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VOLTAGE-GATED SODIUM CHANNELS AND HYPERALGESIA

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■ **Abstract** Physiological and pharmacological evidence both have demonstrated a critical role for voltage-gated sodium channels (VGSCs) in many types of chronic pain syndromes because these channels play a fundamental role in the excitability of neurons in the central and peripheral nervous systems. Alterations in function of these channels appear to be intimately linked to hyperexcitability of neurons. Many types of pain appear to reflect neuronal hyperexcitability, and importantly, use-dependent sodium channel blockers are effective in the treatment of many types of chronic pain. This review focuses on the role of VGSCs in the hyperexcitability of sensory primary afferent neurons and their contribution to the inflammatory or neuropathic pain states. The discrete localization of the tetrodotoxin (TTX)-resistant channels, in particular $Na_V1.8$, in the peripheral nerves may provide a novel opportunity for the development of a drug targeted at these channels to achieve efficacious pain relief with an acceptable safety profile.

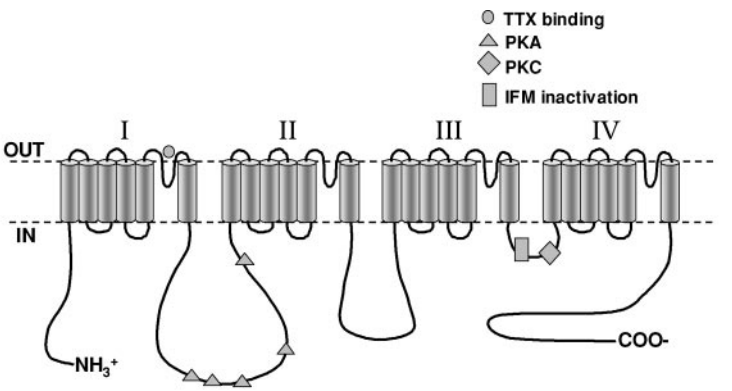
INTRODUCTION

Voltage-gated sodium channels (VGSCs) play a fundamental role in the excitability of all neurons. They are located in the plasma membrane and mediate the influx of sodium ions into the cell in response to local membrane depolarization; sodium influx results in the generation of the action potential. Alteration in VGSC expression and/or function thus has a profound effect on the firing pattern of sensory primary afferent neurons as well as neurons in the central nervous system. Injury to sensory primary afferent neurons often results in abnormal, repetitive discharge or

exaggerated response to subsequent sensory stimuli. Such exaggerated response is believed to contribute to chronic inflammatory and neuropathic pains. Central projection neurons that relay sensory signals to the sensory cortex may also become hyperresponsive, a process termed central sensitization. Both physiological and pharmacological evidence implicate a critical role of VGSCs in the development and maintenance of hyperexcitability observed in primary afferent neurons following nerve and tissue injury. Importantly, use-dependent sodium channel inhibitors are clinically effective in the treatment of many types of chronic pain. This review focuses on VGSCs in sensory afferent neurons and their contribution to nerve and tissue injury-induced pain.

Voltage-Gated Sodium Channels

Each VGSC comprises a large alpha subunit (~260 kDa) and one or more beta subunits (33–36 kDa) (1) (Figure 1). The alpha subunit consists of four homologous domains (I–IV), each containing six transmembrane segments (S1–S6) and a



Subtype	Rat Orthologs	TTX Sensitivity (nM)	Activation Threshold	Inactivation Rate	Tissue Localization
$Na_V1.1$	Brain I	-	Low	Fast	CNS, also in DRG and motor neurons
$Na_V1.2$	Brain IIA	18	Low	Fast	CNS
$Na_V1.3$	Brain III	15	Low	Fast	Embryonic nervous system; adult CNS;
$Na_V1.4$	SkM1	5	Low	Fast	Skeletal muscle
$Na_V1.5$	H1	1,800	Low	Medium	Heart; embryonic DRG
$Na_V1.6$	SCP6, PN4	1	Low	Fast	DRG, motor neurons, also in CNS
$Na_V1.7$	PN1	2	Low	Fast	Mostly DRG, also in CNS
$Na_V1.8$	PN3, SNS	>100,000	High	Slow	DRG (80% small diameter; 20% large
$Na_V1.9$	PN5, NaN	39,000	Low	Medium	DRG (small diameter); also in CNS

Figure 1 Schematic secondary structure of the family of VGSCs, their classification, tissue distribution, and functional characteristics.

pore-forming loop between segments V and VI. The alpha subunit contains all of the machinery necessary for a functional ion channel in addition to the ion pore, including the voltage sensor (in domain IV), an ion selectivity "filter," and a segment responsible for fast inactivation (third intracellular loop between IIIS6 and IVS1, identifiable by the tripeptide motif, IFM). Thus, a single alpha subunit constitutes a functional VGSC. The alpha subunit also contains the majority of sites mediating pharmacological modulation of gating or permeation processes, e.g., the binding site for tetrodotoxin (TTX) resides in domain I. The alpha subunit also contains a number of phosphorylation sites, which enable relatively rapid modulation of channel gating properties (1). Beta subunits appear to serve a number of functions, including targeting and anchoring channels at specific sites in the plasma membrane and modulation of the gating properties of the alpha subunits (2). Genes encoding ten alpha subunits and three beta subunits have been identified (3). The tissue- and cell-specific expression of these channel subtypes can be critical in determining the heterogeneity and functional specialization of many types of cells, including the sensory neurons of the peripheral nervous system that propagate sensory or nociceptive signals to the brain and the spinal cord. Detailed reviews of this topic may be found elsewhere (4, 5).

Sensory Primary Afferent Neurons

Sensory neurons are a heterogeneous population of primary afferent neurons that subserve an array of unique functions, including proprioception, mechanosensation (vibratory, pressure), thermal sensation (cool, warm), as well as nociception. The cutaneous afferent, i.e., sensory neurons that innervate the skin and skeletal muscles, can be differentiated morphologically and functionally. Among these are myelinated, fast-conductance, large-diameter fibers called A-beta fibers, which have a low threshold for activation and mainly conduct information about innocuous touch; the thinly myelinated medium-velocity fibers called A-delta fibers, which are polymodal in nature; and the unmyelinated, slow-conductance small-diameter fibers called C fibers, most of which have high threshold for activation and transmit potentially damaging, noxious inputs. Among the population of nociceptive afferents, there are a number of unique subpopulations (6), including afferents responsive to noxious thermal stimuli (i.e., C-cold fibers); noxious thermal and mechanical stimuli (i.e., C-mechano-heat fibers); and noxious thermal, mechanical, and chemical stimuli (C-polymodal). This heterogeneity has implications for injury-induced pain, as observations indicate that subpopulations of afferents may be far more important than others for the expression of specific pain syndromes. For example, mechanically insensitive afferents (MIAs) appear to be critical for the prolonged burning sensation associated with the application of capsaicin, the pungent component of chili peppers (7).

The most direct way to correlate the expression of sodium channel subtypes and the biophysical properties of sensory neurons is to record from these neurons in vivo; determine their biophysical characteristics, such as stimulus response

properties and action potential conduction velocity; then assess the Na^+ channels present in the neuron by immunohistochemical or molecular biological techniques. Djouhri, Lawson, and coworkers have used this approach to describe the populations of sensory neurons that express $Na_V1.7$ (8), $Na_V1.8$ (9), and $Na_V1.9$ (10). Characterization of sodium channel function in sensory neurons includes patch recording from teased fiber (11), isolated organ preparations (12), or by recording from the sensory neuron cell body in vitro. The most common of these is the isolated sensory neuron cell body preparation.

Based on data obtained in vivo, a number of criteria have been used to distinguish subpopulations of sensory neurons. These include cell body size (13), histological properties (14–20), chemosensitivity (14, 15), and electrophysiological properties (14, 15). Cell body size is used as a criterion based on data from cutaneous afferents indicating that there is a correlation between cell body size and action potential conduction velocity: Neurons with a small cell body diameter tend to give rise to slowly conducting axons, whereas neurons with a large cell body diameter tend to give rise to rapidly conducting axons (21–23). Thus, neurons with a small cell body diameter are considered putative nociceptors (i.e., conduct high threshold noxious input), whereas neurons with a large cell body diameter are considered likely nonnociceptive in nature. Electrophysiological properties may also be used to distinguish nociceptive from nonnociceptive afferents. Because all high-threshold afferents, whether they have rapidly or slowly conducting axons, have an inflection or "hump" on the falling phase of the somal action potential (24), neurons with a hump are likely to be nociceptive, and the converse is also true.

Voltage-Gated Sodium Channels in Sensory Neurons

Use of in situ hybridization and reverse transcriptase–coupled polymerase chain reaction (RT-PCR) techniques indicate that nine of the ten alpha subtypes (25, 26) and all three beta subtypes (27), plus the splice variant of beta 1, beta1A (28), of sodium channels are present in sensory neurons. Although $Na_V1.6$ and $Na_V1.7$ are present in virtually all sensory neurons, $Na_V1.1$, 1.2, 1.8, and 1.9 are differentially expressed among subpopulations of sensory neurons (25). $Na_V1.1$ is preferentially expressed in large-diameter sensory neurons, $Na_V1.8$ is highly expressed in small-diameter neurons and to a lesser extent in subpopulations of medium- and large-diameter neurons, whereas $Na_V1.9$ is only present in small-diameter neurons. $Na_V1.2$ is variably expressed among sensory neurons, with most cells lacking a detectable hybridization signal. $Na_V1.3$ (29) and 1.5 (26) are developmentally regulated such that they are highly expressed in embryonic sensory neurons, but expressed at very low levels in adult sensory neurons. $Na_V1.5$ appears to be present in less than 5% of sensory neurons in the adult rat.

Results from immunohistochemical studies indicate that VGSC subtypes are differentially distributed throughout the neuron. For example, $Na_V1.6$ appears to be the channel most highly localized to nodes of Ranvier (30), whereas $Na_V1.7$,

1.8, and 1.9 are not. In contrast, $Na_V1.7$ appears to be preferentially expressed in axon terminals (31), $Na_V1.8$ is preferentially expressed in the cell body and possibly the terminal arbor, whereas $Na_V1.9$ is expressed throughout neurons that give rise to unmyelinated axons (32). Finally, as discussed below, there is evidence that the cellular distribution of several of these channels changes following injury.

Electrophysiological characterization of VGSCs present in sensory neurons, in combination with the neurotoxin TTX, indicates that there are two general classes of current in sensory neurons: one is blocked by TTX (TTX-sensitive or TTX-S) and the other is insensitive to TTX (TTX-resistant or TTX-R). TTX-S currents are blocked by TTX at concentrations in the low nanomolar range. These VGSCs tend to have a low threshold for activation (between -55 and -40 mV), are rapidly activating, and are rapidly inactivating. Approximately 50% of these channels are available for activation at potentials close to resting membrane potential ($\sim$65 mV) (33). Most TTX-S currents present in sensory neurons recover from inactivation with a relatively slow time course. However, as discussed below, following nerve injury, there is an increase in the rate of recovery that appears to coincide with changes in the expression pattern of TTX-S VGSCs present in sensory neurons (34).

VGSCs that are TTX-R have been further subdivided into several different classes of ionic current on the basis of distinct biophysical properties. One of these TTX-R currents has similar biophysical properties to those of TTX-S channels, with a low threshold for activation and relatively rapid rates of activation and inactivation. This low-threshold TTX-R current has been referred to as TTX- R3 (35) or fast TTX-R current (36). An additional TTX-R current with very low thresholds for activation has also been described [i.e., TTX-R4 (36)]. A more recent analysis of the low-threshold TTX-R current in sensory neurons suggests that this current is carried by $Na_V1.5$ (26).

A second TTX-R current is resistant to TTX at concentrations >10 μM (33, 35, 37–39). This current has a high threshold for both activation (~-36 mV) and steady-state inactivation, activates and inactivates relatively slowly, but recovers from inactivation or reprimes rapidly (33). Furthermore, data from these studies show that this current accounts for the high activation threshold observed in nociceptive afferents. Because the current is still largely available for activation in the presence of sustained membrane depolarization and recovers from inactivation rapidly with membrane hyperpolarization, these properties suggest that this current can sustain low levels of activity when other channel subtypes are inactivated by the depolarization potential (39). This high-threshold TTX-R current has been referred to as TTX-R1 [(35), see also References 36, 40]. There is compelling evidence to suggest that $Na_V1.8$ underlies this high-threshold TTX-R current. Critically, the nuclear injection of $Na_V1.8$ cDNA into sensory neurons isolated from $Na_V1.8$ knockout mice results in the expression of a TTX-R current identical to TTX-R1 (41).

A third TTX-R current is also resistant to TTX at concentrations >10 μM. This current has very unique biophysical properties compared to the rest of the

family of VGSCs. It has a very low threshold for activation (between −90 and −70 mV) and an availability curve with a midpoint of ∼−44 mV (40). These two properties enable current activation over a large voltage range and can have a profound influence on neuronal excitability (42). This current has been referred to as a persistent current. Because the activation rate of this current is very slow, it is unlikely to contribute to the action potential but may contribute to the determination of the resting membrane potential and membrane depolarization associated with subthreshold stimuli (43). $Na_V1.9$ appears to be the channel underlying this persistent current because (*a*) there is a good correlation between the properties of neurons that express the persistent current and those that express $Na_V1.9$ (32, 40), (*b*) this current is detectable in dorsal root ganglia (DRG) neurons from $Na_V1.8$ knockout mice, and (*c*) the sequence of $Na_V1.9$ predicts a channel that will be resistant to TTX (44, 45).

Functional characterization of specific VGSCs in sensory neurons has been inhibited by the lack of selective channel blockers. Classic channel blockers, such as local anesthetics, antiepileptics, and membrane stabilizers, show little specificity among channel subtypes (46, 47). Although pharmacological tools do not yet enable a functional characterization of specific VGSCs in sensory neurons, several novel approaches in combination with available pharmacological tools have yielded important results. First, it is clear that TTX-S channels mediate action potential conduction along both myelinated and unmyelinated axons. This is based on the observation that TTX application to distal axons completely blocks conduction in the vast majority of studies reported to date (12, 24). Thus, even though there is evidence for functional TTX-R channels in axons (11), the density of these channels appears to be insufficient to mediate conduction in the majority (>92%) of unmyelinated and all myelinated axons (48). Given that rapid signaling of nociceptive stimuli requires action potential conduction, this observation illustrates a basis for the effectiveness of blocking TTX-S channels for pain control. Second, it is also clear that the TTX-R channel $Na_V1.8$ contributes to the somal action potential of high threshold sensory neurons in vivo (24). In the presence of sustained membrane depolarization, resulting in the inactivation of TTX-S, $Na_V1.8$ is sufficient to enable action potential generation in the majority of high-threshold afferents (49). However, as is more often the case, $Na_V1.8$ appears to work in conjunction with TTX-S currents in the generation of action potentials. In such cases, the higher threshold for activation and the slower rates of activation and inactivation enable $Na_V1.8$ to have a unique impact on the action potential waveform. TTX-R channels only contribute significantly to ion flux at later stages of the action potential, most importantly during the falling phase (50). At this stage, these channels appear to delay membrane repolarization enabling substantial Ca^{2+} influx. This Ca^{2+} influx has been shown to regulate a number of cellular processes and may be important for initiating transcriptional changes in nociceptive afferents in response to injury.

There is evidence that $Na_V1.8$ channels are present and functional in peripheral terminals of nociceptive afferents. Brock and colleagues used an in vitro

preparation to study corneal afferents (12, 51, 52). These investigators observed that TTX-R channels mediated action potential initiation in polymodal nociceptive afferents, and that these initiation sites are very close to, if not at, the terminal endings (51). Finally, there is evidence that TTX-R currents may contribute to the release of transmitter from the central terminals of nociceptive afferents. This evidence comes from an in vitro preparation utilized to study synaptic interactions between primary afferent and dorsal horn neurons (53). In this preparation, it appears that ATP released from the primary afferent terminal is able to act back on the afferent terminal to facilitate additional release of glutamate. Importantly, the additional glutamate release was dependent on active conduction in the afferent terminal that, in turn, was dependent on the activation of TTX-R channels in the afferent terminal.

SODIUM CHANNELS AND HYPERALGESIA

Somatic/Cutaneous Inflammatory Hyperalgesia

Tissue injury results in local inflammation. Pain is one of the cardinal signs associated with this inflammation, and this pain reflects an increase in the excitability of afferent neurons innervating the injured tissue. This increase in excitability reflects the actions of a number of inflammatory mediators, including ATP, bradykinin, serotonin, cytokines such as TNF alpha, and prostaglandins. That analgesic agents, such as the nonsteroidal antiinflammatory drugs (NSAIDs), act to inhibit the production of prostaglandins from arachidonic acid by blocking cyclo-oxygenases (COX) (54) and are highly efficacious in alleviating inflammatory hyperalgesia (55) suggests that prostaglandins are critical inflammatory mediators that promote pain.

The Effect of Prostaglandins on Sensory Primary Afferent

Prostaglandins are often described as a prototypic hyperalgesic agent because they produce hyperalgesia and/or nociceptor sensitization while producing little direct activation of nociceptive terminals. Prostaglandins have been shown to sensitize nociceptors to all modes of stimuli tested, including mechanical, thermal, and chemical. For example, a continuous infusion of prostaglandin E_2 (PGE_2) increased the frequency of bradykinin-evoked action potentials recorded from the plantar nerve (56) or from the saphenous nerve (57). Several lines of evidence suggest that prostaglandins sensitize primary afferent neurons through a direct action on the sensory neurons. This evidence includes (*a*) the presence of receptors on the sensory neurons, (*b*) time course for behavioral changes, (*c*) absence of other detectable changes in tissue, and probably most compelling, (*d*) the demonstration of sensitization of isolated neurons in vitro. Importantly, use of the isolated neuron in vitro has enabled identification of mechanisms underlying the actions of inflammatory mediators, such as prostaglandins.

The Effect of PGE_2 on Voltage-Gated Sodium Channels

PGE_2 modulates TTX-R sodium current in sensory neurons in a manner consistent with an underlying mechanism of sensitization; the current activates at more hyperpolarized potentials and the magnitude of the current is increased as are its rates of activation and inactivation (49). As discussed above, TTX-R sodium currents are essential for action potential generation in the majority of nociceptive neurons. Thus, the ability of PGE_2 to modulate the activity of these channels presents a highly effective mechanism by which PGE_2 can selectively enhance the excitability of the nociceptive neurons.

Support for a causal relationship between PGE_2-induced hyperalgesia and TTX-R sodium current has been provided by using an antisense deoxynucleotide (ODN) that specifically disrupts the synthesis ("knockdown") of one of the TTX-R VGSCs, $Na_V1.8$ in the DRG in vivo (58). Antisense, but not a control mismatch, ODN treatment reduces the expression of $Na_V1.8$ by $\sim$50%, and rats treated with the antisense ODN show a significant decrease in PGE_2-induced mechanical hyperalgesia (58). Because $Na_V1.8$ is normally expressed predominantly in unmyelinated, nociceptive C fibers, these data show that acute PGE_2- induced hyperalgesia is mediated by nociceptive C fiber activity that is sustained by TTX-R sodium current. The data also implicate $Na_V1.8$ as the critical VGSC subtype that is necessary for the initiation of hyperalgesia.

The Effect of Other Acute Inflammatory Mediators on Voltage-Gated Sodium Channels

To date, a number of acute inflammatory mediators, including adenosine (59), serotonin/5-hydroxytryptamine (5-HT) (60–62), bradykinin (57, 63), endothelin-1 (64–68), and plasma epinephrine (69), have also been demonstrated to directly modulate the excitability of primary afferents. Their direct action on primary afferent indicates that the receptors for these mediators must be expressed on nociceptive neurons. These mediators, with the exception of bradykinin (and possibly ET-1), have been shown to modulate the activity of TTX-R sodium current in a manner similar to that seen for PGE_2 (59, 60, 62, 64). Modulation of TTX-R sodium current thus appears to be a common mechanism that underlies the sensitizing effect of multiple inflammatory mediators.

Neurotrophic Factors and their Effect on Voltage-Gated Sodium Channels

In addition to the inflammatory mediators listed above, which act to alter the activity of VGSCs locally, there are a number of mediators that influence neuronal excitability by regulating gene transcription. The most extensively studied of these molecules, at least with respect to their role in nociceptive processing, include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell–derived neurotrophic factor (GDNF) and related factors. During development,

these compounds act as survival factors. In the adult, they appear to control the phenotype of sensory neurons. Because the concentration of these compounds, particularly that of NGF, is increased in the presence of inflammation, NGF is able to drive phenotypic changes in sensory neurons innervating the site of injury. Consistent with this suggestion is the observation that peripheral administration of NGF induces a localized, delayed hyperalgesia that is long lasting (70–72), suggesting that NGF induces the expression of proteins in the sensory neurons that enhance their excitability. There is evidence that NGF stimulates an upregulation of $Na_V1.8$ in small DRG cells as it enhances the density of TTX-R current in specific subpopulations of sensory neurons (73). In cultured neurons, NGF acutely enhances the excitability of small DRG neurons by enhancing TTX-R current (74). Thus, NGF may enhance nociceptive afferent excitability, in part, by exerting both an acute influence on the gating of TTX-R sodium current (its contribution from $Na_V1.8$ and/or $Na_V1.9$ has not been defined) and a prolonged influence by an increased expression of $Na_V1.8$. On the other hand, NGF has no effect on the expression of $Na_V1.9$ (75). Thus, the increase in TTX-R is likely to be due to the upregulation of $Na_V1.8$.

NGF also stimulates the synthesis of BDNF in DRG neurons positive for NGF receptors, i.e., trkA-positive cells (76). Thus, BDNF is a transmitter in afferent fibers. The function of BDNF has been derived mainly from CNS studies, where BDNF may induce long-term potentiation and may evoke neuronal excitation by activating a sodium current (77). It was shown recently that BDNF may stimulate $Na_V1.9$ through a direct interaction between its activated receptor, called trkB, and $Na_V1.9$ in the central nervous system (78). However, because BDNF has not been found to alter sodium currents in the DRG cells (79), it has yet to be determined whether such action plays any role in inflammatory hyperalgesia.

Experimental Models of Inflammatory Hyperalgesia

Although the pharmacological and in vitro approaches described above have provided compelling evidence that implicate TTX-R sodium channels as an underlying mechanism of nociceptive hypersensitivity, they do present the caveat that the concentrations used in the analyses may not be physiologically relevant (particularly the doses of neurotrophic factors). Thus, the role of TTX-R in inflammatory hyperalgesia has to be validated in experimental models that more closely resemble clinical conditions. A large literature has elucidated many of the mechanisms of cutaneous inflammatory hyperalgesia by employing animal models in which inflammation is induced, typically in a hind limb, by subcutaneous administration of a small amount of a chemical reagent that stimulates a local inflammatory response. The most common reagents used include formalin, carrageenan (a seaweed extract), or complete Freund's adjuvant (CFA). Although these reagents all cause local tissue damage as indicated by mast cell degranulation, neutrophil and macrophage infiltration, plasma extravasation, or tissue necrosis, the extent and the characteristics of the injury, as well as the duration of hyperalgesia, vary substantially among these models. Models of neurogenic inflammation have also been

developed by the local administration of algogenic substances, such as capsaicin, which activate the release of excitatory neurotransmitters (e.g., substance P) from peripheral nociceptive termini that, in turn, stimulate an immune response.

Collective data from these studies also support a role of TTX-R sodium channels in inflammatory hyperalgesia. First, carrageenan- as well as CFA-induced hyperalgesia give rise to a significant upregulation of TTX-R current (79, 80) and the expression of $Na_V1.8$ in the DRG cells (79, 81). Both carrageenan and CFA stimulate the production of NGF in immune cells (82, 83), suggesting that NGF production may be linked to the chemical-induced upregulation of $Na_V1.8$ (73, 84). Second, the use of antisense ODNs that specifically target $Na_V1.8$ to knockdown (i.e., reduce) the expression of this channel subtype in the lumbar DRG is effective in preventing the hyperalgesia measured four days after injection of CFA unilaterally into the rat hind paw (85). Similar results were obtained with an experimental model of urinary bladder inflammation, where knockdown of $Na_V1.8$ was effective in attenuating the persistent inflammation-induced sensitization of bladder C fibers (86). Thus, $Na_V1.8$ appears to contribute not only to the initiation of inflammatory hyperalgesia, but also to its maintenance.

Although the bulk of the data collected to date implicate a role for $Na_V1.8$ in inflammatory hyperalgesia, it should be noted that there is also evidence for contribution of other channels, including $Na_V1.9$ and $Na_V1.7$. Recent evidence suggests that $Na_V1.9$ also may be a target for modulation by inflammatory mediators, as the persistent current is dramatically increased following G-protein activation with the nonhydrolyzable GTP analog, GTPγS (42). The GTPγS-induced increase in persistent current was apparently sufficient to induce spontaneous activity in some neurons. Other lines of evidence implicating a protential role for $Na_V1.9$ come from studies involving neurotrophic factors and channel expression. Specifically, NGF and GDNF induce increase in $Na_V1.9$ expression (75). Evidence in support of a role for $Na_V1.7$ comes from the observation that a brief exposure of NGF results in a dramatic redistribution of the channel to peripheral terminals of sprouting axons (87). It is also worth noting that in at least one in vitro study designed to identify mechanisms underlying 5-HT-induced increases in excitability, an increase in a TTX-S current was observed in some neurons (60).

SODIUM CHANNELS IN NEUROPATHIC PAIN

VGSCs in sensory neurons are thought also to play a critical role in a number of chronic, painful neuropathies that arise from injury to peripheral nerves. Symptoms of neuropathic pain include abnormal hypersensitivity to innocuous touch (allodynia) and noxious mechanical or thermal stimulation (hyperalgesia). Clinical neuropathic pain is often intractable and can arise from a variety of disease states (e.g., diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, AIDS) or traumatic injuries, nerve compression, or chemotherapy.

It has long been appreciated that physical injury to peripheral nerves (e.g., sciatic nerve branches that innervate the foot) that is mimicked experimentally by

transection of the nerves' axon, results in rapid redistribution of VGSCs along the axon and dendrites, and spontaneous firing of the injured nerve (88, 89). The alteration in the excitability of the injured nerve is considered to be critical for the incidence of spontaneous pain in the absence of external stimuli (90). As the activity of VGSCs is necessary for action potential generation in all neurons, the changes in VGSCs associated with a transected nerve implicate a role of VGSCs in the hyperexcitability of the injured nerve.

It is well established that both TTX-R and TTX-S sodium currents are altered upon nerve transection, based on functional and gene expression analysis (44, 91–95). However, the relationship between changes in channel expression and changes in neuronal excitability is tenuous. A recent study involving transection of the vagus neurons demonstrates that axotomy-induced changes in TTX-R and TTX-S currents result in a decrease in excitability (96). Furthermore, given that partial nerve injuries are the ones most commonly associated with the development of pain, the relevance of the nerve transection model to clinical conditions of neuropathic pain arising from injury to peripheral nerve is less clear. However, data from other experimental models of peripheral nerve injury, as well as pharmacological evidence, suggest that the VGSC is a reasonable target for the treatment of neuropathic pain (see below). We limit our discussion to findings obtained from the models of surgically induced injuries to the sciatic nerve (97–101) because they represent the most commonly used models from which our current state of knowledge on the VGSC in neuropathic pain has been derived.

TTX-S and TTX-R Sodium Currents in Neuropathic Pain

The first sciatic nerve injury model involves a complete transection of the sciatic nerve. Because the sciatic nerve is comprised of afferents with cell bodies mainly in L4 and L5 ganglia, such an injury directly damages ∼50% of the neurons in each ganglion. Such injury induces a rapid (days) onset of spontaneous, ectopic discharge from the site of injury, which, unlike activities observed in the presence of inflammation, is primarily carried by rapidly conducting A fibers. In a partial nerve injury model where only the L5 or the L5 and L6 spinal nerves are transected or tightly ligated, similar changes in the A fiber activity are restricted to the injured DRG (102–105) but not among the population of uninjured afferent from L4 (105). In the injured DRG, a significant upregulation of TTX-S current and a reduction in the TTX-R current in the small DRG are observed (34, 48). The increase in TTX-S is thought to be due to an enhanced expression of the channel subtype $Na_V1.3$, which is normally expressed at very low levels in the DRG of adult rats (29, 92, 106). The downregulation of TTX-R in the small DRG is due to decreased expression of the $Na_V1.8$ and $Na_V1.9$ subtypes (44, 94, 95).

$Na_V1.3$, Ectopic Discharge, and Neuropathic Pain

The evidence that supports a role for $Na_V1.3$ in mediating ectopic activity in the injured neurons is based on the following observations: First, the channel is

dramatically upregulated following nerve injury; second, the biophysical properties of the channel should enable the channel to support higher rates of activity; and third, nerve injury is associated with an increase in membrane potential oscillations that appear to underlie spontaneous activity, and these oscillations are TTX-S. Ectopic discharge (and thus $Na_V1.3$ expression) has been proposed to underlie neuropathic pain because the time course for the development of membrane potential oscillations and ectopic activity correlates very well with the time course for the development of neuropathic pain behavior. Furthermore, the ectopic activity can be suppressed by sodium channel blockers such as lidocaine, which is clinically effective in treating neuropathic pain (see below). A recent study using pharmacological doses of GDNF to prevent sensory hypersensitivity in nerve-injured rats showed that this effect was concomitant with a block of A fiber ectopic discharge and normalization of $Na_V1.3$ expression in the injured DRG (105).

On the other hand, lidocaine blocks all VGSCs and is not selective for $Na_V1.3$, whereas GDNF normalizes the nerve injury-induced changes in the expression of many other proteins besides $Na_V1.3$ in the DRG and spinal cord (107); thus, these drugs lack the target specificity to provide a definitive link between $Na_V1.3$ expression and neuropathic pain. Furthermore, $Na_V1.3$ is a TTX-S channel, but TTX applied to the injured nerve only partially reverses neuropathic pain behavior (108).

Some data also question whether $Na_V1.3$ expression alone is sufficient for the onset of ectopic activity (e.g., the channel is upregulated in small DRG neurons, but they do not become spontaneously active) (96, 102, 105). The role of ectopic discharge in the manifestation of neuropathic pain is also not clear. Ectopic activity is exclusively associated with transected fibers, which are incapable of transmitting evoked sensory input. Neuropathic pain states, on the other hand, are generally measured in animal models as diminished response thresholds from evoked stimulation. Furthermore, in at least one experimental nerve injury model, ectopic activity of the injured fibers is highest soon after injury, but is significantly diminished within one week by almost 75% (103), whereas neuropathic pain behavior in the injured animal is maintained at the same level for many months (104, 109). There is also a growing body of evidence implicating a role of the remaining uninjured primary afferent of the sciatic nerve in maintaining sensory hypersensitivity (see below). Thus, ectopic activity of the injured neurons may be insufficient for the manifestation of neuropathic pain, at least as measured routinely in experimental models.

$Na_V1.8$ and Neuropathic Pain

A knockdown of $Na_V1.8$ in neuropathic rats in a model of mononeuropathy (L5/L6 spinal nerve ligation injury) effectively reverses neuropathic pain, bringing the sensory thresholds to thermal and tactile stimuli back to control levels (48, 110). This approach provides direct evidence that the activity of a sodium channel subtype in the sensory primary afferent is necessary for the expression of neuropathic pain.

It also suggests that primary afferent fibers that contain functional $Na_V1.8$ after nerve injury may be "sensitized." The important role of $Na_V1.8$ in action potential generation and the additional observation that this channel subtype also enables the DRG cells to fire repetitively upon stimulation provide functional evidence to support such a hypothesis (111).

As mentioned above, injured primary afferents show a significant downregulation of $Na_V1.8$; thus, the site of action of $Na_V1.8$ is not likely to be in the injured nerve fibers. In the adjacent uninjured L4 DRG cells, however, the level of expression of $Na_V1.8$ (95) and the density and kinetics of the TTX-R current (48) are not different from control, suggesting that the expression of $Na_V1.8$ is maintained. However, a significant upregulation of the channel protein is apparent by day 2 after injury in the sciatic nerve (48). The upregulation of $Na_V1.8$ immunoreactivity is correlated with an increase in TTX-R compound action potential at C fiber conduction velocity. A minor TTX-R, A fiber conduction velocity is also evident. These data demonstrate a functional reorganization of $Na_V1.8$ along unmyelinated fibers and in some myelinated fibers. Antisense mediated knockdown of $Na_V1.8$ immunoreactivity and TTX-R current in these uninjured axons correlate with the reversal of both mechanical and thermal hypersensitivity, suggesting that this reorganization of $Na_V1.8$ activity along the uninjured axons may be necessary for expression of neuropathic pain in the injured rat (48). These as well as other data (112, 113), argue that abnormal activity in the uninjured primary afferent may be critical for the observed hypersensitivity to sensory input in the injured animal. A redistribution of $Na_V1.8$ along the injured sciatic nerve has been also observed in the chronic constriction injury model of neuropathic pain (114), and $Na_V1.8$ immunoreactivity is evident in peripheral nerve tissues from patients with chronic neuropathic pain (115, 116).

The use of antisense oligonucleotides to disrupt the expression and function of $Na_V1.8$ has also been applied to other models of chronic inflammatory and visceral pain (85, 86). These findings further substantiate the role of $Na_V1.8$ in the hypersensitivity of primary afferent neurons, suggesting that the changes in $Na_V1.8$ seen in the L5/L6 spinal nerve injury model may have wider implications and potential clinical relevance.

Transgenic mice lacking $Na_V1.8$ provide an alternative animal model to evaluate the role of $Na_V1.8$ in neuropathic pain (41). Nerve injury elicits thermal hyperalgesia and tactile hypersensitivity by day 3 in both wild-type and $Na_V1.8$-null mutant mice, suggesting that neuropathic pain is developed and maintained despite the lack of $Na_V1.8$ (117). An important confounding factor in the interpretation of the behavioral data in these animals, however, is the uncertain phenotype of the peripheral nervous system of these mice. The $Na_V1.8$-null mutant mice exhibit an upregulation of TTX-S $Na_V1.7$ in the C type DRG neurons and modified activity of the C fibers (41). Other changes that may not be in common with the wild-type control after nerve injury may also occur. Complete elimination of the TTX-R current carried by $Na_V1.8$ has a profound effect on the conductance of other channels, including sodium channel subtypes, the emergence of non-Na^+ action potentials,

and calcium channel activity (111). How these biophysical characteristics may influence the neurons' response to nerve injury is not known, making interpretation of data from this transgenic model difficult.

$Na_V1.9$ and Neuropathic Pain

To date, there is little data implicating a role for $Na_V1.9$ in neuropathic pain. In fact, there are two lines of evidence to suggest the channel contributes little to these behavioral changes. First, based on the kinetic properties of this channel and computer analysis, it has been proposed that this channel is active at the resting membrane potential and may modulate the resting potential of nociceptors and their response to subthreshold stimuli (43). However, under conditions of persistent excitability, most of these channels will be in the inactivated state and not available for opening. Second, antisense oligonucleotide that targets $Na_V1.9$ shows that a knockdown of this channel subtype produces no effect on either thermal hyperalgesia or tactile hypersensitivity in the neuropathic rat (85). The antisense treatment in sham-operated rats also does not show any effect on baseline sensory thresholds.

SODIUM CHANNEL BLOCKERS AS ANTIHYPERALGESIC DRUGS

As mentioned above, a prominent role for VGSCs in the pathophysiology of an injured neuron is supported by the clinical effectiveness of agents that act primarily through a common, use-dependent block of sodium channels, e.g., local anesthetics, type 1b antiarrhythmics, and anticonvulsants (118), in the treatment of many types of chronic, in particular, neuropathic pain (119, 120).

Local Anesthetics/Antiarrhythmics

Although local anesthetic drugs have been considered as alternative therapy in certain types of acute pain (121–125), the predominant focus has been on chronic neuropathic pain syndromes, particularly because many of these appear unresponsive to treatment with standard opioids and nonsteroidal antiinflammatory drugs (119, 120). Local anesthetics have been reported to provide effective relief in painful diabetic polyneuropathy (126–128), neuralgic pain (129–132), lumbar radiculopathies (133, 134), complex regional pain syndrome (CRPS) I and II (135–137), and traumatic peripheral nerve injuries (138–141). A caveat, however, is that the majority of these studies represent clinical series and case reports, whereas only a comparatively small number involve randomized, single or double blind, placebo-controlled trials (142). Moreover, despite this capability for achieving efficacy in many different chronic, intractable pain conditions, the full analgesic potential of these agents has been frequently limited by the onset of numerous adverse, particularly CNS-related, side-effects, e.g., nausea and emesis, dizziness

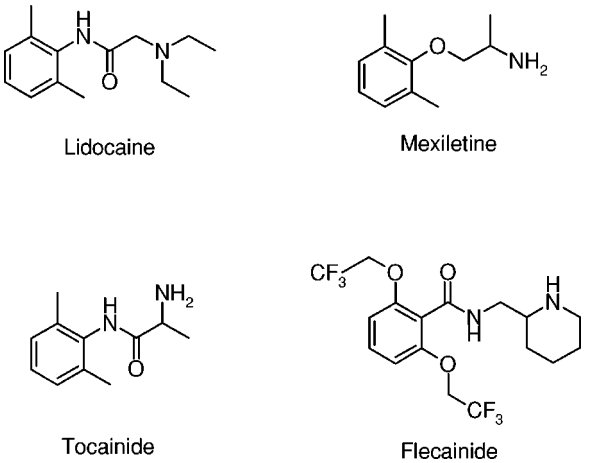


Figure 2 Local anesthetic/type 1b antiarrhythmic drugs used as analgesics.

and light-headedness, somnolence, ataxia, and tinnitus. Cardiotoxicity can also be problematic particularly in the elderly population (143).

Intravenous lidocaine (Figure 2) is by far the most prevalent local anesthetic used for the treatment of neuropathic pain. In addition to the routine acute effect, it has been reported to produce pain relief for several days, an effect that far outlasts drug elimination from the plasma (128, 144, 145). The mechanism(s) related to this phenomenon are presently unknown. Other local anesthetics (see Figure 2) that have been used include flecainide (146, 147) and the oral agents tocainide (129) and type Ib antiarrhythmic agent, mexiletine (127, 139). Mexiletine, in particular, has been used relatively successfully either as a monotherapy or sequentially following an initial lidocaine infusion. Indeed, IV lidocaine has been increasingly advocated as a diagnostic aid for the presence of pain associated with nerve injury (132, 148) and for its predictive value of potential analgesic efficacy of oral local anesthetic agents, such as mexiletine for follow-up therapy (138, 141).

In animal models of neuropathic pain, the local anesthetics appear to have a similar profile to the clinical experience, being effective against mechanical and/or thermal hyperalgesia and tactile and/or cold allodynia but with differential sensitivity and limited efficacy (149–155). In most cases, the ceiling for the analgesic effect was almost always associated with the appearance of side effects, e.g., sedation; loss of righting reflex; and, at high doses, convulsions. In another model representative of facilitated processing of sensory information, the formalin test, lidocaine (149) and mexiletine (153) attenuated both phases of the behavioral response. A critical aspect of the local anesthetic analgesic action is the ability, at low subanesthetic (therapeutic) concentrations, to block the spontaneous and/or evoked repetitive, ectopic impulse activity in afferent fibers that is mediated by both TTX-S and the slowly inactivating TTX-R sodium channels (156–160).

Lidocaine can suppress the generation of this abnormal impulse traffic and restore normal firing rhythm by acting either directly at the site of origin or at distant sites (156–160). Consequently, these agents are able to target injured nerves on the basis of their high-frequency, repetitive firing characteristics, while having minimal impact on normal, somatosensory (i.e., nociceptive) neuronal function.

Anticonvulsants

Since Trousseau in 1885 noted that the paroxysmal component of trigeminal neuralgia was remarkably similar to epilepsy and termed it epileptiform neuralgia, anticonvulsant drugs (see Figure 3) have become among the more commonly used pharmacological interventions for the treatment of chronic pain (for reviews, see 161–163). It has been a common perception, possibly influenced by these early reports, that drugs of this class provide effective and sustained relief only when there is a paroxysmal, lancinating component to the pain, e.g., trigeminal neuralgia (164, 165). Although neuralgic pain remains a primary indication, carbamazepine and, to a more variable extent, diphenylhydantoin (also known as phenytoin) can also be effective analgesics in other types of painful, peripheral neuropathies, such as diabetic neuropathy (166–168). When effective, the general clinical impression of the established anticonvulsants has been that pain relief is almost always obtained concomitantly with numerous adverse side effects (164–166) and/or limitations in efficacy (165, 167). The adverse side-effect profile of these anticonvulsants can be severe and frequently includes CNS effects, such as dizziness, ataxia, lightheadedness, somnolence, and alterations in mood. Hepatic dysfunction and leukopenia have also been reported to occur with carbamazepine. The marginal analgesic efficacy of phenytoin and, to a lesser extent, carbamazepine at doses not associated with side effects is also reflected in most experimental animal models of peripheral nerve injury (150) and inflammation (169).

Recent years have seen the emergence of several novel antiepileptic agents, exemplified by lamotrigine (170), which may also have utility in the treatment of chronic pain but with a much improved therapeutic margin of safety over the established drugs, despite the possible need for higher doses than those required for anticonvulsant activity. Lamotrigine (Figure 3) produces a voltage- and

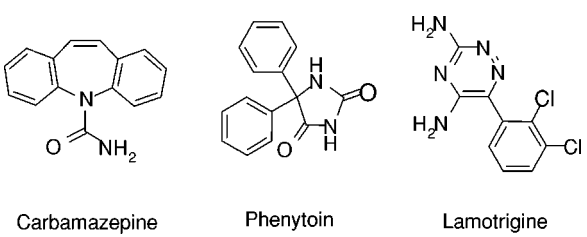


Figure 3 Anticonvulsant drugs used as analgesics.

frequency-dependent block of sodium channels with a subsequent reduction in the presynaptic release of the excitatory amino acids glutamate and aspartate (171, 172). Currently in Phase III trials for neuropathic pain, lamotrigine has been reported to show a promising analgesic effect in trigeminal neuralgia (173); diabetic neuropathy (174); and either postherpetic neuralgia, causalgia, or phantom limb pain (175). However, in a further randomized, double-blind, placebo-controlled study of intractable neuropathic pain, lamotrigine was found to be ineffective (176). Lamotrigine has been found to produce an antihyperalgesic and antiallodynic effect in the rodent models of neuropathic and/or inflammatory pain (169, 177–179), although the effect does appear to be modality specific. In acute pain models, lamotrigine appeared ineffective against an acute, high-threshold thermal noxious stimulus (177, 178), implying a selective interaction with pathways associated with pathophysiological events rather than with normal sensory nociceptive function consistent with its use-dependent block of sodium channels.

Voltage-Gated Sodium Channels in Sensory Neurons as Targets of Local Anesthetics and Anticonvulsants

A principal target of local anesthetic and anticonvulsant drugs in the most prevalent forms of neuropathic pain is most likely the sodium channels located in the peripheral sensory neuron. These channels may play an important role not only in the initial injury discharge but also in spontaneous, ongoing, and stimulus-evoked pain, and dysesthesias characteristic of many types of peripheral neuropathies. In clinical studies, lidocaine applied topically to either the skin (131, 180), region of the nerve supplying the painful foci (145, 181, 182), or neuroma (140) produced complete relief of spontaneous, ongoing, and stimulus-evoked pain. Moreover, in animal models of inflammatory and neuropathic pain, local application of bupivacaine produced a reversal of mechanical hyperalgesia (183) and allodynia (184), respectively. These studies would suggest, therefore, that in chronic pain of inflammatory or neuropathic origin, blockade of sodium channels in the sensory neurons constitutes an important site of action for the antihyperalgesic actions of these drugs.

CONCLUDING REMARKS

In summary, TTX-R sodium current is essential in the establishment of hyperexcitability of sensory neurons that contribute to inflammatory hyperalgesia and nerve injury-induced pain. Data support $Na_V1.8$ as the predominant channel involved in gating this sodium current. It remains to be determined whether selective blockade of either $Na_V1.8$ and/or $Na_V1.9$ or, alternatively, any of the TTX-S channels in peripheral sensory neurons will produce either an improvement in analgesic efficacy or the therapeutic window over currently available nonsubtype selective agents. However, the discrete localization of the TTX-R channels, in particular

$Na_V1.8$, may be the crucial factor in providing a novel opportunity for drugs targeted at these channels to achieve both the desired degree of analgesic efficacy and safety profile.

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