View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Neuron, Vol. 28, 365–368, November, 2000, Copyright ©2000 by Cell Press

Letter to the Editor

Nomenclature of Voltage-Gated Sodium Channels

Voltage-gated sodium channels are critical elements of action potential initiation and propagation in excitable cells because they are responsible for the initial depolarization of the membrane. These channels consist of a highly processed α subunit that is ~260 kDa, associated with auxiliary β subunits (reviewed by Catterall, 2000). Sodium channels in the adult CNS contain β1 (or β3) and β2 subunits, while channels in adult skeletal muscle have only the β1 subunit. 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.

A variety of different sodium channels have been identified by electrophysiological recording, biochemical purification, and molecular cloning (reviewed by Goldin, 2001). The sodium channels are the founding members of the superfamily of ion channels that includes voltage-gated potassium and calcium channels. 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 have been named in many different ways, with no consistent nomenclature for the various isoforms. Some of the channels have been given numerical names. Others have been given names that are based on the tissue of origin for the original clone but often do not reflect the overall tissue distribution of the isoform. In addition, channels derived from different species but encoded by orthologous genes have often been given different names, so that there are multiple synonyms for many of sodium channel isoforms.

To eliminate confusion resulting from the multiplicity of names, we propose a standardized nomenclature for voltage-gated sodium channels (Table 1). This nomenclature is based on the one for voltage-gated potassium channels (Chandy, 1991) that is now in common use. It utilizes a numerical system to define subfamilies and subtypes based on similarities among the amino acid sequences of the channels. A comparable nomenclature has been proposed for voltage-gated calcium channels (Ertel et al., 2000). The name 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 decimal point identifies the specific channel isoform (e.g., $Na_V1.1$). That 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 (Figure 1A). For potassium channels and calcium channels, all the members of distinct subfamilies are less than 50% identical to those of other families, and there is much closer sequence similarity within families (Chandy, 1991; Ertel et al., 2000). The sodium channel

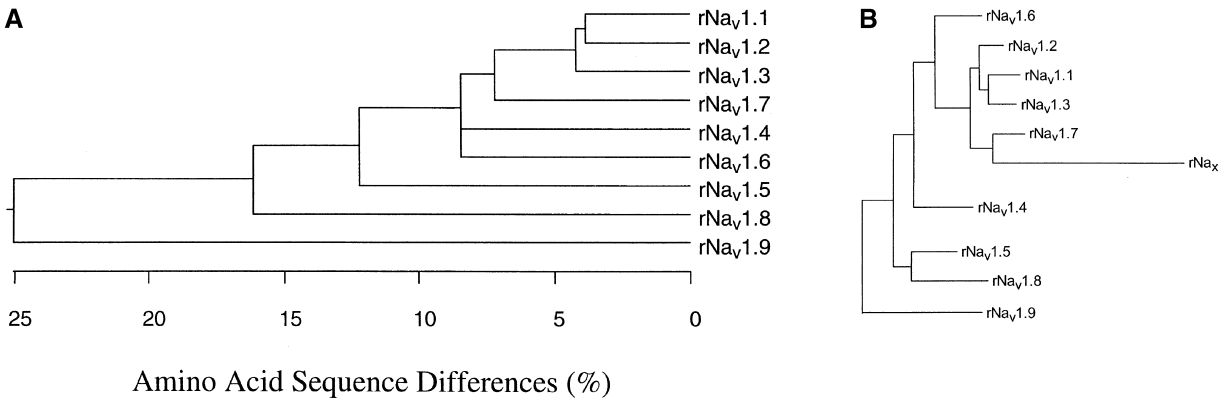

Figure 1. Amino Acid Sequence Similarity and Phylogenetic Relationships of Voltage-Gated Sodium Channel α Subunits

(A) Comparison of amino acid identify for rat sodium channels $Na_V1.1$–$Na_V1.9$. The comparison was performed with Megalign in the program DNAStar (utilizing the Clustal method) for the four domains and the cytoplasmic linker connecting domains III and IV. (B) 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 of the 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.

Table 1. Mammalian Sodium Channel α Subunits

Type	Former Name	Genbank Number[a]	Gene Symbol	Chromosomal Location	Splice Variants	Primary Tissues
$Na_V1.1$	rat I	X03638 (r)	SCN1A	Mouse 2	$Na_V1.1a$	CNS
	HBSCI	X65362 (h)		Human 2q24		PNS
	GPBI	AF003372 (gp)				
	SCN1A					
$Na_V1.2$	rat II	X03639 (r)	SCN2A	Mouse 2	$Na_V1.2a$	CNS
	HBSCII	X61149 (r)		Human 2q23-24		
	HBA	X65361 (h)				
		M94055 (h)				
$Na_V1.3$	rat III	Y00766 (r)	SCN3A	Mouse 2	$Na_V1.3a$	CNS
				Human 2q24	$Na_V1.3b$	
$Na_V1.4$	SkM1, μ1	M26643 (r)	SCN4A	Mouse 11		sk. muscle
		M81758 (h)		Human 17q23-25		
$Na_V1.5$	SkM2	M27902 (r)	SCN5A	Mouse 9		Uninnervated sk.
	H1	M77235 (h)		Human 3p21		muscle, heart
$Na_V1.6$	NaCh6	L39018 (r)	SCN8A	Mouse 15	$Na_V1.6a$	CNS, PNS
	PN4	AF049239 (r)		Human 12q13		
	Scn8a	AF049240 (r)				
	CerIII	U26707 (m)				
		AF049617 (m)				
		AF050736 (h)				
		AF225988 (h)				
		AF003373 (gp)				
$Na_V1.7$	NaS	U35238 (rb)	SCN9A	Mouse 2		PNS
	hNE-Na	X82835 (h)		Human 2q24		Schwann cells
	PN1	U79568 (r)				
		AF000368 (r)				
$Na_V1.8$	SNS	X92184 (r)	SCN10A	Mouse 9		DRG
	PN3	U53833 (r)		Human 3p22-24		
	NaNG	Y09108 (m)				
		U60590 (d)				
$Na_V1.9$	NaN	AF059030 (r)	SCN11A	Mouse 9	$Na_V1.9a$	PNS
	SNS2	AJ237852 (r)		Human 3p21-24		
	PN5	AF118044 (m)				
	NaT	AB031389 (m)				
	SCN12A	AF126739 (h)				
		AF188679 (h)				
		AF109737 (h)				
		AF150882 (h)				
Na_x	$Na_V2.1$	M91556 (h)	SCN7A	Mouse 2		heart, uterus,
	Na-G	M96578 (r)	SCN6A[b]	Human 2q21-23		sk. muscle
	SCL11	Y09164 (r)				astrocytes,
	$Na_V2.3$	L36179 (m)				DRG

[a] The letter in parentheses after each accession number indicates the species of origin for the sequence, as follows: h, human; r, rat; rb, rabbit; m, mouse; gp, guinea pig; d, dog.

[b] This gene was originally assigned symbols *SCN6A* and *SCN7A*, which were mapped in human and mouse, respectively. The two most likely represent the same gene, and the SCN6A symbol will probably be deleted.

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.

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 (Figure 1B). 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 neurons. 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 (Figure 1B), and their amino acid sequences are greater than 74% 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 single position in domain I, and they are expressed in heart and dorsal root ganglion neurons (reviewed in Catterall, 2000; Goldin, 2001). Their genes are located on human chromosome 3p21–24, consistent with a common evolutionary origin. $Na_V1.4$, expressed primarily in skeletal muscle, and $Na_V1.6$, expressed primarily in the CNS, are set apart from these other two closely related groups of sodium channel genes (Figure 1B). Although their amino acid sequences are greater

than 84% identical to the group of sodium channels whose genes are located on chromosome 2 (Figure 1A), their phylogenetic relationship is much more distant when analyzed by parsimony comparison (Figure 1B). 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 HOX 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, phylogenetic relationship, and chromosomal relationship 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, 1991; 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 (Table 1, Na_x). They are ~50% identical to the type 1 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 neurons in the PNS. 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 (Figure 1B), where their gene is also located. Successful functional expression of these atypical sodium channel-like proteins and identification of additional related sodium channels may provide evidence for a second sodium channel family.

Three auxiliary subunits of sodium channels have been defined thus far: β1, β2, and β3. 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). New subunits related to the β subunits should be named β4 to βn. New subunits that are unrelated to β subunits should be named γ, δ, etc.

The family of voltage-gated sodium channels is an expanding collection of different isoforms with distinct tissue distributions and potentially distinct physiological functions. We hope that this new nomenclature will provide a common standard that will make it easier to communicate and compare results concerning the current and future members of this family. This nomenclature has been reviewed and accepted by the Nomenclature Committee of the International Union of Pharmacology, and a full-length review is planned for Pharmacological Reviews.

**Alan L. Goldin,[1] Robert L. Barchi,[2]
John H. Caldwell,[3] Franz Hofmann,[4]
James R. Howe,[5] John C. Hunter,[6]
Roland G. Kallen,[7] Gail Mandel,[8]
Miriam H. Meisler,[9] Yoheved Berwald Netter,[10]
Masahara Noda,[11] Michael M. Tamkun,[12]
Steven G. Waxman,[13] John N. Wood,[14]
and William A. Catterall[15,16]**

[1] Department of Microbiology
and Molecular Genetics
University of California
Irvine, California 92697
[2] Institute of Neuroscience
University of Pennsylvania
Philadelphia, Pennsylvania 19104
[3] Department of Cell and Structural Biology
University of Colorado Medical Center
Denver, Colorado 80262
[4] Institute of Pharmacology
Technical University of Munich
80808 Munich
Germany
[5] Department of Pharmacology
Yale University School of Medicine
New Haven, Connecticut 06510
[6] Center for Biological Research
Neurobiology Business Unit
Roche Bioscience
Palo Alto, California 94304
[7] Department of Biochemistry and Biophysics
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104
[8] Department of Neurobiology
State University of New York
Stony Brook, New York 11790
[9] Department of Human Genetics
University of Michigan
Ann Arbor, Michigan 48109
[10] Cellular Biochemistry
College de France
75231 Paris
France
[11] Division of Molecular Neurobiology
National Institute for Basic Biology
Okazaki 444-8585
Japan
[12] Department of Physiology
Colorado State University
Fort Collins, Colorado 80523
[13] Department of Neurology
Yale University School of Medicine
New Haven, Connecticut 06510
[14] Department of Biology
University College, London
London WC1E 6BT
United Kingdom
[15] Department of Pharmacology
University of Washington
Seattle, Washington 98195

References

Catterall, W.A. (2000). Neuron *26*, 13–25.

Chandy, K.G. (1991). Nature *352*, 26.

Ertel, E.A., Campbell, K.P., Harpold, M.M., Hofmann, F., Mori, Y., Perez-Reyes, E., Schwartz, A., Snutch, T.P., Tanabe, T., Birnbaumer, L., et al. (2000). Neuron *25*, 533–535.

George, A.L., Knittel, T.J., and Tamkun, M.M. (1992). Proc. Natl. Acad. Sci. USA *89*, 554–558.

Goldin, A.L. (2001). Annu. Rev. Neurosci., in press.

Plummer, N.W., and Meisler, M.H. (1999). Genomics *57*, 323–331.

[16]To whom correspondence should be addressed (e-mail: wcatt@u.washington.edu).