Commentary

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Beyond single targets: leveraging degeneracy in sodium channels for osteoarthritis analgesia

Samantha Perez-Miller[a], Rajesh Khanna[a,b,c,*]

Commentary on: Shin SM, Itson-Zoske B, Xu H, Xiang H, Fan F, Hogan QH, Yu H. Sensory neuron-specific block of multifaceted sodium channels mitigates neuropathic pain behaviors of osteoarthritis. Pain Rep 2025. DOI: 10.1097/PR9.0000000000001288.

Voltage-gated sodium channels (Na_Vs), particularly those in nociceptive neurons, are key mediators of pain, making them important therapeutic targets.[2] These channels are responsible for the initiation and propagation of action potentials in peripheral sensory neurons (PSNs).[2] Neurons achieve similar functions using various ion channel combinations, a flexibility known as degeneracy.[7] This flexibility is crucial for maintaining homeostatic excitability and overall function, and it explains how adaptive changes in different ion channels can lead to the same hyperexcitable state, affecting neurons' responsivity to pathological conditions and drugs.[39] Since pain often involves multiple ion channels, a single-target approach may be insufficient due to compensatory mechanisms where the cell adjusts to the inhibition of one channel by upregulating others.[29] Exemplifying this failed one-target approach is the targeting of $Na_V1.7$ channels (see reviews)[4,6,26,41] after the discovery that its absence leads to congenital insensitivity to pain. This discovery sparked a "rush" to develop selective inhibitors, resulting in numerous potent in vitro compounds. However, clinical trials targeting $Na_V1.7$ with inhibitors such as PF-05089771,[22] Vixotrigine,[8] and TV-45070[28] have largely failed to demonstrate effective analgesia in conditions like diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia.[42] Therefore, a more effective strategy may involve a multitarget approach that inhibits several channels simultaneously.

In this issue, Shin et al.,[34] propose an innovative approach to managing neuropathic pain through the development of a sodium channel inhibitory peptide aptamer named Na_ViPA1 (**Fig. 1**). By targeting multiple sodium channels in PSNs, Na_ViPA1 embraces a novel strategy to address channel degeneracy, which contributes to neuronal hyperexcitability associated with chronic pain. A year earlier, the same group had identified Na_ViPA1, which is derived from a segment of the first intracellular loop of $Na_V1.7$, a sodium channel isoform strongly linked to pain syndromes.[33] Although other proteins bind in the cytoplasmic regions of $Na_V1.7$,[3,12,25] Na_ViPA1's design takes advantage of an intrinsically disordered region of $Na_V1.7$, which permits flexible binding interactions with multiple tetrodotoxin (TTX)-sensitive sodium channel isoforms. Specifically, Shin et al. demonstrated that Na_ViPA1 inhibited $Na_V1.7$ along with $Na_V1.6$, $Na_V1.3$, and $Na_V1.1$ channels that contribute to the initiation and propagation of action potentials in peripheral sensory neurons. Importantly, Na_ViPA1 did not affect $Na_V1.5$ (the cardiac isoform) or $Na_V1.8$ (which has distinct kinetics and roles in pain), thus promising a degree of selectivity that could reduce off-target effects and adverse outcomes (**Fig. 1**). The proposed mechanism of action for Na_ViPA1 relies on its interaction with short linear motifs within the targeted Na_V channels, including a polybasic motif and specific serine residues, allowing it to effectively modulate channel function[5,33] (**Fig. 1**).

In their previous work, Shin et al.[33] showed that when Na_ViPA1 is delivered to dorsal root ganglion (DRG) neurons using adeno-associated virus (AAV) vectors for peripherally restricted gene expression, it robustly reduces TTX-sensitive sodium currents. In a rat model of neuropathic pain induced by tibial nerve injury (TNI), DRG injection of AAV6 (a variant that enhances the magnitude of early transgene expression without negatively altering the long-term expression kinetics[37]), encoding Na_ViPA1 led to a marked

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[a] Department of Pharmacology and Therapeutics, College of Medicine, University of Florida, Gainesville, FL, USA, [b] Center for Advanced Pain Therapeutics and Research (CAPToR), College of Medicine, University of Florida, Gainesville, FL, USA, [c] McKnight Brain Institute, College of Medicine, University of Florida, Gainesville, FL, USA

**Corresponding author. Address: Department of Pharmacology & Therapeutics, and Center for Advanced Pain Therapeutics and Research (CAPToR), College of Medicine, University of Florida, Gainesville, FL 32610. E-mail address: r.khanna@ufl.edu (R. Khanna).*

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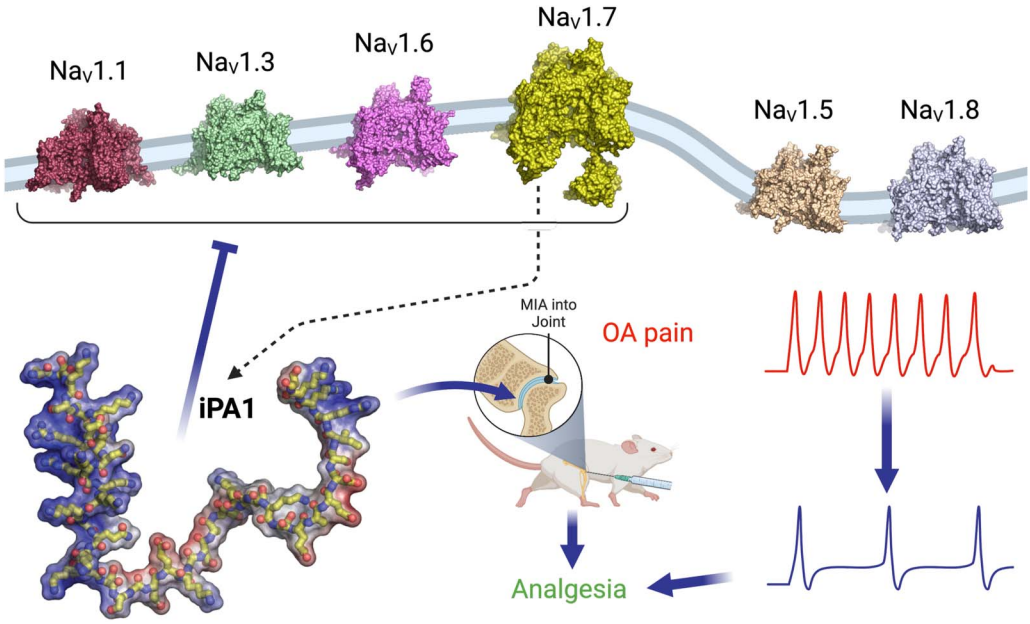

Figure 1. Combined block of multiple voltage-gated sodium channels (Na_Vs) as an effective strategy for osteoarthritis (OA) pain. iPA1, a 45 amino acid peptide identified from the first intracellular loop of the voltage-gated sodium channel $Na_V1.7$, inhibits $Na_V1.1$, $Na_V1.3$, $Na_V1.6$, and $Na_V1.7$—but not $Na_V1.5$ or $Na_V1.8$—currents. iPA1 alleviates pain in the monoiodoacetate (MIA) model of OA pain and reduces neuronal hyperexcitability. Na_V structure PDB IDs: $Na_V1.1$, 7DTD[27]; $Na_V1.3$, 7W77[21]; $Na_V1.6$, 8FHD[9]; $Na_V1.7$, 7W9K[15]; $Na_V1.5$, 7DTC[20]; $Na_V1.8$, 7WE4.[16] The model for Na_ViPA1 was extracted from the AlphaFold[17] model of human $Na_V1.7$ and is shown as ball-stick representation (yellow carbons) and surface representation. The surface is colored according to electrostatics calculated using Adaptive Poisson–Boltzmann Solver (APBS)[18] where blue represents positively charged and red represents negatively charged regions. The N-terminal polybasic motif is outlined. Molecular figures were generated in PyMOL.[36] Figure Created in BioRender.

attenuation of both evoked and spontaneous pain behaviors. Electrophysiological recordings using whole-cell current clamp techniques revealed that Na_ViPA1 expression normalized the heightened excitability of PSNs that is typically observed after nerve injury, suggesting that the peptide restores neuronal homeostasis by counteracting injury-induced hyperexcitability. In addition to in vivo experiments in rat models, the team demonstrated that Na_ViPA1 mediates sodium channel inhibition in human-induced pluripotent stem cell–derived sensory neurons.[33] This cross-species validation not only reinforces the mechanistic rationale for targeting sodium channels but also hints at the translational potential of Na_ViPA1 as a therapeutic modality in human pain conditions.

Capitalizing on the efficacy of this approach[33] and noting that increased activity and abnormal expression of Na_Vs in PSNs lead to their hyperexcitability in osteoarthritis (OA),[14] Shin et al.[34] set out to test if PSNs-specific expression of Na_ViPA1 in vivo could block pain behaviors in the monoiodoacetate (MIA)-model of OA. Delivery of AAV6.2FF-Na_ViPA1 vector into the lumbar 4/5 DRG transduced ~60% of neurons.[34] Robust analgesia of MIA-OA pain was seen in male and female rats injected with Na_ViPA1: an average reduction of 52% in the mild mechanical stimulation von Frey test, 45% in Pin test (noxious mechanical stimulation), 82% in Cold test and 40% in Heat test, as well as a reduction in weight-bearing asymmetry. Using the conditioned place preference test, they found that Na_ViPA1 alleviated ongoing pain caused by MIA, showing that this multipronged inhibitory peptide can also reduce the affective aspect of pain.[34] Furthermore, Na_ViPA1 normalized the action potential firing of PSNs in MIA-OA rats (**Fig. 1**), which indicates that the analgesic effect is, at least in part, due to a reversal of neuronal hyperexcitability. These results align with findings that highlight how targeting peripheral nociceptive input can relieve pain.

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                          1         10        20        30        40          %ID (%Sim)
sp|P35498|Nav1.1/490-533  SSKSAKERRNRRKKRKQKE.QSGGEEKDEDEFQKSESEDSIRRKG 68.9 (73.3)
sp|Q99250|Nav1.2/494-536  SSKSEKELKNRRKKKKQKE.QSGEEEK.NDRVRKSESEDSIRRKG 64.4 (73.3)
sp|Q9NY46|Nav1.3/492-536  SSKSAKEWRNRRKKRRQREHLEGNNKGERDSFPKSESEDSVKRSS 57.8 (75.6)
sp|P35499|Nav1.4/491-499  .....................LEGG.EADGD............  6.7  (6.7)
sp|Q14524|Nav1.5/467-504  APVNSHERRSKRRKR....MSSGTEECGEDRLPKSDSEDGPR... 35.6 (51.1)
sp|Q9UQD0|Nav1.6/484-528  SSKSAKERRNRRKKRKQKELSEGEEKGDPEKVFKSESEDGMRRKA 77.8 (82.2)
sp|Q15858|Nav1.7/469-513  SSKSAKERRNRRKKKNQKKLSSGEEKGDAEKLSKSESEDSIRRKS reference
sp|Q9Y5Y9|Nav1.8/451-482  TSKNASERRHRIKPR....VSEGSTE..DNKSPRSDPY....... 26.7 (40.0)
sp|Q9UI33|Nav1.9/454-468  TPKKRKLFGNKKRKS.............................  8.9 (17.8)
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Figure 2. Sequence alignment of Na_ViPA1 sequences from human Na_V isoforms. Sequences were obtained from UniProt and aligned in JalView[38] using the MAFFT (version 7.310) L-ins-i algorithm.[19] Alignment visualization was created with ESPript 3.0.[30] Sequence identities (%ID) and similarities (%Sim) over the entire 45-amino acid peptide were calculated with the Sequence Manipulation Suite.[35]

Despite its promise, several challenges remain before Na_ViPA1 can be translated into a clinical setting. A major concern is targeting voltage gated sodium channels in peripheral somatosensory neurons that are not involved in the transmission of pain. That Na_ViPA1 affected mild mechanical behavior raises the question of whether it also affects innocuous somatosensory transmission, highlighting a potential limitation. A major concern is the variability inherent in AAV-mediated gene delivery. Differences in viral tropism and long-term expression patterns in humans compared to animal models must be carefully addressed.[13] There are safety concerns regarding high-dose viral therapies in humans, including immune responses and potential adverse effects such as genotoxicity, hepatotoxicity, thrombotic microangiopathy (ie, clotting disorders affecting small blood vessels), and neurotoxicity.[32] Manufacturing AAV vectors is also complex and costly (ie, improving vector quality),[31] which can hinder large-scale production and accessibility.[23] Moreover, although acute inhibition of sodium channels can normalize hyperexcitability, the long-term consequences of sustained inhibition remain unknown. Chronic blockade might lead to unforeseen alterations in sensory processing or neuronal adaptation. There is also the need for deeper molecular characterization to ensure that Na_ViPA1 does not interact adversely with other cellular proteins or ion channels, potentially leading to off-target effects. In addition, the Shin group did not test inhibition of $Na_V1.9$, due to lack of significant homology in the Na_ViPA1 region,[33] $Na_V1.4$, or $Na_V1.2$. The first intracellular loop of $Na_V1.4$ is significantly shorter than other isoforms and has no homologous sequence to Na_ViPA1, explaining why that isoform was not tested. On the other hand, the region in $Na_V1.2$ does share significant homology, ~64% to Na_ViPA1 compared to ~58% for $Na_V1.3$ (**Fig. 2**). Perhaps $Na_V1.2$ was not tested due to expression patterns restricted mainly to the brain.[40] Nevertheless, whether the NaViPA1 peptide inhibits these isoforms may provide additional mechanistic insight, particularly given the high similarity of $Na_V1.2$ and the presence of the well-conserved polybasic motif in $Na_V1.9$ (**Fig. 2**). Although Na_ViPA1 was shown not to affect big-conductance calcium activated potassium (BK) or calcium channels, the possibility that it interacts with other unknown protein-binding targets cannot be excluded. If the peptide binds to the membrane through a lipid-based mechanism, as suggested by their earlier findings,[33] it could influence various proteins with positively charged domains. Adopting a multitargeting polypharmacology approach, while promising, could potentially result in increased off-target effects. Further, it is still unknown *where* along the peripheral nociceptor pathway the actionable target of Na_ViPA1 is located. The two published studies on Na_ViPA1[33,34] cannot rule out that pain reduction from blocking TTX-sensitive Na_Vs may occur by suppressing hyperexcitable afferent input, which could indirectly modulate spinal cord and brain antinociceptive circuits. The identification of the TTX-S $Na_V1.7$ sodium channel in chondrocytes,[10] where it influences chondrocyte stability, suggests it as a promising therapeutic target for OA. This emphasizes the need for OA pain interventions to address multiple levels along the neuraxis, extending beyond just neuronal cells. Testing Na_ViPA1 in clinically relevant models of OA, such as the destabilized medial meniscus or the medial meniscus transection models, would be instructive. This is because the heterogeneity of symptoms in OA means that a single model is unlikely to fully capture the complexity of symptomatic OA, as most clinical cases are idiopathic.

In conclusion, Shin et al.[34] provide compelling evidence that Na_ViPA1, delivered via AAV vectors, represents an innovative strategy for achieving peripheral analgesia in OA pain by targeting multiple sodium channels involved in pain transmission. A promising direction for future research is to use homology-guided mutational analysis of Na_ViPA1 to identify key residues critical for its antinociceptive effect. This could inform the design of pharmacophores that mimic these peptides, ultimately leading to the development of peptidomimetics. This approach has recently been pursued for another nociceptive voltage-gated channel and holds potential for innovative therapeutic strategies.[1,11,24] Despite its promising results and translational potential, further research addressing delivery variability, long-term safety, and molecular specificity is necessary before Na_ViPA1 can be considered a viable clinical treatment for neuropathic pain.

Disclosures

R.K. is the founder of Regulonix LLC, a startup company developing nonopioid drugs for chronic pain. S.P.-M. does not have any conflicts to declare.

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