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Viewpoint

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No Gain, No Pain: $Na_V1.7$ as an Analgesic Target

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ABSTRACT: Chronic pain is one of the most complex and difficult to manage clinical problems, with the therapeutic utility of current-generation analgesics restricted by problems such as dose-limiting side effects, tolerance, and the potential for addiction. The voltage-gated sodium channel $Na_V1.7$ plays a key role in setting the threshold for action potential generation in primary sensory neurons, and humans that lack this channel are completely insensitive to pain. In this Viewpoint, we examine the potential of $Na_V1.7$ as an analgesic target a well as the challenges involved in developing therapeutically useful subtype-selective inhibitors of this ion channel.

KEYWORDS: *Chronic pain, $Na_V1.7$, analgesic, sensory neuron, nociceptor, monoclonal antibody*

Normal pain is a key adaptive response that signals actual or impending danger. In contrast, aberrant long-lasting pain transforms this adaptive response into a debilitating and often poorly managed disease. Chronic pain affects ~20% of the adult population, with higher prevalence in elderly cohorts. The economic cost of chronic pain in the United States is ~$600 billion per annum, more than the combined economic burden of cancer, heart disease, and diabetes.[1] Recent research suggests that an ion channel in sensory neurons might be a key analgesic target for treating chronic pain.

Noxious stimuli that cause pain are sensed by specialized afferent nerve fibers known as primary sensory neurons or nociceptors. These pseudounipolar neurons 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 (Figure 1). The peripheral terminals of these neurons are enriched in specialized channels and receptors that transduce mechanical, thermal, or chemical stimuli into a depolarization of the cell membrane, known as a generator potential. Proximal to these "pain sensors" is a specialized pacemaker zone where this generator potential can be transformed into an action potential (electrogenesis). Arrival of this electrical signal at the central projection of the sensory neuron leads to neurotransmitter release and subsequent activation of second order sensory neurons that carry the encoded signal to the brain, where it is perceived as pain (Figure 1).

Electrogenesis is largely a function of the type and density of voltage-gated sodium (Na_V) channels present in the pacemaker zone. Humans and rodents contain nine Na_V channel subtypes, denoted $Na_V1.1$–$Na_V1.9$. Of the five subtypes present in normal adult sensory neurons, namely, $Na_V1.1$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, the latter three play an important role in pain signaling. The crucial role of $Na_V1.7$ in pain generation was revealed by several remarkable human genetic studies. Gain-of-function mutations in the gene *SCN9A* that encodes $Na_V1.7$ underlie the syndromes erythromelalgia and paroxysmal extreme pain disorder that are characterized by severe episodic pain.[2] In contrast, nonsense mutations in *SCN9A* lead to a congenital insensitivity to pain (CIP).[2] Apart from their inability to sense pain, loss of smell (anosmia) is the only other sensory impairment in individuals with this channelopathy; they have no motor or autonomic dysfunction, and normal sense of proprioception, touch, and temperature discrimination.

Why does $Na_V1.7$ have such a profound impact on pain signaling? $Na_V1.7$ exhibits slower recovery from fast inactivation than other tetrodotoxin-sensitive (TTX-S) Na_V channels, and it exhibits a slow onset of closed-state inactivation. These properties contribute to the propensity of $Na_V1.7$ to generate substantial ramp currents in response to slow, small depolarizations.[2,3] Thus, $Na_V1.7$ is thought to be crucial in setting the threshold for action potential generation in nociceptive neurons.[2] In simplistic terms, $Na_V1.7$ can be viewed as an amplifier of pain signals generated by the receptors ("molecular pickups") at nociceptor terminals. Just as an electric guitar fails to produce a readily audible sound without being plugged into an amplifier, sensory neurons fail to generate a pain signal when the molecular pickups cannot be connected to the $Na_V1.7$ signal amplifier.

The crucial role of $Na_V1.7$ in pain generation has created immense interest in this channel as an analgesic target. However, progress in this area has been slower than anticipated due to the need for therapeutics targeted against $Na_V1.7$ to have very high selectivity over key Na_V channel subtypes such as $Na_V1.5$, which is critical for the rising phase of the cardiac action potential, and $Na_V1.6$, which is essential for action potential generation at nodes of Ranvier in myelinated motor neurons. Off-target activity at other Na_V channel subtypes limits the clinical utility of nonspecific $Na_V1.7$ blockers such as local anesthetics, tricylic antidepressants, and anticonvulsives. Amgen, AstraZeneca, Convergence, Merck, Pfizer, and Xenon have all developed small-molecule $Na_V1.7$ inhibitors, but detailed subtype-selectivity data, particularly over other TTX-S isoforms, has not been reported.

Animal venoms are a rich source of ion channel blockers that are typically more potent than small molecules and have better subtype selectivity due to their larger pharmacophore. ProTx-II,

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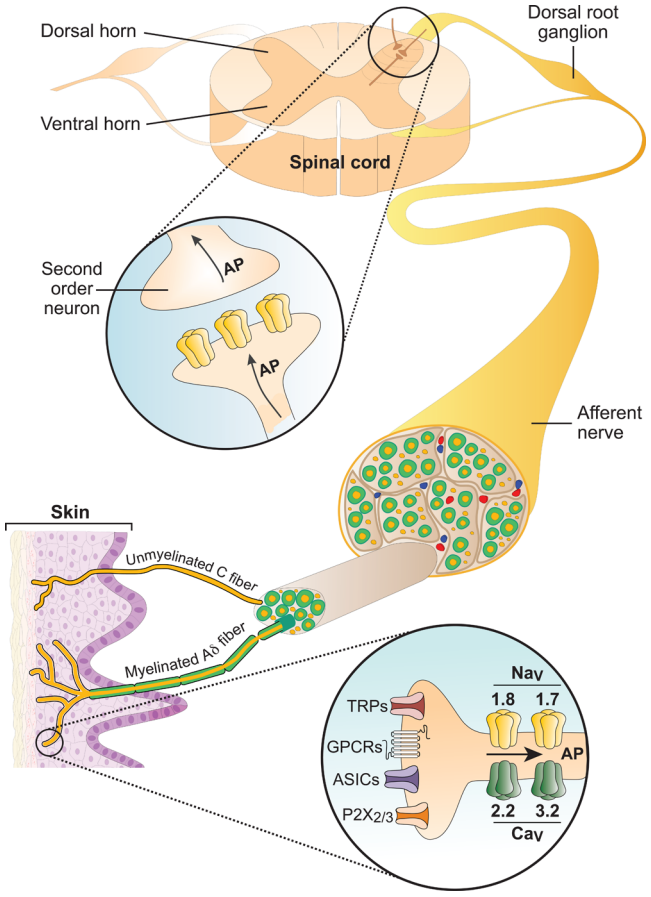

Figure 1. Schematic of the pain signaling pathway. The peripheral endings of small unmyelinated C fibers (orange) and thinly myelinated Aδ fibers (green) arborize in the epidermis of the skin (light purple) where specialized channels and receptors (e.g., acid-sensing ion channels (ASICs), G protein coupled receptors (GPCRs), P2X receptors, and transient receptor potential (TRP) channels) transduce mechanical, thermal, or chemical stimuli into membrane depolarizations. These generator potentials are transformed into an action potential (AP) by ion channels, particularly $Na_V1.7$, in the adjacent pacemaker zone. These action potentials are then transmitted along the afferent sensory fibers, which are enveloped by perineurium (beige) and bundled by the epineurium (mustard) together with capillary blood supply. The central projections of these fibers, whose cell bodies reside in the dorsal root ganglia, terminate in the spinal cord where they synapse with second order neurons of the spinothalamic tract to convey nociceptive signals to higher brain centers. For the sake of clarity, the figure shows only a small selection of the many receptors and ion channels found in the peripheral endings of sensory neurons.

a spider-venom peptide isolated by Merck, was the first $Na_V1.7$ inhibitor reported to have >50-fold selectivity over all other Na_V isoforms. ProTx-II failed to elicit analgesia after intravenous or intrathecal dosing in an inflammatory pain model, which was attributed to its poor pharmacodynamic profile, in particular an extraordinarily slow on-rate and poor penetration into the perineurium. Nonetheless, proof-of-concept for the analgesic efficacy of peptidic $Na_V1.7$ modulators was provided by the recent report that a $Na_V1.7$-selective centipede-venom peptide elicited analgesia in several animal models.[4]

A recent paper by Lee and co-workers[5] suggests that monoclonal antibodies (Mabs) are a viable approach for therapeutic targeting of $Na_V1.7$. Mabs typically have high selectivity, high affinity, and long half-lives, and Mabs targeted against nerve growth factor are in clinical trials for treatment of cancer and osteoarthritis pain. The Mab developed by Lee et al. (SVmab1) was cleverly engineered to target one of the channel voltage-sensors, which are more divergent than the pore region of the channel and thus provide a greater opportunity for achieving subtype selectivity (Figure 2). This strategy resulted

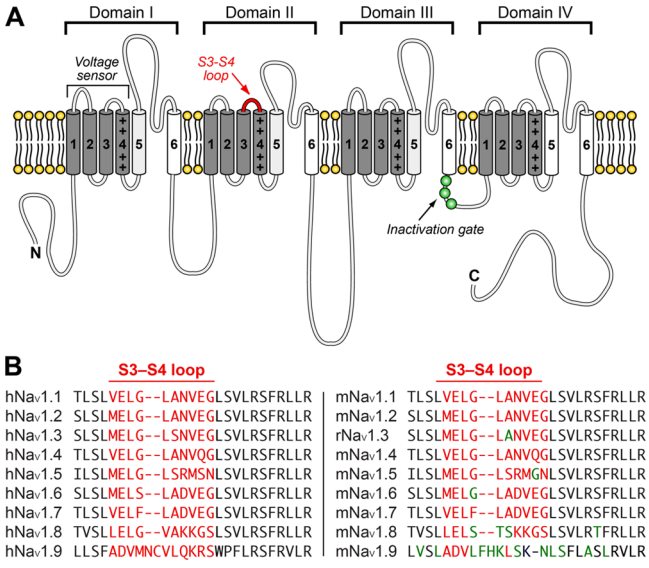

Figure 2. (A) Molecular architecture of Na_V channels. The pore-forming α subunit is composed of four homologous domains, denoted I–IV, connected by intracellular linkers. Each of these domains contains six transmembrane (TM) helical segments (labeled 1–6) joined by intra- or extracellular loops. TM segments 5 and 6 from each domain, along with the intervening membrane re-entrant loops, come together in a circular arrangement to form the channel pore and ion-selectivity filter. TM segments 1–4 of each domain form the voltage-sensing units. The arginine-rich TM segment 4 is responsible for sensing changes in membrane polarization. Sodium channel inactivation is mediated by a short stretch of hydrophobic residues (the "inactivation gate"; green balls) in the intracellular linker connecting domains III and IV. The extracellular S3–S4 loop in domain II (highlighted in red) is the primary binding site for numerous animal toxins and is the epitope targeted by the SVmab1 antibody.[5] (B) Sequence alignment of the domain II S3–S4 region from each of the Na_V subtypes in human (left panel) and mouse (right panel). The mouse $Na_V1.3$ sequence is not available so the rat sequence is shown. The S3–S4 loop epitope used to raise the SVmab1 antibody is highlighted in red, and amino acid residues that differ between the human and mouse sequences are shown in green.

in functional selectivity for $hNa_V1.7$, with no appreciable inhibition of other hNa_V isoforms except for partial effects at $hNa_V1.6$. SVmab1 caused a depolarizing shift in the voltage-dependence of activation and decreased $Na_V1.7$ peak currents, resulting in inhibition of transient and persistent sodium currents and action potentials in small-sized DRG neurons as well as nociceptive synaptic transmission in spinal cord slices.[5] Although the epitope used to develop SVmab1 includes the ProTx-II binding site, SVmab1 exhibited surprising functional difference to ProTx-II, including pronounced use-dependence leading to preferential inhibition of $Na_V1.7$ during fast pulse trains. SVmab1 decreased licking time in a formalin-induced pain model after intravenous, intrathecal, or intraplantar administration and it also inhibited mechanical allodynia in a model of neuropathic pain after intravenous and intrathecal

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delivery, although the analgesic effect was of relatively short duration.

While these data suggest that inhibition of $Na_V1.7$ at any level of the pain pathway—from peripheral sensory nerve endings to spinal projections of these neurons—mediates analgesia, it is unclear which strategy will be most beneficial clinically. It is conceivable that inhibition of $Na_V1.7$ in central terminals that integrate multiple painful stimuli might provide more complete analgesia than inhibition at peripheral sensory nerve endings, where other Na_V isoforms such as $Na_V1.8$ may contribute to action potential initiation and propagation. Alternatively, the analgesic effect observed after intraplantar administration of SVmab1 may at least partially arise from its effect at $Na_V1.6$, as local inhibition of $Na_V1.6$ by conotoxins that lack activity at $Na_V1.7$ decreases pain behavior in a number of models. While the selectivity of SVmab1 at rodent Na_V isoforms was not determined systematically, based on its profile at human isoforms, the dose administered by the intraplantar route—which exposes peripheral sensory nerve endings in the skin to high local concentrations—would be sufficiently high to affect $Na_V1.6$ in addition to $Na_V1.7$.

It is unclear what level of $Na_V1.7$ inhibition is required to elicit effective analgesia, or whether it is possible to achieve a graded analgesic response that eliminates pathological pain while maintaining normal nociceptive function, which is essential to avoid inadvertent self-harm. The effect of SVmab1 on physiological nociceptive responses and normal pain behavior in the absence of pathology has not been assessed, but the profound phenotype seen in CIP suggests that potent $Na_V1.7$ block might result in complete analgesia, which would necessitate careful management in a closely supervised clinical setting, potentially limiting the therapeutic utility of $Na_V1.7$ inhibitors.

$Na_V1.7$ inhibitors clearly hold great promise as universally effective analgesics, and $Na_V1.7$-selective modulators such as SVmab1 are beginning to emerge. However, modality- and pathway-specific treatments that would enable chronic pain patients to lead a normal life are not yet a reality. Much work remains to be done to understand the role played by $Na_V1.7$ in pathological pain states and to determine the best approach for targeting this channel to turn down the gain on pain.

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Notes

The authors declare no competing financial interest.

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