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REVIEW

Voltage-gated Na channels

Sensory neuron sodium channels as pain targets; from cocaine to Journavx (VX-548, suzetrigine)

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Voltage-gated sodium channels underpin electrical signaling in sensory neurons. Their activity is an essential element in the vast majority of pain conditions, making them significant drug targets. Sensory neuron sodium channels play roles not only in afferent signaling but also in a range of efferent regulatory mechanisms. Side effects through actions on other cell types and efferent signaling are thus important issues to address during analgesic drug development. As an example, the human genetic evidence for $Na_V1.7$ as an ideal pain target contrasts with the side effects of $Na_V1.7$ antagonists. In this review, we describe the history and progress toward the development of useful analgesic drugs and the renewed focus on $Na_V1.8$ as a key target in pain treatment. $Na_V1.8$ antagonists alone or in combination with other analgesics are likely to provide new opportunities for pain relief for the vast number of people (about 33% of the population) impacted by chronic pain, particularly present in aging populations.

Introduction

Pain treatment with natural products has been used through the ages (Wood, 2015), and extracts from the coca plant that target sodium channels are still commonly used in South America. Chewing coca plant leaves suppresses tiredness and pain without dramatic numbness. Cocaine was isolated from coca plants in 1862 and found to cause anesthesia by Koller (Goerig et al., 2012). He used cocaine for eye surgery in 1884, and the use of cocaine spread rapidly in the clinical world. The relationship between anesthesia and analgesia is significant for sodium channel blockers, where increasing doses cause first analgesia and then anesthesia. Procaine or novocaine was synthesized in 1905 and was used for anesthesia, but the longer-acting properties of lidocaine proved useful and this drug is widely used to this day (Rahart, 1972; Gordh et al., 2010). In this review, we tell the story of sodium channel isoform identification and their validation as pain targets in sensory neurons, together with recent developments in medicinal chemistry that have provided a number of potential new analgesic drugs. FDA approval of a new effective $Na_V1.8$ antagonist, Suzetrigine, marketed under the brand name Journavx, is a striking advance in pain treatment.

Identifying sodium channels

The remarkable intellectual and experimental feats of the 18th century underpin our present understanding of electrical signaling in the nervous system. An interesting historical overview is provided by Piccolino, (1997). After the discovery that there was a membrane potential across nerves, du Bois-Reymond described the action potential in 1848. Julius Bernstein expounded a membrane theory that involved altered ion permeability to explain electrical propagation. In the mid-20th century, Kenneth Coles at Columbia showed that there was an increase in conductance associated with the action potential, developing the voltage clamp technique subsequently used to great effect (Hodgkin and Huxley, 1952a) to examine the role of different ion fluxes that contribute to action potential propagation. Thus, by the mid-1950s, electrophysiological analysis of electrical signaling in the nervous system had matured, just as genetics turned into a molecular science with the discovery of the structure of DNA, leading eventually to the cloning of ion channels.

Toxins proved essential both for purifying sodium channels and in understanding the structural and molecular determinants of sodium channel gating (Hartshorne and Catterall, 1981). The

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bacterial toxins tetrodotoxin (TTX) and saxitoxin isolated from puffer fish were found to exert their toxic actions through sodium channels by Narahashi in 1964 (Narahashi, 2008). This allowed Catterall to isolate sodium channel proteins and obtain partial protein sequence, facilitating the cloning of the channels. Noda and Numa showed that multiple transcripts of sodium channels existed in the rat brain and isolated cDNA copies of mRNA, finally expressing functional channels in *Xenopus* oocytes (Numa and Noda, 1986) These technical feats have given us a wealth of insights into sodium channel function. The regulation of sodium channel transcription was also studied in the 1990s, and groups led by Anderson and Mandel both identified a regulatory DNA sequence that plays an important role in restricting most sodium channel gene expression to neurons—the neuron-restricted silencing element (Chong et al., 1995; Schoenherr and Anderson, 1995).

The structures of voltage-gated sodium channels (VGSC) are similar. The VGSC gene family comprises nine homologous members *SCN1A–SCN11A*, while the encoded sodium-selective ion channels are numbered from $Na_V1.1$ to $Na_V1.9$. Nax encoded by *SCN7A*, though structurally related to VGSCs, is activated by altered sodium concentrations and is physically associated with the sodium potassium ATPase (Noda and Hiyama 2015). See Table 1. Each α-subunit (~260 kDa) contains four homologous domains comprising six transmembrane segments (see Fig. 1). One α-subunit is sufficient to form a functional channel, but α-subunits associate with β-subunits (*SCN1B–SCN4B*), which modulate channel biophysics and trafficking. The voltage sensors contain repeated motifs of positively charged amino acids followed by hydrophobic residues arranged in 3_{10} helix, placing the positively charged residues on one side of the helix as a linear array. Depolarization of the cell alters the electric field across the cell membrane, resulting in the rapid movement of the D*I–III* S4 voltage sensors and a conformational change in the protein, which opens the ion channel pore. Channel opening caused by membrane depolarization results in a rapid influx of sodium ions and further depolarization of the membrane potential toward the equilibrium potential for sodium (approximately +60 mV in most neurons). VGSCs close within milliseconds of opening. Inactivation of VGSCs is usually incomplete, resulting in a small persistent Na^+ current, which inactivates over a time period of tens of seconds. This can have important functional consequences (e.g., Branco et al., 2016). VGSCs can be divided into two parts with the transmembrane domains S1–S4, contributing to the voltage sensor, and S5–S6 arranging to form the sodium-selective pore. The VGSC inactivation gate contains three amino acids (isoleucine, phenylalanine, and methionine) located in the intracellular loop connecting domains III and IV. Progress has been made in determining the three-dimensional structures of eukaryotic sodium channels using cryo-EM. Shen provided the first cryo-EM structure of a eukaryotic sodium channel (Shen et al., 2017). Other structures followed (Shen et al., 2017; Pan et al., 2018; Fan et al., 2023; Wu et al., 2023; Huang et al., 2024) and were discussed up to 2024 in a review by Huang et al. (2024). However, the conformations present in the multimolecular structures found in a neuronal membrane may be subtle variants on these basic structures. Very interestingly, there is strong evidence that VGSCs exist as dimers linked by 14–3–3 proteins that interact with the first intracellular loop of the channels (Clatot et al., 2017). Indeed, the original work of Hodgkin and Huxley on the ionic basis of action potential generation (Hodgkin and Huxley, 1952a, 1952b) fits well with a model that invokes cooperative activation of closely associated channels (Huang et al., 2012; Kumar et al., 2024) rather than individual channels acting non-cooperatively. Analysis of $Na_V1.7$-interacting proteins in a physiological setting has been carried out with an epitope-tagged $Na_V1.7$ knock-in mouse (Kanellopoulos et al., 2018). Intriguingly, $Na_V1.1$ and $Na_V1.2$, but not other VGSCs, are candidates to bind to $Na_V1.7$.

Table 1. **VGSC genes and channels**

Gene	Ion channel
SCN1A	$Na_V1.1$
SCN2A	$Na_V1.2$
SCN3A	$Na_V1.3$
SCN4A	$Na_V1.4$
SCN5A	$Na_V1.5$
SCN7A	Nax
SCN8A	$Na_V1.6$
SCN9A	$Na_V1.7$
SCN10A	$Na_V1.8$
SCN11A	$Na_V1.9$

Sodium channels and pain

The fact that sodium channel blockers, such as lidocaine, are effective analgesics focused attention on the three sensory neuron isoforms $Na_V1.7$–$Na_V1.9$ found at high levels in the peripheral nervous system. Importantly, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ null mutant mice are viable but show major deficits in pain behavior, making them attractive drug targets. In fact, only $Na_V1.8$ is selectively expressed in sensory neurons, while $Na_V1.7$ and $Na_V1.9$ are found in a variety of central nervous system (CNS) and peripheral nervous system neurons as well. Examination of the RNA-seq database produced by the Linarrson lab (http://mousebrain.org) shows that $Na_V1.7$ is present in almost all sets of CNS neurons, and Nav1.9 is present in the hypothalamus, as well as at very high levels in enteric neurons. There is also expression in non-neuronal tissues of mRNA-encoding $Na_V1.7$ and $Na_V1.9$. The organization of human sodium channel genes and their exons is schematized in Fig. 1. The TTX-resistant channels $Na_V1.9$ and $Na_V1.8$ and the cardiac channel $Na_V1.5$ genes are closely linked on chromosome 3p22.2. $Na_V1.7$ is found on chromosome 2q24.3 adjacent to the unusual sodium channel Nax encoded by *SCN7A*. $Na_V1.1$ is downstream of $Na_V1.7$, and intriguingly, an antisense RNA overlaps with both $Na_V1.1$- and $Na_V1.7$-encoding genes *SCN1A* and *SCN9A*, respectively. This antisense RNA is able to downregulate $Na_V1.7$ expression and is expressed in neurofilament-positive sensory neurons that are linked to proprioception and innocuous sensation (Koenig et al.,

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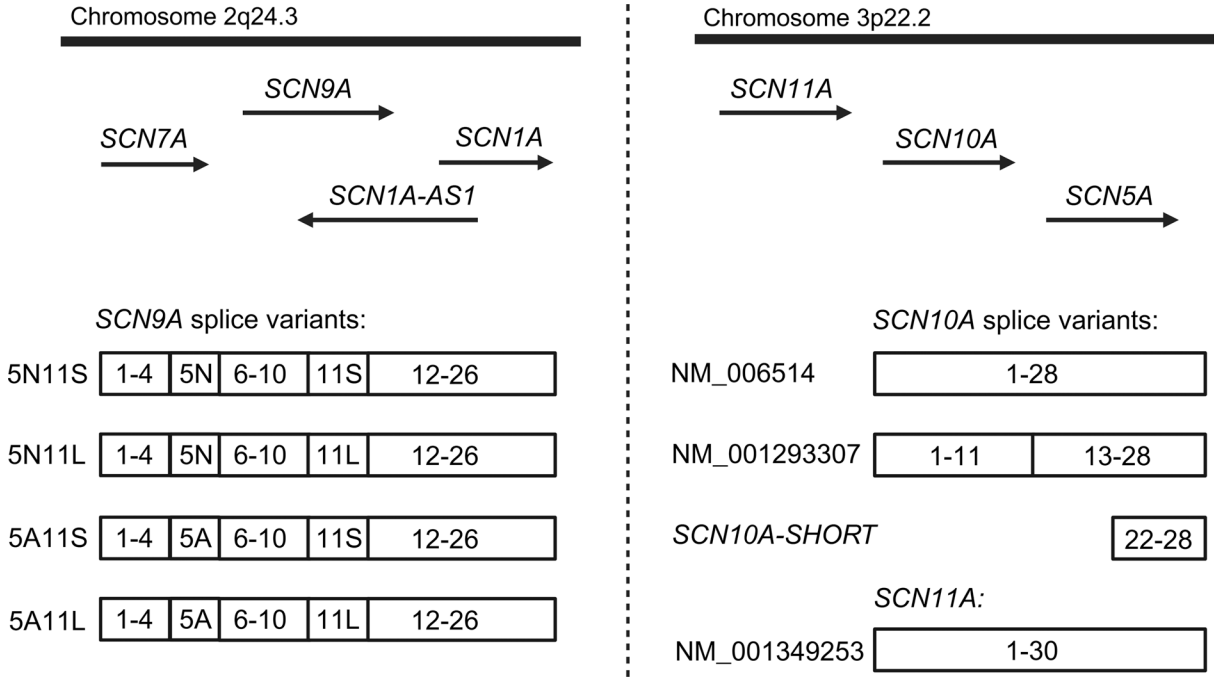

Figure 1. **Human *SCN9A*, *SCN10A*, and *SCN11A* gene footprints and key splice variants.** SCN9A maps to chromosome 2q24.3 and is flanked by SCN7A and SCN1A. A natural antisense transcript overlaps both SCN9A and SCN1A. SCN10A and SCN11A also map to a VGSC gene cluster, which also includes SCN5A on chromosome 3p22.2. There are four SCN9A splice variants expressed in dorsal root ganglia, which differ by the inclusion of one of the mutually exclusive coding exon 5 s (N or A) and a short (S) or long (L) variant of coding exon 11 (Farmer et al., 2012). Alternative splicing of SCN10A, which includes or excludes exon 12, results in a longer or smaller protein isoform, respectively. A short variant comprising exons 22–28 is expressed in the heart. SCN11A has two splice variants (NM_001349253 and NM_014139) that differ in the 5′UTR but encode the same protein.

2015). The activity of the antisense transcript in lowering functional expression of $Na_V1.7$ channels may explain why this ion channel has been linked to pain in humans and mice, while apparently playing no role in other forms of somatosensation.

$Na_V1.7$ was cloned by Gayle Mandel's group at Stoneybrook (Toledo-Aral et al., 1997). They noticed, presciently, that the channel was expressed in the terminals of sensory neurons, consistent with later in vivo observations showing a key role for the channel in neurotransmitter release. However, the channel is very broadly expressed in many parts of the CNS as well as autonomic neurons, where it also plays an essential role.

Embryonic deletion of $Na_V1.7$ in $Na_V1.8^+$ sensory neurons was found by Nassar to result in analgesia (Nassar et al., 2004). Also in 2004, Yang's team showed a link between $Na_V1.7$ human mutations and some rarer forms of erythermalgia (Yang et al., 2004). Waxman's team analyzed a range of these erythermalgia-associated mutants and showed that they were gain-of-function mutations, resulting in increased neuronal activity (Waxman et al., 2014). However, generating transgenic mouse models of the human mutants failed to give an erythermalgia phenotype. Other human mutations linked to defective inactivation of $Na_V1.7$ also caused an increase in pain, particularly evoked by mechanical stimuli (Fertleman et al., 2006). Finally, loss-of-function $Na_V1.7$ humans were found to be pain free (Cox et al., 2006). Thus, $Na_V1.7$ gain-of-function mutations may cause pain in humans, while loss of the channel results in pain-free humans—data that energized pharma companies to develop $Na_V1.7$ antagonists.

Application of the opioid antagonist naloxone substantially reversed the analgesia, implying a role for the opioid system in mouse $Na_V1.7$ null analgesia (Minett et al., 2015). The same effect was observed in human $Na_V1.7$ null pain-free humans (Minett et al., 2015; MacDonald et al., 2021). An induction of preproenkephalin expression was detected in embryonic $Na_V1.7$ null mutant mouse sensory neurons, but this does not explain opioid dependent analgesia, as a similar level of enkephalin induction induced by deletion of the transcription factor NFAT5 does not result in any analgesia (Pereira et al., 2018). This anomaly was resolved by the observation that the opioid signaling system is strongly potentiated in mouse $Na_V1.7$ null mice (Isensee et al., 2017).

The mechanism of analgesia of embryonic $Na_V1.7$ nulls seems to depend in large part on a failure of neurotransmitter release. Glutamate and substance P release are both dramatically downregulated in embryonic $Na_V1.7$ mouse null sensory neurons (MacDonald et al., 2021). $Na_V1.7$ interacts with opioid receptors via proteins like GNAO1 (Iseppon et al., 2024). It is present at high levels in the terminals of sensory neurons (see Figs. 2 and 4) and also binds molecules associated with synaptic vesicle release machinery like synaptotagmin (Kanellopoulos et al., 2018). Thus, its activity at central terminals seems to be crucial for primary afferent signaling to the CNS. It may be necessary for depolarization at central terminals that recruits voltage-gated calcium channels to enable glutamate transmitter release. Other studies of human $Na_V1.7$ null analgesia have provided evidence for a potential role of peripheral neuropathy (McDermott et al., 2019).

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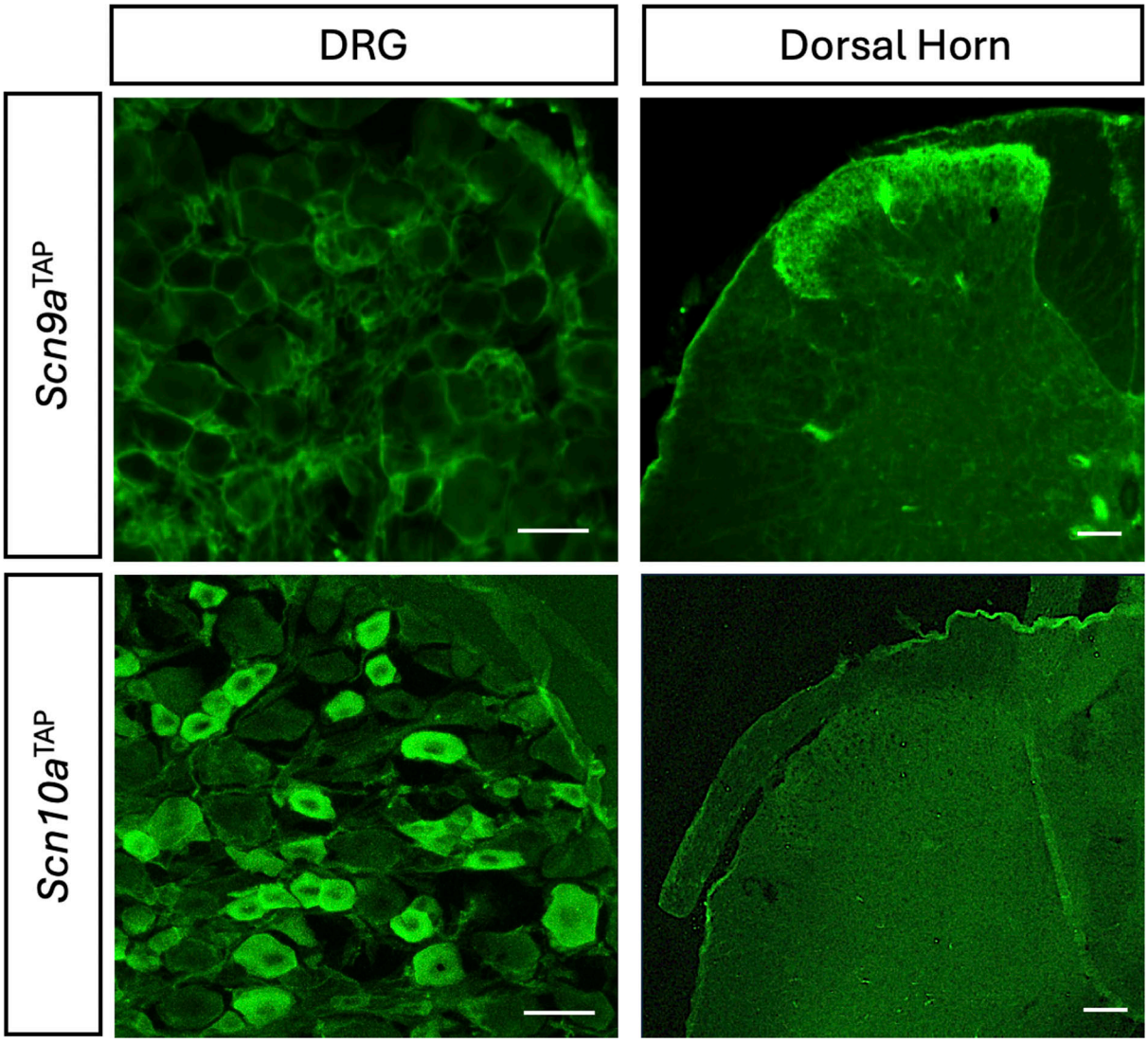

Figure 2. **Different distribution of $Na_V1.8$ and $Na_V1.7$ in the DRG and spinal cord.** The expression of $Na_V1.8$ and $Na_V1.7$ in DRG and the spinal cord was investigated with immunohistochemistry. In brief, the DRG and spinal cord sections from 4% PFA-perfused TAP-tagged $Na_V1.8$ and $Na_V1.7$ knock-in mice were stained with anti-FLAG antibody (1:400; #F1804; Sigma-Aldrich), then followed with goat-anti-mouse IgG conjugated with Alexa 488 (1:1,000; #A-11001; Invitrogen). The staining was visualized and analyzed using Leica TCS SP8 Confocal Microscope System. More details can be found in a previous study (Kanellopoulos et al., 2018). FLAG-tag $Na_V1.8$ expression (in green) is visible in mainly small-diameter DRG neurons in TAP-tagged $Na_V1.8$ mice (A). But it does not appear in the DRG of TAP-tagged $Na_V1.7$ mice (B). FLAG-tagged $Na_V1.7$ expression (in green) is present in lamina I to III of dorsal horn in the spinal cord in TAP-tagged $Na_V1.7$ mice (C) but is absent in the spinal cord of TAP-tagged $Na_V1.8$ knock-in mice (D). Scale bar = 100 µm.

Importantly, if $Na_V1.7$ is partially deleted in adult mice with tamoxifen-inducible Cre recombinase, analgesia is also obtained (Deng et al., 2023). However, in these experiments, in contrast to embryonic nulls, there is a loss of electrical excitability in sensory neurons and no apparent role detected for the opioid system. Embryonic deletion of $Na_V1.7$ does not alter sensory neuron excitability in mice (MacDonald et al., 2021). This difference with the findings in embryonic nulls (MacDonald et al., 2021) supports the view that there are two distinct types of analgesia associated with embryonic or adult loss of $Na_V1.7$ expression. As $Na_V1.7$ is the voltage-gated channel that responds first with action potentials to sensory neuron depolarization, the adult data are convincing. It is possible that $Na_V1.7$ is also enriched at peripheral as well as central terminals.

The viability and normal behavior apart from a lack of pain of embryonic $Na_V1.7$ nulls suggest that developmental compensatory effects rescue the excitability of peripheral neurons. $Na_V1.7$ is the principal human parasympathetic sodium channel and plays an important role in sympathetic neurons as well as throughout the CNS (Kocmalova et al., 2017; Branco et al., 2016) and potentially in insulin release (Zhang et al., 2014). Therefore, there must be compensatory mechanisms, perhaps involving upregulation of other channels in the embryonic nulls to rescue central, autonomic, and sensory neuron excitability. The lack of therapeutic window and autonomic side effects of potent selective $Na_V1.7$ channel blockers also contrasts with the apparent normality of embryonic $Na_V1.7$ null mice and humans (Regan et al., 2024). The hypothesis that expression of

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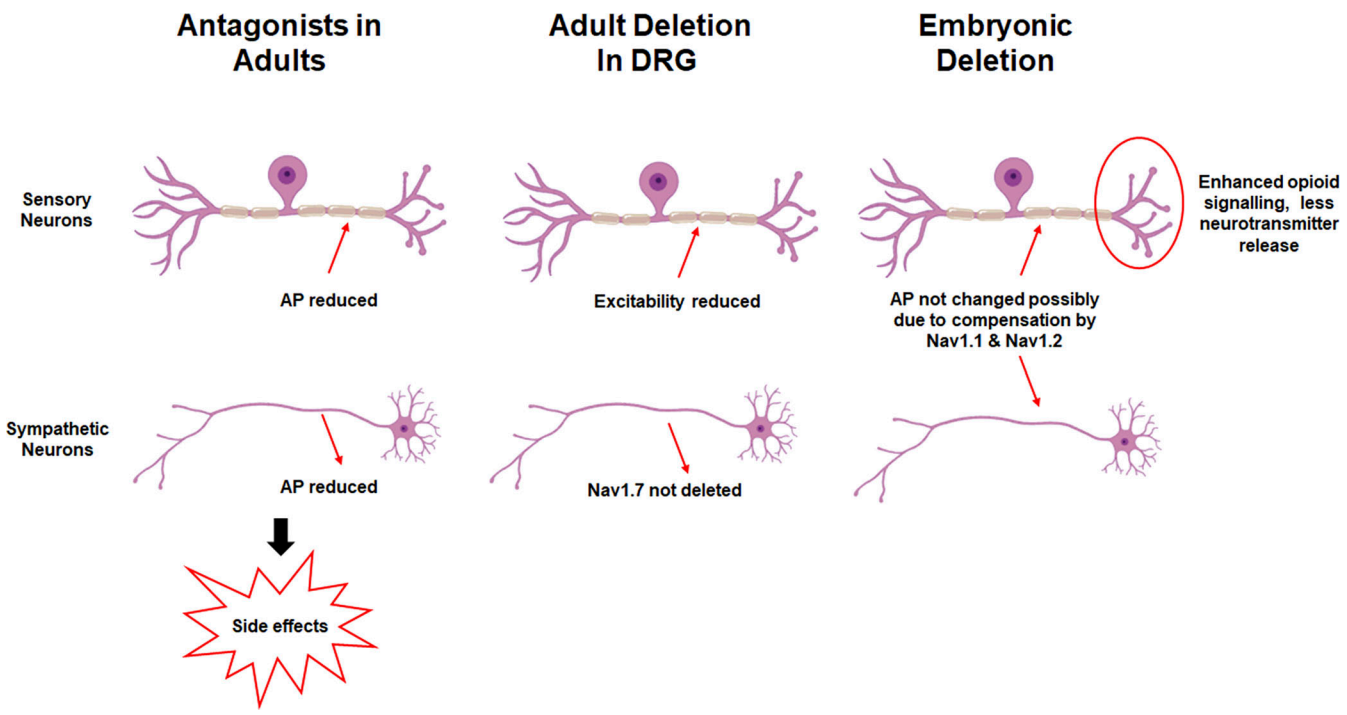

Figure 3. **Analgesia associated with loss of $Na_V1.7$ expression.** Embryonic loss of $Na_V1.7$ leads to viable functional humans and mice, whose only deficit is anosmia (MacDonald et al., 2021; Weiss et al., 2011). Surprisingly, potent antagonists of $Na_V1.7$ are toxic through actions on the autonomic nervous system (Regan et al., 2024). Partially deleting $Na_V1.7$ in adult sensory neurons (but not autonomic neurons) limits action potential propagation to produce analgesia (Deng et al., 2023). In embryonic nulls there is a loss of neurotransmitter release that is opioid dependent, but in adult nulls there is no role for opioids in analgesia.

other ion channels could compensate for the loss of $Na_V1.7$ in embryonic null sensory neurons was tested by measuring proteins levels with mass spectrometry (Iseppon et al., 2024). Sodium channels $Na_V1.1$ and $Na_V1.2$ are upregulated in $Na_V1.7$ embryonic null mice (Iseppon et al., 2024). Intriguingly, many of the upregulated proteins physically interact with $Na_V1.7$ based on immunoprecipitation and mass spectrometry identification (Kanellopoulos et al., 2018).

In summary, embryonic loss-of-function $Na_V1.7$ mutants are likely to have a potentially lethal phenotype owing to effects on cells other than sensory neurons. Developmental compensatory mechanisms by other sodium channels appear to mask this deleterious event Figs. 3 and 4. $Na_V1.7$ antagonists have dangerous side effects that show no therapeutic window with analgesia (Regan et al., 2024). Thus, $Na_V1.7$ channel blockers are not attractive as analgesic drugs.

There are, however, other potential routes to targeting $Na_V1.7$ to affect analgesia. Khanna et al. have focused on the role of collapsin response mediator protein CRMP2 that is regulated by SUMOylating and phosphorylation (Braden et al., 2021). This protein has been shown to bind to and control $Na_V1.7$ functional expression. Targeting it may lower channel activity. Khanna and others have shown that CRMP2 also regulates many other ion channels implicated in somatosensation (Brustovetsky et al., 2014; Ji et al., 2019; Chi et al., 2009), and the fact that there is no serious loss of sympathetic function with the drugs targeting this interaction (Khanna, personal communication) suggests that these useful analgesics are not targeting $Na_V1.7$ alone but also acting on other channels involved in peripheral pain pathways. The channel repertoires within sympathetic and sensory neuron are likely to be distinct. Hence, this approach to pain control remains potentially important, as side effect issues that mitigate against channel blockers may be less significant for broad-spectrum channel-trafficking blockers. Gene therapy approaches have also been explored (Vega-Loza et al., 2020).

$Na_V1.8$

The TTX-resistant sodium channel $Na_V1.8$, was cloned in 1996 (Akopian et al., 1996) and acts as a major contributor to the upstroke of action potentials. The channel is insensitive to blocking with TTX, and its biophysical properties are unusual, allowing it to sustain high-frequency input into the CNS. It is selectively expressed in sensory neurons and has been shown to play an important role, particularly in inflammatory and mechanical pain (Akopian et al., 1999). Antagonists are potent analgesics in preclinical models of neuropathic and inflammatory pain (Ekberg et al., 2006). TTX insensitivity depends upon the presence of a serine residue that on mutagenesis confers normal TTX sensitivity on the channel—just as happens with the heart channel (Sivilotti et al., 1997). The pattern of expression of NaV1.8 is remarkably specific, and it has proved invaluable as a marker for damage-sensing neurons. $Na_V1.8$ is essential in maintaining the excitability of nociceptors at low temperatures, becoming the sole electrical impulse generator at temperatures <10°C. This is caused by enhanced slow inactivation of TTX-sensitive channels in response to cooling, whereas the

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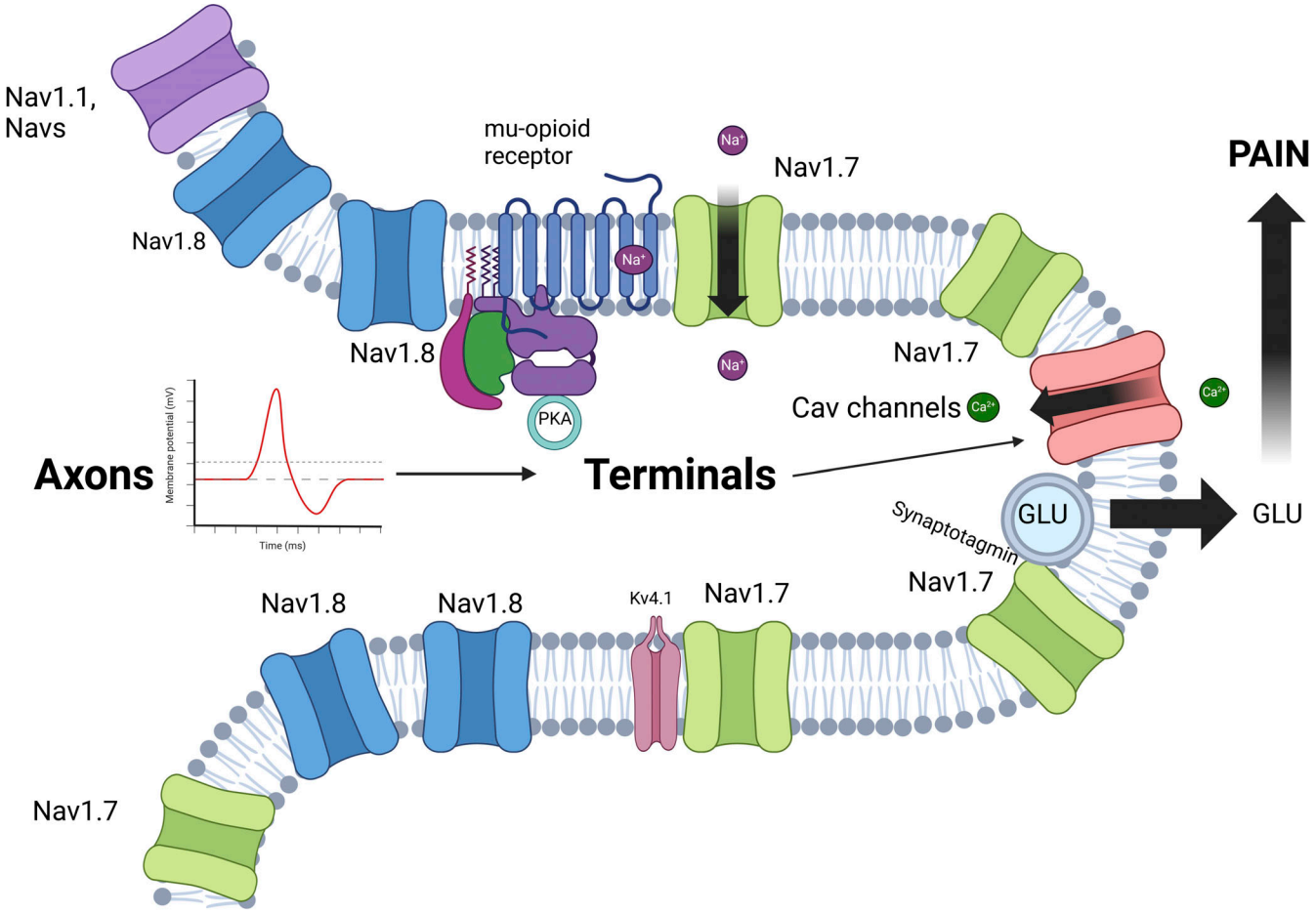

Figure 4. **Distribution and function of $Na_V1.7$ at terminals and $Na_V1.8$ in axons of sensory neurons.** $Na_V1.8$ is principally found in the peripheral axons, while $Na_V1.7$ is concentrated at terminals. There it interacts with components of the synaptic vesicle release machinery (e.g., Synaptotagmin) and may recruit voltage-gated calcium channels to depolarize the central terminal and evoke neurotransmitter release (Kanellopoulos et al., 2018). $Na_V1.7$ is also known to associate with opioid receptors that may be deactivated by sodium that is released with the persistent current associated with $Na_V1.7$. PKA activation downstream of opioid receptors is known to be enhanced in $Na_V1.7$ nulls (Isensee et al., 2017). KV4.1, another target of opioid signaling, associates with $Na_V1.7$. Sodium channels may exist as dimers, and $Na_V1.1$, $Na_V1.6$, $Na_V.1.7$, and other Na_V channels are found in axons as well as $Na_V1.8$. As pain occurs in some conditions (e.g., bone pain) without $Na_V1.7$ or $Na_V1.8$, other sodium channels must be able to contribute to nociceptive input. Much of this input nonetheless comes via $Na_V1.8$-expressing neurons (Haroun et al., 2023).

inactivation of $Na_V1.8$ is cold resistant. (Zimmermann et al., 2007). Antisense oligonucleotides attenuate the development and maintenance of neuropathic pain, while small interfering RNA-selective knockdown of $Na_V1.8$ reverses mechanical allodynia (Dong et al., 2007). However, $Na_V1.8$ knockout mice show neuropathic pain behavior in one pain model, while cancer-induced bone pain is also unaffected by the deletion of the $Na_V1.8$ channel (Haroun et al., 2023). Analysis of knockout mice also shows an important role for $Na_V1.8$ in visceral pain (Heinle et al., 2024). Laird and Cervero showed that both colitis and associated referred pain were markedly diminished in $Na_V1.8$ global null mice (Laird et al., 2002).

Human genetic evidence of a role for $Na_V1.8$ in pain is weaker than that for $Na_V1.7$. For example, no human pain-free null mutants have been identified. However, human erythermalgia mutants have been identified (Kist et al., 2016) that impact on action potential properties. Other mutations, for example A1073V, have been linked to less pain after abdominal surgery (Coates et al., 2019). Many $Na_V1.8$-focused drug development programs were halted after the discovery of a genetic link with cardiovascular problems and Brugada sudden death syndrome and $Na_V1.8$ (Chambers et al., 2010). This issue has been resolved by Christoffels et al., who showed that a cryptic intronic promoter drives the production of a C-terminal fragment named SCN10A-*short*, comprising the last eight transmembrane segments of $Na_V1.8$ in the heart (Man et al., 2021). There, this inactive protein promotes the activity of the heart channel $Na_V1.5$, explaining why the loss of SCN10A-*short* can result in cardiac dysfunction and Brugada sudden death syndrome. The role of this short $Na_V1.8$ protein may explain the absence of human loss-of-function $Na_v1.8$ mutants with diminished pain. The loss of $Na_V1.8$ potentially leads to cardiovascular dysfunction during development that may be lethal. Present antagonists targeting the $Na_V1.8$ channel pore are not compromised by actions on the short form found in the heart.

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The role of $Na_V1.8$ in pain pathways, first obtained through knockout studies, is reinforced by the fact that a range of inflammatory mediators increase $Na_V1.8$ activity. Within the intracellular first and second loops, five serines have been shown to be targets for protein kinase A, activated by prostaglandins (Fitzgerald et al., 1999). Phosphorylation results in enhanced activity and a shift in voltage dependence (Kimourtzis et al., 2024). The inflammatory mediator nerve growth factor (NGF) plays a major role in osteoarthritis and bone cancer pain. It also enhances expression of $Na_V1.8$, but through an indirect route. The calcium-binding protein p11 (S100A10, annexin 2 light chain) traffics $Na_V1.8$ into sensory neuron membranes and is transcriptionally upregulated by NGF (Foulkes et al., 2006). There is no effect of NGF on $Na_V1.8$ gene expression, but the channel is inserted into the membrane through the interaction with NGF-induced p11. p11 is essential for normal levels of expression of $Na_V1.8$ and interacts with the N-terminal region of the channel (Okuse et al., 2002). Other inflammatory mediators, such as tumor necrosis factor, also increase the expression of $Na_V1.8$ through activation of a number of kinases (Chen et al., 2011). Thus, a role for $Na_V1.8$ in pain is well established, and antagonists are clearly of interest as potential analgesics.

$Na_V1.8^+$ neurons have been implicated in a number of other physiological processes through their efferent functions. Most of these studies have relied on killing $Na_V1.8^+$ neurons using a mouse expressing Cre recombinase driven by the $Na_V1.8$ promoter (Nassar et al., 2004). $Na_V1.8$ expression is haplosufficient, so it is possible to drive Cre recombinase from one *Scn10a* allele to explore function of $Na_V1.8$ neurons. The Cre unleashes the actions of diphtheria toxin (or its receptor). The contribution of $Na_V1.8$ itself to these various functions in general remains unexplored, but the activity of $Na_V1.8^+$ neurons has been unambiguously demonstrated. It may therefore be worth appraising effects of new $Na_V1.8$ antagonists on functions other than pain. $Na_V1.8^+$ neutrons have been shown to play a role in feeding and weight control (Bullich-Vilarrubias et al., 2024), as well as immunity (Filtjens et al., 2021), infections, and temperature regulation (Loose et al., 2023). These observations emphasize the intertwined nature of damage-sensing neurons and immune responses in protecting the body from a variety of insults.

Interactions between $Na_V1.7$ and $Na_V1.8$

The relation between $Na_V1.7$ and $Na_V1.8$ channels has been explored through studying sensory neurons in culture (Vasylyev et al., 2024). However, the situation *in vivo* is different. Using epitope-tagged $Na_V1.7$ and $Na_V1.8$, we can see that while $Na_V1.8$ is present at high levels in the peripheral axons of sensory neurons, most $Na_V1.7$ is expressed at the central terminals within the spinal cord, where $Na_V1.8$ is hardly detectable (Figs. 2 and 4).

A similar concentration may occur at peripheral terminals, consistent with a role for $Na_V1.7$ initiating action potentials. An analysis of 1,000 human cadavers showed that there is no $Na_V1.8$ in the human CNS (Osteen et al., 2025). As mentioned earlier, $Na_V1.7$ binds elements of the synaptic release mechanism, such as synaptotagmin, so it is likely that $Na_V1.7$ is closely associated with the voltage-gated calcium channels that are essential for neurotransmitter release. A loss of action potentials and depolarization at central terminals would explain why embryonic nulls do not release glutamate in response to noxious stimuli. Combined with the role of opioids in diminishing neurotransmitter release, this provides a mechanism that explains the pain-free phenotype of embryonic $Na_V1.7$ null mice and humans.

$Na_V1.9$ was cloned by Dib-Hajj et al. (1998) and examined electrophysiologically in sensory neurons from $Na_V1.8$ nulls, where the characteristics of the $Na_V1.9$ channel could be examined in an appropriate cellular context (Cummins et al., 1999). $Na_V1.9$ is a biophysically unique sodium channel which generates TTX-resistant currents that have very slow gating kinetics. The current generated by $Na_V1.9$ is "persistent" and can be activated at potentials close to resting membrane potential (approximately −60 mV), and the channel acts as a modulator of membrane excitability by contributing regenerative inward currents over a strategic membrane potential range both negative to and overlapping with the voltage threshold for other transient sodium channels (Eijkelkamp et al., 2012).

SCN11A knockout mice exhibit a clear analgesic phenotype, confirming that $Na_V1.9$ is an important player in generating hyperalgesia in inflammatory pain states. This appears to be explicable by changes in the properties of distal primary afferents. The response to inflammatory mediators is suppressed in $Na_V1.9$ knockout mice, consistent with the immunocytochemical localization of the channel at unmyelinated nerve endings, and the remarkable functional plasticity of the current, known to be under G-protein pathway control via protein kinase. There is considerable evidence that $Na_V1.9$ plays a role in human pain. Some mutations lead to congenital insensitivity to pain in humans (Woods et al., 2015). However, the pain-free mutants have major problems with gut motility leading to hospitalization, which is understandable as the ion channel is expressed at very high levels in myenteric neurons (Padilla et al., 2007) and has an important role in regulating gut motility (Zhao et al., 2023). $Na_V1.9$ has therefore been abandoned by most teams as an analgesic drug target.

Sodium channel–targeting analgesic drugs

With the complete repertoire of sodium channel genes having been established, it became possible to develop strategies to identify selective antagonists, particularly focusing on $Na_V1.7$ and $Na_V1.8$. Anti-epileptics, such as carbamazepine, have some utility in trigeminal neuralgia or diabetic neuropathy but are principally useful for epilepsy (Wang et al., 2024). A substantial effort has been made to generate $Na_V1.7$ and $Na_V1.8$ antagonists. This has been driven by a hugely informative effort exploiting cryo-EM, mutagenesis, and electrophysiological studies. Insights into the site and mechanism of action of both cocaine and lidocaine have been obtained. Cocaine's action on the human cardiac channel $Na_V1.5$ has been investigated in *Xenopus* oocytes (O'Leary and Chahine, 2002). They found a use-dependent inhibition via the interdomain III–IV linker that is required for the high-affinity component of cocaine inhibition. They also showed that mutation of a conserved aromatic residue (Y1767) in the D4/S6 segment weakened cocaine inhibition. Cocaine

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thus appears to be a general pore blocker that stabilizes sodium channels in an inactivated state.

Lidocaine is also a use-dependent sodium channel pore blocker that interacts with specific regions of sodium channels (Cummins, 2007). The voltage sensor S4 regions in domains 3 and 4 seem to be the site of high-affinity binding for lidocaine when they are in an outward position. The main interest of the pain community now is, of course, the development of isoform-specific sodium channel blockers that have limited side effects compared with general sodium channel antagonists. For such studies, in vivo experiments are essential. Unfortunately, species differences have made analysis of some of the new $Na_V1.8$ antagonists in rodents impossible, and nonhuman primates have been required for studies of human-selective antagonists. This precludes the use of GCaMP imaging studies that are so useful in analyzing peripheral analgesic drug action (Iseppon et al., 2022). However, the production of chimeras between $Na_V1.8$ from species that are susceptible or insensitive to channel block has proved very informative in terms of identifying drug-binding sites (Gilchrist et al., 2024).

$Na_V1.7$ antagonists

The genetic data on human and mouse $Na_V1.7$ gain- and loss-of-function mutants provide irrefutable evidence that $Na_V1.7$ plays a key role in pain pathways. Disappointingly, mechanistic studies of $Na_V1.7$ gain- and loss-of-function mutants demonstrate that this apparently perfect target may not be addressed (see above). $Na_V1.7$ is not peripheral neuron specific (Alexandrou et al., 2016). $Na_V1.7$ plays a key role in sympathetic and parasympathetic function and is present in the vast majority of CNS neurons as well as non-neuronal organs, like the pancreas and synoviocytes (Fu et al., 2024). Studies with a specific Merck antagonist have shown that side effects rule out $Na_V1.7$ antagonists as useful drugs (Regan et al., 2024). Within sensory neurons, a principal role of the channel seems to be at the central terminal within the CNS, contributing to neurotransmitter release. Thus, peripherally targeted antagonists such as Pfizer's PF-05089771007 are unlikely to be useful and indeed have failed. A comprehensive insight into analgesic drug-binding sites on $Na_V1.7$ has been produced using cryo-EM in two detailed and significant papers (Zhang et al., 2022). In the first, three central pore blockers were studied in detail. The xenon compound Xen907 was shown to bind to the S6 region of domain 4, with effects on the fast inactivation gate. Two earlier compounds are also pore blockers. TC-N1752, which closes the inactivation gate via effects on the S2 helix in domain 2, is able to lower formalin-induced pain. IN2 is a pore blocker, which does not cause conformational changes. Electrophysiological studies show that XEN907 and TC-N1752 stabilize $Na_V1.7$ in an inactivated state and delay the recovery from inactivation. Such studies were extended and refined by Wu et al. in a comprehensive analysis of the binding sites of validated $Na_V1.7$ blockers (Wu et al., 2023). Carbamazepine, bupivacaine, and lacosamide all bind to a site beneath the intracellular gate. Binding sites for a number of other analgesic drugs were also mapped. This work is unlikely to be extended now, given the side effect problems of $Na_V1.7$-targeting analgesics (Dormer et al., 2023). MK-2075, a small-molecule selective $Na_V1.7$ inhibitor (human and rhesus half-maximal inhibitory concentration [IC_{50}] = 85 and 161 nmol/liter, respectively) was assessed in rhesus monkeys and in phase I clinical studies to understand the safety of $Na_V1.7$ blockade. Its powerful effects on the autonomic nervous system showed no therapeutic window for analgesia. Genentech's highly potent and selective $Na_V1.7$ inhibitor, GNE-3565, also suffers from the same side effect issues.

$Na_V1.8$ antagonists

Despite relatively weak human genetic data, interest in $Na_V1.8$ antagonists as analgesics was apparent from the first identification of the channel because of the association of a TTX-resistant sodium channel with pain pathways (Elliott and Elliott, 1993). Functional $Na_V1.8$ and $Na_V1.9$ channels are difficult to express in many cell lines, although sensory neuron–derived cell lines such as ND7/23 have proved useful (Wood et al., 1990). In addition, there is divergence in sequence between rodent and human $Na_V1.8$ channels (Gilchrist et al., 2024) that has required a focus on the human channel for the development of useful analgesics.

The first evidence that $Na_V1.8$ was involved in mouse pain came from Jon Levine, who showed that antisense knockdown of $Na_V1.8$ transcripts led to analgesia in a model of prostaglandin E2-evoked hyperalgesia (Khasar et al., 1998). Mouse knockout studies later showed that $Na_V1.8$ had a significant role in inflammatory, mechanical, and visceral pain. The present opioid crisis has further enthused pharma to investigate this target. Abbot laboratories developed a potentially useful drug with micromolar activity that was not followed up in the clinic (Jarvis et al., 2007; Wang et al., 2024). Early clinical studies of Pfizer $Na_V1.8$ antagonists also resulted in their discontinuation (Bagal et al., 2014). However, Vertex persevered with a number of compounds (VX-150 and VX-548—Suzetrigine or Journavx) that reached the clinic, and other groups, for example Latigo, have also developed active molecules that are undergoing clinical trials (Gilchrist et al., 2024; Qin et al., 2023).

Cryo-EM has provided interesting structural insights into sodium channel structure and the interactions of drugs. Structures are, of necessity, determined in the depolarized state that may create difficulties for the study of drug interactions. For example, no information could be gleaned about the binding site of lidocaine on $Na_V1.7$ using cryo-EM (Wu et al., 2023). A tour-de-force cryo-EM structure of $Na_V1.8$ with and without the associated Abbott channel blocker, A-803467, has nonetheless provided insights into $Na_V1.8$ activity. Mutagenesis studies also allow a precise identification of residues involved in channel activity to be obtained (Huang et al., 2022). This information has been further extended to interrogate the mechanism of action of other sodium channel antagonists (Fig. 5) (Wang et al., 2024). As yet the precise site of action of the sole clinically validated $Na_V1.8$ antagonist, Suzetrigine/Journavx, has yet to be determined by cryo-EM, but the binding site has been identified using domain swops between $Na_V1.2$ and $Na_V1.8$. Transferring domain 2 of $Na_V1.8$ to $Na_V1.2$ resulted in Suzetrigine/Journavx sensitivity, and further sequence swaps between $Na_V1.8$ and $Na_V1.2$ identified a KKGS sequence in the VSD11 region that confers

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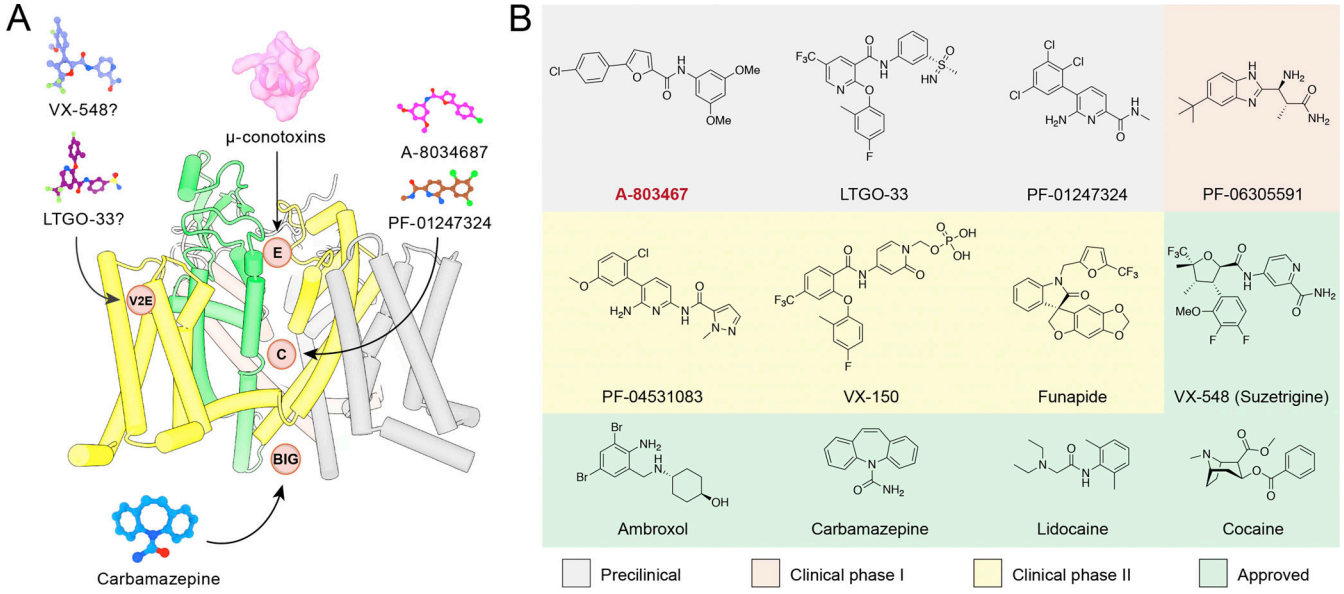

Figure 5. **$Na_V1.8$ is a key target for developing nonaddictive painkillers. (A)** The potential binding sites for various $Na_V1.8$ antagonists are summarized in a figure derived from cryo-EM studies of human $Na_V1.8$ complexed with A-803467 modified from Wang et al. (2024). The extracellular loop region above the pore domain (site E) is targeted by conotoxins, while additional binding sites for small molecules include the central pore region (site C), the extracellular cavity in VSD2 (site V2E), and the region beneath the intercellular gate (site BIG). A Latigo compound LTG-033 may bind to V2E with a role for some identified amino acids identified by mutagenesis studies GVAKKGSLS (Gilchrist et al., 2024). The Vertex drug Journavx (VX-548, Suzetrigine) is also suggested to bind to this site via amino acids KKGS. These findings indicate multiple distinct sites can be targeted to lower sodium channel activity. **(B)** Summary of clinical or investigational $Na_V1.8$ antagonists. Carbamazepine, lidocaine, and cocaine act as nonselective Na_V channel blockers, whereas ambroxol and Journavx preferentially target $Na_V1.8$. Several investigational molecules with diverse chemical structures include A-803467, LTGO-33, PF-01247324, PF-06305591, ANP-230, PF-04531083, and VX-150. Notably, ANP-230 differs from other selective $Na_V1.8$ antagonists by also blocking $Na_V1.7$ and $Na_V1.9$ (Kamei et al., 2024).

selectivity. Suzetrigine thus inhibits $Na_V1.8$ by binding to the protein's second voltage-sensing domain to stabilize the closed state of the channel. This novel allosteric mechanism results in tonic inhibition of $Na_V1.8$. The drug binds to and stabilizes the down state of the VSDII-closed channel, with some reverse use dependence with the activated channel (Osteen et al., 2025). FDA approval has now been granted for Journavx.

The properties of the Vertex inhibitors VX-150 and VX-548 or Suzetrigine/Journavx (Vaelli et al., 2024) have been explored electrophysiologically. Suzetrigine/Journavx is a remarkably potent inhibitor of the human channel with excellent selectivity (IC_{50} 0.27 nM and 30,000-fold selectivity against other sodium channels). At higher concentrations (IC_{50} 200 nM), it is effective on rodent channels. Interestingly, these compounds show similar properties to the abandoned Abbot inhibitor A-887826 in that they appear to bind the closed channel very effectively but "fall-off" the channel on depolarization so that the activated state of the channel does not bind to the drug (reverse use dependence). This is not necessarily a problem in terms of $Na_V1.8$ inhibition. Stabilization of the closed state by some compounds has been discussed (Gilchrist et al., 2024). Trains of action potentials at physiological temperature do not reduce Suzetrigine inhibition (Jo et al., 2025). There is excellent activity of the orally active Suzetrigine/Journavx in some acute human pain models (Jones et al., 2023).

Other orally effective analgesics like Latigo's latest compounds seem to act at similar sites and may demonstrate less reverse use dependence. Recent publications focus on LTGO-33, an orally active potent (nM) and selective (600-fold) sodium channel blocker. The compound that is in phase 2 trials after a successful phase 1 trial is LTG-01, about which less information is currently available. The binding site of LTGO-33 was identified by domain swops and mutagenesis and turns out to also be an extracellular cleft in the second voltage-sensing domain of $Na_V1.8$ (Gilchrist and Bosmans, 2018; Gilchrist et al., 2024).

The development of potent orally active $Na_V1.8$ antagonists is a major achievement in terms of potential new analgesic strategies. Fluorinated compounds are frequently represented in new drugs, and $Na_V1.8$-targeting analgesic drugs are no exception (Chandra et al., 2023). Fluorine aids binding to hydrophobic clefts and also impedes metabolic degradation. There are clearly some similarities between Suzetrigine and LTGO-33 in terms of the incorporation of fluorine residues, and the presence of an amide-linked aromatic ring linked to a further amide structure.

Some issues still remain to be resolved in terms of developing new $Na_V1.8$-targeted analgesics. Does the channel exist as a dimer with other sodium channels that may alter its pharmacology in some sets of neurons? Is reverse use dependence a problem in some chronic pain settings? Evidence against this idea has been presented. Perhaps as importantly, can antagonists potentiate the analgesic actions of other drugs so that they can be given in lower concentrations together. Expensive clinical trials are necessary to answer these important issues.

The future

The route from cocaine to Suzetrigine/Journavx provides a fascinating story of scientific endeavor. Recent developments

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in the sodium channel field have produced a mixture of disappointing ($Na_V1.7$) and positive ($Na_V1.8$) data for the pain community.

Damage-sensing neurons in the periphery drive the vast majority of pain conditions through sodium channel activity. Analgesic drug targets are amply represented on these nociceptive cells, ranging from receptors for inflammatory mediators that change the gain of the neurons (St.-Jacques and Ma, 2014, Bimonte et al., 2021) to receptors that activate nociceptors (Davis et al., 2000). In addition, some drugs, for example codeine or gabapentinoids, act to block neurotransmitter release and signaling to the CNS (Chow et al., 2023). Now with $Na_V1.8$ antagonists, we have the prospect of a new class of drugs that block electrical signaling along the length of the nociceptor axon (Jones et al., 2023). Lidocaine is an extraordinarily useful drug, acting as anesthetic and analgesic through its actions blocking sodium channel activity. However, it blocks all sensory neuron subtypes and can be lethal at high doses (Werdehausen et al., 2011). Suzetrigine/Journavx, unlike lidocaine appears to be specific for nociceptors. Positive results for human pain have already been reported for bunionectomy and diabetic neuropathy (Jones et al., 2023). In contrast, a recent study of back pain gave disappointing results (https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-results-phase-2-study-suzetrigine-treatment). This could be the result of a role for other sodium channels or a consequence of the properties of Suzetrigine (Hondeghem and Snyders, 1990). There are certainly a range of mechanisms involved in different pain states associated with sensory neurons that reinforce the case for combinatorial pain therapies (Bangash et al., 2018). However, the development of effective $Na_V1.8$ antagonists is a major advance, and FDA approval has recently been given for Journavx (https://www.fda.gov/news-events/press-announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain). Such antagonists, used alone or in combination with other analgesics, promise an advance in pain relief that is urgently needed in our aging world.

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