Review article

The role of voltage-gated sodium channels in modality-specific pain pathways

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Pain is a distressing physical and emotional experience associated with actual or potential tissue injury, or an experience described in terms of such injury. The primary function of nociceptors, such as some dorsal root ganglion (DRG) neurons, is to transduce noxious sensory modalities, e.g. mechanical pressure, cold and heat, into electrical impulses and to transmit these to processing centres in the central nervous system (CNS). Modality-specific pain pathways have been identified through in vivo deletion of voltage-gated Na⁺ channels in mouse DRG neurons. Deletion of Na⁺v1.8 channels has been shown to result in loss of mechanosensory and cold-induced pain, but not-heat induced pain, whereas deletion of Na⁺v1.7 channels has been seen to abolish responses to noxious heat and mechanical stimuli. The present review constitutes an attempt to elucidate the mechanisms through which voltage-gated Na⁺ channels are involved in modality-specific pain pathways. It has been found that Na⁺v1.8 and Na⁺v1.9 channels are resistant to slow inactivation upon cooling, maintaining activity even though channels on other sensory afferents may be inactivated. Na⁺v1.7 channel activity is reported to be coupled to substance P release into the dorsal horn of dorsal root ganglion (DRG) neurons in heat-specific pain pathways. Recent research has also offered insight into the role of Na⁺v1.7 and Na⁺v1.9 mutations in pain-related conditions, e.g. inherited erythromelalgia and cold-aggravated pain, respectively, as these influence kinetic parameters, such as open state probability. Therefore, voltage-gated Na⁺ channels appear to be playing an important role in segregating modality-specific pain pathways. The identification of markers for mechanisms implicated in the activation of these pathways could potentially pave the way towards the development of more effective analgesics.

Key words: pain pathways, modality, sodium channels, Na⁺v1.7, Na⁺v1.8, Na⁺v1.9

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Introduction

According to the International Association for the Study of Pain, pain can be defined as an adverse sensory and emotional experience corresponding to actual or potential tissue damage, or an experience that can be described in terms of such damage (Loeser and Treede, 2008). Of note, in the UK alone between one-third and one-half of the population suffers from chronic pain (Fayaz et al., 2016). Damaging stimuli, e.g. extremes in temperature, mechanosensation and injury-related chemicals, activate nociceptors, which are specialized peripheral sensory neurons that transmit the resulting electrical impulses to higher processing centres in the brain (Dubin and Patapoutian, 2010). The cell bodies of nociceptors are located in DRG and trigeminal ganglion, whereas their sensory fibres are classified as small-diameter...
unmyelinated C afferents, medium-diameter myelinated Aδ afferents, and large-diameter myelinated Aβ afferents (Basbaum et al., 2009). Among these afferents, C fibres appear to exhibit polymodality, i.e. the ability to respond to multiple sorts of painful stimuli (Emery et al., 2016). Despite their polymodality, deletion of specific voltage-gated Na⁺ channels in mice has been observed to result in modality-specific deficits in pain, highlighting the existence of specific pain pathways (Emery et al., 2016). The aim of the present paper is to discuss the role of voltage-gated Na⁺ channels in these modality-specific pain pathways.

**Voltage-gated Na⁺ channels**

The voltage-gated Na⁺ channel was first cloned by Noda et al. (1984). Specifically, they sequenced the cDNA for the *Electrophorus electricus* electroplax sodium channel, identified four repeated homology domains, and within each unit they identified clustered regions of positively charged amino acids. Now, it is well established that the four repeated homology domains form the voltage-gated Na⁺-selective aqueous ion channel pore (Wood et al., 2004). Each of these domains (I–IV) has six transmembrane segments (S1–S6) (Cestèle and Catterall, 2000). The positively charged S4 segment is the voltage sensor, whose outward movement at positive membrane potentials exerts force on the S5–S6 linker, thus opening the ion channel (Yarov-Yarovoy et al., 2012). The channels open within the order of a millisecond and their ionic current is also eliminated within a millisecond (Cummins, Sheets, Waxman, 2007). The short intracellular loop connecting domains III and IV is involved in channel inactivation (Cestèle and Catterall, 2000). The four homologous domains collectively form the α subunit of the voltage-gated Na⁺ channels (Wood et al., 2004). Voltage-gated Na⁺ channels themselves are a family of nine structurally related α subunits (Wood et al., 2004; see Table 1). These nine α subunits differ in terms of cellular and tissue expression, subcellular expression, and differential expression profiles during development (Yu and Catterall, 2003). The α subunits can interact with accessory single-transmembrane β subunits that may be influencing the localization and/or membrane stabilization of the α subunits (Cummins, Sheets, Waxman, 2007). Voltage-gated Na⁺ channels are widely known for their role in the initiation and propagation of action potentials. However, in the field of pain, their functions extend beyond that of action potential initiation and propagation, as they are involved significantly in development and mechanisms of chronic pain, given that mutations in Na⁺ channels result in inherited erythromelalgia and paroxysmal extreme pain disorder (Cummins, Sheets, Waxman, 2007). The structure of the voltage-gated Na⁺ channels can be seen under Fig. 1.

**Table 1.** Mammalian voltage-gated Na⁺ channels

<table>
<thead>
<tr>
<th>Name</th>
<th>Gene</th>
<th>Distribution</th>
<th>DRG?</th>
<th>TTXa?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na,1,1 (Type I)</td>
<td>SCN1A1</td>
<td>CNS² Heart</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Na,1,2 (Type II)</td>
<td>SCN2A</td>
<td>CNS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Na,1,3 (Type III)</td>
<td>SCN3A</td>
<td>Foetal DRG</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Na,1,4 (SkM1*)</td>
<td>SCN4A</td>
<td>Muscle</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Na,1,5 (SkM2)</td>
<td>SCN5A</td>
<td>Heart</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Na,1,6 (NaCh6)</td>
<td>SCN8A</td>
<td>DRG CNS</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Na,1,7 (PN15)</td>
<td>SCN9A</td>
<td>DRG SCG³</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Na,1,8 (SNS)</td>
<td>SCN10A</td>
<td>DRG</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Na,1,9 (NaN)</td>
<td>SCN11A</td>
<td>DRG</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Na, (NaG)</td>
<td>SCN7A</td>
<td>Lung nerve</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*DRG, dorsal root ganglia.

TTX, tetrodotoxin-sensitive.

SCN1A, sodium voltage-gated channel alpha subunit 1.

CNS, central nervous system.

SkM1, skeletal muscle type 1.

NaCh6, sodium channel 6.

PN1, peripheral nerve type 1.

SCG, superior cervical ganglion.

SNS, sensory neuron-specific sodium channel.


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Using this technique, they visualized different sets of DRG neurons. Deletion of Nav1.8 expressing sensory neurons that become active upon application of noxious mechanical, cold and heat stimuli. Deletion of Nav1.8 sensory neurons that become active upon application of noxious mechanical, cold and heat stimuli. Deletion of Nav1.8 expressing sensory neurons with mice homozygous for the Nav1.8 channel subunit gene. DTA thus killed Nav1.8-expressing sensory neurons. Using this technique, they visualized different sets of DRG neurons. Deletion of Nav1.8 expressing sensory neurons with mice homozygous for the Nav1.8 channel subunit gene. DTA thus killed Nav1.8-expressing sensory neurons. Using this technique, they visualized different sets of DRG neurons. Deletion of Nav1.8 expressing sensory neurons with mice homozygous for the Nav1.8 channel subunit gene. DTA thus killed Nav1.8-expressing sensory neurons. Using this technique, they visualized different sets of DRG neurons. Deletion of Nav1.8 expressing sensory neurons with mice homozygous for the Nav1.8 channel subunit gene. DTA thus killed Nav1.8-expressing sensory neurons.

Further support for the concept of modality-specific pain pathways has been offered by the study of Emery et al. (2016). They used C57BL/6 mice that expressed the fluorescent Ca²⁺ indicator GCaMP in their DRG neurons, in vivo. Using this technique, they visualized different sets of DRG sensory neurons that become active upon application of noxious mechanical, cold and heat stimuli. Deletion of Nav1.8 channels prevented the activation of mechanical-sensing neurons, but not that of heat-sensing neurons. It also resulted in loss of inflammatory pain, but not loss of neuropathic pain. This not only shows that different pain modalities, e.g. heat, cold, mechanical pressure, are associated with the activation of specific sets of sensory neurons and special pain pathways, but also that voltage-gated Na⁺ channels, such as Nav1.8 channels, may be playing a critical role in the transmission of signals within these modality-specific sets of nociceptors.

The roles of voltage-gated Na⁺ channels in cold-induced pain are summarized by Foulkes and Wood (2007). They suggest that noxious cold temperatures alter neuronal membrane properties, with the passive conductance of K⁺ ‘leak’ channels and the activity of the Na⁺/K⁺ ATPase being reduced. This effectively increases the membrane resistance, rendering depolarizing currents more effective at depolarizing the membrane and reaching the threshold for activation of Nav1.8 channels. Furthermore, they suggest that low temperatures could also act to directly shift the activation threshold for Nav1.8 channels to more negative membrane potentials. A third mechanism that is suggested implicates cold-induced upregulation of p38 MAPK (see Mizushima et al., 2006), which then augments Nav1.8 current density, specifically via phosphorylation at S551 and S556 (Hudmon et al., 2008). However, according to Foulkes and Wood (2007), what is unique about the role of Nav1.8 channels is that they are the only voltage-gated Na⁺ channels that do not inactivate at low temperatures. This, along with tissue specific expression of these channels, is proposed to give rise to modality-specific activation of nociceptors by noxious cold, as shown by the studies of Abrahamsen et al. (2008) and Emery et al. (2016).

Evidence for the effect of noxious cold on the membrane properties, Nav1.8 activation threshold and inactivation of Nav1.8 channels has been offered by Zimmermann et al. (2007). Throughout their study, they made use of the Na⁺ channel blocker tetrodotoxin (TTX) to isolate Nav1.8 currents, as...
Na\textsubscript{1.8} are resistant to it (see Table 1). They first blocked rat mecanochannel-sensitive C fibre nociceptors in vitro at 30°C with 1 μM TTX, rendering the cells unexcitable. Upon cooling, the nociceptors became excitable. Cooling also resulted in slower inactivation kinetics of TTX-sensitive (TTXs) and TTX-resistant (TTXr) Na\textsuperscript{+} currents in DRG neurons. However, this effect was more pronounced in TTXs currents at a holding potential of −80 mV, whereas any differences were abolished at −120 mV. This shows that the slow inactivation threshold was lowered for TTXs upon cooling, that TTXr currents were mainly resistant to shifts in their slow inactivation threshold, whereas cooling led to a small shift in activation threshold towards hyperpolarized potentials for both TTXs and TTXr currents. Given that Na\textsubscript{1.9} channels are also TTXr, Zimmermann et al. (2007) also studied the effect of cooling on Na\textsubscript{1.8}-deficient neurons. In the presence of TTX and at 10°C, Na\textsubscript{1.8}-deficient neurons failed to generate action potentials in response to current injections and mechanical stimuli, whereas wild-type (WT) neurons remained excitable. They confirmed that Na\textsubscript{1.8} knockout results in loss of behavioural responses, e.g. foot-lifting, to noxious cold in the cold-plate test. Finally, whereas TTX and cooling each increased the rheobase current and the chronaxy at all current durations tested in rat skin-nerve terminal preparations, cooling in the presence of TTX decreased the rheobase current regardless of stimulus duration, highlighting an increase in membrane resistance. This, in turn, increases the voltage response of Na\textsubscript{1.8} in response to depolarizing currents.

Despite that Na\textsubscript{1.9} channels were not deemed to be essential in the study by Zimmermann et al. (2007), Lolignier et al. (2015) observed that Na\textsubscript{1.9} function is upregulated in a set of nociceptors responding to cooling, whereas preventing Na\textsubscript{1.9} expression in rodents impairs cold-induced neuronal firing, increases pain threshold to cold, and reduces oxaliplatin-induced cold-pain hypersensitivity. However, in contrast to Na\textsubscript{1.8} channels and what was found by Zimmermann et al. (2007), they observed that cooling-induced slowing of activation and inactivation was voltage-independent. They concluded that Na\textsubscript{1.9} channels act as subthreshold amplifiers in cold modality-specific nociceptors, important in the integration of impulses. In addition, it has been supported that, in Na\textsubscript{1.8} and Na\textsubscript{1.9} knockout mice, Na\textsubscript{1.9} channels play a more modulatory role than Na\textsubscript{1.8} channels in the development of cold allodynia in neuropathic pain, whereas the involvement of both Na\textsubscript{1.8} and Na\textsubscript{1.9} channels in inflammatory pain hypersensitivity may be limited (Leo, D’Hooge, Meert, 2010). A missense mutation (p.V1184A) in SCN1A, the gene encoding Na\textsubscript{1.9} channels, increases the open probability of the mutant channels and the hyperexcitability of DRG neurons, the latter effect being less attenuated at low temperatures compared to WT channels, and has been associated with cold-aggravated pain (Leipold et al., 2015). Therefore, both Na\textsubscript{1.8} and Na\textsubscript{1.9} channels are deemed to be electrophysiologically suitable for the transmission of noxious cold stimuli (Lolignier et al., 2016). Both are resistant to cold-induced inactivation, while channels in other afferents are inactivated by low temperatures, resulting in loss of other sensory modalities (Lolignier et al., 2016).

Heat-evoked pain pathways

The study by Minett et al. (2012) offers insight into the relationship between Na\textsubscript{1.7}-expressing sensory neurons, reflex withdrawal responses to heat, and responses to the hotplate test. Na\textsubscript{1.7} channels were either only deleted from Na\textsubscript{1.8}-expressing sensory neurons through Cre driven by Na\textsubscript{1.8} (Na\textsubscript{1.7}\textsubscript{Nav1.8}) or they were deleted from all sensory neurons through Advillin promoter-driven Cre expression (Na\textsubscript{1.7}\textsubscript{Advill}). Withdrawal responses to heat and mechanical pain were abolished when Na\textsubscript{1.7} channels were deleted from all sensory neurons, whereas withdrawal responses to heat were maintained when Na\textsubscript{1.7} channels were only deleted from Na\textsubscript{1.8}-expressing sensory neurons. Responses to the hotplate test were only abolished when Na\textsubscript{1.7} channels were deleted both from DRG neurons and sympathetic neurons by Wnt1-Cre (Na\textsubscript{1.7}\textsubscript{Wnt1}). At the same time, all conditional Na\textsubscript{1.7} knockout mouse lines (Na\textsubscript{1.7}\textsubscript{Nav1.8}, Na\textsubscript{1.7}\textsubscript{Advill} and Na\textsubscript{1.7}\textsubscript{Wnt1}) responded normally to noxious cold stimuli. This indicates that Na\textsubscript{1.7} channels are not involved in the propagation of noxious cold stimuli. Overall, the study by Minett et al. (2012) offers support for the existence of different subsets of Na\textsubscript{1.7}-expressing neurons for heat-evoked withdrawal responses and responses to the hotplate test.

Several mechanisms have been suggested for the link between Na\textsubscript{1.7} and painful heat responses. Of note, mutations in the gene encoding Na\textsubscript{1.7} channels, SCN9A, conveys inherited erythromelalgia, a condition associated with burning pain (Dib-Hajj et al., 2006). These gain-of-function mutations result in the shift of the activation threshold of Na\textsubscript{1.7} channels towards hyperpolarizing membrane potentials, a shift of steady-state inactivation towards less negative potentials, lower rheobase currents and high-frequency DRG neuronal activity (Dib-Hajj et al., 2005). More specifically, the erythromelalgia mutation Q875E is suggested to form a disulphide bridge between the voltage sensor of domain I and the pore region of domain II, forcing the pore into opened position (Stadler, O’Reilly, Lampert, 2015). In conditions of health, Na\textsubscript{1.7} channels are thought to amplify the transducer currents of heat-sensing channels, e.g. TRPV1 (Shields et al., 2012). Additionally, it has been suggested that burn injury-induced lowering of the Na\textsubscript{1.7} channel activation threshold could be brought about by ERK1/2-mediated modulatory phosphorylation of T531, S535, S608 and S712 in the first intracellular loop (Stamboulian et al., 2010; Shields et al., 2012). Furthermore, Mazzaro and Basbaum (2007) supported that deletion of preprotachykinin-A (PPT-A), the gene that encodes Substance P and Neurokinin A, in mice, decreased the responses of lamina I and V neurons to noxious thermal stimuli, whereas the responses of the laminal neurons to noxious mechanical stimulation did not differ between WT and PPT-A knockout mice. In their study, Minett et al. (2012) also observed that deletion of Na\textsubscript{1.7} in mouse DRG neurons abolished substance P release into the dorsal horn of the DRG neurons and did not result in wind-up upon electrical stimulation of the spinal lamina V wide dynamic range neurons. Therefore, Na\textsubscript{1.7} channel activity could be critical for the release of
substance P and wind-up in spinal pain pathways specific for heat-evoked pain, but not for noxious mechanical stimuli.

Na\(_{1.9}\) channels are also thought to play a role in heat-evoked pain. Lolignier et al. (2011) supported that Na\(_{1.9}\) channels are involved in noxious thermal and mechanical hypersensitivity associated with subacute paw inflammation and chronic ankle inflammation in mice and rats, without any alterations in basal pain thresholds. They also observed increased Na\(_{1.9}\) immunoreactivity in ipsilateral DRG neurons and increased Na\(_{1.9}\) immunolabeling in nerve fibres that surrounded inflamed areas, without any changes in Na\(_{1.9}\) mRNA levels, 24 h after carrageenan (thermal pain-inducing chemical) application, which they attributed to increased transport of Na\(_{1.9}\) channels from the soma towards the nerve terminals. Thus, it may be that, in response to inflammatory thermal and inflammatory mechanical pain, Na\(_{1.9}\) channels are transported to nerve terminals and sensitize nociceptors to noxious heat and mechanical stimuli.

### Involvement in thermal hyperalgesia

Different sets of modality-specific sets of sensory neurons seem to be activated in response to noxious heat or noxious cold (see Fig. 2). As can be seen from the study of Emery et al. (2016), mechanical stimulation of L4 DRG neurons triggers the activation of polymodal sensory neurons and, throughout this review, it appeared that noxious heat- or cold-specific pain pathways overlapped with those for the transmission of noxious mechanical stimuli. It is thus unlikely that there is a distinct neural

**Figure 2.** Modality-specific pain pathways and voltage-gated Na\(^{+}\) channels. Deletion of Na\(_{1.8}\) channels from DRG nociceptors abolishes behavioural responses to noxious cold, but not noxious thermal, stimuli in mice (left) (see Abrahamsen et al. (2008)), whereas deletion of Na\(_{1.7}\) channels from DRG nociceptors impairs withdrawal responses of mice to noxious thermal stimuli, but does not alter behavioural responses to noxious cold stimuli (right) (see Minett et al. (2012)). Cold and thermal nociception seems to be mediated by distinct subsets of DRG nociceptors (left, right). Among the biophysical properties that render Na\(_{1.8}\) and Na\(_{1.9}\) channels effective in transmission of noxious cold stimuli is their resistance to slow inactivation at low temperatures (left) (Zimmermann et al., 2007; Lolignier et al., 2015). On the other hand, Na\(_{1.7}\) channels may be involved in the release of substance P and wind-up in noxious heat-specific pathways (Minett et al., 2012), with Na\(_{1.9}\) channels potentially sensitizing nerve terminals to noxious thermal stimuli (right) (Lolignier et al., 2011).
pathway for the selective propagation of noxious mechanosen-
sory signals. Voltage-gated Na⁺ channels seem to be playing a
critical role in the segregation of noxious cold and noxious heat
modality-specific pathways (see Fig. 2). It is yet unclear whether
Na⁺,1.7 and Na⁺,1.8 channels are selectively expressed in nox-
ious heat- and noxious cold-specific pain pathways, respect-
ively. As was previously mentioned, withdrawal responses to
noxious heat were eliminated in Na⁺,1.7Advill mice, but were
maintained in Na⁺,1.7Nav1.8−/− mice (Minett et al., 2012). Whilst it
is likely that Na⁺,1.7 channels in Na⁺,1.8-negative nociceptors are
essential for the transmission of noxious heat stimuli
(Minett et al., 2012), the possibility that Na⁺,1.7 channels in
Na⁺,1.8-expressing neurons contribute to noxious thermal sen-
sation should not be rejected. It is possible that all Na⁺,1.7-
expressing DRG nociceptors are involved in the propagation of
noxious heat stimuli and that noxious thermal reflexes in
Na⁺,1.7Advill mice were abolished due to a complete knockout
of Na⁺,1.7 channels from all DRG nociceptors, whereas in
Na⁺,1.7Nav1.8−/− mice, the activity of Na⁺,1.7 channels in Na⁺,1.8-
negative DRG nociceptors could have been sufficient to main-
tain the behavioural response in the absence of Na⁺,1.7 channels
in Na⁺,1.8-expressing neurons. It is, therefore, also probable that
Na⁺,1.7 channels in both Na⁺,1.8-negative and Na⁺,1.8-posi-
tive DRG nociceptors are involved in thermal pain sensation. A
direct comparison in thermal pain reflexes between mice that
lack Na⁺,1.7 channels in Na⁺,1.8-negative sensory neurons only
and mice lacking Na⁺,1.7 channels solely in Na⁺,1.8-positive
neurons (Na⁺,1.7Nav1.8−/−) could have offered greater insight
into the involvement of specific Na⁺,1.8-expressing DRG
nociceptors in thermal pain and the expression pattern of
Na⁺,1.7 channels in noxious heat-specific pain pathways.
Our understanding of the expression pattern of Na⁺,1.8
channels in noxious cold-pain pathways is also limited, as
studies have made wide use of global Na⁺,1.8 knockout
mouse lines, e.g. Na⁺,1.8DTA (Abrahamsen et al., 2008), and
not of conditional Na⁺,1.8 knockout mice.

Furthermore, these findings raise the question of whether nociceptors that express both Na⁺,1.7 and Na⁺,1.8 channels
might be polymodal, owing to the modality-specific contribu-
tions of the channels. It has previously been shown that ther-
mal hyperalgesia, but not noxious thermal sensation, is
absent in Na⁺,1.7Nav1.8−/− mice (Nassar et al., 2004; Minett
et al., 2012). This could be attributed to the biophysical prop-
eerties of Na⁺,1.7 and Na⁺,1.8 channels. Na⁺,1.7 channels are
more significant in early stages of electrogenesis in nociceptor
neurons, as they produce graded depolarizations, potentially
boosting subthreshold potentials and resulting in the activa-
tion of Na⁺,1.8 channels that activate at more depolarized
thresholds (Dib-Hajj et al., 2005). Na⁺,1.8 channels maintain
repetitive firing during sustained depolarization (Han,
Huang, Waxman, 2016), generate large persistent currents
and ramp currents, produce spontaneous longer-lasting action
potentials, and increase firing frequency (Han et al.,
2015), potentially contributing to increased sensitivity to nox-
ious thermal pain. Na⁺,1.7Nav1.8−/− mice do not exhibit impair-
ments to noxious thermal detection (Nassar et al., 2004),
likely due to the action of Na⁺,1.7 channels in Na⁺,1.8-negative
nociceptors. However, thermal hyperalgesia is eliminated
(Nassar et al., 2004), potentially due to the absence of the
Na⁺,1.7-mediated graded depolarization that raise the mem-
brane potential of DRG neurons to the threshold for Na⁺,1.8
channel activation. In addition, intrathecal injection of spe-
cific antisense oligonucleotides to Na⁺,1.8, which resulted in
knockdown of Na⁺,1.8 channels in rat DRG neurons, did not
alter the response of rats to noxious mechanical or thermal
stimuli (Lai et al., 2002). However, the antisense oligonu-
cleotides abolished thermal and mechanical hyperalgesia in rats
that had undergone spinal nerve ligation, an effect that was
reversible upon cessation of the antisense oligonucleotide
Treatment (Lai et al., 2002). This could potentially be attribu-
ted to the absence of the large persistent currents and long-
lasing action potentials that are mediated by Na⁺,1.8 channels.
Therefore, whereas it is not clear whether nociceptors that
express both Na⁺,1.7 and Na⁺,1.8 channels can convey both
noxious heat and noxious cold stimuli, they are likely involved
in thermal hyperalgesia.

Special Considerations

In summary, Na⁺,1.7, Na⁺,1.8 and Na⁺,1.9 channels are involved in
modality-specific pain pathways via various mechanisms (see
Fig. 2). Na⁺,1.8 and Na⁺,1.9 channels play an important role in
noxious cold-specific pain pathways, as they appear to be resis-
tant to slow inactivation at low temperatures and remain active
when channels of other afferents are inactivated by noxious
cold. On the other hand, it is proposed that Na⁺,1.7 channels
are essential for the amplification of noxious heat-specific trans-
ducer currents, the release of substance P and wind-up of
responses at the dorsal horn of the spinal cord. Na⁺,1.9 were
seen to be important in noxious thermal and mechanical hyper-
sensitivity in inflammatory pain, potentially via a mechanism
that involved their axonal transport to nerve terminals of DRG
neurons. Gain-of-function mutations in Na⁺,1.7 channels are
essential clinically as they are associated with conditions of
burning pain, such as inherited erythromelalgia, whereas,
recently, an activity-enhancing missense mutation in Na⁺,1.9
channels was associated with cold-aggravated pain (Leipold
et al., 2015). Finally, both Na⁺,1.7 and Na⁺,1.8 channels in
DRG nociceptors that co-express them can contribute to ther-
mal hyperalgesia.

Despite all that has been suggested, some considerations
ought not to be ignored. For example, global Na⁺,1.8 knockout
in mice ablates withdrawal responses to noxious cold stimuli,
but not to chemically-induced, e.g. acetone, noxious cooling
(Minett et al., 2012), highlighting the importance of the experi-
mental protocol used to model cold or thermal pain. Research
findings in rodent models of pain should be translated to
human physiology with a great deal of caution. Whereas
mouse DRG tissues highly express Na⁺,1.8 channels (45% of
total Na⁺ expression) in comparison to Na⁺,1.7 channels
(18%), human DRG tissues express more Na⁺,1.7 channels
(50%) and less Na\textsubscript{1.8} channels (12%) (Chang et al., 2017). Although TTXs and TTXr currents are relatively similar in rat and human DRG neurons, there are also important species differences, a notable example being that there is little evidence that the inactivation of TTXr currents is use-dependent in human DRG neurons (Zhang et al., 2017). Furthermore, whereas Na\textsubscript{1.7} channels likely play a major role in noxious heat-specific somatic pain pathways, they may not be important in visceral pain pathways, given that vast depletion of Na\textsubscript{1.7} channels from colonic sensory neurons in mice did not alter pain reflexes to intracolonic application of capsaicin or mustard oil, or induction of cystitis (Hockley et al., 2017). Like noxious cold-specific pain pathways, visceral pain pathways may implicate TTXr voltage-gated Na\textsuperscript{+} channels (Laird et al., 2002; Saito et al., 2008; Hockley et al., 2014). However, unlike noxious cold-specific pain pathways, knockout of Na\textsubscript{1.8} or Na\textsubscript{1.9} in rodents has been shown to affect the sensitization, but not the detection, of visceral pain (Qi, Zhou, Xu, 2011). This may be because the majority of visceral mucosal mechanosensory are chemosensitive (Sengupta, 2009), responding to inflammatory mediators, e.g. nerve growth factor (NGF), prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) that act to sensitize voltage-gated Na\textsuperscript{+} channels by various signalling transduction mechanisms, e.g. protein kinase A (PKA), protein kinase C (Qi, Zhou, Xu, 2011). The TTXr voltage-gated Na\textsuperscript{+} channels could be involved in hypersensitivity in a manner similar to the one described earlier for thermal hyperalgesia.

These considerations may have important implications in the development of effective analgesics. Any differences between human and rodent DRG neurons in the expression of voltage-gated Na\textsuperscript{+} channels or in their TTXr and TTXs currents can be accompanied by species differences in the pharmacological properties of voltage-gated Na\textsuperscript{+} channels in nociceptor neurons. For example, it has been reported that TTXs currents in human DRG neurons are resistant to the Na\textsubscript{1.7}-selective blocker Pro-Tx II and that the Na\textsubscript{1.7}-selective small molecule inhibitor PF-05 089 771 blocks both TTXs and TTXr currents in human nociceptors (Zhang et al., 2017). In addition, whereas the TTXr blocker A-803 467, which potently blocks human Na\textsubscript{1.8} channels (IC\textsubscript{50} = 8 nM), can significantly limit acute visceral nociceptive responses (Jarvis et al., 2007), selective pharmacological blockade of Na\textsubscript{1.7} channels in the visera is unlikely to be sufficient in targeting chronic visceral pain (Hockley et al., 2017). Nevertheless, future studies could identify markers for mechanisms related to the activation of modality-specific pain pathways, in the hopes of delivering more promising treatments for human pain (Emery et al., 2016).

**Author biography**

Georgios Louloudis recently completed his Neuroscience MSc degree at University College London. He reviewed the scientific literature, wrote the paper and has primary responsibility for the final content. His research interests are centred on neurological disorders, with a key focus on Alzheimer’s disease and dementia. He is broadly interested in the causes, mechanisms of toxicity, prevention, diagnosis and treatment of neurological disorders, and seeks to pursue an academic career in clinical and translational neuroscience.

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