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THE ROLE OF SODIUM CHANNELS IN CHRONIC PAIN

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Abstract

Here we review recent research into the mechanisms of chronic pain that has focused on neuronal sodium channels, a target of classic analgesic agents. We first discuss evidence that specific sodium channel isoforms are essential for the detection and conduction of normal acutely painful stimuli from nociceptors. We then review findings that show changes in sodium channel expression and localization in chronic inflammation and nerve injury in animal and human tissues. We conclude by discussing the role that myelination plays in organizing and maintaining sodium channel clusters at nodes of Ranvier in normal development and how inflammatory processes or nerve injury alter the characteristics of such clusters. Based on these findings, we suggest that chronic pain may in part result from partial demyelination of axons during chronic injury, which creates aberrant sodium channel clusters that serve as sites of ectopic sensitivity or spontaneous activity.

Keywords

sodium channels; chronic pain; nociception; demyelination; nodes of Ranvier

INTRODUCTION

Chronic pain is an exceptionally prevalent pathophysiological condition, and given the high stakes in pain therapy, it is not unexpected that this problem has commanded considerable attention from the biomedical research community. At the outset it should be made clear that the focus of this review is to address a very specific topic, namely the role that sodium channels play in the detection and conduction of painful stimuli in the peripheral nervous system and in the establishment of chronic pain disorders. While recent progress in this field has significant implications for the understanding and treatment for chronic pain, it should be kept in mind that important advances are also being made in other approaches to this subject.

In any case, the pain field has recently been transformed by two general findings: First, it has been shown that *special types of sodium channels (“isoforms”) are selectively expressed in peripheral nociceptive pathways*. The significance of these findings in turn, implies that

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improvements in pain therapeutics may be achieved through the development of compounds that specifically inhibit these selectively expressed isoforms. Second, the *expression of sodium channels dramatically changes in cases of chronic inflammatory and neuropathic conditions*. Thus this finding suggests that sodium channels themselves play a direct role in the establishment of chronic pain states.

SODIUM CHANNEL EXPRESSION AND FUNCTION IN NORMAL PERIPHERAL NOCICEPTIVE PATHWAYS

As the main molecular moiety responsible for generating the propagating axonal action potential, sodium channels will naturally be involved in conducting information from peripheral nervous system (PNS) pain receptors to the central nervous system (CNS). Additionally, there is evidence that sodium channels also play a role in the actual transduction of painful stimuli to electrical impulses at nociceptive receptors themselves^{1, 2}. Naturally, these roles in normal nociception are reflected in the manner in which local anesthetics relieve pain through their sodium channel blocking actions.

Sodium channels are a diverse family of isoforms with unique expression patterns and functions

Early analysis of purified sodium channels showed that the molecular mechanisms for basic sodium channel functions (i.e. sodium selectivity and permeability, voltage-dependent activation and inactivation) were mediated by a single large (~250 kilodalton) polypeptide⁶. However, in many tissues this so-called α -polypeptide is often associated with one or more accessory subunits. These β -subunits appear to play a role in modulating channel function and expression³ and may well play important roles in pain⁴. In any case, for simplicity this article will focus solely on the role of the major α channel polypeptide, to which we now refer to simply as the sodium channel.

Sodium channel polypeptides are not expressed by a single gene. Rather, recombinant DNA studies (i.e. cDNA and gene “cloning”) have shown that sodium channels exist in most organisms as multigene families, the individual gene products of which are known as *isoforms*. Thus at least 9 distinct sodium channel types are currently known to be expressed in mammals (Table 1).

A major current research thrust concerns the reasons for such ion channel diversity. Most investigators agree that there are three basic possibilities: 1) Functional variations may exist among isoforms that are needed for excitation differences required by different cell types. For example, fast channel kinetics are suited for the transmission of high frequencies of action potentials in myelinated fibers, while slow kinetic gating of certain isoforms may be required for the long duration action potentials in smooth muscle or cardiac tissue; 2) Amino acid sequence variations may encode signals that allow channel isoforms to be selectively localized to different membrane areas or specializations (e.g. nodes of Ranvier, neuron dendrites, muscle fiber t-tubules) through interactions with transport, targeting, or clustering molecules; 3) The noncoding region of channel isoform genes may contain unique regulatory elements that would allow cell, tissue or developmentally-specific expression of a given isoform. For example, the regulation of cardiac function probably requires sodium channel expression to respond to very different processes and factors than development of excitability in the nervous system.

Note that these three different explanations are not exclusive of one another, and there is good evidence that all three explanations of ion channel diversity apply in at least one example. Thus there are elegant studies that demonstrate the existence of specific gene regulatory elements and transcription factors that control the specific expression of certain

sodium channel isoforms⁵⁻⁷, while the selective targeting and clustering of channel isoforms has been shown in a number of studies⁶. It is on this latter phenomenon that we now focus as background to our discussion of sodium channels and pain.

Sodium channel isoforms are selectively expressed among excitable tissues

The most direct way to determine the distribution of various sodium channel isoforms in excitable tissues is to use immunohistochemical methods in which antibodies that are specific for each isoform are employed as isoform markers. We and others have made such antibodies to all isoforms, and we have used confocal immunofluorescence microscopy to visualize the distribution of the various channel types in different tissues (Fig. 1). Thus it can be seen clearly that individual isoforms are often selectively expressed in different excitable tissues. For example, Na_v1.6 is the dominant isoform expressed at nodes of Ranvier, while Na_v1.7 is commonly expressed in unmyelinated fibers within the PNS. Alternatively, it is sometimes the case that a given cell type may synthesize two or more different isoforms, but then each is subsequently targeted to a different subcellular domain. For example, in retinal ganglion neurons that form the optic nerve, both Na_v1.2 and 1.6 isoforms are made. Na_v1.2 is expressed selectively in the initial unmyelinated segment of the retinal ganglion cell axon, while Na_v1.6 is expressed selectively at nodes of Ranvier within the optic nerve itself⁸.

Na_v1.7, 1.8, and 1.9 isoforms are selectively expressed in PNS pain pathways

Using immunocytochemical approaches, it has been discovered three sodium channel isoforms are expressed selectively in pain-conducting pathways of the PNS². Thus isoforms Na_v1.7, 1.8, and 1.9 are localized dominantly in peripheral sensory ganglia, including dorsal root ganglia (DRG) and trigeminal ganglia (TGG), to small and medium neuronal somata involved in pain transmission (Fig. 1). Na_v1.7 itself is associated strikingly with pain pathways, as it is expressed highly in both unmyelinated C-fibers that also contain the neuropeptide substance-P (Fig.2) and in free nerve endings in nociceptive receptor fields found in the skin, tooth pulp, and the cornea (Fig. 3).

Evidence that peripheral sodium channel isoforms are functionally important for the detection and conduction of painful stimuli

Indications that specific channel isoforms are involved in chronic pain came from studies in which analgesic drugs were tested for their selectivity to block different sodium channel isoforms. In particular, we have found that certain antiseizure drugs commonly used to treat chronic pain (e.g. carbamazepine) are much more efficacious blockers of Na_v1.7 sodium channels than Na_v1.2 isoforms (Wang and Levinson, unpublished), the latter of which is not predominantly found in peripheral nociceptive neurons or their processes (e.g. see Fig. 1). Recent studies have attempted to more directly address this point using rodent models in which a given isoform is selectively suppressed using RNA antisense approaches⁹ or in transgenic knockout mice. In general such studies have shown that alteration of Na_v1.7, 1.8, or 1.9 expression leads to reduced sensitivity to chronic pain in either inflammatory or neuropathic pain models².

However, from a clinical point of view the most compelling evidence for specific involvement of PNS isoforms in pain comes from the studies of human familial pain disorders¹. In particular, so called “gain of function” mutations in Na_v1.7 function have been shown recently to account for several inherited erythromelalgias and paroxysmal extreme pain disorders¹⁰⁻¹². In these patients, mutations in Na_v1.7 affect the voltage-dependence of channel gating such that channels either open more readily in response to depolarizing stimuli, or they are less affected by inactivation at resting membrane potentials. In either case, it is thought that nociceptor cell bodies, axons, and/or free nerve endings

become highly sensitive to sub-threshold stimuli or even become spontaneously active, thus subjecting the patient to a sensation of pain when none exists.

Perhaps even more spectacular are congenital $\text{Na}_v1.7$ mutations that completely eliminate the sensation of pain in affected individuals¹³. In such individuals, stimuli such as contact with sharp objects or burning hot materials fail to elicit any painful sensations at all. The mutations responsible for this phenotype also completely eliminate the functionality of the $\text{Na}_v1.7$ isoform, providing further proof for the essential role of this channel in pain sensation.

ROLES OF SODIUM CHANNELS IN CHRONIC PAIN STATES

The evidence discussed above supports the necessary role of the $\text{Na}_v1.7$ isoform in normal physiological pain sensations. Certainly a role in physiological pain is important, and this evidence suggests the targeting of a single isoform can alter pain sensations. But what is the role of sodium channels in chronic pain states? Chronic pain is a prevalent problem among the general population,¹⁴ and current treatments are often times ineffective or limited due to undesirable side-effects¹⁵. More specific treatments are needed. In this regard, the enriched peripheral distribution and localization within nociceptors of some of the sodium channel isoforms and the critical role played by sodium channels in neuronal excitability identifies these isoforms as logical targets for the development of new analgesics. Even though pain is typically categorized as either inflammatory or neuropathic¹⁶, many similarities exist between these two conditions¹⁷. These similarities suggest that the same isoforms may be involved with both conditions and offers the hope for the development of isoform-selective blockers to be used in the treatment of a wide variety of pain conditions^{18, 19}. We will briefly describe some of the evidence that supports the involvement of specific isoforms with each of these pain conditions and note that others have also recently reviewed the role of sodium channels in inflammatory and/or neuropathic pain^{20, 21, 22}.

Sodium channels appear to play a role in the maintenance of inflammatory pain states

Inflammatory pain results from the sensitization and activation of peripheral nociceptors by inflammatory mediators. The increased excitability is the net result of mediators on a myriad of different ion channels, including sodium channels²³. Multiple studies have evaluated changes in sodium channels in experimental animals with inflammatory lesions most commonly induced by peripheral injection of either carrageenan or complete Freund adjuvant. The results of these studies typically show increased expression of the $\text{Na}_v1.3$, 1.7, 1.8 and 1.9 isoforms in sensory neuronal cell bodies following the inflammatory lesions^{24, 25, 26–28}. Other studies have used knockout mice or knock-down methods to evaluate the role of specific isoforms in inflammatory pain. The results of these studies strongly implicate $\text{Na}_v1.7$ ^{9, 29} and 1.8^{30, 31} and, to a lesser extent, the 1.9 isoform^{32, 33}. Importantly, peripheral inflammation and nerve growth factor are both associated with a rapid increase in sodium channel production in sensory neurons that was specific for $\text{Na}_v1.7$ when compared to $\text{Na}_v1.8$ ^{34, 35}. On this basis we hypothesized that inflammation-induced $\text{Na}_v1.7$ synthesis was required for maintenance of the critical features of this form of pain, such as hyperalgesia and allodynia. In particular, it is possible that $\text{Na}_v1.7$ expression is increased in nociceptors at the wound site and in the surrounding tissues, thus conferring on them a lower threshold of activation by non-noxious stimuli, perhaps accounting partially for the phenomena of allodynia and hyperalgesia.

While animal studies especially implicate the $\text{Na}_v1.7$ and 1.8 isoforms in experimental inflammatory pain, studies in humans are far fewer. We and others have utilized the human tooth as a model system to examine the effects of inflammation on sodium channel expression within human tissues. Our model compares the expression of sodium channels

within the axons of extracted normal third molars (wisdom teeth) to inflamed molar teeth with decay (cariou lesion) and pain. The use of this model evaluates peripheral nerves and so contrasts with the methods used in most experimental animal studies where expressions are typically evaluated in sensory neurons.

Results of these pulp studies showed the expression of $\text{Na}_v1.8$ at 16.5% of the nodal sites in normal samples³⁶ a variable overall nerve fiber expression of sodium channels in both normal and painful specimens³⁷, while in contrast the nerve fiber expression of $\text{Na}_v1.7$ was significantly increased in painful specimens when compared to normal specimens³⁸. Other findings included a nearly ten-fold increase in the expression of $\text{Na}_v1.7$ at nodes of Ranvier in painful samples³⁸, whereas the nodal expression of $\text{Na}_v1.6$ was not different between normal and painful samples⁸⁴. These findings suggest that inflammation is associated with a novel expression of multiple isoforms at nodes of Ranvier and not a simple replacement of one isoform with another. Since each sodium channel possesses unique gating properties²², the coexpression of multiple isoforms at single sites may well have significant effects on excitability, e.g. such sites may become spontaneously activated (see below).

Although other studies have also reported the increased expression of the $\text{Na}_v1.7$, 1.8 and 1.9 isoforms within nerves in the inflamed human dental pulp^{39, 40, 41}, none have evaluated expressions at nodal sites where the voltage-gated activation of sodium channels is responsible for action potential propagation. Importantly, all painful samples were collected from patients who described constant ongoing pain and the presence of sharp, shooting spontaneous pain episodes over the 24 hour period preceding extraction. Although correlational studies are difficult, it is tempting to suggest that the presence of large sodium channel accumulations within the painful specimens may be linked to spontaneous pain episodes, a common symptom of toothache.

Role of sodium channels in neuropathic pain

Neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory nervous system” by the International Association for the Study of Pain, and although it shares contributions from the immune system with inflammatory pain, other features help distinguish neuropathic pain from inflammatory pain. In particular, such pain is often characterized by extreme ectopic mechanical sensitivity and by spontaneous painful sensations, and these clinical symptoms could in part result from sodium channel activation. Indeed, both animal and human studies have described ectopic activity in neuromas,^{42, 43} and drugs with sodium channel blocking effects used clinically to treat neuropathic pain also inhibit ectopic nerve activity^{44, 45, 46} (reviewed in^{47, 48}). Even so, the results of animal studies are less consistent regarding possible contributions of specific isoforms to neuropathic pain than are seen in inflammatory pain. The results show no effect on neuropathic pain for $\text{Na}_v1.3$, 1.7, 1.8 and 1.9 in knock-out mice^{49, 33, 50, 51}, whereas the use of knock-down techniques show mixed results for $\text{Na}_v1.3$ ^{52, 53}, positive effects for 1.8^{54, 55} and no effect for 1.9⁵⁶.

However, results in these studies may be complicated due to compensatory changes in other isoforms or systems and by off-target effects of knock-down treatments. Thus more recent evidence supports a role for $\text{Na}_v1.7$ and 1.8 in neuropathic pain as shown with specific blockers of these isoforms^{57, 58, 59, 60, 61}. In addition, there are results from humans that implicate these isoforms in neuropathic pain. Most of these human studies have evaluated expressions in excised painful neuromas. Results show a greater concentration of sodium channels in painful neuromas when compared to normal nerve biopsies and this expression is especially prominent in the tips of axons⁶². Other results show an accumulation of $\text{Na}_v1.8$ in painful neuromas^{24, 63} and a causalgic finger⁶⁴, increased expression of both $\text{Na}_v1.7$ and 1.8 in painful human neuromas⁶⁵, and increased expression of $\text{Na}_v1.3$, 1.7 and 1.8 in

painful neuromas when compared to more proximal regions from the same nerves⁶⁶. In contrast, a quantitative study of Na_v1.7 in asymptomatic and painful lingual nerve neuromas found expression that was not correlated with pain symptoms, but this study lacked comparisons to normal nerves⁶⁷. Finally, animal studies also show enhanced Na_v1.8 expression in uninjured axons close to ones with injury⁶⁸, suggesting that diffusible factors may play a role in ectopic isoform expression in nerve injury.

Even though Na_v1.6 is expressed at all nodes of Ranvier in the peripheral and central nervous system⁶⁹, few studies have evaluated possible involvement of this isoform in neuropathic pain. The few studies performed have described an increased or maintenance of expression at nodal sites^{70, 66}, and when these results are considered in relation to the many other studies showing expressions of other isoforms at the site of nerve injury, together they again suggest the possibility of mixtures of isoforms contributing unique gating properties. Even though there is a lack in knowledge regarding how an altered mix of multiple isoforms influences neuronal excitability in pain conditions, the recent results obtained with the use of isoform-specific blocking agents solidify the use of this strategy to treat not only the more clinically challenging neuropathic pain conditions, but also inflammatory pain. A common theme for many studies is increased expression of specific isoforms in both inflammatory and neuropathic pain conditions. In this regard, the techniques used by our group that evaluate overall and site-specific changes of isoforms within focal nerve regions with either of these injuries are appropriate to study possible mechanisms contributing to formation of sodium clusters.

THE FORMATION AND MAINTENANCE OF SODIUM CHANNEL CLUSTERS DEPENDS ON SIGNALS FROM ADJACENT MYELINATING GLIA

The node of Ranvier is a location where sodium channels are found at very high density and where their activation is necessary for saltatory conduction⁷¹. In this regard, the localization of sodium channels at the node of Ranvier represents a key subcellular domain that influences the activity of myelinated fibers. Even though other subcellular domains also contain a high density of sodium channels that play key roles in neuronal excitability, such as the initial segment, the activation of nodal sodium channels in the axons of primary sensory neurons may be especially important due to the special constraints imposed by the pseudounipolar morphology and t-junction connecting the peripheral and central process to the cell body. Some have suggested, and modeling has predicted, that spike formation within the soma may not be necessary for action potential propagation from the peripheral to the central process and central nervous system⁷².

The formation and maintenance of high density sodium channel clusters at nodes of Ranvier in myelinated nerve axons is an example of the selective expression of membrane proteins at extreme distances from their point of synthesis in the neuron soma. Previous work has shown that such exquisite targeting of channels is largely determined by myelinating glia themselves, i.e. Schwann cells or oligodendocytes^{73–75}. Thus in early development, myelinating cells apparently induce the formation of high density sodium channel clusters adjacent to their outer margins on the axonal membrane, and further, these clusters appear to move ahead of the growing glial cell as the myelin wrapping extends along the axon⁷⁴. Stable nodes of Ranvier are then formed when clusters from adjacent myelinating glia approach each other and fuse into a mature, stable cluster (Fig. 4). At present, the actual signaling pathway from myelinating cell to the axon that creates such dense sodium channel clusters is not entirely understood, although it appears to involve interactions of specific membrane receptors, such as gliomedin, on the glial cell with those on the axon^{76, 77}. Interestingly, the localization of sodium channels within axon initial segments is

independent of these extrinsic signals and instead appears as an inherent property of the neuron⁷⁸.

Demyelination is associated with a remodeling and altered expression of sodium channels

Since myelinating glia provides the cues for sodium channel cluster formation, what happens to sodium channel cluster formation in those conditions where myelin is lost? This response could be important, since demyelinating conditions can be associated with pain^{79, 80}. Interestingly, in those acute demyelinating insults that allow a timely remyelination process (within 7–10 days) sodium channel clusters are formed in the new nodes similarly to the manner in which they form during development, i.e. at the ends of remyelinating glia⁷³. But very different results are seen in cases of chronic demyelination or in conditions where myelin fails to form developmentally, since large numbers of amorphous and enlarged channel clusters appear on demyelinated axons and are like those seen in human neuromas^{81–83} (Fig. 5). Importantly, these changes are also seen in the inflamed and painful human dental pulp and at the site of nerve injury in an animal model for neuropathic pain^{38, 84, 37, 70, 85} (Fig. 6). Together, these findings suggest that augmentation and remodeling of sodium channel clusters at demyelinated sites may be an important factor influencing nerve fiber excitability, with broad implications on pain mechanisms.

We suggest that such clusters are the source of both ectopic mechanical and spontaneous pain associated with nerve injury and may even be responsible for the sharp shooting pain sensations described by our patients with inflammatory toothache pain. But how might such clusters form? We hypothesize that injury-induced focal demyelination is responsible. In this scheme, chronic loss of myelin results in changes in the signaling process between glia and nerve that maintains well-defined clusters of channels in myelinated fibers. As a result, larger clusters form in the now extended gap between myelin sheaths. Our results show that such abnormalities can also occur on a smaller scale when nodes start to become locally distorted (Fig. 7); in such cases, nodal clusters first enlarge in the widening gap, then often split into separate clusters. As the gap widens further, we infer that each cluster stays associated with its glial edge to form a “heminode”. Finally, if this demyelinated gap persists long enough, we propose that abnormal, large, amorphous clusters or group of smaller clusters may form in the demyelinated axon. We propose that any or all of such clusters may display spontaneous activity and ectopic sensitivity, thus serving as sources of local chronic pain. This model would also suggest that this process would be prolonged in those clinical conditions where myelinating glia are adversely affected, such as long-standing inflammatory conditions. Furthermore, the similarity in this reorganization of sodium channel clusters seen in both neuropathic and inflammatory conditions suggests some similarities between the two conditions.

The remodeling of sodium channels in injured myelinated fibers includes the increased and abnormal expression of other non-nodal isoforms

A further finding that may have significance for the generation of painful impulses at nerve injury sites is that non-nodal sodium channel isoforms (i.e. non- $\text{Na}_v1.6$ channels) appear to be abundantly expressed in remodeled and newly-appearing clusters in demyelinating areas. Thus both $\text{Na}_v1.7$ and 1.8 isoforms populate such clusters and are even found in some otherwise normal appearing nodes⁸⁶. We suggest that such clusters, which probably are comprised of isoform mixtures, will have novel excitability properties that make them more likely to activate spontaneously or upon ectopic stimulation. If so, the new isoform-specific blockers that target either the $\text{Na}_v1.7$ or 1.8 isoforms may prove to be especially efficacious as new analgesics for both neuropathic and inflammatory pain conditions. Our recent work provides some clues as to why non-nodal isoforms appear in myelinated fibers as a result of

injury. These results show that in the postnatal development of PNS myelin in rodents all neuronal sodium channel isoforms (i.e. $\text{Na}_v1.1$ – 1.3 , $\text{Na}_v1.6$ – 1.9) are initially expressed when nodes of Ranvier are first formed, but they are gradually eliminated from nodal clusters over a course of about 2 weeks in favor of the uniform expression of $\text{Na}_v1.6$ (Fig. 4). Further, such elimination of non-nodal isoforms is delayed in mouse mutants in whom the myelination process is delayed or defective⁸ (Luo, Meijer, Ehring and Levinson, in preparation). Thus we propose that development of compact myelin induces a $\text{Na}_v1.6$ selective targeting program in neurons and that demyelination reverses this process to allow non- $\text{Na}_v1.6$ isoforms to be re-expressed in axons in which significant demyelination has occurred.

APPROACHES TO ADVANCED PAIN THERAPEUTICS

Naturally, as noted above, the realization that the sodium channel isoforms preferentially expressed in the PNS, including $\text{Na}_v1.3$, 1.9 and especially 1.7 and 1.8 , play specific roles in the neurobiology of pain strongly suggests that these isoforms would be excellent targets for new drugs for chronic pain management. Thus a number of groups and companies are actively involved in developing such compounds,^{48, 87} and initial reports (see above) provide support for the effectiveness of these compounds in a wide variety of experimental pain conditions in animals.

In an alternative approach to this problem, collaborative studies have used gene therapy methods to selectively reduce the expression of $\text{Na}_v1.7$ channels in a rodent model of chronic inflammatory pain⁹. This was accomplished by application of a recombinant, non-replicative herpes simplex virus (HSV) that expresses $\text{Na}_v1.7$ antisense mRNA to the rat hindpaw. Inflammation of the paw was induced by injection of complete Freund adjuvant, and the resulting thermal hyperalgesia and mechanical allodynia was characterized. Pain thresholds in treated animals were significantly elevated when compared to control animals injected with non-antisense expressing HSV, and these behavioral changes paralleled reduction in $\text{Na}_v1.7$ channel expression as measured by immunofluorescence. Thus selective reduction of sodium channel isoform expression by gene therapy would appear to be a promising approach to the management of chronic pain. Together, these results provide hope that the future use of such compounds and approaches will provide effective treatment options for the many patients living and suffering with chronic pain.

CONCLUSIONS

Sodium channels appear to play significant roles in the establishment of chronic pain states in addition to their classical roles in the detection and conduction of acute pain stimuli. The finding that only one or a few sodium channel isoforms are involved in these processes suggests that therapeutic approaches that selectively reduce the function of these isoforms will be an important source of advances in the treatment of chronic pain in the future.

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Abbreviations

CNS	central nervous system
DRG	dorsal root ganglion

HSV	<i>Herpes simplex virus</i>
Na_v1.x	sodium channel isoform 1.x
PNS	peripheral nervous system
TGG	trigeminal ganglion

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Figure 1. Images of the subcellular localization of various sodium channel isoforms as seen using isoform-specific immunofluorescence techniques

A: $\text{Na}_v1.6$ channels at nodes of Ranvier (bright dots, 20 $\times$ objective). These are nodes in mouse sciatic nerve axons. B: $\text{Na}_v1.7$ isoform expression in unmyelinated fiber bundles of mouse sciatic nerve (40 $\times$ obj.). C: $\text{Na}_v1.4$ expression in rat skeletal muscle (40 $\times$). Note the intense labeling of postsynaptic sodium channel clusters, while weaker labeling of t-tubules is also apparent (as seen in the z-line labeling pattern). D: $\text{Na}_v1.5$ expression in rat cardiac ventricular myocytes (20 $\times$). Note intense staining of intercalated discs between myocytes and the t-tubule staining pattern. E: Expression of isoforms in the dorsal root ganglion (all at 20 $\times$ obj.). Note that expression of isoforms varies among different sized subpopulations of neurons, i.e. smaller neurons express $\text{Na}_v1.7$ and 1.8, while larger neurons express $\text{Na}_v1.1$ and $\text{Na}_v1.2$.

Figure 2. Selective expression of the $\text{Na}_v1.7$ isoform in presumptive nociceptive C-fibers
These images were taken from immunostained rat sciatic nerve fibers (40 $\times$ objective). **Top:** $\text{Na}_v1.7$ immunofluorescence in unmyelinated fiber bundles. **Bottom:** Substance-P immunoreactivity in same field as top panel. Note the typical punctate pattern of substance-P immunofluorescence in the same fibers that were $\text{Na}_v1.7$ -positive in the top panel. In this panel the brightness has been increased to show the nonspecific autofluorescence in large myelinated fibers that are $\text{Na}_v1.7$ -negative.

Figure 3. Expression of $\text{Na}_v1.7$ in tooth pulp, skin, and cornea

In rat tooth pulp, the pattern of $\text{Na}_v1.7$ immunofluorescence suggests selective localization to fine unmyelinated fibers and free nerve endings in the coronal pulp (60 $\times$ obj.). Similarly, in human skin unmyelinated fiber bundles and presumptive nerve endings are brightly stained for $\text{Na}_v1.7$. The rat cornea whole mount shows a branching $\text{Na}_v1.7$ -positive nerve bundle overlying the stroma.

Figure 4. Formation of nodal sodium channel clusters by myelinating glia during development and in remyelination

This figure depicts the stages of cluster formation in the PNS, starting at the top (A) where Schwann cells in the promyelinating state attach to the axon; at this stage various sodium channel isoforms (represented by multicolored dots) are diffusely distributed throughout the axon and do not cluster. In (B), the Schwann cells have just started to form compact myelin and high density axonal sodium channel clusters containing all isoforms form at their ends. As myelination proceeds (C), the channel clusters move ahead of the extending Schwann cells, fusing with adjacent clusters from the opposite approaching Schwann cell to form a

stable node of Ranvier (D). Finally, the mature nodal sodium channel isoform Na_v1.6 replaces the other isoforms to form a homogenous nodal cluster of Na_v1.6 (E, yellow dots).

Figure 5. Expression of sodium channels in a painful human neuroma

Here the antibody recognized all sodium channel isoforms. Note high density of channels in brightly immunofluorescent fibers found only in the affected portion of the nerve. Also, apparently normal nodes of Ranvier are still found in this tissue (arrows). Scale bar= 10 μ m. Data from England et al. (1996).

Figure 6. Expression of sodium channels in an animal model of chronic nerve injury

Rat infraorbital nerves were chronically inflamed and subjected to mechanical damage. Two weeks later nerves were harvested and immunostained for sodium channels using a non-isoform specific antibody (panels C and D). Nerves were co-stained for caspr, a paranodally-expressed protein, to identify Schwann cell processes adjacent to nodal sodium channel clusters (A and B). Representative confocal micrographs show that the density of sodium channel clusters dramatically increased in the lesioned nerves. Further, the structure of paranodal myelin became distorted in lesioned nerves, and the channel clusters at such aberrant nodes were usually enlarged and asymmetric (compare arrows; see also Fig. 6). Scale bar in A = 10 μ m for all panels. Data from Henry et al. (2006).

Figure 7. Aberrant expression of sodium channels at nodal sites in chronic nerve injury

These images were taken from the same chronic injury model used in Fig. 5. A typical node from a normal infraorbital nerve is shown in A, and the different types of caspr-related sodium channel accumulations commonly seen after a lesion are shown in B-F. The sodium channel clusters (light grey, arrowheads) are either directly adjacent to caspr clusters (black, A-E) or lack an association with caspr (F). Thus the sodium channel accumulations seen in lesioned nerves consist of caspr-associated forms that include typical nodes that appear elongated or “robust” (B), split nodes (C and D), and heminodes (E), while some channel accumulations lack caspr and thus appear “naked” (F). Data from Henry et al. (2006).

Table 1
Mammalian sodium channel isoforms and their known distributions in excitable tissues

Also given are alternative isoform protein and genomic nomenclatures which are often found in the older literature. The function of the Na_v2.x protein as a sodium channel is still uncertain.

Isoform (Standard nomenclature)	Other names in literature	Gene name	Typical distribution
Na _v 1.1	Type I	<i>SCN1A</i>	<i>Dendrites</i>
Na _v 1.2	Type II/IIA	<i>SCN2A</i>	<i>Unmyelin. initial segments</i>
Na _v 1.3	Type III	<i>SCN3A</i>	<i>Early neuronal development</i>
Na _v 1.4	SkM1, μ 1	<i>SCN4A</i>	<i>Skeletal muscle (mature)</i>
Na _v 1.5	H1, SkM2, μ 2	<i>SCN5A</i>	<i>Heart, Immature Skel. musc.</i>
Na _v 1.6	Cer3, PN4	<i>SCN8A</i>	<i><u>Nodes</u>, synapses, dendrites</i>
Na _v 1.7	PN1, hNE-Na, Nas	<i>SCN9A</i>	<i>Unmyelinated PNS (pain)</i>
Na _v 1.8	SNS, PN3	<i>SCN10A</i>	<i>Unmyelinated PNS (pain)</i>
Na _v 1.9	NaN, SNS2	<i>SCN11A</i>	<i>PNS – free nerve endings</i>
Na _v 2.x	ret1, NaG, <i>atypical</i>	<i>SCN7A</i>	<i>Nonmyelinating Schwann c.</i>