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$Na_V1.7$ as a pain target – From gene to pharmacology

Irina Vetter [a,b,*], Jennifer R. Deuis [a], Alexander Mueller [a], Mathilde R. Israel [a], Hana Starobova [a], Alan Zhang [c], Lachlan D. Rash [a,d], Mehdi Mobli [c]

[a] Institute for Molecular Bioscience, Centre for Pain Research, The University of Queensland, St Lucia, Qld 4072, Australia
[b] School of Pharmacy, The University of Queensland, Woolloongabba, Qld 4102, Australia
[c] Centre for Advanced Imaging, The University of Queensland, St. Lucia, Qld 4072, Australia
[d] School of Biomedical Sciences, The University of Queensland, St. Lucia, Qld 4072, Australia

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ABSTRACT

$Na_V1.7$, a subtype of the voltage-gated sodium channel family that is highly expressed in peripheral sensory neurons, remains one of the most promising targets for the treatment of pain. However, despite compelling genetic evidence supporting a key role for $Na_V1.7$ in regulating excitability of peripheral sensory neurons, the development of truly subtype-selective inhibitors has been challenging. Here, we discuss complexities surrounding targeting $Na_V1.7$ pharmacologically for treatment of pain and explore future opportunities for development of effective analgesic $Na_V1.7$ inhibitors.

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1. Introduction

Voltage-gated sodium channels (Na_V) are crucial in the processes of action potential generation and propagation as they provide a path for influx of sodium ions (Na^+) during the rising phase of an action potential. In humans there are nine α-subunit isoforms ($Na_V1.1$–1.9) with distinct expression profiles. Several of these Na_V isoforms have been implicated to have a role in pain, but none more so than $Na_V1.7$, which has received considerable attention based on remarkable human phenotypes resulting from mutations in *SCN9A*, the gene encoding the pore-forming $Na_V1.7$ α-subunit. Notably, loss of function mutations in *SCN9A* cause congenital insensitivity to pain, a rare human condition that leads to the inability to feel pain in the absence of other sensory impairments, other than loss of smell (anosmia). This makes $Na_V1.7$ an attractive pain target, as the phenotype of congenital insensitivity to pain suggests that pharmacological inhibition of $Na_V1.7$ could potentially treat a wide variety of pain types with little to no expected adverse effects. However, efforts to develop selective pharmacological inhibitors have been hampered due to the high level of homology between the Na_V subtypes, and we therefore know surprisingly little about the

Abbreviations: AGRP, agouti-related peptide; CIP, Congenital insensitivity to pain; DRG, dorsal root ganglion; IEM, inherited erythromelalgia; PEPD, paroxysmal extreme pain disorder; POMC, pro-opiomelanocortin; PVH, paraventricular hypothalamic nucleus; Na_V, voltage-gated sodium channel.

* Corresponding author at: Institute for Molecular Bioscience, 306 Carmody Road, Brisbane, St. Lucia, Qld 4072, Australia.
E-mail address: i.vetter@uq.edu.au (I. Vetter).

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therapeutic potential of selective $Na_V1.7$ inhibitors. We review the evidence supporting the validity of $Na_V1.7$ as a therapeutic target for pain, based on the findings from both genetic studies and functional assessment by $Na_V1.7$ modulators described to date.

2. Expression of $Na_V1.7$

Sensory neurons innervate peripheral tissues and provide us with the ability to sense touch, pressure, temperature and pain. They can be broadly classified into Aβ-, Aδ- and C-fibres based on conduction velocity, degree of myelination and size of the cell body. These neurons, whose cell bodies are found in the dorsal root ganglia, have a single axon with a peripheral branch that terminates in the skin or viscera, and a central branch that terminates in the spinal cord. Located at the peripheral terminals of these neurons are a range of specialised ion channels and receptors that respond to noxious stimuli by causing small, localised sub-threshold depolarisations known as generator potentials (Dubin & Patapoutian, 2010).

$Na_V1.7$, previously called PN1 or hNE, was initially identified as a peripheral neuron-specific sodium channel isoform highly expressed in sympathetic, dorsal root and trigeminal ganglia, but not at appreciable levels in the brain (Toledo-Aral et al., 1997) (Fig. 1). The robust expression of $Na_V1.7$ in postnatal and adult peripheral sensory neurons of all sizes has been systematically confirmed both in rodents, primates and humans (Ahmad et al., 2007; Black et al., 1996; Felts, Yokoyama, Dib-Hajj, Black, & Waxman, 1997; Gould et al., 2000; Porreca et al., 1999; Sangameswaran et al., 1997), with 63% of peripherin-positive dorsal root ganglion (DRG), 65% of IB4-positive neurons, 58% of CGRP-positive neurons and 15% of neurofilament-positive cell bodies exhibiting robust $Na_V1.7$ immunolabelling (Black, Frezel, Dib-Hajj, & Waxman, 2012). This pattern of expression is consistent with high intensity staining observed in guinea pig DRG cell bodies giving rise to unmyelinated C-fibre polymodal nociceptors, followed by moderate staining in a significant proportion of high- and low-threshold myelinated Aδ neurons (Djouhri et al., 2003). In contrast, only some cutaneous myelinated Aα/β low-threshold mechanosensitive units, and no muscle spindle low-threshold mechanosensitive units expressed $Na_V1.7$

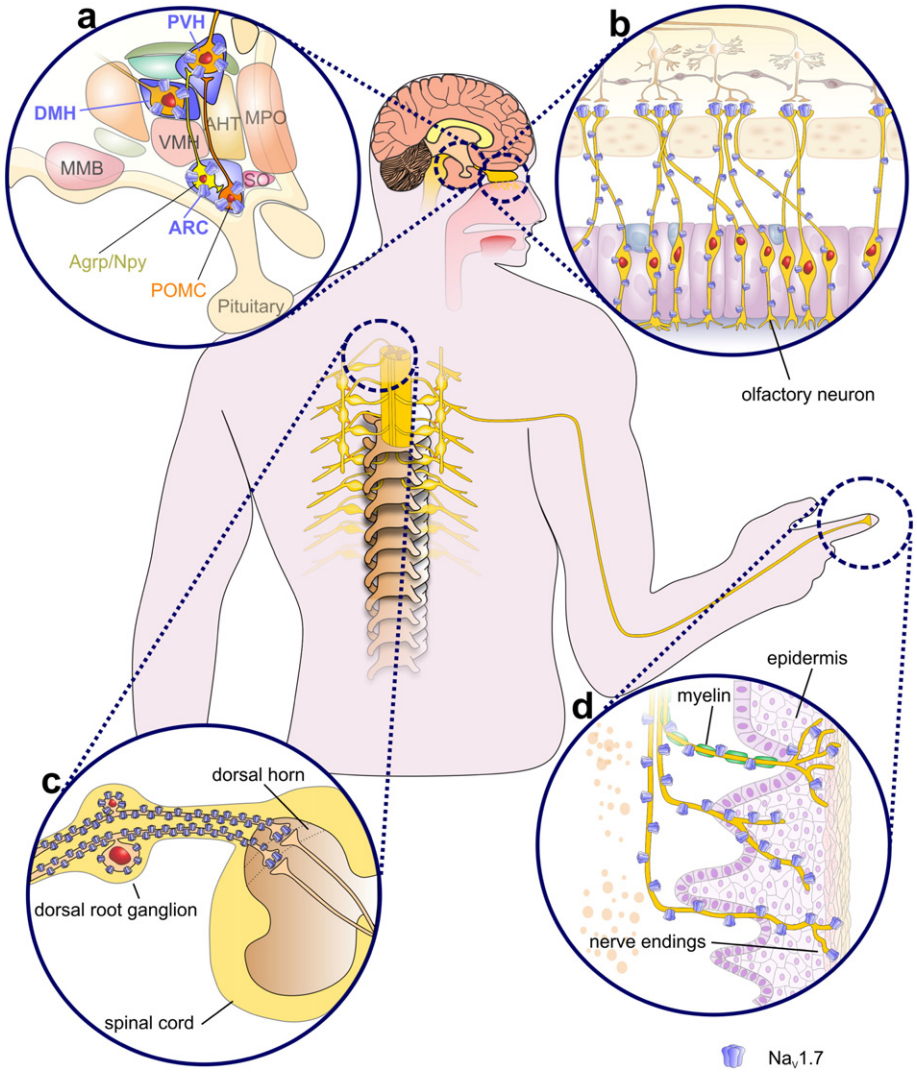

Fig. 1. Expression profile of $Na_V1.7$. a) In the rodent central nervous system, $Na_V1.7$ is expressed in the pituitary gland, subfornical organ as well as several hypothalamic nuclei (Ahmad et al., 2007; Morinville et al., 2007). In the arcuate nucleus (ARC), dorsomedial nucleus (DMH) and paraventricular nucleus (PVH), $Na_V1.7$ is expressed in Agrp, Npy and POMC-expressing neurons where it contributes a persistent current that is crucial for synaptic integration. Note that $Na_V1.7$ expression in these brain regions is substantially lower in primates and humans b) $Na_V1.7$ is expressed along the olfactory sensory nerve from the olfactory epithelium to the branches of the olfactory nerve but absent in mitral and granule neurons receiving synaptic inputs from olfactory sensory neurons. In these neurons, $Na_V1.7$ is crucial for neurotransmitter release and absence of functional $Na_V1.7$ leads to anosmia. c) In sensory neurons, $Na_V1.7$ is expressed in dorsal root ganglion neuron cell bodies, along axons, in the central terminals as well as in d) peripheral nerve terminals. MPO, medial preoptic nucleus; PVH, paraventricular nucleus; SO, supraoptic nucleus; AHT, anterior hypothalamic nucleus; VMH, ventromedial nucleus; MMB, mammillary body; ARC, arcuate nucleus; DMH, dorsomedial nucleus; Agrp, Agouti-related peptide neurons; Npy, Neuropeptide Y neurons; POMC, pro-opiomelanocortin neurons.