



Review

Ion Channel Genes in Painful Neuropathies

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Abstract: Neuropathic pain (NP) is a typical symptom of peripheral nerve disorders, including painful neuropathy. The biological mechanisms that control ion channels are important for many cell activities and are also therapeutic targets. Disruption of the cellular mechanisms that govern ion channel activity can contribute to pain pathophysiology. The voltage-gated sodium channel (VGSC) is the most researched ion channel in terms of NP; however, VGSC impairment is detected in only <20% of painful neuropathy patients. Here, we discuss the potential role of the other peripheral ion channels involved in sensory signaling (transient receptor potential cation channels), neuronal excitation regulation (potassium channels), involuntary action potential generation (hyperpolarization-activated cyclic nucleotide-gated channels), thermal pain (anocetamins), pH modulation (acid sensing ion channels), and neurotransmitter release (calcium channels) related to pain and their prospective role as therapeutic targets for painful neuropathy.



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1. Introduction

Peripheral Neuropathy (PN) is a debilitating illness caused by peripheral nerve damage. Depending on the kind of nerve implicated, this condition impairs sensation, movement, pain transmission, and gland or organ function. Over 50% of individuals experiencing PN report pain symptoms due to a lesion or disease in their somatosensory system [1,2]. As a result, these individuals are classified as Painful PN (PPN) patients, and the pain experience can significantly impact those affected. The current pharmacological treatment of PPN is limited by side effects and often only has moderate efficacy [2]. Despite recent advances in pain research, the pathophysiology of PPN remains largely unknown, hindering the development of novel therapeutic drugs [3].

It is important to acknowledge that there is a correlation between pain perception and genetic variants in Ion Channel Genes (ICGs) [4]. As these ion channels play a critical role in generating, transmitting, and transforming nerve signals in the peripheral nerves, they must be thoroughly examined as promising molecular targets for PPN therapy [5]. Voltage-Gated Sodium Channels (VGSCs) are the most researched ICGs and have been linked to disorders such as congenital insensitivity to pain (CIP), paroxysmal extreme pain disorder (PEPD), erythromelalgia, small fiber neuropathy (SFN), and painful diabetic peripheral neuropathy (PDPN) [6]. While VGSCs play a crucial role in neuronal excitability and pain

processing, alterations in these genes can only account for a portion of the complexity of PPN [7]. Recent studies have shown that other ICGs are involved in pain signaling, modulation, and transmission (Figure 1) [5,8,9]. This review delves into the growing function of ICGs in PPN, aside from VGSCs, which have been previously extensively discussed in recent reviews [7,10,11]. Specifically, we focus on ion channels that have a known connection to pain and/or peripheral neuropathy, such as calcium and potassium channels, hyperpolarization-activated cyclic nucleotide-gated channels (HCN), anoctamins (TMEM16/ANO), transient receptor potential cation channels (TRP), and acid-sensing ion channels (ASIC).

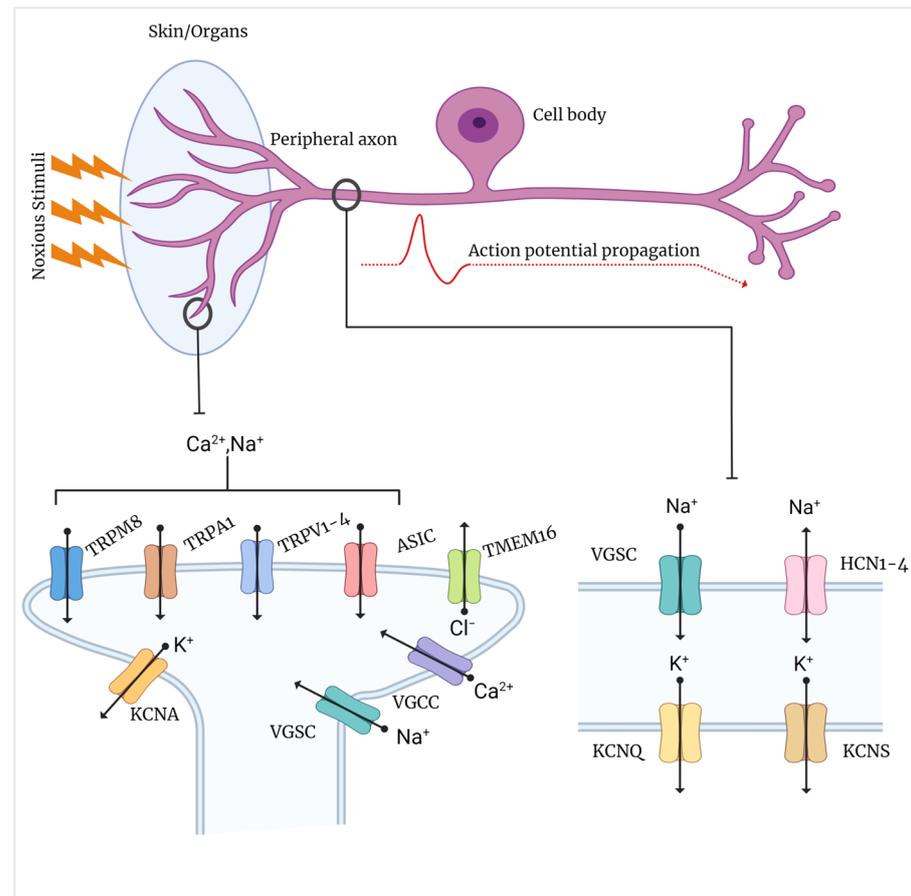


Figure 1. The activation of ion channels at the peripheral terminals in response to unpleasant stimuli causes membrane depolarization and the generation of action potentials in afferent fibers. These action potentials are generated by ion channel activation and propagate along axons to postsynaptic nerve terminals in the spinal dorsal horn. TMEM16 Transmembrane protein 16 (Anoctamins), TRPV Transient Receptor Potential Vanilloid, TRPA1 Transient Receptor Potential Ankyrin 1, TRPM8 Transient Receptor Potential Melastatin 8, ASIC Acid-Sensing Ion Channel, VGCC Voltage-dependent Calcium Channel, VGKC Voltage-Gated Potassium Channel, VGSC Voltage-Gated Sodium Channel, HCN Hyperpolarization-activated, and Cyclic Nucleotide-gated channel [10,12,13].

2. Role of Ion Channels in Painful Peripheral Neuropathy

2.1. Voltage-Gated Ca²⁺ Channels and Calcium Signaling

Voltage-gated calcium channels (VGCCs) in excitable cells help neurons communicate by converting action potentials into calcium ion flows, triggering the release of neurotransmitters. VGCCs consist of a pore-forming α_1 subunit (Ca_v1-3.x) associated with multiple auxiliary subunits ($\alpha_2\delta$, β , and γ), except Cav3.x, which forms T-type Ca²⁺ channel without any auxiliary subunits. Moreover, the γ subunit is only present in calcium channel complexes in skeletal muscle [14]. The α_1 subunit of VGCC creates the pore that facilitates

the influx of calcium ions, whereas the auxiliary subunits are responsible for membrane trafficking, expression, and biophysical property regulation [15,16]. VGCCs are classified into L-, N-, P/Q-, R-, and T-types depending on the voltage required for their activation and biochemical properties. VGCCs in the sensory system can cause pain when their function is disrupted. N-type and T-type channels are studied for pain relief, but the roles of other channels are not well known. Several studies, including both animal and clinical studies, have demonstrated that there is a connection between PPN and VGCCs of the N- (*CACNA1B*), P/Q- (*CACNA1A*), R- (*CACNA1E*), and T-type (*CACNA1G*, *CACNA1H*, and *CACNA1I*) and auxiliary subunits (*CACNA2D1*, *CACNA2D2*, *CACNA2D3*, and *CACNA2D4*) (Table 1).

Table 1. Genetic variants with their known phenotypic and functional effect related to neuropathic pain.

| Gene | Mutation | Type of Evidence | Functional Effect | Phenotype | Reference |
|----------------|----------------|--|-------------------|-------------------------|-----------|
| <i>ANO3</i> | Ser213Phe | Targeted sequencing | N/A | PDPN | [8] |
| | Ile453Val | Targeted sequencing | N/A | PDPN | [8] |
| | Leu984Phe | Targeted sequencing | N/A | PDPN | [8] |
| | Gly1034Arg | Targeted sequencing | N/A | SFN | [9] |
| | Met370Cysfs*? | Targeted sequencing | N/A | SFN | [9] |
| <i>CACNA1A</i> | Pro2455His | WCV patch clamp | GOF | TN | [17] |
| <i>CACNA1H</i> | Arg481Cys | WES | N/A | Writer's cramp and TN | [18] |
| <i>HCN1</i> | Arg405Gln | Targeted sequencing | N/A | PDPN | [8] |
| <i>KCNS1</i> | Ile48Val | SNPs association with greater pain outcome | N/A | Pain after nerve injury | [19] |
| <i>KCNQ3</i> | Val629Ile | Targeted sequencing | N/A | SFN | [9] |
| | Asp569Gly | Targeted sequencing | N/A | SFN | [9] |
| <i>TRPA1</i> | Ser86Ala | WCV patch clamp and calcium imaging | GOF | N/A | [20] |
| | Leu118Val | Targeted sequencing | N/A | PDPN | [8] |
| | Thr311Asn | Targeted sequencing | N/A | SFN | [9] |
| | Ser317Ala | WCV patch clamp and calcium imaging | GOF | N/A | [20] |
| | Tyr327Cys | Targeted sequencing | N/A | SFN | [9] |
| | Arg343Cys | Targeted sequencing and Sanger sequencing | N/A | EM | [21] |
| | Arg393Gln | WES | N/A | TN | [22] |
| | Arg393* | Targeted sequencing | N/A | SFN | [9] |
| | Ser428Ala | WCV patch clamp and calcium imaging | GOF | N/A | [20] |
| | Asn460Ser | Targeted sequencing and Sanger sequencing | N/A | EM | [21] |
| | Cys608* | Targeted sequencing and Sanger sequencing | N/A | EM | [21] |
| | Arg652* | Targeted sequencing | N/A | PDPN, SFN | [8,9] |
| | Met689Val | Targeted sequencing | N/A | SFN | [9] |
| | Ala828Leufs*17 | Targeted sequencing | N/A | PDPN | [8] |

Table 1. Cont.

| Gene | Mutation | Type of Evidence | Functional Effect | Phenotype | Reference |
|-------|----------------|---|---------------------------------------|-----------------------------------|-----------|
| | Asn855Ser | WCV patch clamp | GOF | Episodic pain syndrome | [23] |
| | Ser972Ala | WCV patch clamp and calcium imaging | GOF | N/A | [20] |
| | Lys1046Glu | Targeted sequencing | N/A | SFN | [9] |
| | Ser443Gly | WES | N/A | TN | [22] |
| TRPM2 | Asp624Trp | NGS study | N/A | CN | [24] |
| | Ala890Val | NGS study | N/A | CN | [24] |
| | Val934Ile | NGS study | N/A | CN | [24] |
| | Ala1645Val | WES | N/A | TN | [22] |
| TRPM3 | Arg30Gln | WCV patch clamp and calcium ion imaging | GOF | TN | [22,25] |
| TRPM8 | Asn222Ser | Targeted sequencing | N/A | SFN | [9] |
| | Arg368Trp | Targeted sequencing | N/A | SFN | [9] |
| | Glu479Asp | Targeted sequencing | N/A | PDPN | [8] |
| | Asp665Asn | NGS study | N/A | CN | [24] |
| | Val705Glyfs*79 | Targeted sequencing | N/A | PDPN | [8] |
| | Thr732Ile | Targeted sequencing | N/A | PDPN | [8] |
| | Val915Met | NGS study | N/A | CN | [24] |
| | Thr982Met | Targeted sequencing | N/A | SFN | [9] |
| | Gln85Arg | Whole-cell voltage clamp | GOF | CN after refractive surgery | [24] |
| TRPV1 | Phe305Ser | Targeted sequencing and Sanger sequencing | N/A | EM | [21] |
| | Phe305Cys | Targeted sequencing | N/A | SFN | [9] |
| | Thr450Ala | Targeted sequencing | N/A | SFN | [9] |
| | Gln498* | Targeted sequencing and Sanger sequencing | N/A | EM | [21] |
| | Arg579Cys | Targeted sequencing | N/A | SFN | [9] |
| | Gly568Asp | Case report | N/A | Painful focal plantar keratoderma | [26] |
| TRPV3 | Gly568Cys | NGS study and WCV patch clamp | GOF | OSLP and EM | [26] |
| | Gly568Val | Sanger sequencing | N/A | OSLP | [26] |
| | Gly573Ser | Animal model study | GOF | Severe itching | [27] |
| | Arg416Trp | Sanger sequencing | N/A | OSLP | [26] |
| | Arg416Gln | NGS study and WCV patch clamp | indirectly involved in channel gating | OSLP | [26] |
| | Leu673Phe | Sanger sequencing | moderately affects channel function | Atypical OSLP | [26] |
| | Trp692Ser | Sanger sequencing | severely affects channel function | OSLP | [26] |

Table 1. Cont.

| Gene | Mutation | Type of Evidence | Functional Effect | Phenotype | Reference |
|-------|-----------|-------------------------------|-------------------|-----------------|-----------|
| TRPV3 | Leu669Pro | Targeted sequencing | N/A | SFN | [9] |
| | p.? # | Targeted sequencing | N/A | SFN | [9] |
| | Arg186Gln | NGS study and qRT-PCR | N/A | HMSN2C and HMN8 | [28,29] |
| TRPV4 | Arg232Cys | NGS study and qRT-PCR | N/A | HMSN2C and HMN8 | [30] |
| | Arg269Cys | NGS study and qRT-PCR | N/A | CMT2C | [28] |
| | Arg269His | NGS study and qRT-PCR | GOF | CMT2C | [28,30] |
| | Tyr283Asn | WES | N/A | TN | [22] |
| TRPV4 | Arg316Trp | NGS study and WCV patch clamp | GOF | HMSN2C | [31,32] |
| | Arg316His | NGS study and WCV patch clamp | GOF | HMSN2C | [30] |

GOF, gain-of-function; N/A, not applicable; SNP, single-nucleotide polymorphism; GWAS, genome-wide association studies; NGS, next-generation sequencing; WES, whole exome sequencing; qRT-PCR, real-time quantitative reverse transcription PCR; WCV, whole-cell voltage; PDPN, painful diabetic peripheral neuropathy; SFN, small-fiber neuropathy; EM, erythromelalgia; TN, trigeminal neuralgia; CN, corneal neuralgia; OSLP, Olmsted syndrome with lesional pain; HMSN2C, hereditary motor and sensory neuropathy 2C; HMN8, distal hereditary motor neuropathy type 8; CMT2, Charcot–Marie–Tooth type 2 disease. # changed protein length due to splicing event at position c.1242+1G>A (loss of donor splice site of intron 9).

2.1.1. CACNA1A and CACNA1B

The Ca_v2.1 (P/Q-type) and Ca_v2.2 (N-type) channels, encoded by *CACNA1A* and *CACNA1B*, are expressed at the presynaptic terminals of dorsal root ganglion (DRG) neurons. Ca_v2.1 regulates excitatory neurotransmitter release and somatodendritic cell neural excitability [14,15]. This VGCC was the first to be genetically linked with complex multi-genetic disorders like epilepsy, migraine, and ataxia. Mutations in the *CACNA1A* gene can lead to different conditions. Gain-Of-Function (GOF) mutations are associated with familial hemiplegic migraine 1, while Loss-Of-Function (LOF) mutations have been linked to episodic ataxia type 2. The GOF mutations in this gene have been found to alter channel characteristics and synaptic transmission in the pain pathway [33]. Ca_v2.1 α₁ null mutant mice demonstrated pro-nociceptive responses to inflammatory and Neuropathic Pain (NP) models but anti-nociceptive responses to noxious heat stimuli. In a separate study, mice with a spontaneous mutation in the Ca_v2.1 channel, which reduced the activation voltage sensitivity, showed hypoalgesic responses to heat, mechanical, and chemical stimuli [34]. Recently, a GOF mutation in the *CACNA1A* gene has been linked to trigeminal neuralgia, as mentioned in Table 1. This mutation has been observed to affect channel gate kinetics, indicating that alterations in Ca_v2.1-dependent synaptic transmission in the trigeminal system may contribute to the processing of pain [17].

Ca_v2.2 (N-type) VGCCs are present in the dendritic shafts and presynaptic terminals of neurons in both the central and peripheral nervous systems. They are responsible for transmitting nociceptive signals in the spinal cord's dorsal horn from A-δ and C nerve fibers [34]. Several studies have demonstrated that blocking or deleting Ca_v2.2 channels can alleviate pain. According to research on rodent pain models or in vitro, ω-conotoxins from marine cone snails and spider venom can block Ca_v2.2 channels [35]. Out of these tested animal models, only ω-conotoxin (MVIIA or SNX-111) from *Conus magus* has been clinically approved under the name of Ziconotide (Prialt®) for chronic pain administered intrathecally and is known to have severe neurological and psychiatric side effects [34]. It was recently shown that these channels found in epidermal nerve terminals only play a role in heat sensitivity following nerve damage, not mechanical sensitivity. Because heat sensitivity is a common symptom of capsaicin-induced pain, intraplantar ziconotide

would lead to decreased heat sensitivity in such pain [36]. Another recent study involving *cacna1b* gene knockin mouse with the hemagglutinin tag, post partial sciatic nerve ligation, exhibited an increased expression of the $\text{Ca}_v2.2$ channel in medium/large DRG neurons with a coexpression of a glial cell line-derived neurotrophic factor (GDNF) family ligand receptor (GFR $\alpha 1$) located in low-threshold mechanoreceptors, and the increased expression of the $\text{Ca}_v2.2$ channel was dependent on the auxiliary subunit complex $\alpha\delta-1$; however, the expression of GFR $\alpha 1$ was not. This led to increased $\text{Ca}_v2.2$ channel trafficking to mechanoreceptor terminals, indicating increased neurotransmission [37]. Moreover, the $\text{Ca}_v2.2$ channel forms complexes with μ -opioid receptors and morphine; a μ -opioid receptor agonist inhibits this channel, providing pain relief. However, the effectiveness of morphine is reduced by the alternative splicing of the $\text{Ca}_v2.2$ channel at exons 37a and 37b, as this changes the formation of the channel complex. It seems that a possible solution to this issue is a spider peptide called “Ph $\alpha 1\beta$ ”. This peptide can block both TRPA1 and $\text{Ca}_v2.2$ channels in postoperative mice who have received varying doses of morphine [38]. Regarding the genetic markers in this channel, LOF variants in the $\text{Ca}_v2.2$ channel have been linked to progressive epilepsy dyskinesia, while GOF variants were once thought to be linked with myoclonic dystonia with painful cramps, but this has since been discredited. LOF mutations reduce neurotransmission by affecting Ca^{2+} influx, but the mechanism behind GOF variations is not fully understood [39–41]. A rare genetic variant in the *CACNA1B* gene, which encodes the $\text{Ca}_v2.2$ channel, was found in patients with post-operative pain and high morphine use; however, its impact on the protein requires further investigation for proper phenotypic association [42].

2.1.2. CACNA1G/1H/1I

Neuronal T-type calcium channels $\text{Ca}_v3.1-3$ are encoded by *CACNA1G*, *CACNA1H*, and *CACNA1I*, respectively, and found on the cell bodies and dendrites of neurons. Regarding NP, knockout mice models studies for $\text{Ca}_v3.1$ and $\text{Ca}_v3.3$ have revealed their association with trigeminal NP, while the former channel was also associated with peripheral pain [43,44]. On the other hand, the expression of $\text{Ca}_v3.2$ channels in the lamina I and II of mouse spinal cord and electrophysiological studies have shown their importance in sensory signal processing at the dorsal horn. Moreover, the $\text{Ca}_v3.2^{\text{GFP-Flox}}$ KI mouse model revealed $\text{Ca}_v3.2$'s role in chronic pain and sensory processing. It affects subthreshold and suprathreshold properties in spinal cord neurons; modulates synaptic transmission; and influences action potential features, firing patterns, and spike coding. This unique role has implications for pain pathways and therapeutic potential [43]. In paclitaxel-treated rats, $\text{Ca}_v3.2$ channels were co-localized with Toll-like receptor 4, and inhibiting either gene prevented paclitaxel-induced neuropathy [45]. Comparatively, intrathecal $\text{Ca}_v3.2$ antisense oligonucleotides generated a reduction in T-type currents in DRG neurons, causing a decrease in nociceptive responses in naïve and neuropathic rats, while targeting $\text{Ca}_v3.1$ or $\text{Ca}_v3.3$ had no impact [46]. Medicinal chemistry has led to potential T-type calcium channel blockers for pain, but clinical success is uncertain [47]. $\text{Ca}_v3.2$'s role in pain and its regulation through post-translational modifications present avenues for therapeutic development. Selective inhibitors like 5bk and betulinic acid show promise in neuropathy rodent models, highlighting the potential for targeted pain relief [48]. In a case of pediatric chronic pain, two heterozygous missense variants in the *CACNA1H* gene were discovered, but their functional impact on $\text{Ca}_v3.2$ channels remains uncertain due to variable experimental outcomes [43]. Recently, a rare *CACNA1H* point mutation (Table 1) was demonstrated to segregate in a family with writer's cramp and was also observed in a patient with bilateral trigeminal neuralgia. This point mutation is predicted to affect the different isoforms of the *CACNA1H* gene (\pm exon 26) and influences the current behavior of this channel. Therefore, it is pertinent to study the effect of variants in this channel with respect to different isoforms of the *CACNA1H* gene [18,49]. Other known variants in the *CACNA1H* gene with a possible association with corneal neuralgia are reported in Table 1 [24].

2.1.3. CACNA2D1/D2/D3/D4

The auxiliary subunits $\alpha_2\delta$, β , and γ regulate the biophysical characteristics and trafficking of the α_1 subunit, whereas the α_2 subunit forms a complex with the δ subunit. These subunits, which are separated into complexes $\alpha_2\delta$ -1 to $\alpha_2\delta$ -4, are encoded by the following genes: *CACNA2D1*, *CACNA2D2*, *CACNA2D3*, and *CACNA2D4* [14].

The auxiliary subunit $\alpha_2\delta$ -1 plays a crucial role in calcium channel trafficking and is linked to pain pathways. Following neuropathic injury, $\alpha_2\delta$ -1 is upregulated, and its knockout delays neuropathic hypersensitivity development. This subunit is expressed in DRG neurons, particularly in small neurons, and influences the distribution of $\text{Ca}_v2.2$ channels, while global $\alpha_2\delta$ -1 ablation demonstrates that $\alpha_2\delta$ -1 is vital for directing $\text{Ca}_v2.2$ channels to the cell surface and presynaptic terminals in DRG neurons and the dorsal horn of the spinal cord. Despite disruptions in $\text{Ca}_v2.2$ localization, there were no significant reductions in other presynaptic markers or postsynaptic markers. Meanwhile, synapse density remained relatively unchanged, and the intensity of $\text{Ca}_v2.2$ in puncta clusters was markedly reduced without $\alpha_2\delta$ -1. Further exploration through the use of techniques such as electron microscopy is necessary to understand the potential changes in synaptic morphology that are caused by $\alpha_2\delta$ -1 ablation [50]. After nerve injury, $\alpha_2\delta$ subunit expression increases in peripheral DRG and spinal cord neurons, making $\alpha_2\delta$ a therapeutic target for gabapentinoids like gabapentin, pregabalin, and mirogabalin. These drugs, which are developed for epilepsy, also bind to $\alpha_2\delta$ -1 and $\alpha_2\delta$ -2 subunits, reducing calcium influx and neurotransmission. While mainly used for epilepsy, gabapentinoids effectively alleviate seizures and are approved for such treatment [51].

The newfound role of $\alpha_2\delta$ in connection with thrombospondins (TSPs), especially thrombospondin-4, impacts synaptogenesis by promoting the formation of synapses at the presynaptic terminal. $\text{Cav} \alpha_2\delta$ -1 and thrombospondin-4 upregulation was reported in DRG and spinal dorsal horn neurons in NP mice models. Gabapentin inhibits the interaction of $\text{Cav} \alpha_2\delta$ -1 and thrombospondin-4, resulting in decreased cellular calcium influx, inhibiting neurotransmission, and exerting analgesic effects on sensory neurons in the spinal dorsal horn at the post-synaptic terminal [52]. Moreover, the association of $\alpha_2\delta$ with N-methyl-D-aspartate (NMDA) receptors has opened up new avenues in chronic pain. We know that nerve injury increases $\alpha_2\delta$ -1, intensifying pain signals through spinal cord NMDA receptors. A recent study demonstrated that nerve injury alters histones, reducing histone deacetylase-2 (HDAC2) in the *Cacna2d1* gene promoter in DRG neurons. HDAC2 removal induces lasting pain hypersensitivity, which is reversible via the use of NMDA blockers or gabapentin. Reduced HDAC2 heightens $\alpha_2\delta$ -1 and NMDA activity in the spinal cord; *Cacna2d1* knockout mice have milder pain responses. HDAC2 limits chronic pain by curbing $\alpha_2\delta$ -1. This insight challenges traditional HDAC roles. Restoring HDAC2 function or reducing histone acetylation could offer lasting nerve pain relief [53].

Another study featuring *Cacna2d1* knockout mice reported the significant attenuation of mechanical and cold allodynia in response to sciatic nerve injury when compared with wild-type mice. The $\text{Cav} \alpha_2\delta$ -2 subunit is known to limit axon growth via calcium influx through calcium channels in the PNS. Additionally, *Cacna2d2* gene ablation in vitro or pharmacological inhibition by pregabalin in vivo has been shown to facilitate axon regeneration after spinal cord injury [51]. In comparison, the deletion of the *Cacna2d3* gene in mice models has been associated with analgesia and the obstruction of the somatosensory system (triggered by thermal pain) [51,54]. However, CACNA2D4 variants have not been linked to NP [51].

2.2. Potassium (K⁺) Channels

Potassium (K⁺) channels are the most diverse ion channel family, with approximately 90 K⁺ channels being distinguished by their activation mechanisms and structures. The four major subgroups are as follows: (1) voltage-gated (K_V), (2) calcium-activated (K_{Ca}), (3) two-/tandem-pore domain (K_{2P}), and (4) inwardly rectifying (K_{IR}) [55,56]. In addition to establishing the resting membrane potential, K⁺ channels govern neuronal excitability. This

is especially important in axons, where K⁺ currents assist in governing neuronal firing and modulating the action potential by counteracting the depolarization caused by the other excitatory channels present in axons. Furthermore, the intracellular location of potassium channels at neuron terminals suggests that they might affect cell–cell communication in reward circuitries through dopamine (DA) neurotransmission [56]. This review will further elaborate on potassium channel genes that contribute to painful neuropathies.

2.2.1. KCNA1 and KCNA2

Currents of K_v channels have been detected in peripheral neurons (including DRG) and linked to pain pathways [45]. A decreased density of K_v channels has been observed in multiple pain conditions, such as nerve injury, painful diabetic neuropathy, and inflammation [57,58]. Here, we focus on K_v1.1 and K_v1.2, which are encoded by the *KCNA1* and *KCNA2* genes, respectively. Several animal models have been utilized to understand their function in pain pathophysiology [23,59,60]. In one study, knockout *kcna1* mice exhibited hyperalgesia in several behavioral tests, including the paw flick assay, hot plate assay, and formalin-induced hind paw licking [59]. The downregulation of *KCNA2* has been observed in the DRG of spinal nerve ligation rats, while *KCNA2* over-expression has been shown to diminish injury-induced pain hypersensitivity in rats [23]. Consistent with this, long noncoding *kcna2* antisense RNA silenced *KCNA2* and contributed to NP in rats via reducing the voltage-gated potassium current and increasing DRG excitability [61]. In addition, several studies have linked the epigenetic repression of *KCNA2* with the development of NP [62–67]. Based on the above, K channels could be an appropriate target for pain therapy in specific individuals.

2.2.2. KCNQ2/3/5

KCNQ or K_v7 channels are responsible for the generation of M currents (I_M) that control membrane potential and neuronal excitability in the central and peripheral nervous system [68]. It has been demonstrated that *KCNQ2/3/5* are present in rat nociceptive DRG neurons, and the expression of these three genes has been investigated specifically in NP diabetic rats. In one study, the tested animals had significantly decreased *KCNQ2/3/5* mRNA and protein levels, followed by a reduction in I_M and increased neuronal excitability of DRG. Moreover, mechanical allodynia and thermal hyperalgesia in diabetic rats was attenuated after KCNQ channel activation with retigabine, while the application of a KCNQ inhibitor, XE991, enhanced pain behaviors [69]. A similar effect was observed in another study on orofacial NP rats with downregulated *KCNQ2*, as they exhibited mechanical allodynia, which was alleviated after retigabine administration [70]. Interestingly, GOF mutations of *KCNQ2* and *KCNQ3* confer pain resilience via an effect on peripheral sensory neurons in inherited erythromelalgia individuals with a disease-causing Na_v1.7 variant while *KCNQ3* genetic variants have been also linked to SFN (Table 1) [71,72].

2.2.3. KCNS1 (K_v9.1)

Potassium voltage-gated channel subfamily S member 1 (*KCNS1*), also recognized as K_v9.1, is the only member of the K_vS family with well-documented implications in pain states [57]. A single-nucleotide polymorphism of *KCNS1* has been associated with an increased risk of developing NP, although this does not confer causality (Table 1) [19]. *KCNS1* is highly expressed in neuronal tissues, including the DRG, spinal cord, and brain [73]. It has been shown that the mRNA of *KCNS1* is downregulated after nerve injury in sensory neurons, while K_v9.1 knock-down via siRNA injection has been shown to lead to neuropathic pain behaviors in tested rats [74]. These results were consistent with that of a later study involving transgenic mice lacking *KCNS1* in sensory neurons. The deletion of *KCNS1* increased basal mechanical pain, and after neuropathic injury, the knockout animals exhibited cold and mechanical hypersensitivity [75].

2.3. Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channels

Hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels belong to a gene-family consisting of four isoforms (HCN1-4) [76]. HCNs are known to form integral transmembrane proteins that act as voltage-gated cation channels that conduct both Na⁺ and K⁺ [77]. Members of the HCN family are expressed in different tissues, including the brain, heart, and peripheral neurons, where they are responsible for the generation of cation currents (I_f or I_h). Their action is directly regulated by cyclic nucleotides, mainly cyclic adenosine monophosphate (cAMP), which contributes to the pacemaker activity in cardiac cells and neurons [77,78]. Several studies involving animal models have revealed the role of I_h in NP pathogenesis and pain processing [79]. Moreover, dysfunction in HCN channels, especially HCN1, HCN2, and HCN4 has been linked to multiple neurological and neurodegenerative disorders, including epilepsy, Alzheimer's disease, Parkinson's disease, and NP [80].

2.3.1. HCN1

Among the HCN isoforms expressed in DRG, HCN1 is the most abundant, and it has been detected in all subtypes of sensory neurons, predominantly in large and medium-sized DRG neurons [81]. Several reports have highlighted that HCN current upregulation is closely linked to pathological pain condition [79,82,83]. In particular, the HCN1 role in NP has been investigated using a variety of animal models [84–86]. A significant upregulation of HCN1 pacemaker currents in large-diameter DRG was observed in a spinal nerve ligation (SNL) rat model. The increased density of I_h was accompanied by mechanical allodynia, which was reversed in the SNL rats after the administration of ZD7288, an HCN antagonist [82]. The contribution of I_h to tactile allodynia was also confirmed in chronic constriction nerve injury (CCI) and chronic compression-induced nerve injury rats [87,88]. Moreover, in the second model, hyperalgesia was also observed [87]. In addition to rat studies, in one particular publication, a *HCN1*^{-/-} mouse model was generated to assess the effect of HCN1 deletion on inflammatory hyperalgesia and NP. The HCN1 knockout mice were characterized by ablated I_h, especially in large sensory neurons, and they exhibited decreased cold allodynia compared to wild-type animals [85]. Many strategies have been applied to target HCN1, providing more insight into the possible mechanism of action and potential pain therapy. In addition to the non-specific HCN blocker ZD7288, other components have also been tested [89,90]. Many of these drugs are known to be effective to reverse neuropathy but often cause side effects such as bradycardia [89,91]. Resta et al. reported upregulated I_h current in DRG neurons from a oxaliplatin-induced NP rat model. The selective HCN1 inhibitor MEL57A has been tested and shown to be effective in reducing hyperalgesia and allodynia in neuropathy rats without unwanted cardiac effects [91]. Taken together, these results indicate that HCN1 is a critical component of NP and that it could be specifically targeted to ameliorate pain symptoms.

2.3.2. HCN2

HCN2 is a cAMP-sensitive isoform that has been intensively investigated, especially with respect to NP pathogenesis, often together with cAMP-insensitive HCN1 [84,86,91]. HCN2 is known to colocalize with HCN1 in large and medium-sized DRG neurons [81]. However, its expression in large sensory neurons is lower than HCN1 as HCN2 generally predominates in medium-sized/small DRG neurons [79]. Taking into account that many HCN blockers are nonspecific, the genetic deletion of HCN2 seems to be a valuable tool to understand its function. In one study, global HCN2 deletion in mice resulted in signs of epilepsy, ataxia, and premature death; therefore, mice with selectively ablated *HCN2* in nociceptive neurons expressing Nav1.8 were created to study its pathophysiology [92,93].

Nav1.8-*HCN2*^{-/-} mice display no behavioral manifestation of NP in response to both thermal and mechanical stimuli after nerve injury, according to the authors of [93]. Interestingly, in another study, HCN2 deletion from nociceptors decreased mechanical allodynia but not heat hyperalgesia in inflammatory chronic pain mouse models [83].

Tsantoulas et al. investigated HCN2's role in diabetic neuropathy pain using type 1 and 2 diabetes mice. They found an increased level of cAMP in the somatosensory neurons of the tested animals and proposed that this is the reason why excessive HCN2 activation leads to the firing of repetitive nociceptive nerve fibers and associated effects in diabetic neuropathy pain. In addition to that, it was shown that mechanical allodynia in painful diabetic mice can be reverted via the administration of the HCN blocker ivabradine and HCN2 deletion in small nociceptive neurons [94]. Recently, many researchers' efforts have been dedicated to understanding the contribution of HCN2 to NP states. It has been found that HCN2 induces NP through the upregulation of NR2B and the activation of the CaMKII/CREB cascade in spinal neurons in oxaliplatin-induced NP [95]. Furthermore, decreased HCN2 expression inhibits pro-inflammatory reactions and suppresses nuclear factor NF- κ B activation, which is involved in NP progression [96].

2.3.3. HCN3 and HCN4

HCN3 and HCN4 subunits are expressed in primary sensory neurons; however, their expression level in DRG neurons is lower in comparison to HCN1/2 [79,81]. Although HCN3 was found to be expressed in small, medium, and large sensory neurons, it seems that its role in acute and chronic pain is limited. A study performed on HCN3 knockout mice with nerve damage did not show differences in thermal hyperalgesia in comparison to wild-type animals. *HCN3* gene deletion also did not result in significant changes in mechanical hyperalgesia; however, slightly reduced responses in the pinprick test were observed. Overall, these results indicate that HCN3 is not a major component contributing to NP [97]. HCN4 is known to be expressed in the brain and DRG, predominantly in medium and small sensory neurons [80]. The role of HCN4 in the pathogenesis of epilepsy has been well established, as several pathogenic mutations have been identified [98,99]; nevertheless, this kind of evidence is missing for the NP phenotype.

2.4. Anoctamin Gene Family

The Anoctamin protein family consists of 10 members (ANO1-10). Anoctamins, also known as TMEM16, are involved in ion transport, phospholipid scrambling, and membrane protein regulation [100]. ANO1 (TMEM16A) and ANO3 (TMEM16C), classified as Ca²⁺-activated Cl⁻ channels (CaCCs), are known to play a crucial role in pain processing in sensory neurons [101,102]. Both channels are expressed in nociceptive DRG neurons [100,103].

2.4.1. ANO1

ANO1 is a ligand-gated anion channel that is activated as a result of calcium entering through TRPV1 [102]. ANO1 serves as a heat sensor in somatosensory neurons activated by noxious temperatures >44 °C in the absence of intracellular Ca²⁺. ANO1 activity in DRG is associated with pain hypersensitivity in inflammatory and NP animal models [104]. Conditional *ANO1* knockout mice have showed reduced thermal nociceptive responses [103,105]. Furthermore, *ANO1* knockout mice have exhibited significantly reduced inflammatory hyperalgesia and mechanical allodynia [104]. These findings are consistent with a previous study on bradykinin-induced inflammatory pain rats, which demonstrated that inhibiting ANO1 results in pain attenuation [106]. The inhibition of TRPV1-ANO1 interaction by TRPV1 antagonists could be an alternative way to treat PPN (Table 1) [102]

2.4.2. ANO3

ANO3 functions as a calcium-dependent phospholipid scramblase as ANO3 does not exhibit CaCC activity since it does not produce Cl⁻ currents stimulated by intracellular Ca²⁺ [100]. In one study, the genetic ablation of ANO3 resulted in increased mechanical and thermal sensitivity in TMEM16C knockout mice. Electrophysiological studies have revealed an interaction between ANO3 and sodium-activated potassium Slack channels. In one study, ANO3 did not form an ion channel itself but enhanced the Slack channel's

activity in the DRG neurons and regulated pain processing [101]. Several Variants of Uncertain Significance (VUS) have been reported in SFN and painful DPN (Table 1).

2.5. Transient Receptor Potential (TRP) Cation Channels

The transient receptor potential channel is a super-family of genes known to be associated with nociception and pain perception. This family is divided into twenty-eight elements which are further segregated into six subfamilies found in mammals: ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), polycystin (TRPP), and vanilloid (TRPV). All the TRP genes are non-selective cation-permeable channels that are known to conduct calcium ions (Table 1) [107]. The TRPA, TRPM, and TRPV channels have been shown to be associated with PPN (Table 1).

2.5.1. TRPA1

TRPA1 is a type of transient receptor potential cation channel found in various parts of the body, especially in nociceptive neurons responsible for sensing pain [107]. It serves as a chemosensor, reacting to chemical irritants and causing painful burning sensations. Additionally, it can be activated by cold stimuli, which sets it apart from the TRPM8 channel [108,109].

TRPA1 is coexpressed with TRPV1, influencing thermosensation and contributing to both pain and inflammation [110,111]. In a recent study, systematic therapy with Sigma-1 receptor (an endoplasmic reticulum chaperone) antagonists reduced painful symptoms in an oxaliplatin-induced neuropathy mice model through regulating TRPA1. Targeting TRPA1 with these antagonists has the potential to prevent and treat Chemotherapy-Induced Peripheral Neuropathy (CIPN) and other NP syndromes, opening the door to new pain management therapies [112]. A recent study discovered that TRPA1 in Schwann cells contributes to pain caused by CGRP and capsaicin in mice and rats. TRPA1 antagonists reduced pain in less severe neuropathic pain models and showed some effectiveness in patients with milder neuropathy. TRPA1 might have a role in neurogenic inflammation and moderate nerve injury-related pain, whereas CGRP does not seem to be involved in these conditions [113]. Another study suggested that the co-localized potassium Slack channel could modulate the TRPA1-mediated activation of sensory neurons but not TRPV1-mediated activation [114]. Moreover, a *trpv1-trpa1-trpm3* knockout mice model showed nearly no thermal sensitivity to nociception, indicating that a variety of TRP channel genes engage in thermal hyperalgesia [115].

Certain *TRPA1* genetic markers have been associated with specific characteristics, including central pain hypersensitivity, primary and secondary hyperalgesia, mechanical nociception, and cold hyperalgesia, following inflammation and nerve injury [108,116]. Genetic variants of the *TRPA1* gene have been linked to conditions like familial episodic pain syndrome (FEPS) and cram-fasciculation syndrome (CFS), as mentioned in Table 1 [108,117]. More recently, rare *TRPA1* variants have been shown to be significantly enriched in chronic neuropathic and nociplastic pain patients [116].

2.5.2. TRPM2

The structure of Transient Receptor Potential Cation Channel Subfamily Melastatin Member 2 (TRPM2) is similar to other TRPM channels, except for the presence of a nucleoside diphosphate-linked moiety x motif 9 (NUDT9) homologous motif at its C-terminal side [107]. When adenosine phosphate-ribose binds to this motif, it modifies the channel's gating, enabling the influx of calcium and sodium ions. TRPM2 can be activated by various stimuli, such as adenine dinucleotide, reactive oxygen species (ROS), and intracellular calcium ions [118]. Studies in mice have indicated that TRPM2 expression in macrophages and spinal glial cells aggravates inflammatory signals associated with pain, influencing the pathophysiology of inflammation and NP [119–122]. However, the precise mechanism of TRPM2 in NP is not fully understood. A recent study investigated the potential of hesperidin (HES) to alleviate diabetic neuropathy (DNP) through TRPM2 channel modulation.

HES treatment in diabetic rats lowered hyperglycemia, pain sensitivity, and nerve damage by controlling TRPM2 channel activity. This suggests that HES could potentially mitigate DNP by targeting the TRPM2 channel [123].

In addition to its role in pain, rare missense variants of TRPM2 have been associated with several other conditions, including bipolar disorder, amyotrophic lateral sclerosis, Parkinson's disease, trigeminal neuralgia, and corneal neuralgia [22,24,124]. Table 1 shows the rare missense variants reported for trigeminal and corneal neuralgia.

2.5.3. TRPM3

The transient receptor potential melastatin-3 (TRPM3) channel is present in various tissues, including the DRG and cardiac and pancreatic cells [125]. It can be activated by sphingosine, pregnenolone sulfate (a neuro-steroid), hypo-osmolality, and temperatures above 37 °C [125,126]. TRPM3 is involved in thermal hyperalgesia and insulin secretion in humans [127,128]. Studies in TRPM3 null mice showed the channel's role in thermal hyperalgesia during inflammation [129,130]. The G $\beta\gamma$ subunit of heterotrimeric G proteins blocks TRPM3, leading to pain reduction and providing insights into the pain-relieving mechanisms of opioid analgesics [131]. TRPM3 has VUS variants associated with developmental and epileptic encephalopathy and trigeminal neuralgia (shown in Table 1) [22,132]. As mentioned before, the ablation of the combination of these three genes (*trpa1-trpv1-trpm3*) in mice models contributed to thermal nociception. The inhibition of all three channels with a single drug or other therapeutic options could be a promising approach for alleviating thermal hyperalgesia [115]. Moreover, in mice model studies, TRPM3 channel activity has been shown to be increased after oxaliplatin treatment, while mice lacking TRPM3 supposedly do not experience cold and mechanical pain. Also, the intraperitoneal injection of isosakuranetin, a TRPM3 inhibitor, has been shown to reduce pain behavior in mice. Thus, the findings mentioned above indicate that TRPM3 could be a new target for oxaliplatin-related-CIPN [133].

2.5.4. TRPM8

The Transient Receptor Potential Cation Channel Subfamily Melastatin Member 8 (TRPM8), also referred to as cold-menthol receptor 1, was among the initial channels identified as cold sensors [134]. TRPM8 is found in primary afferent nerve fibers of the A δ and C types located in the DRG, as well as in the bladder and prostate [135–137]. As a non-specific cation channel, TRPM8 plays a role in regulating calcium ion balance. It responds to cold temperatures (8–28 °C), alterations in pH, and various cooling agents like methanol, icilin, and eucalyptol [134,138,139]. Cold hyperalgesia, a heightened sensitivity to cold, can be induced by chemotherapy in cancer patients. Mouse models with NP treated via chemotherapy drugs such as oxaliplatin and vincristine have been observed to display a significant rise in TRPM8 mRNA levels in DRG neurons. Consequently, either eliminating the TRPM8 gene or using drugs that counter TRPM8's effects seemingly alleviates NP in these models [140,141]. However, a recent study suggested that after oxaliplatin or paclitaxel treatment, TRPM8-expressing trigeminal neurons exhibit higher vulnerability rather than DRG neurons [142]. Morphine-triggered cold hyperalgesia activates the μ -opioid receptor, leading to the excitation of DRG neurons that express TRPM8 [143]. Meanwhile, in another study, RGM8-51, a TRPM8 antagonist, was effective in decreasing cold hyperalgesia in an oxaliplatin-induced PN mouse model and relieved NP rats of cold, mechanical, and heat hypersensitivity after sciatic nerve constriction [144]. Another investigation explored Aju-I in diabetic NP. Aju-I treatment in rats reduced hyperglycemia, pain hypersensitivity, and pancreas damage induced by diabetes. It also mitigated histopathological changes in nerves and the spinal cord, decreasing oxidative stress and modulating TRPV1/TRPM8 nociceptors [145]. The only documented GOF VUS within *TRPM8*, rs200774365 (Arg30Gln), has been linked to trigeminal neuralgia [25].

2.5.5. TRPV1

The Transient Receptor Potential cation channel Vanilloid 1 (TRPV1) is expressed in both somatic and visceral afferent neurons present at both spinal cord and peripheral junctions [146]. It functions as a polymodal nociceptor, responding to a diverse range of noxious stimuli such as vanilloids, protons, heat (≥ 42 °C), lipids, and voltage changes. Given its multi-faceted gating mechanisms, TRPV1 has garnered attention as a potential molecular target for various pain-related conditions, including hyperalgesia, inflammatory pain, hypersensitivity, and acute burning pain [13,146–148]. Over the past decade, significant efforts have been made to investigate the role of TRPV1 in pain modulation. Researchers have developed a variety of antagonists and genetic animal models to explore its function. However, while these antagonists have demonstrated efficacy in treating NP based on their modality, some have exhibited the unintended consequence of inducing hypo- or hyperthermia in animal models or patients [149]. Some of the recent animal model studies on rodent species have explored different types of therapeutic approaches, as outlined in Table 2. Studies involving TRPV1-null mice have provided valuable insights into its role. These mice display reduced sensitivity to thermal pain in response to inflammation, suggesting the involvement of TRPV1 in thermal hyperalgesia [150]. As indicated before, the trio TRP channel knockout model of *trpa1-trpv1-trpm3* has revealed that multiple TRP channel genes likely collaborate in orchestrating thermal sensations and nociception [115].

Considering these findings, TRPV1 emerges as an attractive molecular target, particularly for individuals suffering from peripheral polyneuropathy (PPN) and NP. Extensive pharmacological and genetic research has focused on modulating TRPV1's activity. Despite these efforts, the genetic landscape of rare functional variants contributing to or causing NP remains largely unexplored. However, from their studies on NP, Ślęczkowska et al. and Katz et al. obtained potentially causal and pathogenic variants, as listed in Table 1 [9,151]. It is worth noting that Katz et al. highlighted a rare homozygous TRPV1 functional variant that renders the channel completely non-functional, resulting in reduced heat sensitivity and heightened cold sensitivity [151].

Table 2. Summary of recent rodent studies on the therapeutic use of TRPV1-related mechanisms in various pain conditions.

| Disease/Condition | Therapeutic Approach | References |
|---------------------------------|--|------------|
| CIPN | TRPV1 siRNA into a druggable approach | [152] |
| PDPN | Potential target blocking GPR177-WNT5a-TRPV1 axis | [153] |
| PDPN | Alpha-lipoic acid and capsaizepine together inhibits TRPV1 channel | [154] |
| PDPN | Ajugarin-I treatment reduces TRPV1/TRPM8 expression | [145] |
| NP | Pregablin reduces pain perception via PKC ϵ /TRPV1 pathway | [155] |
| Side-effects of opioids post-NP | Potential target such as β -arrestin 2 that regulates bi-directionally TRPV1 and μ -opioid receptors | [156] |
| NP | Cannabidiol for acute NP partially inhibits 5-HT1A and TRPV1 | [157] |

2.5.6. TRPV3

TRPV3 (Transient Receptor Potential cation channel Vanilloid 3) is highly expressed in skin and hair follicle keratinocytes, as well as in DRG [158]. TRPV3 is involved in cutaneous development and maintenance and results in an itchy sensation [159]. TRPV3 is activated at a mild temperature of ~ 33 °C [160]. Unlike other TRP channels, TRPV3 becomes sensitized after repeated stimulation rather than desensitization [161]. The heat-induced activation of TRPV3 leads to increased channel expression and releases a substance called thymic stromal lymphopoietin, which is a potent itch inducer [162]. Moreover, GOF variants in *TRPV3* have been associated with severe pain, along with itchiness [162], and VUS has been associated with several different pain disorders, including SFN (Table 1) [9,26,163]. Additionally, citrusinine-II, a plant-derived medication, is known to block the TRPV3 channel to relieve pain and itchiness (Table 1) [164].

2.5.7. TRPV4

TRPV4, also known as Osmosensitive Transient Receptor Potential Channel 4, is similar to TRPV2 and found in sensory neurons, non-neuronal cells, and keratinocytes. TRPV4 is activated by mild warm temperatures (~30–35 °C) and hypo-osmolarity, much like TRPV3 [159,165]. Todaka et al. discovered that mice lacking TRPV4 exhibit changes in sensory peripheral neurons when exposed to hypo-osmolarity and mechanical nociception [166]. The TRPV4 gene is extensively expressed in the brain and spinal cord, including regions like the DRG, TG, nodose ganglion, and hypothalamic neurons [167]. According to Bagnell et al., TRPV4, along with the small GTPase RhoA, forms a sensitive signaling complex that contributes to detrimental changes in cell structure during neurological injuries and diseases. Thus, they suggest that targeting TRPV4 with drugs could prevent these harmful effects, offering new possibilities for treating neurological conditions that currently lack effective treatments [168]. The authors of another study drawn a similar conclusion, stating that after nerve injury, TRPV4 activation causes mechanical pain and triggers TRPV4-dependent microgliosis. Moreover, TRPV4's involvement in increasing neuronal excitability, dendritic spine remodeling, and spinal neuroplasticity through microglia-derived lipocalin-2 has been noted in the literature, thereby making the channel a more plausible target for NP [169]. Pathological TRPV4 variants can lead to ion channel dysfunction, resulting in motor issues and axonal neuropathies such as spinal muscular atrophy, distal hereditary motor neuropathy, and Charcot–Marie–Tooth disease 2C [170]. The pathological TRPV4 variants mentioned in the literature are detailed in Table 1.

2.6. Acid-Sensing Ion Channels (ASICs)

ASICs are a family of four voltage-independent amiloride-sensitive cationic channels (ASIC-4) that are permeable to cations, primarily Na⁺. Extracellular protons activate ASICs, and they are abundant in the central nervous system and peripheral nerves. Several studies have suggested that ASIC1-3 plays a role in the pathophysiology of chronic, inflammatory, and neuropathic pain. In one study, an increased expression of ASIC1a, ASIC2, and ASIC3 mRNA was observed in DRG after inflammation [171]. However, in ASIC1^{-/-} and ASIC2^{-/-} mice, a lack of ASIC expression was associated with increased pain behavior, primarily during formalin injection [172]. Blocking ASIC1a with PcTx1 or specific antisense oligonucleotides has been shown to reduce thermal and mechanical hypersensitivity in CFA animals [173]. Citric acid stimulates and potentiates ASIC1, resulting in nociceptive responses induced by subcutaneous acid infusion [174]. Chen et al. found that ASIC3^{-/-} knockout mice were more sensitive to moderate- to high-intensity pain stimuli. However, mice lacking ASIC3 were hypertensive to high-intensity thermal stimulation but did not exhibit increased pain behaviors after formalin injection [175]. ASIC3 activation via acid and pruritogen has been shown to mediate itchiness, which is a common symptom of NP [176].

3. Conclusions

With a primary focus on ion channels, the field of neuropathic pain genetics is continuously expanding, leading to the discovery of new genes and variants. This provides opportunities to link genetic data with mechanistic studies and patient characteristics. This paper aims to integrate this information to optimize therapeutic approaches and identify novel treatment possibilities. Most of the ion channel genes discussed in this review are associated with hyperalgesia or allodynia, except for HCN3, which is not linked to pain, and ANO3 and HCN4, which indirectly impact pain perception. Variants in ion channel genes are also associated with specific clinical manifestations of NP and PPN, such as cold-induced pain (TRPA1 and TRPM8), inflammatory pain (CACNA1A, ANO1, TRPV1, TRPM2, and ASIC3), itch-related pain (ASIC3 and TRPV3), and chemotherapy-induced pain (CACNA1H, TRPV2, and TRPM8). This genetic complexity makes pain treatment challenging, as generalized approaches may not be very effective. Targeting

multiple ion channels with drugs might offer a more suitable solution for a broader range of patients. For instance, drugs targeting TRPV1 can impact various underlying causes due to its interactions with several ion channels. However, it is important to note that TRPV1-targeting drugs tend to attenuate rather than completely reverse pain responses. Thus, developing drugs that target multiple ion channels for pain relief could prove more effective. Given the observed genetic heterogeneity in PPN patients, personalized medical treatment based on each patient's genetic and clinical profiles may be more beneficial. This individualized approach aims to address specific clinical features, leading to an increased treatment response.

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References

1. Watson, J.C.; Dyck, P.J.B. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. *Mayo Clin. Proc.* **2015**, *90*, 940–951. [[CrossRef](#)] [[PubMed](#)]
2. Cavalli, E.; Mammana, S.; Nicoletti, F.; Bramanti, P.; Mazzon, E. The Neuropathic Pain: An Overview of the Current Treatment and Future Therapeutic Approaches. *Int. J. Immunopathol. Pharmacol.* **2019**, *33*, 2058738419838383. [[CrossRef](#)]
3. Yan, Y.Y.; Li, C.Y.; Zhou, L.; Ao, L.Y.; Fang, W.R.; Li, Y.M. man Research Progress of Mechanisms and Drug Therapy for Neuropathic Pain. *Life Sci.* **2017**, *190*, 68–77. [[CrossRef](#)] [[PubMed](#)]
4. Zorina-Lichtenwalter, K.; Parisien, M.; Diatchenko, L. Genetic Studies of Human Neuropathic Pain Conditions: A Review. *Pain* **2018**, *159*, 583. [[CrossRef](#)] [[PubMed](#)]
5. Shinu, P.; Morsy, M.A.; Nair, A.B.; Al Mouslem, A.K.; Venugopala, K.N.; Goyal, M.; Bansal, M.; Jacob, S.; Deb, P.K. Novel Therapies for the Treatment of Neuropathic Pain: Potential and Pitfalls. *J. Clin. Med.* **2022**, *11*, 3002. [[CrossRef](#)] [[PubMed](#)]
6. Sopacua, M.; Hoeijmakers, J.G.J.; Merkies, I.S.J.; Lauria, G.; Waxman, S.G.; Faber, C.G. Small-Fiber Neuropathy: Expanding the Clinical Pain Universe. *J. Peripher. Nerv. Syst.* **2019**, *24*, 19–33. [[CrossRef](#)]
7. Bennett, D.L.; Clark, X.A.J.; Huang, J.; Waxman, S.G.; Dib-Hajj, S.D. The Role of Voltage-Gated Sodium Channels in Pain Signaling. *Physiol. Rev.* **2019**, *99*, 1079–1151. [[CrossRef](#)]
8. Ślęczkowska, M.; Almomani, R.; Marchi, M.; de Greef, B.T.A.; Sopacua, M.; Hoeijmakers, J.G.J.; Lindsey, P.; Salvi, E.; Bönhof, G.J.; Ziegler, D.; et al. Peripheral Ion Channel Gene Screening in Painful-and Painless-Diabetic Neuropathy. *Int. J. Mol. Sci.* **2022**, *23*, 7190. [[CrossRef](#)]
9. Ślęczkowska, M.; Almomani, R.; Marchi, M.; Salvi, E.; de Greef, B.T.A.; Sopacua, M.; Hoeijmakers, J.G.J.; Lindsey, P.; Waxman, S.G.; Lauria, G.; et al. Peripheral Ion Channel Genes Screening in Painful Small Fiber Neuropathy. *Int. J. Mol. Sci.* **2022**, *23*, 14095. [[CrossRef](#)]
10. Goodwin, G.; McMahon, S.B. The Physiological Function of Different Voltage-Gated Sodium Channels in Pain. *Nat. Rev. Neurosci.* **2021**, *22*, 263–274. [[CrossRef](#)]
11. Bigsby, S.; Neapetung, J.; Campanucci, V.A. Voltage-Gated Sodium Channels in Diabetic Sensory Neuropathy: Function, Modulation, and Therapeutic Potential. *Front. Cell. Neurosci.* **2022**, *16*, 994585. [[CrossRef](#)] [[PubMed](#)]

12. Waxman, S.G.; Zamponi, G.W. Regulating Excitability of Peripheral Afferents: Emerging Ion Channel Targets. *Nat. Neurosci.* **2014**, *17*, 153–163. [[CrossRef](#)]
13. González-Ramírez, R.; Chen, Y.; Liedtke, W.B.; Morales-Lázaro, S.L. TRP Channels and Pain. In *Neurobiology of TRP Channels*; CRC Press: Boca Raton, FL, USA, 2017; pp. 125–148. [[CrossRef](#)]
14. Dolphin, A.C.; Lee, A. Presynaptic Calcium Channels: Specialized Control of Synaptic Neurotransmitter Release. *Nat. Rev. Neurosci.* **2020**, *21*, 213–229. [[CrossRef](#)] [[PubMed](#)]
15. Rajagopal, S.; Ponnusamy, M. Voltage-Dependent Calcium Channels: From Physiology to Diseases. In *Calcium Signaling: From Physiology to Diseases*; Springer: Singapore, 2017; pp. 61–72. [[CrossRef](#)]
16. Haworth, A.S.; Brackenbury, W.J. Emerging Roles for Multifunctional Ion Channel Auxiliary Subunits in Cancer. *Cell Calcium* **2019**, *80*, 125–140. [[CrossRef](#)] [[PubMed](#)]
17. Gambeta, E.; Gandini, M.A.; Souza, I.A.; Ferron, L.; Zamponi, G.W. A CACNA1A Variant Associated with Trigeminal Neuralgia Alters the Gating of Cav2.1 Channels. *Mol. Brain* **2021**, *14*, 4. [[CrossRef](#)]
18. Huang, M.; Nibbeling, E.A.R.; Lagrand, T.J.; Souza, I.A.; Groen, J.L.; Gandini, M.A.; Zhang, F.X.; Koelman, J.H.T.M.; Adir, N.; Sinke, R.J.; et al. Rare Functional Missense Variants in CACNA1H: What Can We Learn from Writer’s Cramp? *Mol. Brain* **2021**, *14*, 18. [[CrossRef](#)]
19. Costigan, M.; Belfer, I.; Griffin, R.S.; Dai, F.; Barrett, L.B.; Coppola, G.; Wu, T.; Kiselycznyk, C.; Poddar, M.; Lu, Y.; et al. Multiple Chronic Pain States Are Associated with a Common Amino Acid-Changing Allele in KCNS1. *Brain* **2010**, *133*, 2519–2527. [[CrossRef](#)]
20. Meents, J.E.; Fischer, M.J.M.; McNaughton, P.A. Sensitization of TRPA1 by Protein Kinase A. *PLoS ONE* **2017**, *12*, e0170097. [[CrossRef](#)]
21. Zhang, Z.; Schmelz, M.; Segerdahl, M.; Quiding, H.; Centerholt, C.; Juréus, A.; Carr, T.H.; Whiteley, J.; Salter, H.; Kvernebo, M.S.; et al. Exonic Mutations in SCN9A (NaV1.7) Are Found in a Minority of Patients with Erythromelalgia. *Scand. J. Pain* **2014**, *5*, 217–225. [[CrossRef](#)]
22. Di Stefano, G.; Yuan, J.H.; Cruccu, G.; Waxman, S.G.; Dib-Hajj, S.D.; Truini, A. Familial Trigeminal Neuralgia—A Systematic Clinical Study with a Genomic Screen of the Neuronal Electrogenome. *Cephalalgia* **2020**, *40*, 767–777. [[CrossRef](#)]
23. Fan, L.; Guan, X.; Wang, W.; Zhao, J.Y.; Zhang, H.; Tiwari, V.; Hoffman, P.N.; Li, M.; Tao, Y.X. Impaired Neuropathic Pain and Preserved Acute Pain in Rats Overexpressing Voltage-Gated Potassium Channel Subunit Kv1.2 in Primary Afferent Neurons. *Mol. Pain* **2014**, *10*, 1744–8069. [[CrossRef](#)] [[PubMed](#)]
24. Yuan, J.H.; Schulman, B.R.; Effraim, P.R.; Sulayman, D.H.; Jacobs, D.S.; Waxman, S.G. Genomic Analysis of 21 Patients with Corneal Neuralgia after Refractive Surgery. *Pain Rep.* **2020**, *5*, e826. [[CrossRef](#)] [[PubMed](#)]
25. Gualdani, R.; Yuan, J.-H.; Effraim, P.R.; Di Stefano, G.; Truini, A.; Cruccu, G.; Dib-Hajj, S.D.; Gailly, P.; Waxman, S.G. Trigeminal Neuralgia TRPM8 Mutation: Enhanced Activation, Basal [Ca²⁺]_i and Menthol Response. *Neurol. Genet.* **2021**, *7*, e550. [[CrossRef](#)] [[PubMed](#)]
26. Zhong, W.; Hu, L.; Cao, X.; Zhao, J.; Zhang, X.; Lee, M.; Wang, H.; Zhang, J.; Chen, Q.; Feng, C.; et al. Genotype–Phenotype Correlation of TRPV3-Related Olmsted Syndrome. *J. Investig. Dermatol.* **2021**, *141*, 545–554. [[CrossRef](#)]
27. Yoshioka, T.; Imura, K.; Asakawa, M.; Suzuki, M.; Oshima, I.; Hirasawa, T.; Sakata, T.; Horikawa, T.; Arimura, A. Impact of the Gly573Ser Substitution in TRPV3 on the Development of Allergic and Pruritic Dermatitis in Mice. *J. Investig. Dermatol.* **2009**, *129*, 714–722. [[CrossRef](#)]
28. Landouré, G.; Zdebik, A.A.; Martinez, T.L.; Burnett, B.G.; Stanescu, H.C.; Inada, H.; Shi, Y.; Taye, A.A.; Kong, L.; Munns, C.H.; et al. Mutations in TRPV4 Cause Charcot-Marie-Tooth Disease Type 2C. *Nat. Genet.* **2010**, *42*, 170. [[CrossRef](#)]
29. Echaniz-Laguna, A.; Dubourg, O.; Carlier, P.; Carlier, R.Y.; Sabouraud, P.; Péréon, Y.; Chapon, F.; Thauvin-Robinet, C.; Laforêt, P.; Eymard, B.; et al. Phenotypic Spectrum and Incidence of TRPV4 Mutations in Patients with Inherited Axonal Neuropathy. *Neurology* **2014**, *82*, 1919–1926. [[CrossRef](#)]
30. Klein, C.J.; Shi, Y.; Fecto, F.; Donaghy, M.; Nicholson, G.; McEntagart, M.E.; Crosby, A.H.; Wu, Y.; Lou, H.; McEvoy, K.M.; et al. TRPV4 Mutations and Cytotoxic Hypercalcemia in Axonal Charcot-Marie-Tooth Neuropathies. *Neurology* **2011**, *76*, 887–894. [[CrossRef](#)]
31. Auer-Grumbach, M.; Olschewski, A.; Papi, L.; Kremer, H.; McEntagart, M.E.; Uhrig, S.; Fischer, C.; Fröhlich, E.; Bálint, Z.; Tang, B.; et al. Alterations in the Ankyrin Domain of TRPV4 Cause Congenital Distal SMA, Scapuloperoneal SMA and HMSN2C. *Nat. Genet.* **2010**, *42*, 160. [[CrossRef](#)]
32. Deng, H.X.; Klein, C.J.; Yan, J.; Shi, Y.; Wu, Y.; Fecto, F.; Yau, H.J.; Yang, Y.; Zhai, H.; Siddique, N.; et al. Scapuloperoneal Spinal Muscular Atrophy and CMT2C Are Allelic Disorders Caused by Alterations in TRPV4. *Nat. Genet.* **2010**, *42*, 165–169. [[CrossRef](#)]
33. Hommersom, M.P.; van Prooije, T.H.; Pennings, M.; Schouten, M.I.; van Bokhoven, H.; Kamsteeg, E.J.; van de Warrenburg, B.P.C. The Complexities of CACNA1A in Clinical Neurogenetics. *J. Neurol.* **2022**, *269*, 3094–3108. [[CrossRef](#)] [[PubMed](#)]
34. Antunes, F.T.T.; Campos, M.M.; Carvalho, V.D.P.R.; da Silva Junior, C.A.; Magno, L.A.V.; de Souza, A.H.; Gomez, M.V. Current Drug Development Overview: Targeting Voltage-Gated Calcium Channels for the Treatment of Pain. *Int. J. Mol. Sci.* **2023**, *24*, 9223. [[CrossRef](#)] [[PubMed](#)]
35. Hoppanova, L.; Lacinova, L. Voltage-Dependent CaV3.2 and CaV2.2 Channels in Nociceptive Pathways. *Pflügers Arch.—Eur. J. Physiol.* **2022**, *474*, 421–434. [[CrossRef](#)] [[PubMed](#)]

36. DuBreuil, D.M.; Soto, E.J.L.; Daste, S.; Meir, R.; Li, D.; Wainger, B.; Fleischmann, A.; Lipscombe, D. Heat But Not Mechanical Hypersensitivity Depends on Voltage-Gated CaV2.2 Calcium Channel Activity in Peripheral Axon Terminals Innervating Skin. *J. Neurosci.* **2021**, *41*, 7546–7560. [[CrossRef](#)]
37. Nieto-Rostro, M.; Patel, R.; Dickenson, A.H.; Dolphin, A.C. Nerve Injury Increases Native CaV2.2 Trafficking in Dorsal Root Ganglion Mechanoreceptors. *Pain* **2023**, *164*, 1264. [[CrossRef](#)]
38. Tonello, R.; Trevisan, G.; Luckemeyer, D.; Castro-Junior, C.J.; Gomez, M.V.; Ferreira, J. Ph α 1 β , a Dual Blocker of TRPA1 and Cav2.2, as an Adjuvant Drug in Opioid Therapy for Postoperative Pain. *Toxicol.* **2020**, *188*, 80–88. [[CrossRef](#)]
39. Gorman, K.M.; Meyer, E.; Grozeva, D.; Spinelli, E.; McTague, A.; Sanchis-Juan, A.; Carss, K.J.; Bryant, E.; Reich, A.; Schneider, A.L.; et al. Bi-Allelic Loss-of-Function CACNA1B Mutations in Progressive Epilepsy-Dyskinesia. *Am. J. Hum. Genet.* **2019**, *104*, 948–956. [[CrossRef](#)]
40. Groen, J.L.; Andrade, A.; Ritz, K.; Jalalzadeh, H.; Haagmans, M.; Bradley, T.E.J.; Jongejan, A.; Verbeek, D.S.; Nürnberg, P.; Denome, S.; et al. CACNA1B Mutation Is Linked to Unique Myoclonus-Dystonia Syndrome. *Hum. Mol. Genet.* **2015**, *24*, 987–993. [[CrossRef](#)]
41. Cherian, A.; Chandarana, M.; Susvirkar, A.A.; Divya, K.P.; Saraf, U.U.; Krishnan, S. Abnormal Saccades Differentiate Adolescent Onset Variant Ataxia Telangiectasia from Other Myoclonus Dystonia. *Ann. Indian Acad. Neurol.* **2021**, *24*, 630. [[CrossRef](#)]
42. Loke, M.F.; Wei, H.; Yeo, J.; Sng, B.L.; Sia, A.T.; Tan, E.C. Deep Sequencing Analysis to Identify Novel and Rare Variants in Pain-Related Genes in Patients with Acute Postoperative Pain and High Morphine Use. *J. Pain Res.* **2019**, *12*, 2755. [[CrossRef](#)]
43. Weiss, N.; Zamponi, G.W. Genetic T-Type Calcium Channelopathies. *J. Med. Genet.* **2020**, *57*, 1–10. [[CrossRef](#)] [[PubMed](#)]
44. Montero, M.; Goins, A.; Cmarko, L.; Weiss, N.; Westlund, K.N.; Alles, S.R.A. Trigeminal Neuropathic Pain Is Alleviated by Inhibition of Cav3.3 T-Type Calcium Channels in Mice. *Channels* **2020**, *15*, 31–37. [[CrossRef](#)] [[PubMed](#)]
45. Li, Y.; Tatsui, C.E.; Rhines, L.D.; North, R.Y.; Harrison, D.S.; Cassidy, R.M.; Johansson, C.A.; Kosturakis, A.K.; Edwards, D.D.; Zhang, H.; et al. Dorsal Root Ganglion Neurons Become Hyperexcitable and Increase Expression of Voltage-Gated T-Type Calcium Channels (Cav3.2) in Paclitaxel-Induced Peripheral Neuropathy. *Pain* **2017**, *158*, 417. [[CrossRef](#)] [[PubMed](#)]
46. Ovsepian, S.V.; Waxman, S.G. Gene Therapy for Chronic Pain: Emerging Opportunities in Target-Rich Peripheral Nociceptors. *Nat. Rev. Neurosci.* **2023**, *24*, 252–265. [[CrossRef](#)]
47. Snutch, T.P.; Zamponi, G.W. Recent Advances in the Development of T-type Calcium Channel Blockers for Pain Intervention. *Br. J. Pharmacol.* **2018**, *175*, 2375. [[CrossRef](#)]
48. Cai, S.; Gomez, K.; Moutal, A.; Khanna, R. Targeting T-Type/Cav3.2 Channels for Chronic Pain. *Transl. Res.* **2021**, *234*, 20. [[CrossRef](#)]
49. Souza, I.A.; Gandini, M.A.; Zamponi, G.W. Splice-Variant Specific Effects of a CACNA1H Mutation Associated with Writer’s Cramp. *Mol. Brain* **2021**, *14*, 145. [[CrossRef](#)]
50. Nieto-Rostro, M.; Ramgoolam, K.; Pratt, W.S.; Kulik, A.; Dolphin, A.C. Ablation of α 2 δ -1 Inhibits Cell-Surface Trafficking of Endogenous N-Type Calcium Channels in the Pain Pathway in Vivo. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E12043–E12052. [[CrossRef](#)]
51. Dolphin, A.C. Voltage-Gated Calcium Channel α 2 δ Subunits: An Assessment of Proposed Novel Roles. *F1000Research* **2018**, *7*, 1830. [[CrossRef](#)]
52. Finnerup, N.B.; Kuner, R.; Jensen, T.S. Neuropathic Pain: From Mechanisms to Treatment. *Physiol. Rev.* **2021**, *101*, 259–301. [[CrossRef](#)]
53. Zhang, J.; Chen, S.R.; Zhou, M.H.; Jin, D.; Chen, H.; Wang, L.; DePinho, R.A.; Pan, H.L. HDAC2 in Primary Sensory Neurons Constitutively Restrains Chronic Pain by Repressing A2 δ -1 Expression and Associated NMDA Receptor Activity. *J. Neurosci.* **2022**, *42*, 8918–8935. [[CrossRef](#)]
54. Landmann, J.; Richter, F.; Oros-Peusquens, A.M.; Shah, N.J.; Classen, J.; Neely, G.G.; Richter, A.; Penninger, J.M.; Bechmann, I. Neuroanatomy of Pain-Deficiency and Cross-Modal Activation in Calcium Channel Subunit (CACN) A2 δ 3 Knockout Mice. *Brain Struct. Funct.* **2018**, *223*, 111–130. [[CrossRef](#)]
55. Andres-Bilbe, A.; Castellanos, A.; Pujol-Coma, A.; Callejo, G.; Comes, N.; Gasull, X. The Background K⁺ Channel TRESK in Sensory Physiology and Pain. *Int. J. Mol. Sci.* **2020**, *21*, 5206. [[CrossRef](#)] [[PubMed](#)]
56. McCoy, M.T.; Jayanthi, S.; Cadet, J.L. Potassium Channels and Their Potential Roles in Substance Use Disorders. *Int. J. Mol. Sci.* **2021**, *22*, 1249. [[CrossRef](#)] [[PubMed](#)]
57. Busserolles, J.; Tsantoulas, C.; Eschalier, A.; García, J.A.L. Potassium Channels in Neuropathic Pain: Advances, Challenges, and Emerging Ideas. *Pain* **2016**, *157* (Suppl. 1), S7–S14. [[CrossRef](#)]
58. Takeda, M.; Tsuboi, Y.; Kitagawa, J.; Nakagawa, K.; Iwata, K.; Matsumoto, S. Potassium Channels as a Potential Therapeutic Target for Trigeminal Neuropathic and Inflammatory Pain. *Mol. Pain* **2011**, *7*, 5. [[CrossRef](#)] [[PubMed](#)]
59. Clark, J.D.; Tempel, B.L. Hyperalgesia in Mice Lacking the Kv1.1 Potassium Channel Gene. *Neurosci. Lett.* **1998**, *251*, 121–124. [[CrossRef](#)]
60. Zhao, Q.; Fan, L.; Wang, J.; Deng, X.; Zou, J. Relationship between Pain Behavior and Changes in KCNA2 Expression in the Dorsal Root Ganglia of Rats with Osteoarthritis. *Pain Res. Manag.* **2020**, *2020*, 4636838. [[CrossRef](#)]
61. Zhao, X.; Tang, Z.; Zhang, H.; Atianjoh, F.E.; Zhao, J.Y.; Liang, L.; Wang, W.; Guan, X.; Kao, S.C.; Tiwari, V.; et al. A Long Noncoding RNA Contributes to Neuropathic Pain by Silencing *Kcna2* in Primary Afferent Neurons. *Nat. Neurosci.* **2013**, *16*, 1024–1031. [[CrossRef](#)]

62. Liang, L.; Gu, X.; Zhao, J.Y.; Wu, S.; Miao, X.; Xiao, J.; Mo, K.; Zhang, J.; Lutz, B.M.; Bekker, A.; et al. G9a Participates in Nerve Injury-Induced Kcna2 Downregulation in Primary Sensory Neurons. *Sci. Rep.* **2016**, *6*, 37704. [[CrossRef](#)]
63. Mo, K.; Wu, S.; Gu, X.; Xiong, M.; Cai, W.; Atianjoh, F.E.; Jobe, E.E.; Zhao, X.; Tu, W.F.; Tao, Y.X. MBD1 Contributes to the Genesis of Acute Pain and Neuropathic Pain by Epigenetic Silencing of Oprm1 and Kcna2 Genes in Primary Sensory Neurons. *J. Neurosci.* **2018**, *38*, 9883–9899. [[CrossRef](#)] [[PubMed](#)]
64. Zhao, J.Y.; Liang, L.; Gu, X.; Li, Z.; Wu, S.; Sun, L.; Atianjoh, F.E.; Feng, J.; Mo, K.; Jia, S.; et al. DNA Methyltransferase DNMT3a Contributes to Neuropathic Pain by Repressing Kcna2 in Primary Afferent Neurons. *Nat. Commun.* **2017**, *8*, 14712. [[CrossRef](#)] [[PubMed](#)]
65. Sun, L.; Gu, X.; Pan, Z.; Guo, X.; Liu, J.; Atianjoh, F.E.; Wu, S.; Mo, K.; Xu, B.; Liang, L.; et al. Contribution of DNMT1 to Neuropathic Pain Genesis Partially through Epigenetically Repressing Kcna2 in Primary Afferent Neurons. *J. Neurosci.* **2019**, *39*, 6595–6607. [[CrossRef](#)]
66. Zhang, J.; Rong, L.; Shao, J.; Zhang, Y.; Liu, Y.; Zhao, S.; Li, L.; Yu, W.; Zhang, M.; Ren, X.; et al. Epigenetic Restoration of Voltage-Gated Potassium Channel Kv1.2 Alleviates Nerve Injury-Induced Neuropathic Pain. *J. Neurochem.* **2021**, *156*, 367–378. [[CrossRef](#)] [[PubMed](#)]
67. Jiang, M.; Wang, Y.; Wang, J.; Feng, S.; Wang, X. The Etiological Roles of MiRNAs, LncRNAs, and CircRNAs in Neuropathic Pain: A Narrative Review. *J. Clin. Lab. Anal.* **2022**, *36*, e24592. [[CrossRef](#)] [[PubMed](#)]
68. Rivera-Arconada, I.; Roza, C.; Lopez-Garcia, J.A. Enhancing M Currents: A Way out for Neuropathic Pain? *Front. Mol. Neurosci.* **2009**, *2*, 10. [[CrossRef](#)]
69. Yu, T.; Li, L.; Liu, H.; Li, H.; Liu, Z.; Li, Z. KCNQ2/3/5 Channels in Dorsal Root Ganglion Neurons Can Be Therapeutic Targets of Neuropathic Pain in Diabetic Rats. *Mol. Pain* **2018**, *14*, 1744806918793229. [[CrossRef](#)]
70. Ling, J.; Erol, F.; Viatchenko-Karpinski, V.; Kanda, H.; Gu, J.G. Orofacial Neuropathic Pain Induced by Oxaliplatin: Downregulation of KCNQ2 Channels in V2 Trigeminal Ganglion Neurons and Treatment by the KCNQ2 Channel Potentiator Retigabine. *Mol. Pain* **2017**, *13*, 1744806917724715. [[CrossRef](#)]
71. Mis, M.A.; Yang, Y.; Tanaka, B.S.; Gomis-Perez, C.; Liu, S.; Dib-Hajj, F.; Adi, T.; Garcia-Milian, R.; Schulman, B.R.; Dib-Hajj, S.D.; et al. Resilience to Pain: A Peripheral Component Identified Using Induced Pluripotent Stem Cells and Dynamic Clamp. *J. Neurosci.* **2019**, *39*, 382–392. [[CrossRef](#)]
72. Yuan, J.-H.; Estacion, M.; Mis, M.A.; Tanaka, B.S.; Schulman, B.R.; Chen, L.; Liu, S.; Dib-Hajj, F.B.; Dib-Hajj, S.D.; Waxman, S.G. KCNQ Variants and Pain Modulation: A Missense Variant in Kv7.3 Contributes to Pain Resilience. *Brain Commun.* **2021**, *3*, fcab212. [[CrossRef](#)]
73. Richardson, F.C.; Kaczmarek, L.K. Modification of Delayed Rectifier Potassium Currents by the Kv9.1 Potassium Channel Subunit. *Hear. Res.* **2000**, *147*, 21–30. [[CrossRef](#)] [[PubMed](#)]
74. Tsantoulas, C.; Zhu, L.; Shaifta, Y.; Grist, J.; Ward, J.P.T.; Raouf, R.; Michael, G.J.; McMahon, S.B. Sensory Neuron Downregulation of the Kv9.1 Potassium Channel Subunit Mediates Neuropathic Pain Following Nerve Injury. *J. Neurosci.* **2012**, *32*, 17502–17513. [[CrossRef](#)] [[PubMed](#)]
75. Tsantoulas, C.; Denk, F.; Signore, M.; Nassar, M.A.; Futai, K.; McMahon, S.B. Mice Lacking Kcns1 in Peripheral Neurons Show Increased Basal and Neuropathic Pain Sensitivity. *Pain* **2018**, *159*, 1641–1651. [[CrossRef](#)] [[PubMed](#)]
76. Chen, S.; Wang, J.; Siegelbaum, S.A. Properties of Hyperpolarization-Activated Pacemaker Current Defined by Coassembly of HCN1 and HCN2 Subunits and Basal Modulation by Cyclic Nucleotide. *J. Gen. Physiol.* **2001**, *117*, 491–503. [[CrossRef](#)] [[PubMed](#)]
77. Sartiani, L.; Mannaioni, G.; Masi, A.; Romanelli, M.N.; Cerbai, E. The Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels: From Biophysics to Pharmacology of a Unique Family of Ion Channels. *Pharmacol. Rev.* **2017**, *69*, 354–395. [[CrossRef](#)]
78. Santoro, B.; Chen, S.; Lüthi, A.; Pavlidis, P.; Shumyatsky, G.P.; Tibbs, G.R.; Siegelbaum, S.A. Molecular and Functional Heterogeneity of Hyperpolarization-Activated Pacemaker Channels in the Mouse CNS. *J. Neurosci.* **2000**, *20*, 5264–5275. [[CrossRef](#)]
79. Jiang, Y.Q.; Sun, Q.; Tu, H.Y.; Wan, Y. Characteristics of HCN Channels and Their Participation in Neuropathic Pain. *Neurochem. Res.* **2008**, *33*, 1979–1989. [[CrossRef](#)]
80. Rivolta, I.; Binda, A.; Masi, A.; DiFrancesco, J.C. Cardiac and Neuronal HCN Channelopathies. *Pflugers Arch. Eur. J. Physiol.* **2020**, *472*, 931–951. [[CrossRef](#)]
81. Tu, H.; Deng, L.; Sun, Q.; Yao, L.; Han, J.S.; Wan, Y. Hyperpolarization-Activated, Cyclic Nucleotide-Gated Cation Channels: Roles in the Differential Electrophysiological Properties of Rat Primary Afferent Neurons. *J. Neurosci. Res.* **2004**, *76*, 713–722. [[CrossRef](#)]
82. Chaplan, S.R.; Guo, H.Q.; Lee, D.H.; Luo, L.; Liu, C.; Kuei, C.; Velumian, A.A.; Butler, M.P.; Brown, S.M.; Dubin, A.E. Neuronal Hyperpolarization-Activated Pacemaker Channels Drive Neuropathic Pain. *J. Neurosci.* **2003**, *23*, 1169–1178. [[CrossRef](#)]
83. Schnorr, S.; Eberhardt, M.; Kistner, K.; Rajab, H.; Käfer, J.; Hess, A.; Reeh, P.; Ludwig, A.; Herrmann, S. HCN2 Channels Account for Mechanical (but Not Heat) Hyperalgesia during Long-Standing Inflammation. *Pain* **2014**, *155*, 1079–1090. [[CrossRef](#)] [[PubMed](#)]
84. Acosta, C.; McMullan, S.; Djouhri, L.; Gao, L.; Watkins, R.; Berry, C.; Dempsey, K.; Lawson, S.N.; Zhang, Z. HCN1 and HCN2 in Rat DRG Neurons: Levels in Nociceptors and Non-Nociceptors, NT3-Dependence and Influence of CFA-Induced Skin Inflammation on HCN2 and NT3 Expression. *PLoS ONE* **2012**, *7*, e50442. [[CrossRef](#)] [[PubMed](#)]
85. Momin, A.; Cadiou, H.; Mason, A.; McNaughton, P.A. Role of the Hyperpolarization-Activated Current I_h in Somatosensory Neurons. *J. Physiol.* **2008**, *586*, 5911–5929. [[CrossRef](#)]

86. Liu, H.; Zhou, J.; Gu, L.; Zuo, Y. The Change of HCN1/HCN2 mRNA Expression in Peripheral Nerve after Chronic Constriction Injury Induced Neuropathy Followed by Pulsed Electromagnetic Field Therapy. *Oncotarget* **2017**, *8*, 1110–1116. [[CrossRef](#)] [[PubMed](#)]
87. Yao, H.; Donnelly, D.F.; Ma, C.; LaMotte, R.H. Upregulation of the Hyperpolarization-Activated Cation Current after Chronic Compression of the Dorsal Root Ganglion. *J. Neurosci.* **2003**, *23*, 2069–2074. [[CrossRef](#)] [[PubMed](#)]
88. Kitagawa, J.; Takeda, M.; Suzuki, I.; Kadoi, J.; Tsuboi, Y.; Honda, K.; Matsumoto, S.; Nakagawa, H.; Tanabe, A.; Iwata, K. Mechanisms Involved in Modulation of Trigeminal Primary Afferent Activity in Rats with Peripheral Mononeuropathy. *Eur. J. Neurosci.* **2006**, *24*, 1976–1986. [[CrossRef](#)]
89. Ramírez, D.; Zúñiga, R.; Concha, G.; Zúñiga, L. HCN Channels: New Therapeutic Targets for Pain Treatment. *Molecules* **2018**, *23*, 2094. [[CrossRef](#)]
90. Mayar, S.; Memarpoor-Yazdi, M.; Makky, A.; Eslami Sarokhalil, R.; D’Avanzo, N. Direct Regulation of Hyperpolarization-Activated Cyclic-Nucleotide Gated (HCN1) Channels by Cannabinoids. *Front. Mol. Neurosci.* **2022**, *15*, 848540. [[CrossRef](#)]
91. Resta, F.; Micheli, L.; Laurino, A.; Spinelli, V.; Mello, T.; Sartiani, L.; Di Cesare Mannelli, L.; Cerbai, E.; Ghelardini, C.; Romanelli, M.N.; et al. Selective HCN1 Block as a Strategy to Control Oxaliplatin-Induced Neuropathy. *Neuropharmacology* **2018**, *131*, 403–413. [[CrossRef](#)]
92. Ludwig, A.; Budde, T.; Stieber, J.; Moosmang, S.; Wahl, C.; Holthoff, K.; Langebartels, A.; Wotjak, C.; Munsch, T.; Zong, X.; et al. Absence Epilepsy and Sinus Dysrhythmia in Mice Lacking the Pacemaker Channel HCN2. *EMBO J.* **2003**, *22*, 216–224. [[CrossRef](#)]
93. Emery, E.C.; Young, G.T.; Berrococo, E.M.; Chen, L.; McNaughton, P.A. HCN2 Ion Channels Play a Central Role in Inflammatory and Neuropathic Pain. *Science* **2011**, *333*, 1462–1466. [[CrossRef](#)]
94. Tsantoulas, C.; Lainez, S.; Wong, S.; Mehta, I.; Vilar, B.; McNaughton, P.A. Hyperpolarization-Activated Cyclic Nucleotide-Gated 2 (Hcn2) Ion Channels Drive Pain in Mouse Models of Diabetic Neuropathy. *Sci. Transl. Med.* **2017**, *9*, eaam6072. [[CrossRef](#)] [[PubMed](#)]
95. Liu, X.; Zhang, L.; Jin, L.; Tan, Y.; Li, W.; Tang, J. HCN2 Contributes to Oxaliplatin-Induced Neuropathic Pain through Activation of the CaMKII/CREB Cascade in Spinal Neurons. *Mol. Pain* **2018**, *14*, 1744806918778490. [[CrossRef](#)] [[PubMed](#)]
96. Huang, H.; Zhang, Z.; Huang, D. Decreased HCN2 Channel Expression Attenuates Neuropathic Pain by Inhibiting Pro-Inflammatory Reactions and NF-KB Activation in Mice. *Int. J. Clin. Exp. Pathol.* **2019**, *12*, 154–163.
97. Lainez, S.; Tsantoulas, C.; Biel, M.; McNaughton, P.A. HCN3 Ion Channels: Roles in Sensory Neuronal Excitability and Pain. *J. Physiol.* **2019**, *597*, 4661–4675. [[CrossRef](#)] [[PubMed](#)]
98. Becker, F.; Reid, C.A.; Hallmann, K.; Tae, H.S.; Phillips, A.M.; Teodorescu, G.; Weber, Y.G.; Kleefuss-Lie, A.; Elger, C.; Perez-Reyes, E.; et al. Functional Variants in HCN4 and CACNA1H May Contribute to Genetic Generalized Epilepsy. *Epilepsia Open* **2017**, *2*, 334–342. [[CrossRef](#)]
99. Campostrini, G.; Difrancesco, J.C.; Castellotti, B.; Milanese, R.; Gnechi-Ruscione, T.; Bonzanni, M.; Bucchi, A.; Baruscotti, M.; Ferrarese, C.; Franceschetti, S.; et al. A Loss-of-Function HCN4 Mutation Associated with Familial Benign Myoclonic Epilepsy in Infancy Causes Increased Neuronal Excitability. *Front. Mol. Neurosci.* **2018**, *11*, 269. [[CrossRef](#)] [[PubMed](#)]
100. Pedemonte, N.; Galletta, L.J. Structure and Function of TMEM16 Proteins (Anoctamins). *Physiol. Rev.* **2014**, *94*, 419–459. [[CrossRef](#)]
101. Huang, F.; Wang, X.; Ostertag, E.M.; Nuwal, T.; Huang, B.; Jan, Y.N.; Basbaum, A.I.; Jan, L.Y. TMEM16C Facilitates Na(+)-Activated K+ Currents in Rat Sensory Neurons and Regulates Pain Processing. *Nat. Neurosci.* **2013**, *16*, 1284–1290. [[CrossRef](#)]
102. Takayama, Y.; Uta, D.; Furue, H.; Tominaga, M. Pain-Enhancing Mechanism through Interaction between TRPV1 and Anoctamin 1 in Sensory Neurons. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 5213–5218. [[CrossRef](#)]
103. Cho, H.; Oh, U. Anoctamin 1 Mediates Thermal Pain as a Heat Sensor. *Curr. Neuropharmacol.* **2013**, *11*, 641. [[CrossRef](#)] [[PubMed](#)]
104. Lee, B.; Cho, H.; Jung, J.; Yang, Y.D.; Yang, D.J.; Oh, U. Anoctamin 1 Contributes to Inflammatory and Nerve-Injury Induced Hypersensitivity. *Mol. Pain* **2014**, *10*, 1744–8069. [[CrossRef](#)]
105. Cho, H.; Yang, Y.D.; Lee, J.; Lee, B.; Kim, T.; Jang, Y.; Back, S.K.; Na, H.S.; Harfe, B.D.; Wang, F.; et al. The Calcium-Activated Chloride Channel Anoctamin 1 Acts as a Heat Sensor in Nociceptive Neurons. *Nat. Neurosci.* **2012**, *15*, 1015–1021. [[CrossRef](#)]
106. Liu, B.; Linley, J.E.; Du, X.; Zhang, X.; Ooi, L.; Zhang, H.; Gamper, N. The Acute Nociceptive Signals Induced by Bradykinin in Rat Sensory Neurons Are Mediated by Inhibition of M-Type K+ Channels and Activation of Ca2+-Activated Cl- Channels. *J. Clin. Investig.* **2010**, *120*, 1240–1252. [[CrossRef](#)] [[PubMed](#)]
107. Nilius, B.; Flockerzi, V. (Eds.) *Handbook of Experimental Pharmacology 222*; Springer: Berlin/Heidelberg, Germany, 2014; Volume 222, ISBN 9783642542145.
108. Meents, J.E.; Ciotu, C.I.; Fischer, M.J.M. Trpa1: A Molecular View. *J. Neurophysiol.* **2019**, *121*, 427–443. [[CrossRef](#)] [[PubMed](#)]
109. Kremeyer, B.; Lopera, F.; Cox, J.J.; Momin, A.; Rugiero, F.; Marsh, S.; Woods, C.G.; Jones, N.G.; Paterson, K.J.; Fricker, F.R.; et al. A Gain-of-Function Mutation in TRPA1 Causes Familial Episodic Pain Syndrome. *Neuron* **2010**, *66*, 671–680. [[CrossRef](#)] [[PubMed](#)]
110. Gouin, O.; L’Herdelle, K.; Lebonvallet, N.; Le Gall-Ianotto, C.; Sakka, M.; Buhé, V.; Plée-Gautier, E.; Carré, J.L.; Lefeuvre, L.; Misery, L.; et al. TRPV1 and TRPA1 in Cutaneous Neurogenic and Chronic Inflammation: Pro-Inflammatory Response Induced by Their Activation and Their Sensitization. *Protein Cell* **2017**, *8*, 644–661. [[CrossRef](#)] [[PubMed](#)]
111. Baral, P.; Udit, S.; Chiu, I.M. Pain and Immunity: Implications for Host Defence. *Nat. Rev. Immunol.* **2019**, *19*, 433–447. [[CrossRef](#)]
112. Marcotti, A.; Fernández-Trillo, J.; González, A.; Vizcaíno-Escoto, M.; Ros-Arlanzón, P.; Romero, L.; Vela, J.M.; Gomis, A.; Viana, F.; De La Peña, E. TRPA1 Modulation by Sigma-1 Receptor Prevents Oxaliplatin-Induced Painful Peripheral Neuropathy. *Brain* **2023**, *146*, 475–491. [[CrossRef](#)]

113. De Logu, F.; De Siena, G.; Landini, L.; Marini, M.; Souza Monteiro de Araujo, D.; Albanese, V.; Preti, D.; Romitelli, A.; Chieca, M.; Titiz, M.; et al. Non-Neuronal TRPA1 Encodes Mechanical Allodynia Associated with Neurogenic Inflammation and Partial Nerve Injury in Rats. *Br. J. Pharmacol.* **2023**, *180*, 1232–1246. [[CrossRef](#)]
114. Zhou, F.; Metzner, K.; Engel, P.; Balzulat, A.; Sisignano, M.; Ruth, P.; Lukowski, R.; Schmidtko, A.; Lu, R. Slack Potassium Channels Modulate TRPA1-Mediated Nociception in Sensory Neurons. *Cells* **2022**, *11*, 1693. [[CrossRef](#)] [[PubMed](#)]
115. Vandewauw, I.; De Clercq, K.; Mulier, M.; Held, K.; Pinto, S.; Van Ranst, N.; Segal, A.; Voet, T.; Vennekens, R.; Zimmermann, K.; et al. A TRP Channel Trio Mediates Acute Noxious Heat Sensing. *Nature* **2018**, *555*, 662–666. [[CrossRef](#)]
116. Marchi, M.; Salvi, E.; Andelic, M.; Mehmeti, E.; D'Amato, I.; Cazzato, D.; Chiappori, F.; Lombardi, R.; Cartelli, D.; Devigili, G.; et al. TRPA1 Rare Variants in Chronic Neuropathic and Nociceptive Pain Patients. *Pain* **2022**, *164*, 2048–2059. [[CrossRef](#)] [[PubMed](#)]
117. Nirenberg, M.J.; Chaouni, R.; Biller, T.M.; Gilbert, R.M.; Paisán-Ruiz, C. A Novel TRPA1 Variant Is Associated with Carbamazepine-Responsive Cramp-Fasciculation Syndrome. *Clin. Genet.* **2018**, *93*, 164–168. [[CrossRef](#)]
118. Wang, H.; Song, T.; Wang, W.; Zhang, Z. TRPM2 Participates the Transformation of Acute Pain to Chronic Pain during Injury-Induced Neuropathic Pain. *Synapse* **2019**, *73*, e22117. [[CrossRef](#)]
119. Haraguchi, K.; Kawamoto, A.; Isami, K.; Maeda, S.; Kusano, A.; Asakura, K.; Shirakawa, H.; Mori, Y.; Nakagawa, T.; Kaneko, S. TRPM2 Contributes to Inflammatory and Neuropathic Pain through the Aggravation of Pronociceptive Inflammatory Responses in Mice. *J. Neurosci.* **2012**, *32*, 3931. [[CrossRef](#)]
120. Jang, Y.; Cho, P.S.; Yang, Y.D.; Hwang, S.W. Nociceptive Roles of TRPM2 Ion Channel in Pathologic Pain. *Mol. Neurobiol.* **2018**, *55*, 6589–6600. [[CrossRef](#)] [[PubMed](#)]
121. Malko, P.; Syed Mortadza, S.A.; McWilliam, J.; Jiang, L.H. TRPM2 Channel in Microglia as a New Player in Neuroinflammation Associated With a Spectrum of Central Nervous System Pathologies. *Front. Pharmacol.* **2019**, *10*, 239. [[CrossRef](#)]
122. Nazıroğlu, M. Activation of TRPM2 and TRPV1 Channels in Dorsal Root Ganglion by NADPH Oxidase and Protein Kinase C Molecular Pathways: A Patch Clamp Study. *J. Mol. Neurosci.* **2017**, *61*, 425–435. [[CrossRef](#)]
123. Bayir, M.H.; Yıldızhan, K.; Altındağ, F. Effect of Hesperidin on Sciatic Nerve Damage in STZ-Induced Diabetic Neuropathy: Modulation of TRPM2 Channel. *Neurotox. Res.* **2023**, 1–10. [[CrossRef](#)]
124. Sita, G.; Hrelia, P.; Graziosi, A.; Ravegnini, G.; Morroni, F. TRPM2 in the Brain: Role in Health and Disease. *Cells* **2018**, *7*, 82. [[CrossRef](#)] [[PubMed](#)]
125. Thiel, G.; Rubil, S.; Lesch, A.; Guethlein, L.A.; Rössler, O.G. Transient Receptor Potential TRPM3 Channels: Pharmacology, Signaling, and Biological Functions. *Pharmacol. Res.* **2017**, *124*, 92–99. [[CrossRef](#)] [[PubMed](#)]
126. Farooqi, A.A.; Javeed, M.K.; Javed, Z.; Riaz, A.M.; Mukhtar, S.; Minhaj, S.; Abbas, S.; Bhatti, S. TRPM Channels: Same Ballpark, Different Players, and Different Rules in Immunogenetics. *Immunogenetics* **2011**, *63*, 773–787. [[CrossRef](#)]
127. Vriens, J.; Voets, T.; Vriens JorisVriens, J. Sensing the Heat with TRPM3. *Pflügers Arch.—Eur. J. Physiol.* **2018**, *470*, 799–807. [[CrossRef](#)]
128. Wagner, T.F.J.; Loch, S.; Lambert, S.; Straub, I.; Mannebach, S.; Mathar, I.; Düfer, M.; Lis, A.; Flockerzi, V.; Philipp, S.E.; et al. Transient Receptor Potential M3 Channels Are Ionotropic Steroid Receptors in Pancreatic Beta Cells. *Nat. Cell Biol.* **2008**, *10*, 1421–1430. [[CrossRef](#)] [[PubMed](#)]
129. Krügel, U.; Straub, I.; Beckmann, H.; Schaefer, M. Primidone Inhibits TRPM3 and Attenuates Thermal Nociception in Vivo. *Pain* **2017**, *158*, 856. [[CrossRef](#)] [[PubMed](#)]
130. Silverman, H.A.; Chen, A.; Kravatz, N.L.; Chavan, S.S.; Chang, E.H. Involvement of Neural Transient Receptor Potential Channels in Peripheral Inflammation. *Front. Immunol.* **2020**, *11*, 2742. [[CrossRef](#)]
131. Behrendt, M.; Gruss, F.; Enzeroth, R.; Dembla, S.; Zhao, S.; Crassous, P.A.; Mohr, F.; Nys, M.; Louros, N.; Gallardo, R.; et al. The Structural Basis for an On-off Switch Controlling Gβγ-Mediated Inhibition of TRPM3 Channels. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 29090–29100. [[CrossRef](#)]
132. Dyment, D.A.; Terhal, P.A.; Rustad, C.F.; Tveten, K.; Griffith, C.; Jayakar, P.; Shinawi, M.; Ellingwood, S.; Smith, R.; van Gassen, K.; et al. De Novo Substitutions of TRPM3 Cause Intellectual Disability and Epilepsy. *Eur. J. Hum. Genet.* **2019**, *27*, 1611–1618. [[CrossRef](#)]
133. Aloi, V.D.; Coutinho Pinto, S.J.P.; Van Bree, R.; Luyten, K.; Voets, T.; Vriens, J. TRPM3 as a Novel Target to Alleviate Acute Oxaliplatin-Induced Peripheral Neuropathic Pain. *Pain* **2023**, *164*, 2060–2069. [[CrossRef](#)]
134. McKemy, D.D.; Neuhauser, W.M.; Julius, D. Identification of a Cold Receptor Reveals a General Role for TRP Channels in Thermosensation. *Nature* **2002**, *416*, 52–58. [[CrossRef](#)]
135. Huang, Y.; Fliegert, R.; Guse, A.H.; Lü, W.; Du, J. A Structural Overview of the Ion Channels of the TRPM Family. *Cell Calcium* **2020**, *85*, 102111. [[CrossRef](#)] [[PubMed](#)]
136. Weyer, A.D.; Lehto, S.G. Development of TRPM8 Antagonists to Treat Chronic Pain and Migraine. *Pharmaceuticals* **2017**, *10*, 37. [[CrossRef](#)]
137. De Caro, C.; Cristiano, C.; Avagliano, C.; Bertamino, A.; Ostacolo, C.; Campiglia, P.; Gomez-Monterrey, I.; La Rana, G.; Gualillo, O.; Calignano, A.; et al. Characterization of New TRPM8 Modulators in Pain Perception. *Int. J. Mol. Sci.* **2019**, *20*, 5544. [[CrossRef](#)] [[PubMed](#)]
138. González-Muñiz, R.; Bonache, M.A.; Martín-Escura, C.; Gómez-Monterrey, I. Recent Progress in TRPM8 Modulation: An Update. *Int. J. Mol. Sci.* **2019**, *20*, 2618. [[CrossRef](#)] [[PubMed](#)]

139. Andersson, D.A.; Chase, H.W.N.; Bevan, S. TRPM8 Activation by Menthol, Icilin, and Cold Is Differentially Modulated by Intracellular PH. *J. Neurosci.* **2004**, *24*, 5364–5369. [[CrossRef](#)]
140. Wu, B.; Su, X.; Zhang, W.; Zhang, Y.-H.; Feng, X.; Ji, Y.-H.; Tan, Z.-Y. Oxaliplatin Depolarizes the IB4⁻ Dorsal Root Ganglion Neurons to Drive the Development of Neuropathic Pain Through TRPM8 in Mice. *Front. Mol. Neurosci.* **2021**, *14*, 690858. [[CrossRef](#)]
141. Khan, A.; Shal, B.; Khan, A.U.; Ullah, R.; Baig, M.W.; ul Haq, I.; Seo, E.K.; Khan, S. Suppression of TRPV1/TRPM8/P2Y Nociceptors by Withametin via Downregulating MAPK Signaling in Mouse Model of Vincristine-Induced Neuropathic Pain. *Int. J. Mol. Sci.* **2021**, *22*, 6084. [[CrossRef](#)]
142. Caudle, R.M.; Neubert, J.K. Effects of Oxaliplatin on Facial Sensitivity to Cool Temperatures and TRPM8 Expressing Trigeminal Ganglion Neurons in Mice. *Front. Pain Res.* **2022**, *3*, 868547. [[CrossRef](#)]
143. Iftinca, M.; Basso, L.; Flynn, R.; Kwok, C.; Roland, C.; Hassan, A.; Defaye, M.; Ramachandran, R.; Trang, T.; Altier, C. Chronic Morphine Regulates TRPM8 Channels via MOR-PKC β Signaling. *Mol. Brain* **2020**, *13*, 61. [[CrossRef](#)]
144. Martín-Escura, C.; Medina-Peris, A.; Spear, L.A.; de la Torre Martínez, R.; Olivos-Oré, L.A.; Barahona, M.V.; González-Rodríguez, S.; Fernández-Ballester, G.; Fernández-Carvajal, A.; Artalejo, A.R.; et al. β -Lactam TRPM8 Antagonist RGM8-51 Displays Antinociceptive Activity in Different Animal Models. *Int. J. Mol. Sci.* **2022**, *23*, 2692. [[CrossRef](#)] [[PubMed](#)]
145. Khan, A.; Wang, F.; Shal, B.; Khan, A.U.; Zahra, S.S.; ul Haq, I.; Khan, S.; Rengasamy, K.R. Anti-Neuropathic Pain Activity of Ajugarin-I via Activation of Nrf2 Signaling and Inhibition of TRPV1/TRPM8 Nociceptors in STZ-Induced Diabetic Neuropathy. *Pharmacol. Res.* **2022**, *183*, 106392. [[CrossRef](#)] [[PubMed](#)]
146. Messeguer, A.; Planells-Cases, R.; Ferrer-Montiel, A. Physiology and Pharmacology of the Vanilloid Receptor. *Curr. Neuropharmacol.* **2005**, *4*, 1–15. [[CrossRef](#)] [[PubMed](#)]
147. Brandt, M.R.; Beyer, C.E.; Stahl, S.M. TRPV1 Antagonists and Chronic Pain: Beyond Thermal Perception. *Pharmaceuticals* **2012**, *5*, 114–132. [[CrossRef](#)]
148. Kumar, R. Endogenous and Exogenous Vanilloids Evoke Disparate TRPV1 Activation to Produce Distinct Neuronal Responses. *Front. Pharmacol.* **2020**, *11*, 903. [[CrossRef](#)]
149. Iftinca, M.; Defaye, M.; Altier, C. TRPV1-Targeted Drugs in Development for Human Pain Conditions. *Drugs* **2021**, *81*, 7–27. [[CrossRef](#)]
150. Mickle, A.D.; Shepherd, A.J.; Mohapatra, D.P.; Edu, A.D.M.S.; Szallasi, A.; Huang, S.M. Nociceptive TRP Channels: Sensory Detectors and Transducers in Multiple Pain Pathologies. *Pharmaceuticals* **2016**, *9*, 72. [[CrossRef](#)]
151. Katz, B.; Zaguri, R.; Edvardson, S.; Maayan, C.; Elpeleg, O.; Lev, S.; Davidson, E.; Peters, M.; Kfir-Erenfeld, S.; Berger, E.; et al. Nociception and Pain in Humans Lacking a Functional TRPV1 Channel. *J. Clin. Investig.* **2023**, *133*, e153558. [[CrossRef](#)]
152. Akhilesh; Uniyal, A.; Gadepalli, A.; Tiwari, V.; Allani, M.; Chouhan, D.; Ummadisetty, O.; Verma, N.; Tiwari, V. Unlocking the Potential of TRPV1 Based siRNA Therapeutics for the Treatment of Chemotherapy-Induced Neuropathic Pain. *Life Sci.* **2022**, *288*, 120187. [[CrossRef](#)]
153. Xie, Y.K.; Luo, H.; Zhang, S.X.; Chen, X.Y.; Guo, R.; Qiu, X.Y.; Liu, S.; Wu, H.; Chen, W.B.; Zhen, X.H.; et al. GPR177 in A-Fiber Sensory Neurons Drives Diabetic Neuropathic Pain via WNT-Mediated TRPV1 Activation. *Sci. Transl. Med.* **2022**, *14*, eab2557. [[CrossRef](#)]
154. Yazgan, B.; Yazgan, Y.; Naziroglu, M. Alpha-Lipoic Acid Modulates the Diabetes Mellitus-Mediated Neuropathic Pain via Inhibition of the TRPV1 Channel, Apoptosis, and Oxidative Stress in Rats. *J. Bioenerg. Biomembr.* **2023**, *55*, 179–193. [[CrossRef](#)] [[PubMed](#)]
155. Zhang, X.; Peng, L.; Liu, D. Pregabalin Alleviates Neuropathic Pain via Inhibition of the PKC ϵ /TRPV1 Pathway. *Neurosci. Lett.* **2022**, *766*, 136348. [[CrossRef](#)] [[PubMed](#)]
156. Wang, X.; Bao, C.; Li, Z.; Yue, L.; Hu, L. Side Effects of Opioids Are Ameliorated by Regulating TRPV1 Receptors. *Int. J. Environ. Res. Public Health* **2022**, *19*, 2387. [[CrossRef](#)]
157. Aguiar, D.D.; da Costa Oliveira, C.; Fonseca, F.C.S.; de Almeida, D.L.; Campos Pereira, W.V.; Guimaraes, F.S.; Perez, A.C.; Duarte, I.D.G.; Romero, T.R.L. Peripherally Injected Canabidiol Reduces Neuropathic Pain in Mice: Role of the 5-HT1A and TRPV1 Receptors. *Biochem. Biophys. Res. Commun.* **2023**, *660*, 58–64. [[CrossRef](#)]
158. Xiao, R.; Tang, J.; Wang, C.; Colton, C.K.; Tian, J.; Zhu, M.X. Calcium Plays a Central Role in the Sensitization of TRPV3 Channel to Repetitive Stimulations. *J. Biol. Chem.* **2008**, *283*, 6162–6174. [[CrossRef](#)] [[PubMed](#)]
159. Zubcevic, L.; Herzik, M.A.; Wu, M.; Borschel, W.F.; Hirschi, M.; Song, A.S.; Lander, G.C.; Lee, S.-Y. Conformational Ensemble of the Human TRPV3 Ion Channel. *Nat. Commun.* **2018**, *9*, 4773. [[CrossRef](#)]
160. Singh, A.K.; McGoldrick, L.L.; Sobolevsky, A.I. Structure and Gating Mechanism of the Transient Receptor Potential Channel TRPV3. *Nat. Struct. Mol. Biol.* **2018**, *25*, 805–813. [[CrossRef](#)]
161. Deng, Z.; Maksaev, G.; Rau, M.; Xie, Z.; Hu, H.; Fitzpatrick, J.A.J.; Yuan, P. Gating of Human TRPV3 in a Lipid Bilayer. *Nat. Struct. Mol. Biol.* **2020**, *27*, 635–644. [[CrossRef](#)]
162. Larkin, C.; Chen, W.; Szabó, I.L.; Shan, C.; Dajnoki, Z.; Szegedi, A.; Buhl, T.; Fan, Y.; O'Neill, S.; Walls, D.; et al. Novel Insights into the TRPV3-Mediated Itch in Atopic Dermatitis. *J. Allergy Clin. Immunol.* **2021**, *147*, 1110–1114.e5. [[CrossRef](#)]
163. Peters, F.; Kopp, J.; Fischer, J.; Tantcheva-Poór, I. Mutation in TRPV3 Causes Painful Focal Plantar Keratoderma. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, e620–e622. [[CrossRef](#)]

164. Han, Y.; Luo, A.; Kamau, P.M.; Takomthong, P.; Hu, J.; Boonyarat, C.; Luo, L.; Lai, R. A Plant-Derived TRPV3 Inhibitor Suppresses Pain and Itch. *Br. J. Pharmacol.* **2021**, *178*, 1669–1683. [[CrossRef](#)] [[PubMed](#)]
165. Deng, Z.; Paknejad, N.; Maksaev, G.; Sala-Rabanal, M.; Nichols, C.G.; Hite, R.K.; Yuan, P. Cryo-EM and X-Ray Structures of TRPV4 Reveal Insight into Ion Permeation and Gating Mechanisms. *Nat. Struct. Mol. Biol.* **2018**, *25*, 252–260. [[CrossRef](#)] [[PubMed](#)]
166. Todaka, H.; Taniguchi, J.; Satoh, J.I.; Mizuno, A.; Suzuki, M. Warm Temperature-Sensitive Transient Receptor Potential Vanilloid 4 (TRPV4) Plays an Essential Role in Thermal Hyperalgesia. *J. Biol. Chem.* **2004**, *279*, 35133–35138. [[CrossRef](#)] [[PubMed](#)]
167. Aroke, E.N.; Powell-Roach, K.L.; Jaime-Lara, R.B.; Tesfaye, M.; Roy, A.; Jackson, P.; Joseph, P.V. Taste the Pain: The Role of TRP Channels in Pain and Taste Perception. *Int. J. Mol. Sci.* **2020**, *21*, 5929. [[CrossRef](#)]
168. Bagnell, A.M.; Sumner, C.J.; McCray, B.A. TRPV4: A Trigger of Pathological RhoA Activation in Neurological Disease. *Bioessays* **2022**, *44*, e2100288. [[CrossRef](#)]
169. Hu, X.; Du, L.; Liu, S.; Lan, Z.; Zang, K.; Feng, J.; Zhao, Y.; Yang, X.; Xie, Z.; Wang, P.L.; et al. A TRPV4-Dependent Neuroimmune Axis in the Spinal Cord Promotes Neuropathic Pain. *J. Clin. Investig.* **2023**, *133*, e161507. [[CrossRef](#)]
170. Deng, S.; Feely, S.M.E.; Shi, Y.; Zhai, H.; Zhan, L.; Siddique, T.; Deng, H.X.; Shy, M.E. Incidence and Clinical Features of TRPV4-Linked Axonal Neuropathies in a USA Cohort of Charcot–Marie–Tooth Disease Type 2. *NeuroMolecular Med.* **2020**, *22*, 68–72. [[CrossRef](#)]
171. De Logu, F.; Geppetti, P. Ion Channel Pharmacology for Pain Modulation. *Handb. Exp. Pharmacol.* **2019**, *260*, 161–186. [[CrossRef](#)]
172. Staniland, A.A.; McMahan, S.B. Mice Lacking Acid-Sensing Ion Channels (ASIC) 1 or 2, but Not ASIC3, Show Increased Pain Behaviour in the Formalin Test. *Eur. J. Pain* **2009**, *13*, 554–563. [[CrossRef](#)]
173. Duan, B.; Wu, L.J.; Yu, Y.Q.; Ding, Y.; Jing, L.; Xu, L.; Chen, J.; Xu, T. Le Upregulation of Acid-Sensing Ion Channel ASIC1a in Spinal Dorsal Horn Neurons Contributes to Inflammatory Pain Hypersensitivity. *J. Neurosci.* **2007**, *27*, 11139–11148. [[CrossRef](#)]
174. Yang, Y.L.; Lai, T.W. Citric Acid in Drug Formulations Causes Pain by Potentiating Acid-Sensing Ion Channel 1. *J. Neurosci.* **2021**, *41*, 4596–4606. [[CrossRef](#)] [[PubMed](#)]
175. Chen, C.C.; Zimmer, A.; Sun, W.H.; Hall, J.; Brownstein, M.J.; Zimmer, A. A Role for ASIC3 in the Modulation of High-Intensity Pain Stimuli. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 8992–8997. [[CrossRef](#)] [[PubMed](#)]
176. Hachisuka, J.; Chiang, M.C.; Ross, S.E. Itch and Neuropathic Itch. *Pain* **2018**, *159*, 603–609. [[CrossRef](#)] [[PubMed](#)]

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