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

John N. Wood[1], Nieng Yan[2,3], Jian Huang [3], Jing Zhao[1], Armen Akopian[4], James J Cox[1], C. Geoff Woods[5] and Mohammed Nassar [6]

1) Molecular Nociception Group, Wolfson Institute for Biomedical Research, UCL, Gower Street, London WC1E 6BT, UK J.Wood@ucl.ac.uk, Jing02.zhao@ucl.ac.uk, J.J.Cox@ucl.ac.uk

2) Beijing Frontier Research Center for Biological Structures, State Key Laboratory of Membrane Biology, Tsinghua-Peking Joint Center for Life Sciences, School of Life Sciences, Tsinghua University, Beijing 100084, China; nyan@tsinghua.edu.cn

3) Institute of Bio-Architecture and Bio-Interactions (IBABI), Shenzhen Medical Academy of Research and Translation, Guangming District, Shenzhen 518107, Guangdong, China; huangjian@smart.org.cn

4) Department of Endodontics, The School of the Dentistry, UTHSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78229, US Akopian@uthscsa.edu

5) Cambridge Institute for Medical Research, Keith Peters Building, Biomedical Campus, Hills Rd, Cambridge CB2 0XY, UK CW347@cam.ac.uk

6) School of Biosciences, Firth Court, University of Sheffield, Sheffield S10 2TN, UK M.Nassar@sheffield.ac.uk

Summary Sensory neuron sodium channel Nav1.8 is essential for many pain conditions, and new antagonists hold significant promise for pain treatment.

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Abstract

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 Nav1.7 as an ideal pain target contrasts with the side effects of Nav1.7 antagonists. In this review we describe the history and progress towards the development of useful analgesic drugs and the renewed focus on Nav1.8 as a key target in pain treatment. Nav1.8 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, Bacon and van Zundert 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, 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 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 Nav1.8 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 signalling 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 1952) to examine the role of different ion fluxes that contribute to action potential propagation. Thus, by the mid-1950s, electrophysiological analysis of electrical signalling 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 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, Tapia-Ramirez 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 Figure 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. Depolarisation 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 depolarisation results

in a rapid influx of sodium ions and further depolarisation of the membrane potential towards the equilibrium potential for sodium (~+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) (Branco, Tozer 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 (IFM)) 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-electron microscopy. Shen provided the first cryo-EM structure of a eukaryotic sodium channel (Shen, Zhou et al. 2017). Other structures followed (Shen, Zhou et al. 2017, Pan, Li et al. 2018, Fan, Huang et al. 2023, Wu, Huang et al. 2023, Huang, Pan and Yan 2024) discussed up to 2024 in a review by Huang et al.(Huang, Pan and Yan 2024) However, the conformations present in the multi-molecular structures found in a neuronal membrane may be subtle variants on these basic structures. Very interestingly, there is strong evidence that voltage gated sodium channels exist as dimers linked by 14-3-3 proteins that interact with the first intracellular loop of the channels (Clatot, Hoshi et al. 2017). Indeed, the original work of Hodgkin and Huxley on the ionic basis of action potential generation (Hodgkin and Huxley 1952, Hodgkin and Huxley 1952) fits well with a model that invokes co-operative activation of closely associated channels (Huang, Volgushev and Wolf 2012, Kumar, Gupta and Ghosh 2024) rather than individual channels acting non-cooperatively. Analysis of Nav1.7 interacting proteins in a physiological setting has been carried out with an epitope-tagged Nav1.7 knock-in mouse (Kanellopoulos, Koenig et al. 2018). Intriguingly, Nav1.1 and Nav1.2, but not other voltage gated sodium channels are candidates to bind to Nav1.7. Nav1.1

Table 1.

Voltage-gated sodium channel genes and channels

Gene	Ion Channel
SCN1A	Nav1.1
SCN2A	Nav1.2
SCN3A	Nav1.3
SCN4A	Nav1.4
SCN5A	Nav1.5
SCN7A	Nax
SCN8A	Nav1.6
SCN9A	Nav1.7
SCN10A	Nav1.8
SCN11A	Nav1.9

Sodium channels and pain

The fact that sodium channel blockers such as lidocaine are effective analgesics focussed attention on the three sensory neuron isoforms $Na_V1.7$–$Na_V1.9$ found at high levels in the peripheral nervous system. Importantly, Nav1.7, Nav1.8 and Nav1.9 null mutant mice are viable but show major deficits in pain behaviour, 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 CNS and PNS neurons as well. Examination of the RNA-seq database produced by the Linarrson lab (Mouse.brain.org) shows that Nav1.7 is present in almost all sets of central nervous system 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 Nav1.7 and Nav1.9. The organisation of human sodium channel genes and their exons is schematised in figure 1. The TTX-resistant channels Nav1.9, Nav1.8 and the cardiac channel Nav1.5 genes are closely linked on chromosome 3p22.2. Nav1.7 is found on chromosome 2q24.3 adjacent to the unusual sodium channel Nax encoded by *SCN7A*. Nav1.1 is downstream of Nav1.7, and intriguingly, an antisense RNA overlaps with both Nav1.1 and Nav1.7 encoding genes *SCN1A* and *SCN9A* respectively. This antisense RNA is able to

downregulate Nav1.7 expression , and is expressed in neurofilament-positive sensory neurons that are linked to proprioception and innocuous sensation (Koenig, Werdehausen et al. 2015). The activity of the antisense transcript in lowering functional expression of Nav1.7 channels may explain why this ion channel has been linked to pain in humans and mice, whilst apparently playing no role in other forms of somatosensation.

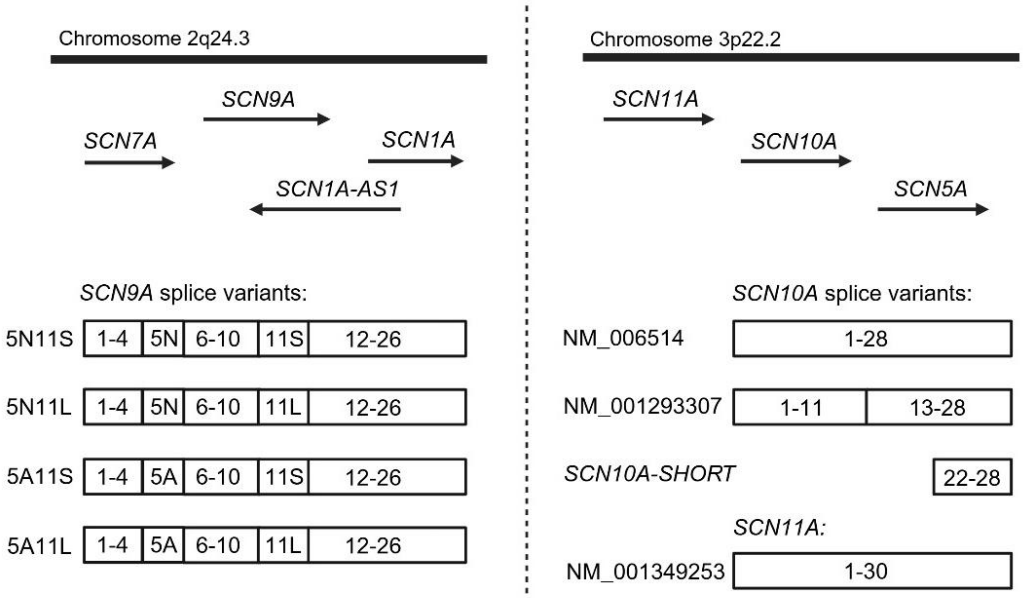

Figure 1 Human *SCN9A*, *SCN10A* and *SCN11A* gene footprints and key splice variants.

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 voltage-gated sodium channel 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 5s (N or A) and a short (S) or long (L) variant of coding exon 11 (Farmer, Cox 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.

Nav1.7 was cloned by Gayle Mandel's group at Stoneybrook (Toledo-Aral, Moss 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 central nervous system as well as autonomic neurons where it also plays an essential role.

Embryonic deletion of $Na_v1.7$ in Nav1.8+ sensory neurons was found by Nassar to result in analgesia (Nassar, Stirling et al. 2004) . Also in 2004, Yang's team showed a link between Nav1.7 human mutations and some rarer forms of erythermalgia (Yang, Wang 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, Merkies 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 Nav1.7 also caused an increase in pain, particularly evoked by mechanical stimuli (Fertleman, Baker et al. 2006). Finally, loss of function Nav1.7 humans were found to be pain-free (Cox, Reimann et al. 2006). Thus Nav1.7 gain of function mutations cause pain in humans, whilst loss of the channel results in pain-free humans – data that energized Pharma companies to develop Nav1.7 antagonists.

Application of the opioid antagonist naloxone substantially reversed the analgesia, implying a role for the opioid system in mouse Nav1.7 null analgesia (Minett, Pereira et al. 2015). The same effect was observed in human Nav1.7 null pain-free humans (Minett, Pereira et al. 2015, MacDonald, Sikandar et al. 2021). An induction of preproenkephalin expression was detected in embryonic Nav1.7 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, Millet et al. 2018). This anomaly was resolved by the observation that the opioid signaling system is strongly potentiated in mouse Nav1.7 null mice (Isensee, Krahé et al. 2017).

The mechanism of analgesia of embryonic Nav1.7 nulls seems to depend in large part on a failure of neurotransmitter release. Glutamate and substance P release are both dramatically down-regulated in embryonic Nav.1.7 mouse null sensory neurons (MacDonald, Sikandar et al. 2021). Nav1.7 interacts with opioid receptors via proteins like GNAO1 (Iseppon, Kanellopoulos et al. 2024). It is present at high levels in the terminals of sensory neurons (see Figure 3) and also binds molecules associated with synaptic vesicle release machinery like synaptotagmin (Kanellopoulos, Koenig 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 Nav1.7 null analgesia have provided evidence for a potential role of peripheral neuropathy (McDermott, Weir et al. 2019).

Importantly, if $Na_v1.7$ is partially deleted in adult mice with tamoxifen-inducible Cre recombinase, analgesia is also obtained (Deng, Dourado 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 Nav1.7 does not alter sensory neuron excitability in mice (MacDonald, Sikandar et al. 2021). This difference with the findings in embryonic nulls (MacDonald, Sikandar et al. 2021) supports the view that there are two distinct types of analgesia associated with embryonic or adult loss of Nav1.7 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 [22]. It is possible that Nav1.7 is also enriched at peripheral as well as central terminals.

The viability and normal behavior apart from a lack of pain of embryonic Nav1.7 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, Kollarik et al. 2017) (Branco, Tozer et al. 2016) and potentially in insulin release (Zhang, Chibalina 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 Nav1.7 channel blockers also contrasts with the apparent normality of embryonic Nav1.7 null mice and humans (Regan, Morissette et al. 2024). The hypothesis that expression of other ion channels could compensate for the loss of Nav1.7 in embryonic null sensory neurons was tested by measuring proteins levels with mass spectrometry (Iseppon, Kanellopoulos et al. 2024). Sodium channels Nav1.1 and Nav1.2 are upregulated in Nav1.7 embryonic null mice (Iseppon, Kanellopoulos et al. 2024). Intriguingly, many of the upregulated proteins physically interact with Nav1.7, based on immunoprecipitation and mass spectrometry identification (Kanellopoulos, Koenig et al. 2018).

In summary, embryonic loss of function Nav1.7 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 (Figure 2) . Nav1.7 antagonists have dangerous side effects that show no therapeutic window with analgesia (Regan, Morissette et al. 2024). Thus Nav1.7 channel blockers are not attractive as analgesic drugs.

There are however other potential routes to targeting Nav1.7 to effect analgesia. Khanna et al have focussed on the role of collapsin response mediator protein CRMP2 that is regulated by SUMOylating and phosphorylation (Braden, Stratton et al. 2022). This protein has been shown to bind to and control Nav1.7 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, Pellman et al. 2014, Ji, Hu et al. 2019) (Chi, Schmutzler 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 Nav1.7 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, Van et al. 2020).

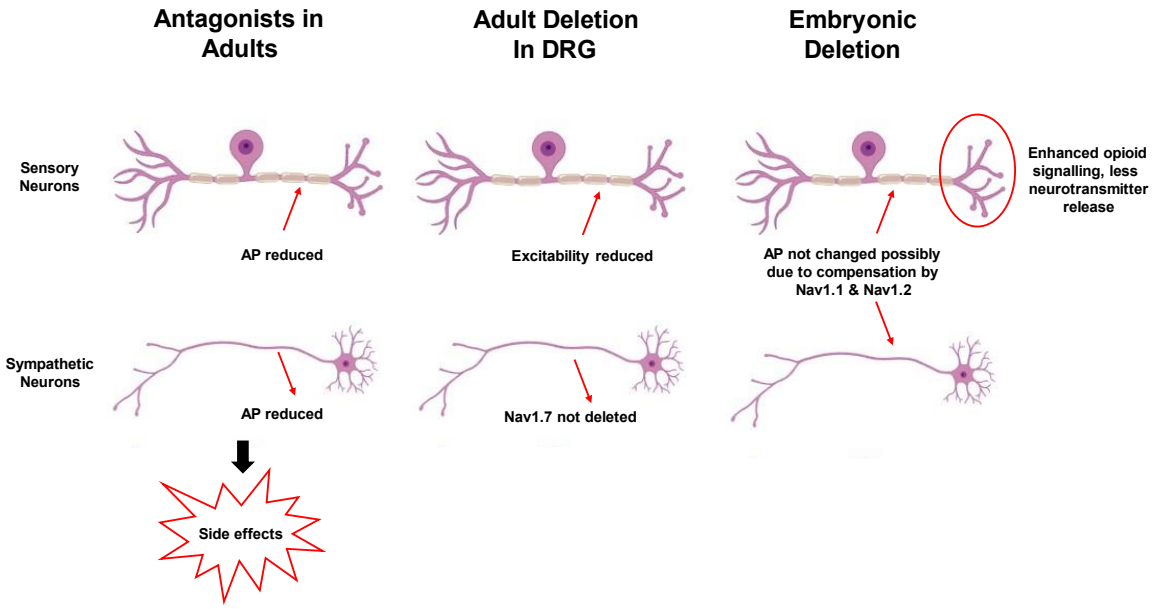

Figure 2 Analgesia associated with loss of Nav1.7 expression.

Embryonic loss of Nav1.7 leads to viable functional humans and mice whose only deficit is anosmia (MacDonald, Sikandar et al. 2021) (Weiss, Pyrski et al. 2011). Surprisingly, potent antagonists of Nav1.7 are toxic through actions on the autonomic nervous system (Regan, Morissette et al. 2024) Partially deleting Nav1.7 in adult sensory neurons (but not autonomic neurons) limits action potential propagation to produce analgesia (Deng, Dourado 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.

Nav1.8 The tetrodotoxin-resistant sodium channel Na_v 1.8, was cloned in 1996 (Akopian, Sivilotti and Wood 1996) and acts as a major contributor to the upstroke of action potentials. The channel is insensitive to block with TTX and its biophysical properties are unusual, allowing it to sustain high frequency input into the central nervous system. It is selectively expressed in sensory

neurons and has been shown to play an important role particularly in inflammatory and mechanical pain (Akopian, Souslova et al. 1999). Antagonists are potent analgesics in preclinical models of neuropathic and inflammatory pain (Ekberg, Jayamanne et al. 2006). Tetrodotoxin 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, Okuse 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 inactivation of $Na_V1.8$ is cold resistant. (Zimmermann, Leffler 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, Goregoaker et al. 2007). However, $Na_V1.8$ knockout mice show neuropathic pain behaviour in one pain model, whilst cancer-induced bone pain is also unaffected by the deletion of the Nav1.8 channel (Haroun, Gossage et al. 2023). Analysis of knockout mice also shows an important role for Nav1.8 in visceral pain (Heinle, Dalessio et al. 2024). Laird and Cervero showed that both colitis and associated referred pain were markedly diminished in Nav1.8 global null mice (Laird, Souslova et al. 2002).

Human genetic evidence of a role for Nav1.8 in pain is weaker than that for Nav1.7. For example, no human pain free null mutants have been identified. However human erythermalgia mutants have been identified (Kist, Sagafos et al. 2016) that impact on action potential properties. Other mutations, for example A1073V, have been linked to less pain after abdominal surgery (Coates, Kim 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, Zhao 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 8 transmembrane segments of $Na_v1.8$ in the heart (Man, Bosada 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 Nav1.8 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 Nav1.8 channel pore are not compromised by actions on the short form found in the heart.

The role of Nav1.8 in pain pathways, first obtained through knock-out studies, is reinforced by the fact that a range of inflammatory mediators increase Nav1.8 activity. Within the intracellular first and second loops, five serines have been shown to be targets for protein kinase A, activated by prostaglandins (Fitzgerald, Okuse et al. 1999). Phosphorylation results in enhanced activity and a shift in voltage-dependence (Kimourtzis, Rangwani 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 Nav1.8, but through an indirect route. The calcium binding protein p11 (S100A10, annexin 2 light chain) traffics Nav1.8 into sensory neuron membranes and is transcriptionally upregulated by NGF (Foulkes, Nassar et al. 2006). There is no effect of NGF on Nav1.8 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 Nav1.8 and interacts with the N-terminal region of the channel (Okuse, Malik-Hall et al. 2002). Other inflammatory mediators such as Tumor Necrosis Factor (TNF) also increase the expression of Nav1.8 through activation of a number of kinases (Chen, Pang et al. 2011). Thus a role for Nav1.8 in pain is well established, and antagonists are clearly of interest as potential analgesics.

Nav1.8+ neurons have been implicated in a number of other physiological processes through their efferent functions. Most of these studies have relied on killing Nav1.8+ neurons using a mouse expressing Cre recombinase driven by the Nav1.8 promoter (Nassar, Stirling et al. 2004). Nav1.8 expression is haplosufficient, so it is possible to drive Cre recombinase from one *Scn10a* allele to explore function of Nav1.8 neurons. The Cre unleashes the actions of diphtheria toxin (or its receptor). The contribution of Nav1.8 itself to these various functions in general remains unexplored, but the activity of Nav1.8+

neurons has been unambiguously demonstrated. It may therefore be worth appraising effects of new Nav1.8 antagonists on functions other than pain. Nav1.8+ neutrons have been shown to play a role in feeding and weight control (Bullich-Vilarrubias, Romani-Perez et al. 2024), as well as immunity (Filtjens, Roger et al. 2021), infections and temperature regulation (Loose, Lischka et al. 2023). These observations emphasise the intertwined nature of damage sensing neurons and immune responses in protecting the body from a variety of insults.

Interactions between Nav1.7 and Nav1.8

The relation between Nav1.7 and Nav1.8 channels has been explored through studying sensory neurons in culture (Vasylyev, Zhao et al. 2024). However, the situation *in vivo* is different. Using epitope-tagged Nav1.7 and Nav1.8, we can see that whilst Nav1.8 is present at high levels in the peripheral axons of sensory neurons, most Nav1.7 is expressed at the central terminals within the spinal cord, where Nav1.8 is hardly detectable (Figure 2).

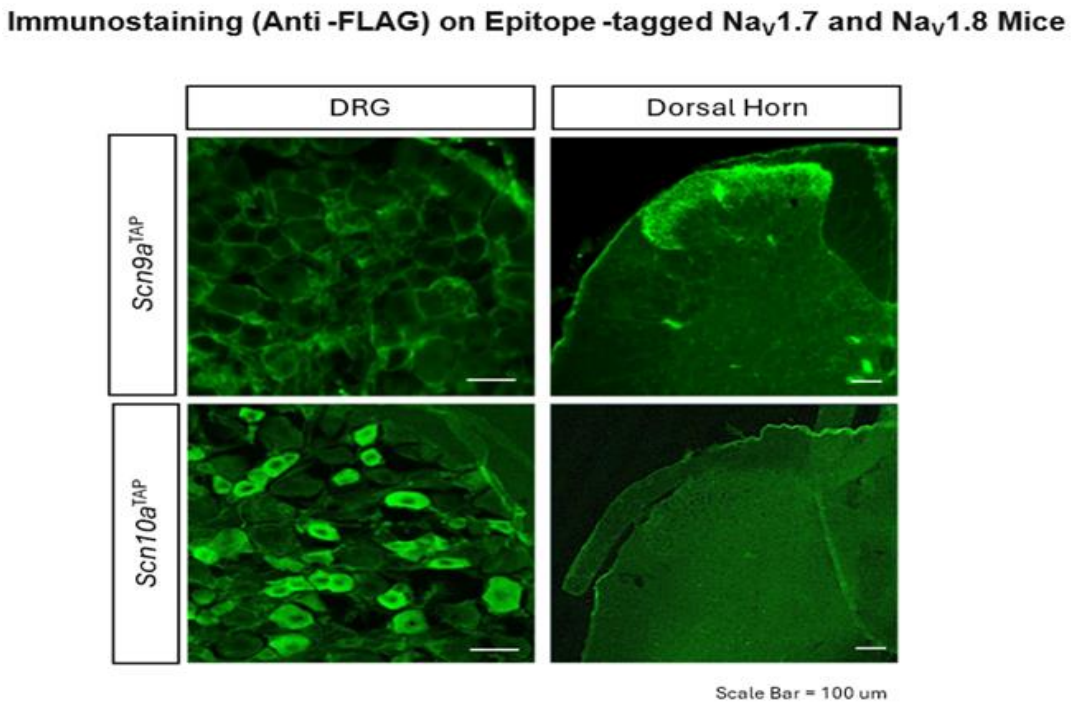

Figure 3. Different distribution of $Na_V1.8$ and $Na_V1.7$ in the DRG and spinal cord.

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; Sigma #F1804), then followed with goat-anti-mouse IgG conjugated with Alexa 488 (1:1000; Invitrogen #A-11001). The staining was visualized and analysed using Leica TCS SP8 Confocal Microscope System. More details can be found in a previous study (Kanellopoulos A. H., et. al., EMBO 2018).

A-B. 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).

C-D. 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.

A similar concentration may occur at peripheral terminals, consistent with a role for Nav1.7 initiating action potentials. An analysis of 1000 human cadavers showed that there is no Nav1.8 in the human central nervous system (Osteen, Immani et al. 2025). As mentioned earlier, Nav1.7 binds elements of the synaptic release mechanism such as synaptotagmin, so it is likely that Nav1.7 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 Nav1.7 null mice and humans.

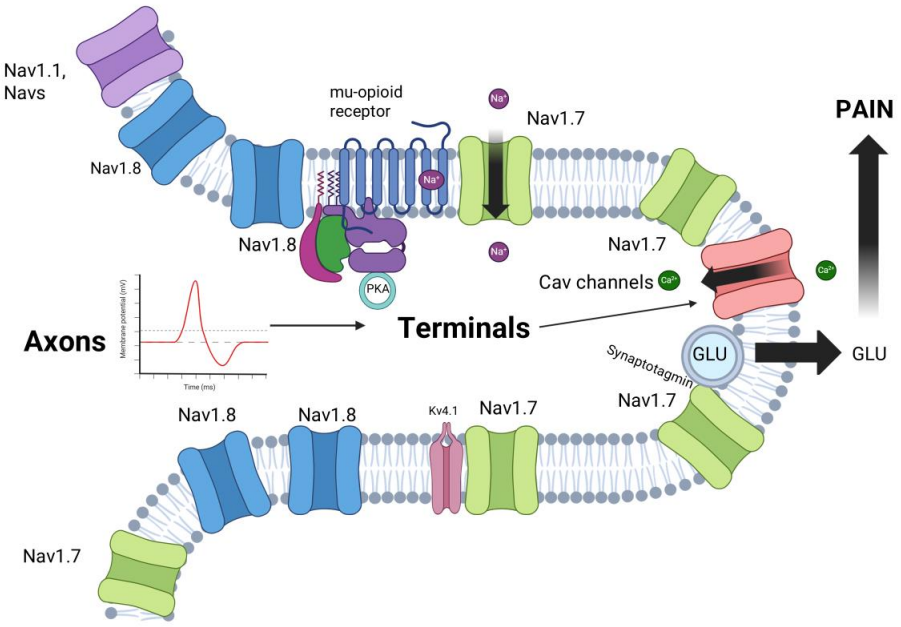

Figure 4 Distribution and function of Nav1.7 at terminals and Nav1.8 in axons of sensory neurons

Nav1.8 is principally found in the peripheral axons, whilst Nav1.7 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, Koenig et al. 2018). Nav1.7 is also known to associate with opioid receptors that may be de-activated by sodium that is released with the persistent current associated with Nav1.7. PKA activation downstream of opioid receptors is known to be enhanced in Nav1.7 nulls (Isensee, Krahé et al. 2017). KV4.1, another target of opioid signaling, associates with Nav1.7. Sodium channels may exist as dimers, and Nav1.1, Nav1.6, Nav.1.7 and other Nav channels are found in axons as well as Nav1.8. As pain occurs in some conditions (e.g. bone pain) without Nav1.7 or Nav1.8, other sodium channels must be able to contribute to nociceptive input. Much of this input nonetheless comes via Nav1.8 expressing neurons (Haroun, Gossage et al. 2023).

Nav1.9 was cloned by Sulayman Dibb Hajj (Dib-Hajj, Tyrrell et al. 1998) and examined electrophysiologically in sensory neurons from Nav1.8 nulls, where the characteristics of the Nav1.9 channel could be examined in an appropriate cellular context (Cummins, Dib-Hajj 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 (~–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, Linley 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 localisation 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 Nav1.9 plays a role in human pain. Some mutations lead to congenital insensitivity to pain in humans (Woods, Babiker et al. 2015). However, the pain-free mutants have major problems with gut motility leading to hospitalisation which is understandable as the ion channel is expressed at very high levels in myenteric neurons (Padilla, Couble et al. 2007) and has an important role in regulating gut motility (Zhao, Zhou and Shi 2023). Nav1.9 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 Nav1.7 and Nav1.8. Anti-epileptics such as Carbamazepine have some utility in trigeminal neuralgia or diabetic neuropathy but are principally useful for epilepsy(Wang, Huang et al. 2024). A substantial effort has been made to generate Nav1.7 and Nav1.8 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 Nav1.5 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 thus appears to be a general pore blocker that stabilises 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 to general sodium channel antagonists. For such studies *in vivo* experiments are essential. Unfortunately, species differences have made analysis of some of the new Nav1.8 antagonists in rodents impossible and non-human primates have been required for studies of human-selective antagonists. This precludes the use of GCaMP imaging studies that are so useful in analysing peripheral analgesic drug action (Iseppon, Linley and Wood 2022). However, the production of chimeras between Nav1.8 from species that are susceptible or insensitive to channel block has proved very informative in terms of identifying drug binding sites (Gilchrist, Yang et al. 2024)

Nav1.7 antagonists

The genetic data on human and mouse Nav1.7 gain and loss-of-function mutants provides irrefutable evidence that Nav1.7 plays a key role in pain pathways. Disappointingly, mechanistic studies of Nav1.7 gain and loss of function mutants demonstrate that this apparently perfect target may not be addressed (see above). Nav1.7 is not peripheral neuron-specific (Alexandrou, Brown et al. 2016). Nav1.7 plays a key role in sympathetic and parasympathetic function, and is present in the vast majority of central

nervous system neurons as well as non-neuronal organs like the pancreas and synoviocytes (Fu, Vasylyev et al. 2024). Studies with a specific Merck antagonist have shown that side effects rule out Nav1.7 antagonists as useful drugs (Regan, Morissette et al. 2024). Within sensory neurons, a principal role of the channel seems to be at the central terminal within the central nervous system, 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 Nav1.7 has been produced using cryo-EM in two detailed and significant papers (Zhang, Shi 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 NaV1.7 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 Nav1.7 blockers (Wu, Huang 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 Nav1.7 targeting analgesics (Dormer, Narayanan 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/L, 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 Nav1.7 inhibitor, GNE-3565 also suffers from the same side effect issues.

Nav1.8 antagonists

Despite relatively weak human genetic data, interest in Nav1.8 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 Nav1.8 and Nav1.9 channels are difficult to express in many cell lines, although sensory neuron-derived cell lines such as ND7/23 have proved useful (Wood, Bevan et al. 1990). In addition, there is divergence in sequence between rodent and human Nav1.8 channels (Gilchrist, Yang et al. 2024) that has required a focus on the human channel for the development of useful analgesics.

The first evidence that Nav1.8 was involved in mouse pain came from Jon Levine who showed that antisense knockdown of Nav1.8 transcripts led to analgesia in a model of prostaglandin E2-evoked hyperalgesia (Khasar, Gold and Levine 1998). Mouse knockout studies later showed that Nav1.8 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, Honore et al. 2007) (Wang, Huang et al. 2024). Early clinical studies of Pfizer Nav1.8 antagonists also resulted in their discontinuation (Bagal, Chapman 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, Yang et al. 2024) (Qin, Wei et al. 2023).

Cryo-electron microscopy 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 Nav1.7 using cryo-EM (Wu, Huang et al. 2023). A tour-de-force cryo-EM structure of Nav1.8 with and without the associated Abbott channel blocker, A-803467, has nonetheless provided insights into Nav1.8 activity. Mutagenesis studies also allow a precise identification of residues involved in channel activity to be obtained (Huang, Jin et al. 2022). This information has been further extended to interrogate the mechanism of action of other sodium channel antagonists (Wang, Huang et al. 2024). As yet the precise site of action of the sole clinically validated Nav1.8 antagonist, Suzetrigine/Journavx, has yet to be determined by cryo-EM, but the binding site has been identified using domain swops between Nav1.2 and

Nav1.8. Transferring domain 2 of Nav1.8 to Nav1.2 resulted in Suzetrigine/Journavx sensitivity, and further sequence swaps between NaV1.8 and Nav1.2 identified a KKGS sequence in the VSD11 region that confers selectivity. Suzetrigine thus inhibits $Na_V1.8$ by binding to the protein's second voltage sensing domain (VSD2) 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, Immani et al. 2025) . FDA approval has now been granted for Journavx.

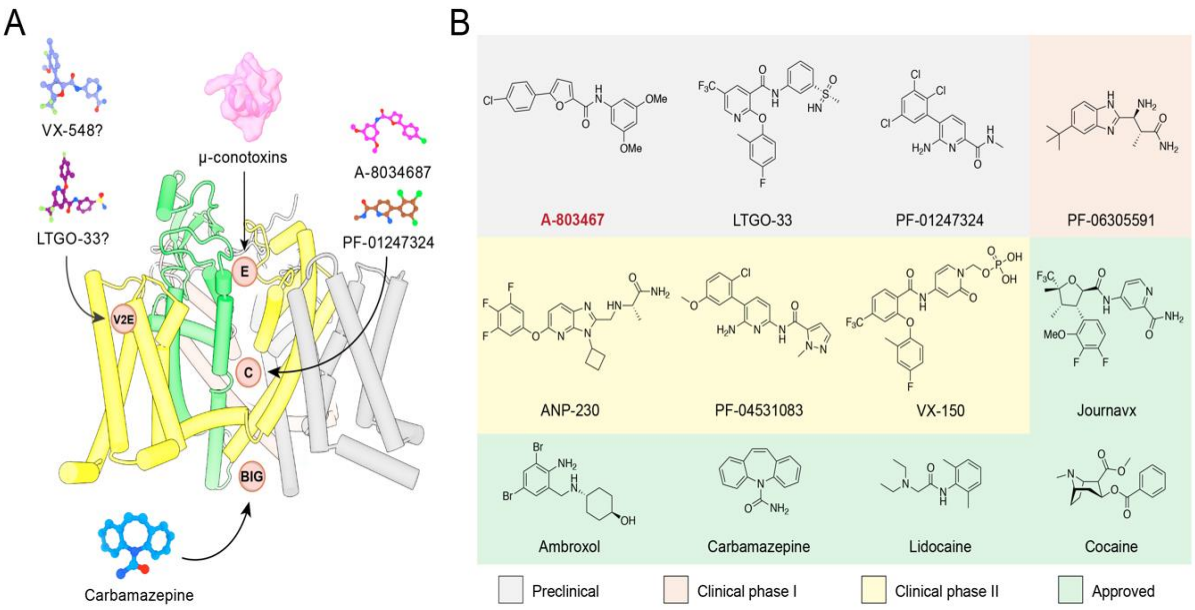

Figure 5 $Na_v1.8$ is a key target for developing non-addictive painkillers. *(A) The potential binding sites for various $Na_v1.8$ antagonists are summarized in a figure derived from cryo-EM studies of human Nav1.8 complexed with A-803467 modified from (Wang, Huang et al. 2024). The extracellular loop 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, Yang 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 non-selective 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, Kudo et al. 2024)

The properties of the Vertex inhibitors VX-150 and VX-548 or Suzetrigine/Journavx (Vaelli, Fujita et al. 2024) have been explored electrophysiologically. Suzetrigine/Journavx is a remarkably potent inhibitor of the human channel with excellent selectivity (IC50 0.27nM and 30,000 fold selectivity against other sodium channels). At higher concentrations (IC50 200nM) 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 depolarisation 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 Nav1.8 inhibition. Stabilization of the closed state by some compounds has been discussed (Gilchrist, Yang et al. 2024). Trains of action potentials at physiological temperature do not reduce Suzetrigine inhibition (Jo, Fujita et al. 2025). There is excellent activity of the orally active Suzetrigine/Journavx in some acute human pain models (Jones, Correll 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. As with Vertex, electrophysiological data on LTGO-33 was obtained at room temperature so we have little information about reverse use dependence at physiological temperatures. 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 Nav1.8 (Gilchrist and Bosmans 2018, Gilchrist, Yang et al. 2024).
The development of potent orally active Nav1.8 antagonists is a major achievement in terms of potential new analgesic strategies. Fluorinated compounds are frequently represented in new drugs, and Nav1.8 targeting analgesic drugs are no exception (Chandra, Singh et al. 2023). Fluorine aids binding to hydrophobic clefts and also impedes metabolic degradation. There are clearly some similarities between Suzetrigine and LTGO0033 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 Nav1.8-targetted 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 endeavour**.** Recent developments in the sodium channel field have produced a mixture of disappointing (Nav1.7) and positive (Nav1.8) 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, Cascella et al. 2021) to receptors that activate nociceptors (Davis, Gray et al. 2000). In addition, some drugs, for example codeine or gabapentinoids act to block neurotransmitter release and signalling to the central nervous system (Chow, Stevens et al. 2023). Now with Nav1.8 antagonists we have the prospect of a new class of drugs that block electrical signalling along the length of the nociceptor axon (Jones, Correll et al. 2023).

Lidocaine is an extraordinarily useful drug, acting as anaesthetic and analgesic through its actions blocking sodium channel activity. However, it blocks all sensory neuron subtypes and can be lethal at high doses (Werdehausen, Braun 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, Correll 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 2024). 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, Alles et al. 2018). However, the development of effective Nav1.8 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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