockerzi V, and Hofmann F (1995) Structure and functional expression of a new member of the tetrodotoxin-sensitive voltage-activated sodium channel family from human neuroendocrine cells. *EMBO J* **14:**1084–1090.

4. Belcher SM, Zerillo CA, Levenson R, Ritchie JM, and Howe JR (1995) Cloning of a sodium channel α subunit from rabbit Schwann cells. *Proc Natl Acad Sci USA* **92:**11034–11038.

5. Beckers M-C, Ernst E, Belcher S, Howe J, Levenson R, and Gros P (1996) A new sodium channel α-subunit gene (*Scn9a*) from Schwann cells maps to the *Scn1a, Scn2a*, *Scn3a* cluster of mouse chromosome 2. *Genomics* **36:**202–205.

6. Kozak CA and Sangameswaran L (1996) Genetic mapping of the peripheral sodium channel genes, *Scn9a* and *Scn10a*, in the mouse. *Mamm Genome* 7:787–792.

7. Rush AM, Bräu ME, Elliott AA, and Elliott JR (1998) Electrophysiological properties of sodium current subtypes in small cells from adult rat dorsal root ganglia. *J Physiol (Lond)* **511:**771–789.

8. Cestèle S, Qu Y, Rogers JC, Rochat H, Scheuer T, and Catterall WA (1998) Voltage sensor-trapping: enhanced activation of sodium channels by β-scorpion toxin bound to the S3-S4 loop in domain II. *Neuron* **21:**919–931.

9. Rogers JC, Qu Y, Tanada TN, Scheuer T, and Catterall WA (1996) Molecular determinants of high affinity binding of α-scorpion toxin and sea anemone toxin in the S3-S4 extracellular loop in domain IV of the Na^+ channel α subunit. *J Biol Chem* **271:**15950–15962.

10. Chevrier P, Vijayaragavan K, and Chahine M (2004) Differential modulation of $Na_v1.7$ and $Na_v1.8$ peripheral nerve sodium channels by the local anesthetic lidocaine. *Br J Pharmacol* **142:**576–584.

11. Felts PA, Yokoyama S, Dib-Hajj S, Black JA, and Waxman SG (1997) Sodium channel α-subunit mRNAs I, II, III, NaG, Na6 and hNE (PN1): different expression patterns in developing rat nervous system. *Mol Brain Res* **45:**71–82.

12. Cummins TR, Howe JR, and Waxman SG (1998) Slow closed-state inactivation: a novel mechanism underlying ramp currents in cells expressing the hNE/PN1 sodium channel. *J Neurosci* **18:**9607–9617.

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.

14. Cummins TR, Dib-Hajj SD, and Waxman SG (2004) Electrophysiological properties of mutant $Na_V1.7$ sodium channels in a painful inherited neuropathy. *J Neurosci* **24:**8232–8236.

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.

1. Cummins TR and Waxman SG (1997) Down-regulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. *J Neurosci* **17:**3503–3514.

2. Sleeper AA, Cummins TR, Hormuzdiar W, Tyrrell L, Dib-Hajj SD, Waxman SG, and Black JA (2000) Changes in expression of two tetrodotoxin-resistant sodium channels and their currents in dorsal root ganglion neurons following sciatic nerve injury, but not rhizotomy. *J Neurosci* **20:**7279–7289.

3. Akopian AN, Sivilotti L, and Wood JN (1996) A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature* **379:**257–262.

4. Djouri L, Fang X, Okuse K, Wood JN, Berry CM, and Lawson SM (2003) The TTX-resistant sodium channel Nav1.8 (SNS/PN3): expression and correlation with membrane properties in rat nociceptive primary afferent neurons. *J Physiol (Lond)* **550:**739–752.

5. Renganathan M, Cummins TR, and Waxman SG (2001) Contribution of $Na_v1.8$ sodium channels to action potential electrogenesis in DRG neurons. *J Neurophysiol* **86:**629–640.

6. Sivilotti L, Okuse K, Akopian AN, Moss S, and Wood JN (1997) A single serine residue confers tetrodotoxin insensitivity on the rat sensory-neuron-specific sodium channel SNS. *FEBS Lett* **409:**49–52.

7. Akopian AN, Souslova V, England S, Okuse K, Ogata N, Ure J, Smith A, Kerr BJ, McMahon SB, Boyce S, et al. (1999) The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat Neurosci* **2:**541–548.

8. Tanaka M, Cummins TR, Ishikawa K, Dib-Hajj SD, Black JA, and Waxman SG (1998) SNS Na^+ channel expression increases in dorsal root ganglion neurons in the carrageenan inflammatory pain model. *Neuroreport* **9:**967–972.

9. Dib-Hajj SD, Ishikawa I, Cummins TR, and Waxman SG (1997) Insertion of a SNS-specific tetrapeptide in the S3-S4 linker of D4 accelerates recovery from inactivation of skeletal muscle voltage-gated Na channel μ1 in HEK293 cells. *FEBS Lett* **416:**11–14.

10. Cummins TR, Black JA, Dib-Hajj SD, and Waxman SG (2000) GDNF up-regulates expression of functional SNS and NaN sodium channels and their currents in axotomized DRG neurons. *J Neurosci* **20:**8754–8761.

11. Okuse K, Malik-Hall M, Baker MD, Poon W-YL, Kong H, Chao M, and Wood JN (2002) Annexin II light chain regulates sensory neuron-specific sodium channel expression. *Nature (Lond)* **417:**653–656.

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.

1. Cummins TR, Dib-Hajj SD, Black JA, Akopian AN, Wood JN, and Waxman SG (1999) A novel persistent tetrodotoxin-resistant sodium current in SNS-null and wild-type small primary sensory neurons. *J Neurosci* **19:**RC43.

2. Sleeper AA, Cummins TR, Hormuzdiar W, Tyrrell L, Dib-Hajj SD, Waxman SG, and Black JA (2000) Changes in expression of two tetrodotoxin-resistant sodium channels and their currents in dorsal root ganglion neurons following sciatic nerve injury, but not rhizotomy. *J Neurosci* **20:**7279–7289.

3. Herzog RI, Cummins TR, and Waxman SG (2001) Persistent TTX-resistant Na^+ current affects resting potential and response to depolarization in simulated spinal sensory neurons. *J Neurophysiol* **86:**1351–1364.

4. Fang X, Djouri L, Black JA, Dib-Hajj SD, Waxman SG, and Lawson SN (2002) The presence and role of the TTX-resistant sodium channel $Na_V1.9$ in nociceptive primary afferent neurons. *J Neurosci* **22:**7425–7434.

5. Baker MD, Chandra SY, Ding Y, Waxman SG, and Wood JN (2003) GTP-induced tetrodotoxin-resistant Na current regulates excitability in mouse and rat small diameter sensory neurones. *J Physiol (Lond)* **548:**373–382.

6. Cummins TR, Black JA, Dib-Hajj SD, and Waxman SG (2000) GDNF up-regulates expression of functional SNS and NaN sodium channels and their currents in axotomized DRG neurons. *J Neurosci* **20:**8754–8761.

7. Rush AM and Waxman SG (2004) PGE2 increases the tetrodotoxin-resistant $Na_V1.9$ sodium current in mouse DRG neurons via G-proteins. *Brain Res* **1023:**264–271.