RESURGENCE OF SODIUM CHANNEL RESEARCH

Alan L Goldin
Department of Microbiology and Molecular Genetics, University of California Irvine, California 92697-4025; e-mail: agoldin@uci.edu

Key Words cloning, expression, mutations, resurgent current

Abstract  A variety of isoforms of mammalian voltage-gated sodium channels have been described. Ten genes encoding sodium channel α subunits have been identified, and nine of those isoforms have been functionally expressed in exogenous systems. The α subunit is associated with accessory β subunits in some tissues, and three genes encoding different β subunits have been identified. The α subunit isoforms have distinct patterns of development and localization in the nervous system, skeletal and cardiac muscle. In addition, many of the isoforms demonstrate subtle differences in their functional properties. However, there are no clear subfamilies of the channels, unlike the situation with potassium and calcium channels. The subtle differences in the functional properties of the sodium channel isoforms result in unique conductances in specific cell types, which have important physiological effects for the organism. Small alterations in the electrophysiological properties of the channel resulting from mutations in specific isoforms cause human diseases such as periodic paralysis, long QT syndrome, and epilepsy.

INTRODUCTION

Voltage-gated sodium channels are the primary molecules responsible for the rising phase of action potentials in electrically excitable cells. Because of their fundamental importance, much of the early work on ion channels involved characterizing the electrophysiological and biochemical properties of sodium channels. In recent years, however, the rapidly expanding number and diversity of potassium and calcium channels has overshadowed the field of sodium channel research, particularly given the fact that all voltage-gated sodium channels are relatively similar. For a number of reasons this situation is beginning to change with a resurgence of interest in the biology of sodium channels. First, a variety of different sodium channel isoforms have been identified, cloned, functionally expressed, and characterized. Second, these isoforms are distinct in terms of developmental and regional expression, and they demonstrate subtle differences in their electrophysiological characteristics. These different properties can result in distinct conductances that are physiologically significant to the organism, such as resurgent currents that are uniquely expressed in cerebellar Purkinje cells. Finally, minor changes in the
properties of specific isoforms result in human diseases of muscle, heart, and the nervous system. The purpose of this review is to summarize the distinguishing characteristics of the different sodium channel isoforms. This review does not include detailed information about the structure and function of voltage-gated sodium channels because this topic has recently been reviewed by Catterall (1).

The voltage-gated sodium channel consists of a highly processed $\alpha$ subunit, $\sim 260$ kDa, that is associated with accessory $\beta$ subunits in some tissues, such as brain and muscle (2, 3). Although sodium channels are not as varied as potassium and calcium channels, sodium channels with different functional or pharmacological properties have been observed by electrophysiological recording. Consistent with this variation, a number of different $\alpha$ subunit isoforms have been detected by biochemical purification and molecular cloning. Unfortunately, the cDNA clones have been named in many different ways, often based on the tissue of origin for the clone, which does not always reflect the overall distribution of the specific isoform. To add to the confusion, the same isoform from different species has been assigned multiple names. Recently, a systematic nomenclature for sodium channels has been proposed (4). This nomenclature is similar to the ones that were developed for potassium (5) and calcium (6) channels, and it has been used for the purposes of this review.

The isoforms have been classified as a single family based on evolutionary relationships, and the names are assigned in numerical order. 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 Na$_v$1 is the only subfamily), and the number following the decimal point identifies the specific channel isoform (e.g. Na$_v$1.1). That number has been assigned according to the approximate order in which each gene was identified, with some exceptions. Splice variants of each family member are identified by lowercase letters following the numbers (e.g. Na$_v$1.1a). The assigned names appear in Table 1, along with the original names, the gene names, Genbank Accession numbers, various characteristics of each isoform, and the references. The relationships among the various isoforms are shown as a phylogenetic tree in Figure 1, which is similar to the tree determined by Plummer & Meisler (7).

Previously, the mammalian sodium channels had been divided into three subfamilies, based on sequence comparisons (reviewed in 8). However, this distinction is not supported by the phylogenetic tree (Figure 1) in which there is no clear separation of sodium channels into separate subfamilies, unlike the case with potassium and calcium channels. Therefore, in this review, the mammalian sodium channel isoforms have all been classified as members of a single family, Na$_v$1.x (Table 1). There are 10 distinct sodium channel isoforms. Na$_v$1.1–1.8 were previously classified as type 1 channels, as the sequences of these isoforms have the most similarity. Na$_v$1.9 consists of an isoform that is approximately 50% identical to most of the other channels, so that it was originally considered to represent a separate family, type 3 (9). Na$_v$1.9 is not significantly more divergent than any of the other
Figure 1  The proposed phylogenetic tree for mammalian voltage-gated sodium channel \( \alpha \) subunits was generated using sequences of channels for which the full-length coding regions have been determined, as listed in Table 1. This tree represents the optimal tree based on parsimony analysis of nucleotide sequences. To perform the analysis, the amino acid sequences for all the isoforms were aligned using Clustal W (135). 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* (136). 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. The numbers at the nodes indicate the bootstrap values for 100 replications. The scale bar represents 500 substitutions. The species of origin is indicated as follows: h = Homo sapiens (human), r = Rattus norvegicus (rat), m = Mus musculus (mouse), c = Canis familiaris (dog), o = Oryctolagus cuniculus (rabbit).

 isoforms based on phylogeny, however, so that it does not clearly define a new subfamily (Figure 1). Na_x includes isoforms with sequences that are also approximately 50% identical to the other sodium channels, and these were originally considered to represent a new family, type 2 (10). Based on phylogeny, however, Na_x appears to be a very late branch that diverged from Na_1.7. Because none of the Na_x channels have been functionally expressed, it is possible that these
<table>
<thead>
<tr>
<th>Channel name</th>
<th>Original name</th>
<th>Species</th>
<th>Splice variants</th>
<th>Function</th>
<th>TTX IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>Tissue</th>
<th>Size</th>
<th>Gene symbol</th>
<th>Chromosomal location&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Genebank access #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na&lt;sub&gt;1.1&lt;/sub&gt;</td>
<td>rat I (12)</td>
<td>Rat</td>
<td>Na&lt;sub&gt;1.1&lt;/sub&gt;a</td>
<td>Yes (99)</td>
<td>10 nM (99)</td>
<td>CNS</td>
<td>2009</td>
<td>SCN1A</td>
<td>M 2 [36] (29) H 2q24 (137)</td>
<td>X03638</td>
</tr>
<tr>
<td>HBSCI (16)</td>
<td>Human</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A (18)</td>
<td>Human</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPBI (17)</td>
<td>Guinea pig</td>
<td>Yes (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;1.2&lt;/sub&gt;</td>
<td>rat II (12)</td>
<td>Rat</td>
<td>Na&lt;sub&gt;1.2&lt;/sub&gt;a</td>
<td>Yes (20, 111)</td>
<td>10 nM (111) 9 nM (99)</td>
<td>CNS</td>
<td>2005</td>
<td>SCN2A</td>
<td>M 2 [36] (29) H 2q23–24 (16, 138)</td>
<td>X03639 X61149 X65361 M94055</td>
</tr>
<tr>
<td>rat IIA (20)</td>
<td>Human</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBSCI (16)</td>
<td>Human</td>
<td>Yes (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBA (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;1.3&lt;/sub&gt;</td>
<td>rat III (13, 112)</td>
<td>Rat</td>
<td>Na&lt;sub&gt;1.3&lt;/sub&gt;a</td>
<td>Yes (112, 139)</td>
<td>2 nM (112) 15 nM (139)</td>
<td>CNS</td>
<td>1951</td>
<td>SCN3A</td>
<td>M 2 [36] (29) H 2q24 (140)</td>
<td>Y00766</td>
</tr>
<tr>
<td>Na&lt;sub&gt;1.4&lt;/sub&gt;</td>
<td>SkM1, &lt;i&gt;µ&lt;/i&gt;1 (45)</td>
<td>Rat</td>
<td>Yes (45)</td>
<td>5 nM (45)</td>
<td>Skeletal muscle</td>
<td>1840</td>
<td>SCN4A</td>
<td></td>
<td></td>
<td>M26643</td>
</tr>
<tr>
<td>SkM1 (48, 49)</td>
<td>Human</td>
<td>Yes (143)</td>
<td>25 nM (143)</td>
<td>Skeletal muscle</td>
<td>1836</td>
<td></td>
<td></td>
<td></td>
<td>M18758</td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;1.5&lt;/sub&gt;</td>
<td>SkM2 (46)</td>
<td>Rat</td>
<td>Yes (61)</td>
<td>2 µM (61)</td>
<td>Denervated skeletal muscle, heart</td>
<td>2018</td>
<td>SCN5A</td>
<td>M 9 [70] (144) H 3p21 (144)</td>
<td>M27902</td>
<td></td>
</tr>
<tr>
<td>rH1 (47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;1.6&lt;/sub&gt;</td>
<td>H1 (50)</td>
<td>Human</td>
<td>Yes (50)</td>
<td>6 µM (50)</td>
<td>Heart</td>
<td>2016</td>
<td>SCN8A</td>
<td>M 15 [64] (15) H 12q13 (15, 23)</td>
<td>M77235 L39018</td>
<td></td>
</tr>
<tr>
<td>NaCh6 (14)</td>
<td>Rat</td>
<td>Na&lt;sub&gt;1.6&lt;/sub&gt;a</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PN4 (21)</td>
<td>Rat</td>
<td>Yes (21)</td>
<td>1 nM (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AF049239 AF049240 U26707 AF049617 AF050736 AF225988</td>
</tr>
<tr>
<td>Scn8a (15, 22)</td>
<td>Mouse</td>
<td>Yes (22)</td>
<td>6 nM (22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scn8a (23)</td>
<td>Human</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Na&lt;sub&gt;i&lt;/sub&gt;,1.7</td>
<td>Guinea pig</td>
<td>Yes (70)</td>
<td>4 nM (70)</td>
<td>PNS</td>
<td>1984</td>
<td>SCN9A</td>
<td>M 2 [36] 2 (145, 146)</td>
<td>AF003373</td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;i&lt;/sub&gt;,1.8</td>
<td>Rat</td>
<td>Yes (72)</td>
<td>25 nM (72)</td>
<td>Medullary thyroid Ca Schwann cell</td>
<td>1977</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nax (73)</td>
<td>Rabbit</td>
<td>No</td>
<td></td>
<td></td>
<td>184</td>
<td>U35238</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;i&lt;/sub&gt;,1.9</td>
<td>SNS (74)</td>
<td>Rat</td>
<td>Yes (74)</td>
<td>~60 µM (74)</td>
<td>PNS (DRG)</td>
<td>1957</td>
<td>SCN10A</td>
<td>M 9 [67] (146)</td>
<td>X92184</td>
<td></td>
</tr>
<tr>
<td>Na&lt;sub&gt;i&lt;/sub&gt;,1.9a</td>
<td>SNS2 (78)</td>
<td>Rat</td>
<td>Yes (78)</td>
<td>1 µM (78)</td>
<td>PNS</td>
<td>1765</td>
<td>SCN11A</td>
<td>M 9 [71] (79, 147)</td>
<td>AJ237852</td>
<td></td>
</tr>
<tr>
<td>NaN (9)</td>
<td>Rat</td>
<td>No</td>
<td>PNS</td>
<td>1765</td>
<td>AF059030</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNS</td>
<td>Rat</td>
<td>Yes</td>
<td>1765</td>
<td>AF126739</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN (9)</td>
<td>Mouse</td>
<td>No</td>
<td>1765</td>
<td>AF118044</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN (79)</td>
<td>Mouse</td>
<td>No</td>
<td>1765</td>
<td>AB031389</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN (80)</td>
<td>Human</td>
<td>No</td>
<td>1791</td>
<td>AF188679</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN12A (81)</td>
<td>Human</td>
<td>No</td>
<td>1791</td>
<td>AF109737</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN (88)</td>
<td>Rat</td>
<td>No</td>
<td>Heart uterus muscle</td>
<td>1682</td>
<td>SCN6A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H 2q21–23 (148)</td>
<td>M91556</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCL11 (87)</td>
<td>Rat</td>
<td>No</td>
<td>Astrocytes</td>
<td>Partial</td>
<td>SCN7A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>M 2 [41] (149)</td>
<td>M96578</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN (86)</td>
<td>Mouse</td>
<td>No</td>
<td>Heart uterus muscle</td>
<td>1681</td>
<td></td>
<td>Y09164</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Complete species names are as follows: Rat = *Rattus norvegicus*, Human = *Homo sapiens*, Mouse = *Mus musculus*, Guinea pig = *Cavia porcellus*, Dog = *Canis familiaris*, Rabbit = *Oryctolagus cuniculus*.

<sup>b</sup>Chromosomal locations are shown for mouse (M) and human (H) chromosomes.

<sup>c</sup>Human map location for SCN9A is inferred from the mouse mapping data.

<sup>d</sup>SCN6A and SCN7A most likely represent the same gene, as they were mapped in human and mouse, respectively (7).
genes do not encode voltage-gated sodium channels. Therefore, these genes have not been assigned numerical names in the proposed nomenclature, although they are discussed in this review.

Although the sequences of the mammalian sodium channels are sufficiently similar so that there are no distinct subfamilies, some of the isoforms are more closely related to each other from an evolutionary point of view, as indicated by the phylogenetic tree (Figure 1) and the chromosomal localization (Table 1) (7). The genes for five isoforms (Na\textsubscript{\alpha}1.1, Na\textsubscript{\alpha}1.2, Na\textsubscript{\alpha}1.3, Na\textsubscript{\alpha}1.7, and Na\textsubscript{\alpha}) are located on chromosome 2 in mouse and human, and all but Na\textsubscript{\alpha} are tightly clustered in both species. These five isoforms are also more closely related to each other in the phylogenetic tree. The genes for the three isoforms that are resistant to nanomolar concentrations of tetrodotoxin (Na\textsubscript{\alpha}1.5, Na\textsubscript{\alpha}1.8, and Na\textsubscript{\alpha}1.9) are located on chromosome 9 in mouse and 3 in human, and these isoforms are closely related in the phylogenetic tree. The genes for two isoforms (Na\textsubscript{\alpha}1.4 and Na\textsubscript{\alpha}1.6) are located on two different chromosomes, and each can be considered a separate group. The organization of the sodium channel genes is consistent with the hypothesis that the four groups of sodium channel genes resulted from the early genomic duplications that generated the four vertebrate HOX clusters and that additional duplications on chromosomes 2 and 9 in mouse (2 and 3 in human) generated the two sodium channel gene clusters (7).

The sodium channel isoforms are discussed based on the tissue in which they are most abundant. Four sodium channel isoforms, Na\textsubscript{\alpha}1.1, Na\textsubscript{\alpha}1.2, Na\textsubscript{\alpha}1.3 and Na\textsubscript{\alpha}1.6, are expressed at high levels in the central nervous system (CNS) (Table 1). Two isoforms are abundant in muscle: Na\textsubscript{\alpha}1.4 in adult skeletal muscle and Na\textsubscript{\alpha}1.5 in embryonic and denervated skeletal muscle and heart muscle. Three isoforms, Na\textsubscript{\alpha}1.7, Na\textsubscript{\alpha}1.8 and Na\textsubscript{\alpha}1.9, are expressed primarily in the peripheral nervous system. The channels making up the Na\textsubscript{\alpha} isoform are considered atypical because the sequences contain significant differences in regions that are critical for channel function, and this is the only isoform that has not been expressed in an exogenous system (10). Because of the lack of expression, it is possible that this isoform does not encode a functional, voltage-gated sodium channel. Na\textsubscript{\alpha} channels are expressed in a variety of tissues, including heart, uterus, muscle, astrocytes, and the dorsal root ganglion (DRG). Complementary DNA clones encoding the three accessory \(\beta\) subunits, Na\textsubscript{\alpha}\(\beta\)1.1, Na\textsubscript{\alpha}\(\beta\)1.2 and Na\textsubscript{\alpha}\(\beta\)1.3, have also been isolated, and these are listed in Table 2. The relationship among the three \(\beta\) subunits is shown as a phylogenetic tree in Figure 2.

### SODIUM CHANNEL \(\alpha\) SUBUNITS

#### Central Nervous System Channels

Na\textsubscript{\alpha}1.1, Na\textsubscript{\alpha}1.2, Na\textsubscript{\alpha}1.3, and Na\textsubscript{\alpha}1.6 are expressed abundantly in the CNS. In addition, Na\textsubscript{\alpha}1.5 is present in limbic regions of the brain (11), but this isoform is discussed with the channels expressed in muscle. Na\textsubscript{\alpha}1.1, Na\textsubscript{\alpha}1.2, and Na\textsubscript{\alpha}1.3 cDNAs were originally isolated from the rat CNS and were called types (or rat...
TABLE 2  Mammalian sodium channel \( \beta \) subunits

<table>
<thead>
<tr>
<th>Name</th>
<th>Gene symbol</th>
<th>Original name</th>
<th>Species</th>
<th>Splice variants</th>
<th>Tissue</th>
<th>Size(^a)</th>
<th>Chromosomal location(^b)</th>
<th>Genbank access #</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Na}_\beta 1.1 )</td>
<td>SCN1B</td>
<td>( \beta 1 ) (98)</td>
<td>Rat</td>
<td>CNS</td>
<td>218 [199]</td>
<td>M 7 [10] (150)</td>
<td>M91808</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \beta 1 ) (151)</td>
<td>Human</td>
<td>CNS</td>
<td>218 [199]</td>
<td>H 19q13 (152)</td>
<td>L10338</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \beta 1 ) (153)</td>
<td>Rabbit</td>
<td>CNS</td>
<td>218 [199]</td>
<td>U35382</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Na}_\beta 2.1 )</td>
<td>SCN2B</td>
<td>( \beta 2 ) (95)</td>
<td>Rat</td>
<td>CNS</td>
<td>215 [186]</td>
<td>M 9 [26] (154)</td>
<td>U37026</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \beta 2 ) (155)</td>
<td>Human</td>
<td>CNS</td>
<td>215 [186]</td>
<td>H 11q22-qter (155)</td>
<td>AF007783</td>
<td></td>
</tr>
<tr>
<td>( \text{Na}_\beta 3.1 )</td>
<td>SCN3B</td>
<td>( \beta 3 ) (97)</td>
<td>Rat</td>
<td>CNS</td>
<td>215 [191]</td>
<td>U37147</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \beta 3 ) (97)</td>
<td>Human</td>
<td>CNS</td>
<td>215 [191]</td>
<td>H 11q23.3 (97)</td>
<td>AF243396</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The numbers in brackets indicate the sizes of the processed proteins. 
\(^b\) Chromosomal locations are shown for mouse (M) and human (H) chromosomes.

I, II, and III (12, 13). \( \text{Na}_1.6 \) cDNA was isolated from rat brain, retina, and DRG (NaCh6) (14) and from mouse brain (Scn8a) (15). Partial cDNA clones have since been isolated for \( \text{Na}_1.1 \) from human (HBSCI) (16) and guinea pig (GPBI) (17), and the full-length sequence has been determined from human (SCN1A) (18). Partial cDNA clones for \( \text{Na}_1.2 \) have also been isolated from human and called HBSCII (16) and HBA (19). A splice variant of \( \text{Na}_1.2 \), originally termed rat IIA (20), has often been considered synonymously with rat II. Full-length sequences of \( \text{Na}_1.6 \) have been isolated from rat (PN4) (21), mouse (Scn8a) (22), and human (Scn8a) (23), and a partial clone has been isolated from guinea pig (CerIII) (17).

The \( \text{Na}_1.1 \) isoform was originally identified in the CNS (12), although it has since been shown to be expressed at high levels in the PNS (24). In contrast, the levels of \( \text{Na}_1.2 \) and \( \text{Na}_1.3 \) are significantly higher in the CNS than in the PNS (24). \( \text{Na}_1.6 \) is the most abundantly expressed channel in the CNS, and it can also be detected in DRG cells (14). Each of these isoforms is present in neurons (14, 25) and glia (14, 26, 27), although the function of the channels in glial cells is not well understood (28). All of the CNS isoforms are inhibited by nanomolar concentrations of tetrodotoxin (TTX).

The genes for the CNS sodium channels have been localized on mouse and human chromosomes (Table 1). \( \text{Na}_1.1, \text{Na}_1.2, \) and \( \text{Na}_1.3 \) are clustered on chromosome 2 in mice and humans. In the mouse, \( \text{Na}_1.2 \) and \( \text{Na}_1.3 \) are within 600 kb by physical mapping, and \( \text{Na}_1.1 \) and \( \text{Na}_1.2 \) are within 0.7 centimorgan by genetic linkage (29). Alternative splicing of all four isoforms has been demonstrated, which has resulted in isoforms termed \( \text{Na}_1.1a, \text{Na}_1.2a, \text{Na}_1.3a, \text{Na}_1.3b, \) and \( \text{Na}_1.6a \) (21, 23, 30–33).

The isoforms in the CNS are present at different times in development, which has been studied most extensively in the rat. \( \text{Na}_1.1, \text{Na}_1.2, \) and \( \text{Na}_1.6 \) are present at significant levels in the adult CNS. \( \text{Na}_1.1 \) expression increases during the third postnatal week and peaks at the end of the first postnatal month, after which levels decrease by about 50% in the adult (34). \( \text{Na}_1.2 \) expression also increases during the third postnatal week, but then continues to increase until reaching maximal
Figure 2  The proposed phylogenetic tree for mammalian voltage-gated sodium channel β subunits was generated using sequences of the cDNA clones listed in Table 2. This unrooted tree represents the optimal tree based on parsimony analysis using a branch-and-bound search, following the procedures described in the legend to Figure 1. The scale bar represents 100 substitutions. The species of origin is indicated as follows: \( h = Homo sapiens \) (human), \( r = Rattus norvegicus \) (rat), \( o = Oryctolagus cuniculus \) (rabbit).

levels during adulthood (34, 35). \( \text{Na}_v 1.6 \) was detected during the embryonic period in brain (33), and levels increased shortly after birth and peaked by 2-weeks of age (23, 36, 37). This is the most abundantly expressed isoform in the CNS during adulthood (14). Levels of \( \text{Na}_v 1.3 \) peak at birth but remain detectable at a lower level in adulthood (35–37).

Different isoforms are present in different locations in the adult CNS. \( \text{Na}_v 1.1 \) is the predominant channel in the caudal regions and the spinal cord. Levels of \( \text{Na}_v 1.2 \) are highest in the rostral regions (35, 38). Specifically, \( \text{Na}_v 1.1 \) was detected at high levels in the cell bodies within the hippocampus, cerebellum, spinal cord, brainstem, cortex, substantia nigra, and caudate (34, 39), and \( \text{Na}_v 1.2 \) was observed at high levels in the axons within the globus pallidus, hippocampus, and thalamus (34). There is no rostral-caudal gradient of \( \text{Na}_v 1.6 \) mRNA (14), but it is present in a somato-dendritic distribution in output neurons of the cerebellum, cerebral cortex, and hippocampus (40), as well as in Purkinje cells in the cerebellar granule cell layer (41, 42). This isoform is present in both sensory and motor pathways, and its subcellular distribution includes axons, nodes, dendrites, cell bodies,
and pre- and post-synaptic sites (42, 43). In the cerebellum, Na\(\textsubscript{1.1}\) is detectable in Purkinje cells but not in granule cells, and Na\(\textsubscript{1.2}\) is expressed in both Purkinje (25) and granule cells (44).

Skeletal and Heart Muscle Channels

Two sodium channel isoforms (Na\(\textsubscript{1.4}\) and Na\(\textsubscript{1.5}\)) are expressed at significant levels in skeletal or cardiac muscle. Na\(\textsubscript{1.4}\) was originally isolated from rat skeletal muscle and was called SkM1 or \(\mu\textsubscript{1}\) (45). Na\(\textsubscript{1.5}\) was isolated from rat skeletal muscle and called SkM2 (46), and it was also isolated from rat heart and called rH1 (47). Human versions of both isoforms have since been isolated and given the same names, SkM1 and H1 (48–50).

Expression of the Na\(\textsubscript{1.4}\) and Na\(\textsubscript{1.5}\) isoforms has been characterized most extensively in the rat. Na\(\textsubscript{1.4}\) is expressed at high levels in adult skeletal muscle, at low levels in neonatal skeletal muscle, and not at all in brain or heart (51). Na\(\textsubscript{1.5}\) is present at high levels in heart, but not in liver, kidney, or uterus (46, 47). This isoform was not originally detected in brain, but more sensitive approaches have demonstrated expression in the piriform cortex and subcortical limbic nuclei (11), which may explain the observation of sodium currents in the entorhinal cortex, with properties similar to those in cardiac muscle (52). Na\(\textsubscript{1.5}\) is not observed in adult skeletal muscle, but it is detectable in neonatal skeletal muscle and after denervation of adult muscle (46). Although both isoforms are present in denervated skeletal muscle, the increase in the level of sodium channel mRNA following denervation results from an induction of Na\(\textsubscript{1.5}\) expression (53).

The two muscle sodium channel isoforms can easily be distinguished from each other and from the CNS isoforms on the basis of toxin sensitivity. Sodium channels present in adult skeletal muscle are sensitive to nanomolar concentrations of TTX, as are the CNS channels. These channels are also sensitive to nanomolar concentrations of \(\mu\) conotoxin GIIIA, to which the CNS channels are resistant (54, 55). Similar sensitivities are observed when the Na\(\textsubscript{1.4}\) channel is expressed in an exogenous system (45, 56). In addition, Na\(\textsubscript{1.4}\) is inhibited by nanomolar concentrations of \(\mu\) conotoxin PIIIA, whereas Na\(\textsubscript{1.2}\) is approximately 15-fold less sensitive, and Na\(\textsubscript{1.7}\) requires micromolar concentrations for inhibition (57).

Sodium channels expressed in cardiac muscle cells are resistant to nanomolar concentrations of TTX, and require micromolar concentrations for inhibition (58). On the other hand, these channels are more sensitive to inhibition by lidocaine than are CNS channels (59). Similar sensitivities are observed when the Na\(\textsubscript{1.5}\) channel is expressed in \textit{Xenopus} oocytes, with an IC\(\textsubscript{50}\) between 2 and 6 \(\mu\text{M}\) for TTX (60, 61). The presence of a cysteine instead of an aromatic residue in the pore region of domain I (the TTX resistance site) in Na\(\textsubscript{1.5}\) is primarily responsible for the relative resistance to TTX (62–64). The same substitution is responsible for the greater sensitivity of Na\(\textsubscript{1.1}\) to block by cadmium and zinc (62–65).

The electrophysiological properties of Na\(\textsubscript{1.4}\) and Na\(\textsubscript{1.5}\) are generally similar to those of the CNS channels, but with some important distinctions. Na\(\textsubscript{1.5}\) has a
more negative voltage-dependence of steady-state inactivation than either Na\textsubscript{v} 1.4 or any of the CNS isoforms (66, 67). Na\textsubscript{v} 1.5 also inactivates more rapidly than either Na\textsubscript{v} 1.4 or the CNS isoforms when the \(\alpha\) subunit is expressed alone in \textit{Xenopus} oocytes (61, 68), and co-expression of the \(\beta 1\) subunit does not accelerate inactivation of Na\textsubscript{v} 1.5 (69).

Peripheral Nervous System Channels

Three sodium channel isoforms, Na\textsubscript{v} 1.7, Na\textsubscript{v} 1.8, and Na\textsubscript{v} 1.9, are expressed primarily in the PNS. In addition, Na\textsubscript{v} 1.1 (24) and Na\textsubscript{v} 1.6 (14, 21), discussed above with the other CNS channels, are present at lower levels in the PNS. Na\textsubscript{v} 1.7 has been isolated from rat DRG (PN1) (70, 71), from human medullary thyroid cancer cells (hNE-NA) (72), and a partial clone has been isolated from rabbit Schwann cells (Nas) (73). Na\textsubscript{v} 1.8 was isolated from rat DRG and called both SNS (74) and PN3 (75), and it has been isolated from mouse (SNS) (76) and dog nodose ganglion (NaNG) (77). Na\textsubscript{v} 1.9 was isolated from rat DRG and called NaN (9), SNS2 (78), and PN5. It has also been isolated from mouse and called NaN (9) and NaT (79). One clone isolated from human DRG was called NaN (80), and another clone isolated from human brain was considered to represent a new isoform, and thus called SCN12A (81). However, this channel most likely represents the human version of the Na\textsubscript{v} 1.9 isoform, based on the phylogenetic tree (Figure 1).

Na\textsubscript{v} 1.1, which was discussed earlier with the CNS channels, is present at high levels in DRG and the lower spinal cord and at lower levels in sciatic nerve (24). Na\textsubscript{v} 1.6 is abundantly expressed in the PNS, having been detected in both gray and white matter in the spinal cord and in all diameter cells in the DRG, including both motor and primary sensory neurons (41, 43). In addition, this channel is present at the nodes of Ranvier in the sciatic nerve, spinal cord, and optic nerve, locations at which the other isoforms were not detected (41–43).

Na\textsubscript{v} 1.7 is widespread in the PNS, present in all types of DRG neurons, in Schwann cells, and in neuroendocrine cells (70, 72, 73). Within neurons, Na\textsubscript{v} 1.7 is localized to the neurite terminals, thus it is likely to have an important role in shaping the action potential (71). It is expressed in PC12 cells in which the level is induced by NGF (82, 83). The channel is sensitive to nanomolar concentration of TTX (70, 72), is slowly inactivating in oocytes, and is not modulated by the \(\beta 1\) or \(\beta 2\) subunits (70).

The expression of Na\textsubscript{v} 1.8 is more localized and found primarily in small-diameter sensory neurons of the DRG and trigeminal ganglion, in which the channel has been observed during both neonatal and adult periods (74–76, 80). This limited localization may have clinical significance because the C fibers that transmit nociceptive impulses are small-diameter neurons (74, 75). The Na\textsubscript{v} 1.8 channel is more resistant to TTX than any of the other isoforms, with an IC\textsubscript{50} of greater than 50 \(\mu\)M (74, 75). Resistance is from the presence of a serine rather than an aromatic residue at the TTX resistance site in domain I. Na\textsubscript{v} 1.8 demonstrates
slow inactivation in oocytes without modulation by the β subunits (75). Mutant mice that completely lack Na,1.8 are viable and express only TTX-sensitive, slow current in DRG neurons (84).

The Na,1.9 channel is expressed in small fibers (sensory neurons) of the DRG and trigeminal ganglion, and the level of expression is down-regulated after axotomy (9, 80). Axonal injury of DRG neurons also leads to expression of Na,1.3, which is not normally present in these cells (85). The Na,1.9 channel is resistant to nanomolar concentrations of TTX, but it is half maximally blocked by 1 µM TTX (78).

Atypical Sodium Channels

The Na, sodium channels were originally considered to be members of a different gene family (type 2), in that these sequences are less than 50% identical to those of the other sodium channel isoforms (10, 86, 87). Three different full-length clones have been isolated. The channel originally called Na,2.1 was isolated from human heart (10), SCL11 was isolated from rat DRG (87), and the channel originally called Na,2.3 was isolated from a mouse atrial tumor cell line (86). A partial clone (Na-G) was also isolated from rat astrocytes (88). It is likely that these clones represent the same isoform because the sequences are quite similar and they were derived from three different species (7). The phylogenetic tree is consistent with this interpretation (Figure 1). Therefore, in this review, these channels have all been classified as NaX. The NaX isoform is present at high levels in heart, skeletal muscle, and uterus, at low levels in brain, kidney, and spleen, and not at all in liver or smooth muscle. This isoform has also been detected in astrocytes, suggesting that it may represent a glial-specific channel.

The NaX isoform has been considered an atypical sodium channel because there are sequence differences in two major regions shown to be critical for normal sodium channel function (10). First, there are significantly fewer charges in the S4 regions, which are essential for voltage-sensitive gating (89, 90). Second, the interdomain III-IV linker, which is involved in fast inactivation (91, 92), is poorly conserved. In particular, the critical IFM residues that form the nucleus of the inactivating particle have been replaced with IFI. However, it is not possible to evaluate the functional significance of these differences because none of these channels has been functionally expressed in an exogenous system, despite numerous efforts (86, 87). There are a number of possible reasons for the inability to observe functional currents from any of these channels. The channels may require accessory subunits that have not yet been identified, or the full-length sequences may contain cloning artifacts. It is possible that these sequences represent pseudogenes, although the fact that all three clones contain uninterrupted reading frames makes this hypothesis less likely. It is also possible that the NaX isoform does not represent a true voltage-gated sodium channel (87), which is why it has not been assigned a number in the proposed nomenclature (4).
SODIUM CHANNEL β SUBUNITS

Many of the mammalian sodium channel α subunits are associated with accessory β subunits in vivo. Two β subunits were originally identified by biochemical purification. The β1 subunit is noncovalently attached to the α subunit, and the β2 subunit is covalently linked to the α subunit by disulfide bonds (93). Channels in the adult CNS are associated with both β1 and β2 subunits, and channels in adult skeletal muscle are associated with just β1 (3). Complementary DNA clones encoding both of these subunits have been isolated from rat and human (Table 2). In addition, cDNA clones encoding a β3 subunit have been isolated from the same two species, and a splice variant of the β1 subunit has been identified in rat (94). The sequences of the three β subunits are not homologous, but they are all clearly related based on the phylogenetic tree (Figure 2). Each of the β subunit sequences predicts a protein with an amino-terminal signal sequence and single membrane-spanning region, indicative of an extracellular amino terminus. All three β subunits contain immunoglobulin-like folds similar to those found in neural cell adhesion molecules (95–97). The β3 subunit RNA is expressed in a complementary fashion to β1 subunit RNA in the CNS, which suggests that α subunits may be associated with either β1 or β3 (97).

Co-expression of the β1 subunit with many of the α subunits in Xenopus oocytes modulates the electrophysiological properties of the channel, including accelerating inactivation and shifting the voltage-dependence of steady-state inactivation in the negative direction (22, 98, 99). These effects require the extracellular domain of the β1 subunit, but not the intracellular domain (100–102). The region on the α subunit that is most important for modulation by β1 includes the extracellular loops between S2 and S6 in domain IV (103). Co-expression of the β3 subunit modulates gating of the α subunit sodium channels to a lesser extent than does co-expression of β1 (97), and co-expression of the β2 subunit modulates α subunit gating the least of the β subunits (95). The β subunits are also important for sodium channel interactions with cellular proteins. The β2 subunit significantly increases membrane capacitance, which may indicate that it is involved in insertion of the channels into the cellular membrane (104, 105). Both β1 and β2 interact with the extracellular matrix proteins tenascin-C and tenascin-R, suggesting that the proteins may function as cellular adhesion molecules (106, 107). Consistent with this hypothesis, both β1 and β2 subunits recruit ankyrin to sites of cell-cell contact, and this recruitment requires the cytoplasmic domains of the subunits (108).

FUNCTIONAL ROLES OF DIFFERENT CHANNEL ISOFORMS

Functional differences among the sodium channel isoforms have been inferred from correlation between electrophysiological recordings from native tissues and identification of the isoforms present in those tissues. One example that has
been extensively studied is the sodium current in cerebellar Purkinje cells, which demonstrates unique persistent and resurgent properties (109, 110). Three isoforms (Nav 1.1, Na v 1.2, and Na v 1.6) have been detected in these cells (17, 25), and Vega-Saenz de Miera et al (17) suggest that Na v 1.1 mediates a transient current in Purkinje neurons whereas Na v 1.6 mediates a persistent current. Raman et al (110) examined the persistent and resurgent currents in normal Purkinje cells and in cells from mice containing a null mutation for Na v 1.6. Both currents were greatly reduced in cells lacking Na v 1.6, suggesting that this channel is a major contributor to persistent and resurgent currents.

One means of determining whether the different sodium channel isoforms mediate distinct conductances is to examine the properties of each isoform in isolation, which is most easily performed using an exogenous expression system. All four of the sodium channel isoforms that have been identified thus far in the CNS have been functionally expressed in exogenous systems (Table 1). The electrophysiological properties of the isoforms examined in *Xenopus* oocytes are generally similar, particularly when compared with the great variation observed for the voltage-gated potassium and calcium channels. All the isoforms demonstrate fast inactivation, are blocked by nanomolar concentrations of TTX, and are modulated by the β1 and β2 subunits (20–22, 95, 98, 99, 111).

There are subtle differences, however. In the absence of β subunits, the Na v 1.6 channel inactivates more rapidly than any of the other isoforms (22), and the Na v 1.3 channel inactivates significantly more slowly (112). Co-expression of the β subunits results in similar inactivation kinetics for Na v 1.1, Na v 1.2, and Na v 1.6 (22), but Na v 1.3 inactivates with biphasic kinetics, suggesting only partial modulation by the β1 subunit (113). The Na v 1.6 isoform has a more positive voltage-dependence of activation and a more negative voltage-dependence of steady-state inactivation compared with Na v 1.1 and Na v 1.2 in the absence of the β subunits (22). However, co-expression of the β subunits causes a large hyperpolarizing shift in the voltage dependence of activation for Na v 1.6, with no significant effect on the voltage-dependence of steady-state inactivation. Therefore, the voltage-dependent properties of Na v 1.1, Na v 1.2, and Na v 1.6 are generally similar in the presence of the β subunits.

There are significant differences among the three isoforms with respect to persistent current (22). Na v 1.2 has the least amount of persistent current at all depolarizations, with less than 1%. Na v 1.1 demonstrates a persistent current that is large at negative potentials (greater than 5%) and decreases with more positive membrane potentials. In contrast, Na v 1.6 demonstrates a persistent current that increases with more positive membrane potentials, reaching a maximum of greater than 5% at the most positive potentials. These results are consistent with the hypothesis that Na v 1.6 channels mediate a persistent current that is largest when an action potential is fired, which might play a critical role in the repetitive firing of action potentials seen in Purkinje neurons. However, the persistent current from Na v 1.1 may also have important consequences for the firing properties of Purkinje neurons.

The resurgent current in cerebellar Purkinje cells is a small sodium current elicited by a waveform that simulates an action potential (109, 110). This current
was observed both in normal Purkinje cells and in cells from mice lacking Na\textsubscript{v}1.6, but it was much larger in the normal Purkinje cells expressing Na\textsubscript{v}1.6. These results suggest that Na\textsubscript{v}1.6 is the primary sodium channel responsible for the resurgent current. However, no resurgent current was observed from Na\textsubscript{v}1.6 channels when they were expressed in \textit{Xenopus} oocytes, either in the presence or absence of the \(\beta\) subunits (22). In addition, no resurgent current was observed in oocytes expressing Na\textsubscript{v}1.1, Na\textsubscript{v}1.2, or various combinations of the three isoforms (22). There are several possible reasons for the lack of resurgent current from Na\textsubscript{v}1.6 channels expressed in \textit{Xenopus} oocytes. First, it is possible that the Na\textsubscript{v}1.6 channel undergoes post-translational modification in Purkinje neurons, which may change some of the electrophysiological properties of the channel. Second, there may be accessory proteins other than the \(\beta\) subunits in Purkinje neurons that could alter the properties of the channel. Third, it is possible that the resurgent current may be a property of one specific splice variant of the Na\textsubscript{v}1.6 sodium channel, since multiple splice variants exist (21, 23, 33). All of these alternatives are based on the hypothesis that resurgence depends on cellular properties or factors in addition to the specific sodium channel isofrm. Consistent with this hypothesis, resurgent current was not observed in mouse spinal neurons, in which Na\textsubscript{v}1.6 is the major component of sodium current density (114).

**CLINICAL SIGNIFICANCE OF SODIUM CHANNELS**

A number of human diseases have been identified that result from aberrant sodium channel activity. Mutations in Na\textsubscript{v}1.4 have been shown to cause three neuromuscular diseases: hyperkalemic periodic paralysis (HYPP), paramyotonia congenita (PMC), and the potassium-aggravated myotonias (115). HYPP is a disease in which increased levels of serum potassium lead to muscle hypoexcitability and paralysis. PMC patients experience cold-induced weakness and paralysis that is aggravated by increased muscle activity. These diseases are inherited in an autosomal-dominant manner and result from mutations in many different regions of the channel, each of which causes defects in either voltage-dependent activation or inactivation (115). Mutations in Na\textsubscript{v}1.5 have been shown to cause long QT syndrome, which is also inherited in a dominant manner (116). The mutations that cause long QT syndrome are located in multiple regions of the channel, and they all cause defects in sodium channel inactivation (117, 118).

There is less information about the effects of sodium channel abnormalities in the CNS. Mutations in Na\textsubscript{v}1.6 have been identified as causing a number of diseases in mice. Unlike the muscle disorders, the Na\textsubscript{v}1.6 mutations are recessive, causing a variety of symptoms ranging from mild ataxia to dystonia, paralysis, and juvenile lethality (119). The mutations include \textit{med} and \textit{med}\textsuperscript{tg}, both of which result in complete disruption of the Na\textsubscript{v}1.6 gene (15, 120, 121), and \textit{med}\textsuperscript{po}, which is a single point mutation of alanine to threonine in the domain III S4-S5 linker (122). This mutation produces an ataxic phenotype that is most likely caused by changes in the voltage-dependent properties of the Na\textsubscript{v}1.6 channel (122, 123). Limbic seizures and
behavioral abnormalities were observed in transgenic mice expressing an Na_1.2 mutation that caused a small increase in persistent current (124). The seizures progressed in severity with age, ultimately leading to premature death (124).

Recently, two types of general epilepsy with febrile seizures plus (GEFS+ type 1) have been demonstrated to result from mutations in human CNS sodium channel genes. GEFS+ type 1 results from a mutation in the gene encoding the β1 subunit (SCN1B) (125), and GEFS+ type 2 results from mutations in the gene encoding Na_1.1 (SCN1A) (18). Both types of GEFS+ are autosomal-dominant disorders. The mutation in the β1 subunit replaces a conserved cysteine in an extracellular immunoglobulin-like fold, which prevents modulation of the α subunit when expressed in Xenopus oocytes (125). Two mutations in Na_1.1 have been identified thus far, one in domain II S4 and the other in domain IV S4 (18). The domain IV mutation, which is a substitution of histidine for arginine, shifted the voltage dependence of steady-state inactivation in the positive direction and caused slower inactivation when it was made in the Na_1.2 channel and examined in Xenopus oocytes (126). However, the effects of either of these mutations in the original Na_1.1 channel have not been examined. The Na_1.1 isoform may be particularly important for the generation of epileptic seizures, as the ratio of mRNA encoding Na_1.1 was increased compared with that encoding Na_1.2 in specific brain regions of patients undergoing surgery to relieve intractable seizures (127).

A number of studies have suggested that changes in the expression of specific sodium channel isoforms contribute to the pathophysiology of inflammatory pain (128, 129) and that aberrant expression of TTX-resistant currents are involved (130, 131). The two TTX-resistant sodium channel isoforms present in the PNS are Na_1.8 and Na_1.9. Both channels are expressed in small-diameter sensory DRG neurons, which include the C fibers that transmit noxious impulses (9, 74, 75, 80). In addition, both isoforms are observed at increased levels in some peripheral nerve fibers proximal to injury in humans (132). The importance of Na_1.9 in nociceptive transmission is suggested by the localization of this isoform in un-myelinated fibers, at some nodes of thinly myelinated fibers, and in corneal terminals that are primarily nociceptive (133). There is more direct evidence for the role of Na_1.8 in neuropathic pain. The symptoms of experimental, neuropathic pain can be attenuated by interfering with the expression of Na_1.8 (134). In addition, mutant mice lacking Na_1.8 demonstrate significant analgesia to noxious mechanical stimuli and other defects in the ability to respond to painful stimuli, indicating that this isoform is involved in pain pathways (84). The data strongly suggest that these isoforms, particularly Na_1.8, have important roles in the transmission of painful impulses in the nervous system.

CONCLUSIONS

The mammalian voltage-gated sodium channels represent a collection of isoforms with distinct patterns of expression and subtle differences in functional properties. There are no clear subfamilies of the isoforms, unlike the situation with
potassium and calcium channels. The relative similarity of electrophysiological characteristics reflects the fact that sodium channels carry out the fundamental role of membrane depolarization during an action potential. However, the subtle differences can result in unique conductances in specific cell types, which have important physiological effects for the organism. In addition, mutations leading to small alterations in channel properties result in human diseases of muscle, heart, and the nervous system.

ACKNOWLEDGMENTS

I thank Dr. Miriam Meisler for critical reading of the manuscript and Dr. George Gutman for help with the phylogenetic analysis. Work in the author’s laboratory is supported by grants from the National Institutes of Health, American Heart Association, and The National Alliance for Research on Schizophrenia and Depression.

Visit the Annual Reviews home page at www.AnnualReviews.org

LITERATURE CITED

sodium channel SCN8A predicts a truncated two-domain protein in fetal brain and non-neuronal cells. J. Biol. Chem. 272:24008–15


sodium channel transcripts during development and in response to denervation. Dev. Biol. 142:360–67
67. Nuss HB, Tomaselli GF, Marban E. 1995. Cardiac sodium channels (hH1) are intrinsically more sensitive to block by lidocaine than are skeletal muscle (\(\mu\)1) channels. J. Gen. Physiol. 106:1193–209


107. Xiao Z-C, Ragsdale DS, Malhotra JD, Mattei LN, Braun PE, et al. 1999. Tenascin-R is a functional modulator of
sodium channel β subunits. *J. Biol. Chem.* 274:26511–17


