Ion channels in nociceptors

Recent developments

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Nociceptors are specialized high-threshold sensory afferents from dorsal root ganglion (DRG) or other primary sensory (e.g., trigeminal) neurons that innervate the skin, muscle, joints, and viscera and respond to noxious or potentially damaging stimuli. Nociceptors express a unique repertoire of voltage-gated sodium (Na^+) channels (Na_v), potassium (K^+) and calcium (Ca^{2+}) channels, as well as cation channels of the transient receptor potential (TRP), acid-sensing ion channel (ASIC), and purinergic P2X families. These channels are responsible for the basic properties of nociceptors, including the lack of spontaneous activity and high threshold of activation. Products of inflammation or axonal injury trigger changes in the expression and function of these channels, resulting in increased excitability (reduced threshold of activation) of nociceptors. This process, known as peripheral nociceptor sensitization, manifests with spontaneous nociceptor activity (resulting in spontaneous pain), increased responsiveness and size of receptor fields for noxious stimulation (primary and secondary hyperalgesia), and nociceptor responses to innocuous mechanical or thermal stimuli (allodynia). These features characterize neuropathic and inflammatory pain. The wide variety of chemical signals that elicit nociceptor sensitization act via several types of receptors expressed in nociceptors, including G-protein-coupled receptors and tyrosine kinase receptors, which affect the expression or sensitivity of cation channels, particularly $Na_v1.7$, $Na_v1.8$, $Na_v1.9$, TRP vanilloid 1 (TRPV1), and TRP ankyrin 1 (TRPA1) channels. Gain-of-function mutations affecting these channels are linked to familial syndromes characterized by episodic pain sporadic painful small fiber neuropathies (SFN); loss-of function mutations are associated with congenital insensitivity to pain. There are extensive and excellent reviews on all these subjects.[1–15]

GENERAL FEATURES OF NOCICEPTORS

Functional diversity. Nociceptors are unencapsulated endings of small myelinated (Aδ) or unmyelinated (C) axons from small DRG and other sensory (e.g., trigeminal) ganglia. The primary neurotransmitter in all nociceptors is L-glutamate. The central projections from these first-order nociceptive neurons terminate primarily in the dorsal horn. Nociceptors constitute a heterogeneous population, both from the functional and neurochemical standpoints. There are 2 main groups of nociceptors. Medium diameter myelinated (Aδ) afferents mediate acute, well-localized "first" or fast pain; small diameter unmyelinated "C" fibers convey poorly localized, "second" or slow pain. Electrophysiologic studies have further subdivided Aδ and C nociceptors into several classes. Aδ nociceptors include type I high threshold mechanical (HTM) nociceptors that respond to both mechanical and chemical stimuli but have relatively high heat thresholds (>50°C), and type II HTM that have a much lower heat threshold but a very high mechanical threshold. Unmyelinated C fibers are highly heterogeneous. Most are polymodal and are referred to as heat and mechanically sensitive C-afferents; others include C-heat nociceptors and C-mechano-cold nociceptors. There is a population of C-fiber nociceptors that is insensitive to mechanical stimuli in the absence of tissue inflammation; these silent or mechanically insensitive afferents constitute

GLOSSARY

$5\text{-}HT_3R$ = $5\text{-}HT_3$ receptor; **12-HPETE** = 12-hydroperoxyeicosatetraenoic acid; **ASIC** = acid-sensing ion channel; **ATP** = adenosine triphosphate; **BDNF** = brain-derived neurotrophic factor; **CGRP** = calcitonin gene-related peptide; **DRG** = dorsal root ganglion; **GDNF** = glial-derived neurotrophic factor; **HCN** = hyperpolarization-activated cyclic nucleotide-gated; **HTM** = high threshold mechanical; **IE** = inherited erythromelalgia; **K_{ATP}** = adenosine triphosphate–gated K^+ channel; **Mrg** = mas-related G-coupled protein receptor; **Na_v** = voltage-gated sodium (Na^+) channel; **NGF** = nerve growth factor; **PEPD** = paroxysmal extreme pain disorder; **PIP_2** = phosphatidylinositol 4,5 biphosphate; **PLC** = phospholipase C; **SFN** = small fiber neuropathy; **Slack** = sequence like a Ca^{2+}-activated K^+ channel; **TASK1** = 2-pore, acid-sensitive K^+ channel; **TLR** = Toll-like receptor; **TMEM16** = transmembrane protein 16; **TRAAK** = 2-pore weak inwardly rectifying K^+ channel-related arachidonic acid–stimulated K^+ channel; **TREK1** = 2-pore weak inwardly rectifying K^+ channel-related potassium channel-1; **TRESK** = 2-pore weak inwardly rectifying K^+ channel-related spinal cord K^+ channel; **TRP** = transient receptor potential; **TRPA1** = transient receptor potential ankyrin 1; **TRPM8** = transient receptor potential melastatin 8; **TRPV1** = transient receptor potential vanilloid 1; **TWIK1** = 2-pore weak inwardly rectifying K^+ channel.

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approximately 15%–20% of cutaneous C-fiber afferents in the human skin. Approximately 5% of C-fibers are "itch" fibers; they respond to histamine and other pruritogens but are insensitive to mechanical stimuli.[16] Studies in vitro show that most small or medium human DRG neurons can be classified as nociceptors; they respond directly to stimuli that elicit pain (e.g., adenosine triphosphate [ATP]) or itch (e.g., histamine) and are activated or sensitized by inflammatory mediators (such as bradykinin or prostaglandin E_2).[17] Microneurographic recordings from individual unmyelinated C fibers in humans allow functional differentiation based on electrophysiologic properties. Nociceptors exhibit pronounced activity-dependent hyperpolarization and reduced conduction velocity in response to repetitive stimulation; this property separates C-polymodal, C-cold, and C-mechano-insensitive fibers[18] and characterizes their different responses to lidocaine[19] and other properties.

BIOCHEMICAL DIVERSITY Nociceptors, particularly C fibers, also differ in their biochemical phenotype. There is a peptidergic population of C nociceptors that synthesizes substance P and calcitonin gene-related peptide (CGRP) and expresses the tyrosine kinase A receptor for nerve growth factor (NGF) as well as TRPV1 and TRPA1 channels (figure). A nonpeptidergic population of C nociceptors expresses the c-Ret receptor for glial-derived neurotrophic factor (GDNF), the IB4 isolectin, and $P2X_3$ receptors. A specific population of nonpeptidergic nociceptive DRG neurons selectively respond to histamine and other pruritic chemicals; these itch neurons express G-protein-coupled receptors of the mas-related G-coupled protein receptor (Mrg) family, particularly MrgA3.[20] However, this subdivision is an oversimplification, as they are several examples of DRG neurons with overlapping phenotypes.[1,2]

Efferent function of nociceptors. Peptidergic nociceptors, in addition to conveying afferent input to the dorsal horn, also have an efferent function (they have been referred to as sensorimotor nerves). They antidromically release substance P and CGRP in a Ca^{2+}-dependent fashion; these neuropeptides have an important role both in maintenance of normal function and in response to tissue injury. Substance P and CGRP released at the site of tissue injury trigger vasodilation, increased vascular permeability, and release of local mediators (autacoids) from mastocytes and other cells. This response is referred to as neurogenic inflammation.

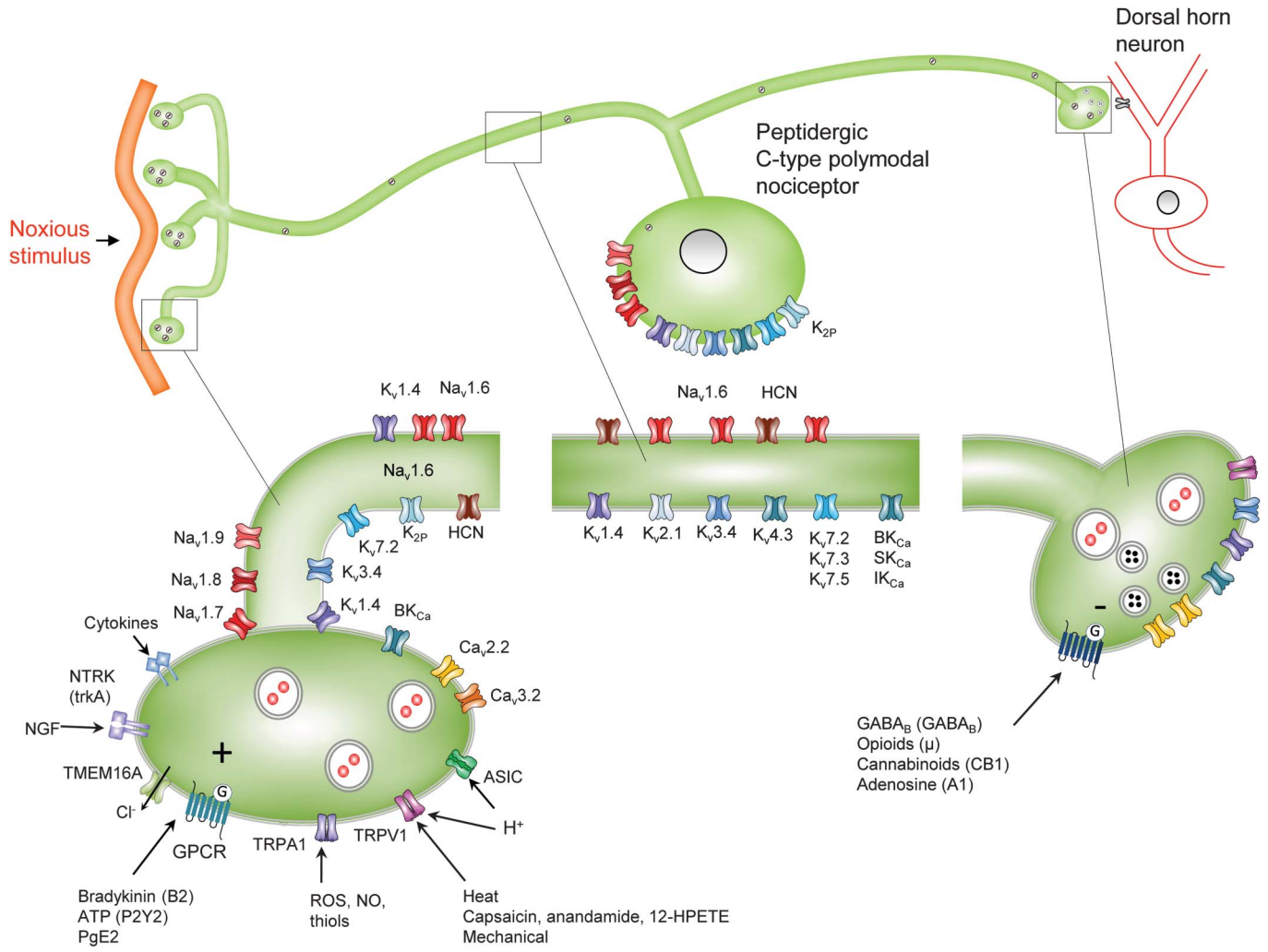
CHANNELS CONTROLLING EXCITABILITY OF NOCICEPTORS Nociceptors express a unique repertoire of ion channels (table 1).

Voltage-gated sodium channels. Several Na_v channels are key determinants of nociceptor excitability. They include $Na_v1.7$ (encoded by the *SCN9A* gene), $Na_v1.8$ (encoded by the *SCN10A* gene), and $Na_v1.9$ (encoded by the *SCN11A* gene).[15] $Na_v1.7$ is expressed in both large and small diameter DRG neurons, as well as in sympathetic ganglion neurons and olfactory sensory neurons.[4] In nociceptors, $Na_v1.7$ is present in the soma and axons of peptidergic and nonpeptidergic nociceptive DRG neurons, including their peripheral terminals (epidermal nerve fibers) and central terminals in the dorsal horn.[4,21] $Na_v1.7$ produces a low threshold, rapidly activating and inactivating current that has slow recovery from inactivation. This allows the channel to produce a substantial current in response to small, slow depolarizations (ramp current); this boosts subthreshold stimuli and increases nociceptor probability to reach threshold for action potential firing.[22,23] In a subset of DRG neurons, $Na_v1.7$ may also produce resurgent currents that support burst firing repolarization following a strong depolarization.[4] $Na_v1.8$ has higher threshold of activation than $Na_v1.7$ but carries most (80%–90%) of the current underlying the depolarization phase (upstroke) of the action potential in C-type DRG neurons.[24]

$Na_v1.8$ mediates a current that is slowly inactivated by depolarization; this supports repetitive firing of DRG neurons in response to sustained depolarization.[24] $Na_v1.9$, which is almost selectively expressed in small DRG neurons, has a hyperpolarized voltage dependence of activation close to the resting membrane potential, a slow gating kinetics, and a broad overlap between activation and steady-state inactivation.[25] $Na_v1.9$ may produce a persistent Na^+ current that amplifies the response of nociceptors to subthreshold depolarizing inputs.[25]

Potassium channels. Nociceptors express different subtypes of K^+ channels. They include several types of voltage-gated K^+ channels (K_v), 2-pore K^+ channels (K_{2P}), Ca^{2+}-activated K^+ channels (K_{Ca}), Na^+-activated K^+ channels (K_{Na}), and, to a lesser extent, inward rectifying K^+ channels (K_{ir}).[5,6] These channels dampen the excitability of nociceptors. K_v channels regulate resting membrane potential; action potential threshold, shape, firing frequency and adaptation; and neurotransmitter release. For example, $K_v1.1$ is activated at modest membrane depolarizations and mediates slowly inactivating, delayed-rectifier type currents responsible for action potential repolarization. $K_v2.1$ primarily influences membrane repolarization and interspike hyperpolarization during repetitive firing; $K_v3.4$ mediates a rapidly inactivating current that accelerates repolarization and may restrict Ca^{2+}-dependent neurotransmitter release at the level

Figure Ion channels in peptidergic-C-fiber nociceptors



Nociceptors, particularly C fibers, are highly heterogeneous. A peptidergic population of C nociceptors express substance P and calcitonin gene-related peptide in addition to L-glutamate, which is their primary neurotransmitter. Other markers of these peptidergic C-nociceptors are the tyrosine kinase A (TrkA) receptor for nerve growth factor (NGF) and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) and ankyrin 1 (TRPA1) channels. Nociceptors also express a unique repertoire of voltage-gated sodium (Na_v) and calcium (Ca_v); a wide variety of potassium (K^+) channels, including voltage-gated (K_v), calcium (Ca^{2+})-activated (K_{Ca}), and 2-pore (K_{2P}) channels; acid-sensitive cation channels (ASIC); hyperpolarization-activated cyclic nucleotide-gated (HCN) channels; and Ca^{2+}-activated chloride (Cl^-) channels of the transmembrane protein 16 (TMEM16) family. The activity of these channels is regulated by products of inflammation, including protons (H^+), prostaglandin E_2 (PGE_2), adenosine triphosphate (ATP), and bradykinin, acting via their respective G-protein-coupled receptors (GPCRs) via G_q- or G_s-triggered pathways. As well as cytokines, NGF, reactive oxygen species (ROS), nitric oxide (NO), and 12-hydroperoxyeicosatetraenoic acid (12-HPETE) also directly sensitize TRPV1 and TRPA1 channels. Neurotransmitter release at the level of the dorsal horn is negatively regulated by several signals acting via Gi/o coupled receptors, including γ-aminobutyric acid (GABA), opioids, cannabinoids (CB1 receptors), and adenosine (A1 receptors).

of the dorsal horn. $K_v1.4$ and K_v 4.3 activate and inactivate rapidly and mediate A-type currents that limit action potential threshold, duration, and firing frequency. K_v7 channels (including $K_v7.2$, $K_v7.3$, and $K_v7.5$) are enriched in the axon initial segment and peripheral terminal of nociceptors; they open near resting membrane potential and mediate a low threshold noninactivating M (for muscarinic receptor modulated) current (I_M) that acts as a voltage clamp that stabilizes the resting membrane potential and regulates both action potential threshold and accommodation within action potential trains.

The K_{Ca} channels provide a feedback inhibition that slows repetitive firing frequency (spike frequency adaptation) and limits Ca^{2+} influx at nerve terminals. Among these channels, the BK_{Ca} (big conductance) channel is activated both by intracellular Ca^{2+} and depolarization and may be particularly relevant due to functional coupling with TRPV1 channels in nociceptors.[26] The K_{Na} channel Slack (sequence like a Ca^{2+}-activated K^+ channel) is responsible for a delayed outward current that contributes to a long-lasting slow hyperpolarization that follows repetitive firing and regulates neuronal excitability and

Table 1 Ion channels in nociceptors

Channel	Function	Comments (including findings in experimental models)
$Na_v1.7$	Threshold channel; large ramp current that amplifies subthreshold stimuli	Also expressed in sympathetic ganglia and olfactory neurons; upregulated in the setting of inflammation and nerve injury
$Na_v1.8$	Most of the current underlying the action potential; supports repetitive action potential firing	Upregulated by NGF in the setting of accumulation at site of axonal injury
$Na_v1.9$	Slow activation at voltage close to the RMP and ultraslow inactivation; amplifies and prolongs small subthreshold depolarizations and depolarizes the RMP	Downregulated in axonal injury; activated in response to inflammatory mediators
$K_v1.1$	Mediates slowly inactivating, delayed-rectifier currents responsible for action potential repolarization	Downregulated in axon injury; forms a complex with CASPR2 that is target of autoantibodies
$K_v2.2$	Influences membrane repolarization and interspike hyperpolarization during repetitive firing	Downregulated after nerve or oxaliplatin-induced injury
$K_v3.4$	Rapidly inactivating current that accelerates repolarization and may restrict Ca^{2+}-dependent neurotransmitter release	Downregulated in axon injury and diabetic neuropathy
$K_v4.3$, $K_v1.4$	Fast activation and inactivation; mediate A-type currents that limit action potential threshold, duration, and firing frequency	Downregulated in the setting of injury via REST
K_v7 ($K_v7.2$, $K_v7.3$, and $K_v7.5$)	Open near RMP and mediate a low-threshold noninactivating M current that stabilizes the RMP and regulates action potential threshold and accommodation	Downregulated in the setting of injury via REST; activated by retigabine and flupirtine
K_{Ca}	Activated by $Ca2^+$ accumulated during neuronal firing; provides a feedback inhibition that slows repetitive action potential firing; BK_{Ca} is functionally coupled to TRPV1	Reduced expression after axotomy; inhibited by PGE2 and other inflammatory mediators
K_{Na}	Na^+-activated K^+ channel that contributes to a long-lasting slow hyperpolarization that follows repetitive firing	Downregulated by internalization during inflammation
K_2P	Constitutively open; generates background "leak" current that stabilizes the RMP below firing threshold	TRESK downregulated in axon injury; TASK downregulated during inflammation
$Ca_v1.2$ (L)	May contribute to nociceptor excitability and peripheral release of neuropeptides	Upregulated after axotomy; mediates neuropathic pain
$Ca_v2.2$ (N)	Located in presynaptic terminals and triggers release of glutamate, substance P, and CGRP both at central and peripheral terminals of nociceptors	The $\alpha2\delta$ subunit increases membrane expression of the $\alpha1$ subunit, is upregulated in inflammatory and neuropathic pain, and is the target of gabapentin and pregabalin
$Ca_v3.2$ (T)	Promotes burst firing; may promote glutamate release from nociceptive terminals in the dorsal horn	May contribute to central mechanisms of pain
TRPV1	Activated by noxious heat, low pH, capsaicin, and bioactive lipids such as anandamide; critically involved in heat-induced pain and acid-evoked sensitization	Target on multiple inflammatory mediators triggering nociceptor sensitization
TRPA1	Molecular integrator of many exogenous and endogenous noxious stimuli, including oxygen and nitrogen free radicals	Coexpressed with TRPV1 in a subset of peptidergic nociceptors; upregulated during inflammation
TRPM8	Activated by both innocuous and noxious cold	Contributes to cold allodynia in the setting of oxaliplatin-induced and other neuropathies
ASIC	Activated by acidic pH; permeable to Na^+ and elicits cell depolarization	ASIC3 is pH sensor for muscle pain triggered by lactic acid
HCN	Activated by hyperpolarization; permeable to Na^+ and K^+ and constitutively open near RMP; positively modulated by cAMP	HCN2 has a role in inflammatory and neuropathic pain; HCN1 may contribute to cold hyperalgesia and allodynia in oxaliplatin-induced neuropathy
TMEM16A (ANO1)	Ca^{2+}-activated Cl^- channel; elicits Cl^- efflux resulting in membrane depolarization and triggering of action potentials	Activated by bradykinin and heat
$P2X_3$	Activated by ATP; permeable to Na^+, K^+, and Ca^{2+}	Mediates mechanosensory transduction in viscera and participates in somatic and visceral pain
$5\text{-}HT_3R$	Activated by serotonin, permeable to Na^+ and Ca^{2+}	Contributes to persistent nociceptive processing in the setting of injury

Abbreviations: ASIC = acid-sensing ion channel; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CASPR2 = contactin-associated protein 2; CGRP = calcitonin gene-related peptide; HCN = hyperpolarization-activated cyclic nucleotide-gated; Na_v = voltage-gated sodium (Na^+) channels; NGF = nerve growth factor; PGE_2 = prostaglandin E_2; REST = RE1-silencing transcription factor; RMP = resting membrane potential; TASK = 2-pore, acid-sensitive K^+ channel; TMEM16 = transmembrane protein 16; TRESK = 2-pore weak inwardly rectifying K^+ channel–related spinal cord K^+ channel; TRPA1 = transient receptor potential ankyrin 1; TRPM8 = transient receptor potential melastatin 8; TRPV1 = transient receptor potential vanilloid 1.

adaptation.[27] Slack channels are abundantly expressed in nonpeptidergic nociceptive DRG neurons.

Many K_{2P} channels are constitutively open and generate a background "leak" current that stabilizes the resting membrane potential below firing threshold. DRG neurons express many members of the K_{2P} channel family, including 2-pore weak inwardly rectifying K^+ channel (TWIK1) and the following

TWIK-related channels: TWIK-related spinal cord K^+ channel (TRESK), TWIK-related potassium channel-1 (TREK1), TWIK-related arachidonic acid–stimulated K^+ channel (TRAAK), and 2-pore, acid-sensitive K^+ channel (TASK1). TRESK and TREK1 may be responsible for most of the background K^+ conductance in nociceptors. TREK1 is coexpressed with TRPV1 channels in nociceptors and, like TRAAK, is sensitive to heat and mechanical stimuli. Small to medium diameter DRG express the inward rectifying K^+ channel subunits Kir6.1, Kir6.2, and SUR1, which form the ATP-gated K^+ channel (K_{ATP}). Whereas this channel has a relatively minor role in setting the baseline excitability of DRG cells, it may have a role in pathologic conditions.[28]

Voltage-gated Ca^{2+} channels. Nociceptors express L-type ($Ca_v1.2$), N-type ($Ca_v2.2$), and T-type ($Ca_v3.2$ and $Ca_v3.3$) channels.[7] The role of L-channels in normal nociceptor function is poorly defined but is suggested by the antinociceptive effects of $Ca_v1.2$ silencing in experimental models of neuropathic pain. The N-type ($Ca_v2.2$) channels are located in presynaptic terminals and trigger release of glutamate, substance P, and CGRP both at central and peripheral terminals of nociceptors. Genetic ablation studies indicate that $Ca_v2.2$ channels contribute to chronic pain. The α2δ subunit of high-voltage gated Ca^{2+} channels, including the N-type channels, increases the membrane expression of the functional α1 subunit[29]; the α2δ subunit is upregulated in experimental models of inflammatory and neuropathic pain,[30] and is the target of gabapentin and pregabalin.[29,30] Presynaptic T-type ($Ca_v3.2$) channels also promote glutamate release from nociceptive terminals in the dorsal horn.[31]

TRP channels. TRP channels are homotetrameric nonselective cation channels with high permeability to Ca^{2+} and act as multimodal receptors.[8] TRPV1, TRPA1, and transient receptor potential melastatin 8 (TRPM8) are present in nociceptors and define different nociceptor populations. TRPV1-expressing nociceptors contain neuropeptides and mediate sensitivity to noxious heat; a subset of TRPV1-positive neurons coexpress TRPA1, which responds to several chemical signals, including products of oxidative and nitrosative stress; and TRPM8-expressing neurons mediate sensitivity to cold.[8] TRP channels are intrinsically sensitive to phosphoinositide lipids, particularly phosphatidylinositol 4,5 biphosphate (PIP_2), and are therefore modulated by G-protein-coupled receptors linked to the Gq–phospholipase C (PLC) pathway, with different effects according to the TRP channel type.

TRPV1 is a marker of peptidergic nociceptors and is activated by noxious heat (>43°C), low pH (5.2), capsaicin, and bioactive lipids such as anandamide.[32] Studies in knock-out mice indicate that TRPV1 is critical for heat-induced pain and acid-evoked sensitization of cutaneous and visceral nociceptors. Protons function both as TRPV1 agonists and as positive allosteric modulators of TRPV1.[32] TRPV1 is tonically inhibited by PIP_2 via lipid–protein interactions; signals that trigger PLC-mediated hydrolysis of PIP_2 relieve TRPV1 from this inhibitory interaction. TRPA1 is a molecular integrator of many exogenous and endogenous noxious stimuli, including oxygen free radicals and other inflammatory agents released at the site of injury, thus promoting nociceptor sensitization.[33–35] TRPA1 is activated by PLC-evoked release of Ca^{2+} from intracellular stores and amplifies the responses initiated by other Ca^{2+} channels, such as TRPV1.[35] TRPM8 is expressed in ~15%–30% of C-fibers and a minor proportion of Aδ fibers, in general different from those expressing TRPV1/TRPA1.[36] TRMP8 is activated by innocuous cool to noxious cold temperatures (<30°C), as well as cooling agents such as menthol. Genetic studies indicate that TRMP8 is the principal transducer of cool and cold stimuli and contributes to cold hypersensitivity during injury.[37] Unlike TRPV1 channels, TRMP8 require PIP_2 for activation; decreased PIP_2 in response to inflammatory mediators promotes TRMP8 desensitization.[38]

Acid-sensing channels. ASICs are voltage-independent cation channels that are activated by acidic pH; they are primarily permeable to Na^+ and elicit cell depolarization, leading to secondary intracellular accumulation of Ca^{2+}.[39] Among these channels, ASIC1a, ASIC1b, ASIC 2a and 2b, and ASIC3 are expressed in sensory neurons of the DRG and trigeminal ganglion. ASIC3 is an essential pH sensor for pain and is primarily located in nociceptive fibers innervating the skeletal and cardiac muscle, joints, and bone; in these tissues, anaerobic metabolism leads to buildup of lactic acid and protons, which activate ASICs.[39]

Hyperpolarization-activated cyclic nucleotide-gated channels. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are activated by membrane hyperpolarization; they are permeable to Na^+ and K^+ and are constitutively open at voltages near the resting membrane potential. In many cases, activation is facilitated by direct interaction with cyclic adenosine monophosphate. Opening of HCN channels elicits membrane depolarization toward threshold for action potential generation and reduces membrane resistance and thus the magnitude of excitatory and inhibitory postsynaptic potentials.[40–42] Nociceptive neurons express both HCN1 and HCN2[43]; evidence from experimental models suggests that HCN channels,

particularly HCN2, have a prominent role in both inflammatory and neuropathic pain.[44,45] Selective knockout studies indicate that HCN1 channels may also have a contributory role in cold hyperalgesia and allodynia in the setting of oxaliplatin-induced neuropathy.[46]

TMEM16/anoctamin channels. Transmembrane protein 16 (TMEM16) proteins, also known as anoctamins, are involved in a variety of functions that include ion transport, phospholipid scrambling, and regulation of other membrane proteins.[47] TMEM16A (anoctamin 1, ANO1) is a Ca^{2+}-activated Cl^- channel; because of the relatively high intracellular Cl^- concentration, opening of TMEM16A/ANO1 channels elicits Cl^- efflux, resulting in membrane depolarization and triggering of action potentials. TMEM16A is expressed in nociceptors[48] and, like TRPV1, is activated by bradykinin[49] and heat.[50] Nociceptive DRG neurons also express the TMEM16C/ANO3 channel, which colocalizes with Slack, the protein forming the K_{Na} channel; this interaction enhances its Na^+ sensitivity of K_{Na}, thereby eliciting membrane hyperpolarization and reducing nociceptor firing.[51]

Purinergic P2X receptors. Purinergic signaling mediated by ATP acting via ionotropic P2X and metabotropic P2Y receptors has an important role in transmission of nociceptive information.[11,52] P2X receptors are permeable to Na^+, K^+, and Ca^{2+} and are involved in mechanosensory transduction and both somatic and visceral pain.[11] $P2X_3$ and to a lesser extent P2X2/3 hetrodimers are the most common subtypes in nociceptors and are expressed in nonpeptidergic nociceptive DRG neurons. The P2Y receptors including P2Y1 and P2Y2 are G-protein-coupled receptors that are expressed in nociceptors and may interact with TRPV1, promoting its response to heat and protons in the setting of inflammatory or neuropathic pain.[11] Purinergic receptors expressed in microglia, including $P2X_4$, $P2X_7$, and $P2Y_{12}$ receptors, also participate in mechanisms of central sensitization in response to nerve injury.[11,52]

Serotonin 5-HT_3 receptors. The 5-HT_3 receptor (5-HT_3R) is a ligand-gated ion channel that is expressed in a minority of nociceptors. The 5-HT_3R is not required for acute nociception in response to physiologic stimuli but contributes to persistent nociceptive processing in the setting of injury.[53] 5-HT_3Rs in the dorsal horn may mediate descending serotonergic facilitation from the rostral ventromedial medulla in part via interactions with glial cells.[54]

NOCICEPTOR SENSITIZATION

Recordings from C nociceptors show several electrophysiologic abnormalities both in patients with neuropathic pain and in experimental models of nerve injury. They include spontaneous impulse generation, sensitization to mechanical, heat, and cold stimuli, and polyspike responses.[55,56] The spontaneous discharge is of low frequency and random, requiring both spatial and temporal summation at the level of the dorsal horn to elicit the experience of pain.[55,56] The abnormal activity of nociceptors reflects peripheral sensitization, which occurs in the setting of inflammation or nerve injury. Sensitized nociceptors develop spontaneous activity, resulting in spontaneous pain, increase in their receptor fields, and response not only to noxious but also to innocuous mechanical or thermal stimuli.[57–59]

Inflammation. Nociceptor sensitization primarily reflects upregulation of cation channels by products of inflammation. This subject has been extensively reviewed[1,2] and few points are emphasized here. Chemical mediators released either from nociceptive terminals or local cells at the site of injury include substance P, CGRP, bradykinin, eicosanoids and related lipids (prostaglandins, thromboxanes, leukotrienes, and endocannabinoids), NGF, brain-derived neurotrophic factor (BDNF) cytokines, chemokines, proteases, and nitric oxide.[1,2] These mediators elicit upregulation of ion channels in nociceptors both by altering their expression or membrane trafficking of the channels and via interactions with G protein–coupled or tyrosine kinase receptors.[1,2,60–63]

There is redundancy of both transduction pathways and targets for peripheral nociceptor sensitization. TRPV1 is a core downstream target for inflammatory signals, including protons, bradykinin, histamine, prostaglandin E_2, ATP, and NGF. For example, bradykinin, acting via B_2 receptors coupled with Gq- PLC-PIP2 transduction pathway, relieves TRPV1 from its inhibitory interactions with PIP_2, increasing its sensitivity to heat and chemical stimuli.[8] Bradykinin may also increase TRPV1 sensitivity via activation of phospholipase A2-lipoxygenase pathway, which converts arachidonic acid to eicosanoids such as 12-hydroperoxyeicosatetraenoic acid (12-HPETE); 12-HPETE, like capsaicin and endovanilloids, can bind directly to and activate TRPV1.[60] TRPA1 is also modulated indirectly by bradykinin and is an important mediator of sensitization in response to oxidative or nitrative stress or endogenous thiol-reactive electrophiles produced during tissue injury and inflammation. Bradykinin may also elicit pain by acting on other targets; for example, release of intracellular Ca^{2+} in response to bradykinin leads to nociceptor depolarization by simultaneously closing M-type K^+ channels and opening TMEM16A/ANO1 channels.[49,64] Like bradykinin, NGF may elicit nociceptors sensitization by several mechanisms;

it directly activates TRPV1 via phosphorylation triggered by PLC, mitogen-activated protein kinase, and phosphoinositide 3-kinase, and promotes expression of pronociceptive proteins, such as substance P, TRPV1, and $Na_v1.8$. $Na_v1.9$ is upregulated during inflammation via GTP-dependent mechanisms.[25] Inflammatory mediators, through the activation of protein kinase A, elicit internalization of Slack and thereby sensitize primary afferent nociceptors to mechanical, thermal, and osmotic stimuli.[65] Pathogen-associated molecular patterns and extracellular microRNAs, acting via Toll-like receptors (TLRs), may contribute to nociceptor sensitization; for example, miRNA-let-7b induces rapid inward currents and action potentials in DRG neurons by activating TLR7 receptors coupled to TRPA1 channels.[66]

Axonal injury. Axonal injury results in increased expression of $Na_v1.7$ and $Na_v1.8$ at the injury site. $Na_V1.7$ accumulates at nerve endings together with extracellular receptor activated kinase 1 and 2, which phosphorylate the channel and reduce its activation threshold; $Na_v1.8$ accumulation may reflect in part increased axonal mRNA transport.[67] In contrast, peripheral axon transection results in downregulation of $Na_v1.9$; this may reflect lack of trophic support by GDNF.[25]

In the setting of axonal injury, there is reduced expression of several types of K^+ channels, including K_v1, K_v2, K_v3, K_v7, BK_{Ca}, TREK, or K_{ATP}.[5,6] This may reflect transcriptional inhibition by the transcription factor RE1-silencing transcription factor, which is induced by injury or inflammation[68,69] and may act via BDNF signaling.[70] Retigabine is an anticonvulsant agent that enhances $K_v7.2/K_v7.3$ activation and M currents in axotomized nociceptive fibers.[5,6] There is upregulation of several types of voltage-gated Ca^{2+} channels in neuropathic pain models. $Ca_v1.2$ upregulation elicits nociceptor hyperexcitability and allodynia[71]; $Ca_v1.2$ knockdown using silencing RNA reversed neuropathic pain.[72] There is also upregulation of the $\alpha2\delta$ subunit of high-voltage gated Ca^{2+} channels,[30] as well as $Ca_v3.2$ (T) channels,[73] in experimental models of neuropathic pain.

Experimental models show that painful neuropathy induced by some chemotherapeutic agents involves upregulation and excessive activation of TRP channels in nociceptors. For example, TRPV1 and TRPA1 are involved in thermal hyperalgesia induced by cisplatinum[74]; TRPA1 and TMP8 mediate pain and cold allodynia induced by oxaliplatin.[75–78] Experimental models show that TRPA1, which is sensitive to products of oxidative and nitrosative stress, contributes to different types of inflammatory and neuropathic pain.[79]

CLINICAL CORRELATIONS Mutations of *SCN9A* (encoding $Na_v1.7$), *SCN10A* (encoding $Na_v1.8$), and *SCN11A* (encoding $Na_v1.9$) may result in channel gain of function or loss of function (table 2). Gain-of-function mutations increase nociceptive DRG excitability and manifest with familial episodic pain syndromes or painful SFN; mutations resulting in channel loss of function result in congenital insensitivity to pain. The clinical consequences and physiologic basis of sodium channelopathies have been extensively reviewed[4,12–15,80,81] and few aspects are emphasized here.

Sodium channelopathies associated with paroxysmal pain. ***Inherited erythromelalgia.*** Erythromelalgia is characterized by severe burning pain and erythema in the feet, hands, and occasionally the nose and ears.

Table 2 Inherited channelopathies associated with abnormal nociceptive processing

Phenotype	Disorder (gene)	Effect of mutation
Inherited pain disorders	Inherited erythromelalgia (*SCN9A*)	$Na_v1.7$ gain of function
	Paroxysmal extreme pain disorder (*SCN9A*)	$Na_v1.7$ gain of function
	Familial episodic pain syndrome type III (*SCN11A*)	$Na_v1.8$ gain of function
	Familial episodic pain syndrome type 1 (*TRPA1*)	TRPA1 gain of function
Congenital insensitivity to pain	*SCN9A* mutation	$Na_v1.7$ loss of function
	HSAN II B (*SCN9A*)	$Na_v1.7$ loss of function
	(*SCN11A* mutation)	$Na_v1.9$ gain of function (and secondary loss of $Na_v1.7$ and $Na_v1.8$ function)
Painful small fiber neuropathy	*SCN10A*	$Na_v1.7$ gain of function in nociceptor, may be associated with loss of function in autonomic ganglia and axonal loss
	SCN10A	$Na_v1.8$ gain of function

Abbreviations: Na_v = voltage-gated sodium (Na^+) channel; TRPA1 = transient receptor potential ankyrin 1.

The pain is initially episodic and precipitated by warmth, exercise, prolonged standing, and sometimes alcohol, and is typically relieved by cooling. Inherited erythromelalgia (IE, also referred to as primary erythermalgia) has a clinical onset in infancy or early childhood and is an autosomal dominant disorder associated with missense mutations of the *SCN9A* gene.[82] These mutations result in gain of function of $Na_v1.7$ channels by increasing probability of channel activation, slowing channel deactivation, and increasing their response to graded stimuli,[83] thereby making nociceptors hyperexcitable.[4] The magnitude of dysfunction of the mutant channel increases at higher temperatures[84] and determines the age at onset of symptoms[85]; some adult-onset cases with no family history may present with de novo mutations.[86] Carbamazepine and mexiletine are nonselective, activity-dependent Na_v blockers that may be efficacious in relieving symptoms in some but not all cases[87,88]; structural modeling and mutant cycle analysis may predict the responsiveness of the mutant $Na_v1.7$ channel to these drugs.[89]

Paroxysmal extreme pain disorders. Paroxysmal extreme pain disorder (PEPD) is an autosomal recessive disorder of onset in infancy. It is characterized by paroxysmal episodes of rectal, perineal, ocular, and mandibular pain, which may be triggered by defection, eating, or strong emotions.[90,91] Pain is associated with autonomic manifestations including flushing, lacrimation, rhinorrhea, bradycardia, and apnea.[90] Flushing can present in a harlequin pattern that alternate between the left and right sides during different episodes.[90,91] PEPD is also associated with gain-of-function *SCN9A* mutations; these mutations do not alter $Na_v1.7$ activation threshold but impair $Na_v1.7$ fast inactivation, leading to a persistent current and generation of resurgent Na^+ currents.[92,93] The findings that a single $Na_v1.7$ mutation associated with functional changes characteristic of both IE (such as reduced activation threshold) and PEPD (impaired fast inactivation) produced a mixed clinical phenotype with characteristics of both disorders suggest that these mutants are part of a physiologic continuum.[94] Patients with PEPD often respond to carbamazepine but response duration varies among patients.[90]

Missense mutations in the *SCN11A* gene causing gain of function $Na_v1.9$ channel and DRG hyperexcitability were reported in 2 Chinese families with autosomal dominant episodic pain syndrome.[95] Clinical characteristics include intense pain localized principally to the distal lower extremities and occasionally in the upper body, especially in the joints of fingers and arms; episodic pain appeared late in the day and relapsed once every 2–5 days in fashion with variable number of recurrences; the pain exacerbated with fatigue, was associated with excessive sweating, and was relieved by application of heat or by oral anti-inflammatory analgesics. Severe pain decreased with age in all affected individuals.[95]

Painful SFN. SFNs are characterized by neuropathic pain and autonomic dysfunction. Faber et al.[96] identified *SCN9A* gene variants producing gain of function of $Na_v1.7$ in approximately 30% of a cohort of idiopathic SFN patients; these variants altered fast inactivation, slow inactivation, or resurgent currents rendering DRG neurons hyperexcitable. Autonomic symptoms vary in spectrum and severity according to the mutation and depending on its impact on sympathetic ganglion neurons, which also express $Na_v1.7$ channels.[15] Increased depolarization in response to some mutations may increase DRG neuron and reduce sympathetic ganglion neuron excitability by a mechanism of depolarization block.[97] Whereas pain in SFN is typically of distal onset, there is also variability in the distribution and triggers of the pain both within and between families harboring the same variant; some patients may present with pain in the face or scalp, or pain and redness triggered by exposure to warmth.[98]

Hoeijmakers et al.[99] described a novel gain-of-function *SCN9A* ($Na_v1.7$) mutation resulting in a syndrome characterized by burning pain in hands and feet triggered by warmth and relieved by cold; autonomic manifestations (profuse sweating, episodic dry eyes and mouth, hot flashes, diarrhea or constipation, end erectile dysfunction); muscle cramps; and small hands and feet (acromesomelia). There was reduced intraepidermal nerve density, suggesting that small nerve fiber dysfunction may have contributed to distal limb underdevelopment in this syndrome.[99] The mechanism of axonal degeneration in *SCN9A* channelopathies is undetermined. Increased intracellular Na^+ load may lead to enhanced activity of the axonal Na^+-Ca^{2+} exchanger, resulting in intracellular Ca^{2+} accumulation and presumably axonal injury.[100] Gain-of-function *SCN10A* mutations associated with increased $Na_v1.8$ channel responses and DRG neuron hyperexcitability have also been identified in patients with painful SFN.[101]

Sodium channelopathies associated with insensitivity to pain. ***Congenital insensitivity to pain.*** Inactivating *SCN9A* mutations leading to loss of $Na_v1.7$ function produce congenital insensitivity to pain associated with congenital anosmia, without affecting intelligence or other neurologic functions.[102–105] $Na_v1.8$ channels cannot compensate for $Na_v1.7$ loss, because $Na_v1.8$ has a higher threshold of activation, preventing them from opening in response to small changes in membrane potential needed for initial transduction of nociceptive signals. Anosmia reflects the prominent role of $Na_v1.7$ channels in sensory transduction in olfactory neurons.[106]

Congenital insensitivity to pain has more recently been linked to gain-of-function *SCN11A* mutations.[107] These patients have hyperhidrosis in the absence of precipitating factors and severe gastrointestinal dysfunction, including episodes of diarrhea and constipation. Intelligence is normal and, unlike the case loss-of-function *SCN9A* mutations, the sense of smell is preserved.[107] Gain-of-function *SCN11A* increases $Na_v1.9$ function by interfering with voltage-dependent inactivation; this results in sustained depolarization that leads to inactivation of $Na_v1.7$ and $Na_v1.8$, resulting in conduction block of nociceptors, hence the insensitivity to pain.[107]

Hereditary sensory and autonomic neuropathy type IID. Compound heterozygous nonsense *SCN9A* mutations have been linked to a syndrome characterized by loss of pain and temperature sensation and anhidrosis; other features include hyposmia, hearing loss, and bone dysplasia.[108] This phenotype, referred to as hereditary sensory and autonomic neuropathy type IID, is characterized by reduced amplitude compound sensory action potential loss of intraepidermal nerve fibers as well as large myelinated fibers.[108]

Other disorders. ***Familial episodic pain syndrome due to TRPA1 mutations.*** Kremeyer et al.[109] described an autosomal dominant familial episodic pain disorder linked to gain-of-function mutation of the *TRPA1* gene encoding the TRPA1 channel. These patients experience severe episodes of pain affecting mainly the thorax and arms but occasionally radiating to the abdomen and legs; the episodes are triggered by cold exposure or hunger, last about 60–90 minutes, and are accompanied by sweating, generalized pallor, peribuccal cyanosis, tachycardia, breathing difficulties, and abdominal wall stiffness.[109] Neurologic examination, nerve conduction studies, and intraepidermal nerve fiber density are normal. Consistent with the sensitivity of TRPA1 to chemical irritants, these patients are hypersensitive to mustard oil.[109]

Genetic variants and risks of developing chronic acquired pain syndromes. As suggested from studies in experimental animals, polymorphisms of genes encoding different types of ion channels in nociceptors may increase pain perception and predispose to development of chronic pain syndromes in humans. These include not only the genes discussed above but also *TRPV1*, *CACNA2D3* (encoding the $\alpha2\delta3$ subunit of high-voltage activated Ca^{2+} channels), *KCNS1* (encoding the K_v9 subunit that is clinically silent but may affect other functional α-subunits of voltage-gated K^+ channels), and *P2RX7* (encoding an ATP-gated channel present in microglia and involved in central mechanism of pain sensitization).[13] However, as recently discussed for the case of Na^+ channels, the functional implications of sequence variants have to be assessed following strict criteria.[14]

Autoimmune potassium channelopathies. Reduced activity of a variety of K^+ channels is associated with increased nociceptor activity.[5,6] Klein et al.[110] reviewed the prevalence and characteristics of pain in 316 patients seropositive for voltage-gated K^+ channel complex–immunoglobulin G directed against leucine-rich glioma activated-1 or contactin-associated protein 2. Among these patients, 50% had pain either in isolation (28%) or with accompanying neurologic manifestations (72%); the pain had subacute onset, chronic course, and neuropathic, nociceptive, regional, or diffuse characteristics.[110] Neuronal hyperexcitability manifesting with hyperhidrosis, heat-pain hyperalgesia, or EMG excitability was 25-fold more common in these patients than in control patients. These results indicate that, in some cases with subacute onset of symptoms, chronic unexplained pain may be manifestation of voltage-gated K^+ channel complex autoimmunity, likely reflecting hyperexcitability of nociceptive pathways.[110]

PERSPECTIVE Over the past several years, experimental studies have provided increasing insight into the neurochemical and functional heterogeneity of nociceptors and the signals involved in nociceptor sensitization as a fundamental mechanism of neuropathic and inflammatory pain. Central to this process are changes in the expression and function of a large variety of ion channels. More recently, clinical studies integrating phenotypic characterization, genetics, and in vitro elucidation of the functional effects of mutations have clearly established that Na_v (and TRPA1) nociceptor channelopathies are an important cause of episodic pain disorders, insensitivity to pain, and painful SFN. Some evidence indicates that autoimmune K_v channelopathies may at least contribute to otherwise unexplained pain. Not surprisingly, the identification of specific ion channels as the target of these disorders, together with abundant evidence in experimental models, has provided the stimulus for the development of channel-specific pharmacotherapy for neuropathic pain. An integrated approach to elucidate the specific channel dysfunction underlying abnormal nociceptor activity and its responsiveness to drugs in specific human pain disorders will hopefully provide therapeutically relevant information.

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