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REVIEW

Transient Receptor Potential Channels: Multiple Modulators of Peripheral Neuropathic Pain in Several Rodent Models

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Abstract

Neuropathic pain, a prevalent chronic condition in clinical settings, has attracted widespread societal attention. This condition is characterized by a persistent pain state accompanied by affective and cognitive disruptions, significantly impacting patients' quality of life. However, current clinical therapies fall short of addressing its complexity. Thus, exploring the underlying molecular mechanism of neuropathic pain and identifying potential targets for intervention is highly warranted. The transient receptor potential (TRP) receptors, a class of widely distributed channel proteins, in the nervous system, play a crucial role in sensory signaling, cellular calcium regulation, and developmental influences. TRP ion channels are also responsible for various sensory responses including heat, cold, pain, and stress. This review highlights recent advances in understanding TRPs in various rodent models of neuropathic pain, aiming to uncover potential therapeutic targets for clinical management.

Keywords Neuropathic pain · Transient receptor potential · Neuropathic pain model · Molecular mechanisms · Ion channel · Treatment

Overview of Neuropathic Pain

Pain, deemed the fifth vital sign, serves as a protective mechanism in response to tissue injury, triggering rapid danger signals and promoting healing [1]. However, when pain transitions from acute to chronic, the persistent distressing sensation significantly impacts the quality of life. Neuropathic pain, a prevalent chronic condition, arises from lesions or diseases affecting the peripheral and/or central somatosensory nervous system [2]. Recently, it was redefined by the International Association for the Study of Pain as "Chronic neuropathic pain is chronic pain caused by a lesion or disease of the somatosensory nervous system". Moreover, it can be categorized into peripheral and central neuropathic pain [3], stemming from many pathogenic factors, such as cancer, diabetes, viral infections, chemotherapy, and traumatic nerve injury [4]. Clinical presentations range from nerve compression (e.g., due to a tumor [5] or disc rupture in the spine, resulting in low back and/or leg pain [6], or nerve compression in the wrist, resulting in carpal tunnel syndrome) [7], nerve damage caused by diseases that affect the nerves (e.g., diabetes, herpes zoster, or chemotherapeutics) [8–10], to central neuropathic pain associated with conditions like post-stroke pain [11], multiple sclerosis-related pain [12], Parkinson's disease-related pain [13] or spinal cord disease-related pain [14]. Characteristic symptoms of neuropathic pain include persistent spontaneous pain, hyperalgesia, and allodynia [15, 16]. Patients with chronic pain often experience psychological distress such as insomnia [17], depression [18], mental disorders, and even suicidal tendencies [19]. Millions of individuals worldwide suffer from neuropathic pain, significantly impacting their quality of life [20]. Current clinical treatments include opioids, calcium ion modifiers (pregabalin or gabapentin), and antidepressants [21]. However, these pharmacological interventions often lack stability in pain control and can lead to drug resistance, addiction, and side effects. Interventional therapies such as nerve pulse modulation exist [22], but struggle with recurrence control. Given the limitations in available therapeutic options, the pursuit of new targets remains essential.

The mechanisms of neuropathic pain are complex, involving alterations in neuronal cell membrane ion channel activities (Na^+ [23, 24], K^+ [25], and Ca^{2+} [26]), immune cell

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proliferation and activation (microglia [1, 27], astrocytes [28], and macrophages [29]), and dysregulation of the immune microenvironment [30] within the nervous systems. Among these mechanisms, TRP receptors, widely present in sensory neurons, play a pivotal role. They respond to various stimuli, such as temperature, pressure, and chemicals [31], converting them into electrophysiological signals that elevate intracellular calcium ion levels, thereby initiating action potentials and neurotransmitter release [32, 33]. In the initial stages, before apparent nerve damage, abnormalities in electrical activity, synaptic alterations, and chronic inflammation arise [34, 35]. Additionally, TRP receptors expressed in neuro-immune cells such as microglia, macrophages, and astrocytes influence intracellular ion levels and modulate the neuroinflammatory response via the altered proliferative state [36–38]. Moreover, tissue damage exacerbated this response, leading to abnormal production of pro-inflammatory mediators [39] and intensifying neuroimmune interactions [29, 40, 41]. Therefore, TRP receptors emerge as promising potential targets for neuropathic pain therapy.

Biofunction of TRP Ion Channels in Pain

TRP proteins, as transmembrane entities, are widely distributed in the nervous system. Comprised of four subunits, forming a tetramer, each subunit boasts six transmembrane domains. The fifth and sixth domains create a non-selective cation channel pore [42], defining the TRP ion channels' structure. In mammals, TRP channels constitute six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin) [43]. They possess a bio-ability to detect and react to a range of stimuli, such as temperature, pressure, pH, and chemical substances, thereby regulating intracellular calcium concentration and membrane potential [44, 45]. These ion channels significantly influence diverse physiological and pathological processes, spanning sensory signaling, cell proliferation, cell death, inflammation, pain, respiratory system diseases, and neurodegenerative conditions [31]. Within the TRP subfamilies, which vary in activation mechanisms and functional properties, TRPC, TRPV, TRPA, and TRPM stand out as potential targets for pain treatment.

The TRPC subfamily includes seven members (TRPC1-7), which are activated by diacylglycerol (DAG) produced by phospholipase C or G protein-coupled receptors (GPCRs) [46]. Their roles involve mediating calcium entry and amplifying intracellular calcium signals [47]. In cases of nerve injury or dysfunction, changes in TRPC channel expression and function in the nervous systems contribute to persistent or recurrent neuropathic pain, impacting neuronal excitability, plasticity, and neuroinflammation [48]. Notably, in peripheral nerve injury models, TRPC1, TRPC4, TRPC5, and TRPC6 overexpression in the injured sciatic nerve was associated with tactile hypersensitivity [49, 50].

The TRPV subfamily in mammals, comprising six members (TRPV1-6), exhibits responsiveness to diverse physical and chemical stimuli, particularly TRPV1-4's thermal activation [51]. Therefore, they play a vital role in sensing temperature, pain, and inflammation. Highly expressed in the spinal dorsal horn and sciatic nerve, TRPVs correlate with spontaneous pain and tactile hypersensitivity [52]. For instance, TRPV1 responds to capsaicin and high temperatures, influencing thermal sensation and pain signal transmission [53]. TRPV4, on the other hand, conducts cutaneous tactile pressure sensation via class A and C fibers and facilitates mechanical stimuli perception [54, 55].

The TRPM subfamily, comprising eight members (TRPM1-8), responds readily to various physical and chemical stimuli, such as temperature and menthol. These channels are primarily related to sensation, neuroprotection, cell proliferation, and cell death [56, 57]. TRPM8, recognized as the primary cold receptor in mammals, is activated at temperatures below 28 °C [58], contributing to cold sensation and neuroprotection [59]. Similarly, TRPM2 and TRPM3 exhibit sensitivity to mechanical and thermal stimuli, holding potential as therapeutic targets [60, 61].

The TRPA family, with seven members where TRPA1 is exclusive to humans, is activated by endogenous inflammatory mediators and exogenous harmful stimuli, contributing to the development of acute and chronic pain and inflammation [62, 63]. TRPA1 can also be activated by mustard oil and mechanical force [64]. It acts as a sensor for temperature, chemical, and mechanical stimuli, mediating biological effects like pain stimulation and playing a critical role in nociceptive responses [65, 66].

TRP channels are intricate and multifaceted proteins crucial for perceiving and regulating the intracellular and extracellular environment. In sensory transduction, TRP is commonly expressed in C- and Aδ sensory nerve fibers that sense mechanical tension and temperature variation (Table 1). Understanding the molecular mechanisms underlying pain signal transduction through TRP channels offers new avenues for developing novel analgesics [79, 80], emphasizing the need for more in-depth research into these channels to explore neuropathic pain mechanisms and potential treatments.

Diverse Models of Neuropathic Pain

To identify therapeutic targets and develop novel treatments, several animal models of neuropathic pain have been established that mimic neuronal tissue damage or nervous system dysfunction. This review specifically

Table 1 TRP expression on different sensory nerve receptors in neuropathic pain models

TRPs		Subset of sensory neurons	References
TRPC	TRPC1	Mechanoreceptors (Aβ-fibers for innocuous mechanical force, slowly adapting Aδ-mechanoreceptors or unmyelinated C-fibers for noxious mechanical force)	[67]
	TRPC6	Mechanoreceptors; Thermoreceptors (warm and cold)	[68, 69]
TRPV	TRPV1	Thermoreceptors; Mechanoreceptors; (C- and Aδ-fibers)	[55, 70, 71]
	TRPV4	Thermoreceptors (warm); Mechanoreceptors (C- and Aδ-fibers)	[54, 55, 72]
TRPA	TRPA1	Thermoreceptors (cold); Mechanoreceptors (C- and Aδ-fibers)	[55, 73, 74]
TRPM	TRPM2	Thermoreceptors (warm); Mechanoreceptors (C- and Aδ-fibers)	[55, 60, 75]
	TRPM3	Thermoreceptors (cold); Mechanoreceptors (C- and Aδ-fibers)	[61, 76]
	TRPM8	Thermoreceptors (cool); Mechanoreceptors (C- and Aδ-fibers)	[55, 77, 78]

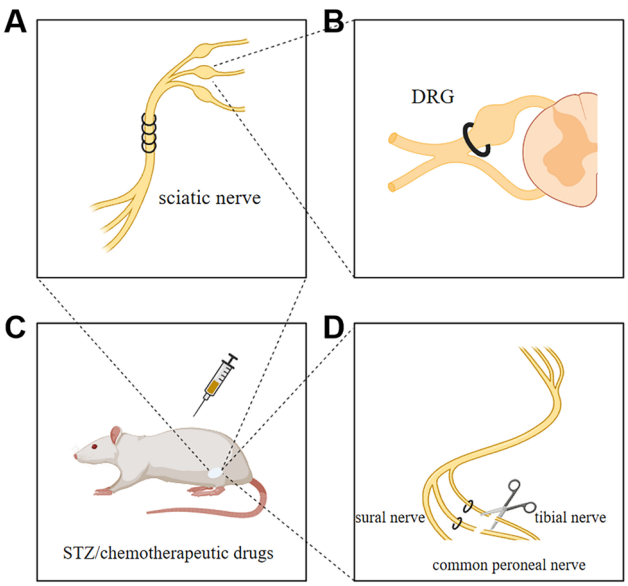

Fig. 1 Diverse models of peripheral neuropathic pain. **A** The CCI model is established by ligating the main trunk of the sciatic nerve. **B** Ligation of the distal dorsal root ganglion used to build the SNL model. **C** Peripheral nerve sensitization (DNP/CIPN) is caused by injections of STZ or chemotherapeutic drugs. **D** The SNI model ligates the tibial nerve and the common peroneal nerve, leaving the sural nerve intact

focuses on common models of peripheral neuropathic pain rather than central neuropathic pain. Peripheral neuropathic pain holds clinical significance due to its high prevalence across various chronic diseases, and extensive research has been conducted in this domain. Commonly studied peripheral neuropathic pain models include chronic constriction injury of the sciatic nerve (CCI), spared nerve injury (SNI), spinal nerve ligation (SNL), diabetic neuropathic pain (DNP), and chemotherapy-induced peripheral neuropathy (CIPN) [81] (Fig. 1). Rodent models serve as valuable tools for controlling experimental variables and mimicking molecular and cellular mechanisms of human diseases. However, they present certain challenges: (1) Rodent models are not completely consistent with the phenotypic and clinical features of human diseases, such as pain sensitivity and drug response [82]. (2) The method of pain assessment in rodent models relies on objective indicators such as behavior, physiology, and neuro-electrophysiology, neglecting subjective factors such as emotion, cognition, and societal impact associated with human diseases [83]. Therefore, such differences need to be considered.

The CCI model, widely employed in studying peripheral nerve neuropathic pain, involves surgically detaching the biceps femoris muscle under anesthesia to expose and isolate the sciatic nerve trunk. Three or four loose chromic gut (or 4–0 silk ligatures, spaced 1 mm apart) are placed around the sciatic nerve until a slight twitch is observed in the lower limbs [84]. Behavioral changes, including mechanical and thermal hyperalgesia, chemical hyper-reactivity, and cold allodynia, worsen within a week and peak in the second-week post-surgery, with the most severe pain-related behaviors persisting for more than two months [84, 85]. In the SNL model, ligation of the L5 and L6 spinal nerves triggers mechanical and thermal hyperalgesia and spontaneous pain within 24–48 h, persisting approximately four months [86, 87]. The SNI model involves ligating the common peroneal and tibial nerves using a 5–0 silk suture. Their distal ends were transected, but the sural nerve was preserved [88]. This model induces mechanical and thermal hyperalgesia and allodynia within four days after the injury, persisting for several weeks (up to a half year) [89]. The advantage of the SNI model is the robustness of the response without significant lameness in the lower limb. Nociception and hyperresponsiveness of C fibers in a DNP model are induced by the subcutaneous injection of streptozotocin (STZ), persisting for approximately 2–3 weeks [90, 91]. Similarly, in the CIPN model, animals were induced to develop thermal and mechanical hypersensitivity through chemotherapeutic drugs such as paclitaxel [92], cisplatin [93], and oxaliplatin [94]. Numerous studies demonstrate the critical roles of TRPs

Table 2 Role of TRPs pathway in different neuropathic pain models

Model	TRPs	Regulation	Biological function	Tissue	Species	References
CCI	TRPM8	up	TRPM8 deficient mice exhibit flaws in specific behaviors (icilin-induced jumping and cold sensitivity)	DRGs	male and female C57 mice	[95]
CCI	TRPM8	up	Inhibition of TRPM8 expression alleviates responses to mechanical and cold stimuli and reduces nociceptive hypersensitivity	DRGs	male SD rat	[77]
CCI	TRPM2	up	TRPM2 knockdown drastically inhibited the iNOS expression and NO generation, with decreased ROS generation	spinal cord; DRGs	male SD rat	[75]
CCI	TRPM3	up	Genetic deletion or inhibitors of TRPM3 inhibited heat and mechanical hypersensitivity by reducing the increase in levels of the early genes c-Fos and pERK	spinal cord; DRGs	male and female mice	[76]
CCI	TRPA1	up	TRPA1 knockout alleviates alanine-induced cold-sensing pain behavior	L4-5 DRGs	male C57 mice	[96]
CCI	TRPV1	up	Baicalin can relieve mechanical and thermal pain and provide analgesia through the TRPV1-ERK pathway	L4-6 DRGs	male SD rat	[70]
CCI	TRPV1/TRPA1	up	HIG attenuates CCI-induced thermal nociceptive sensitization and mechanical pain sensitization, and reduces inflammatory responses and oxidative stress via TRPV1/TRPA1 receptors	L4-5 DRGs	male SD rat	[71]
CCI	TRPC6	up	Dexmedetomidine may reduce neuropathic pain responses by inhibiting TRPC6 expression and alleviating neuroinflammatory responses	L4-6 DRGs	male SD rat	[69]
SNI	TRPML3	up	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPV1	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPA1	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPC3	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPC4	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPC5	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPM6	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPM8	down	/	L4-5 DRGs	male SD rat	[97]
SNI	TRPA1	up	TRPA1 receptor is involved in the development of sensitivity to mechanical and cold stimuli after nerve injury	DRGs	dude mouse	[78]
SNI	TRPM8	down	TRPM8 has been implicated in the development of sensitivity to mechanical and cold stimuli following nerve injury	DRGs	dude mouse	[78]

Table 2 (continued)

Model	TRPs	Regulation	Biological function	Tissue	Species	References
SNI	TRPM2	up	TRPM2 expression in macrophages and microglia exacerbates peripheral and spinal pro-nociceptive inflammatory responses and contributes to the pathogenesis of neuropathic pain	sciatic nerve; spinal cord	C57BL/6 J mice	[60]
SNI	TRPC6	up	Inhibition of TRPC6 expression attenuates inflammatory factor levels and activated proliferation of microglia in the dorsal horn of the spinal cord, resulting in relief of mechanical and cold sensory pain	spinal cord	male SD rat	[68]
SNI	TRPV1	/	TRPV1 is not associated with mechanically abnormal nociception due to Aβ fiber sensitization, but it does contribute to the enhanced discharge and mechanical nociceptive hypersensitivity	/	male Wistar rat	[98]
SNL	TRPA1	up	TRPA1 is participating in the electrical activity of Aδ fibers and is strongly associated with abnormal mechanical nociception and cold nociceptive hypersensitivity	DRG	rat	[73]
SNL	TRPA1/ TRPM8	/	The agonist iclin of TRPM8 and TRPA1 activates DRG neurons in vitro and plays an important role in cold sensory hypersensitivity	DRG/spinal cord	male SD rat	[99]
SNL	TRPA1	up	Blocking TRPA1 in primary sensory neurons reverses cold pain hypersensitivity caused by inflammation and nerve damage	L4-5 DRGs	male SD rat	[74]
SNL	TRPM8/ TRPA1	/	The agonist iclin of TRPM8 and TRPA1 reduces voltage-gated calcium channel currents in injured dorsal root ganglion neurons	DRGs	male Wistar rat	[100]
DNP	TRPM8	up	Inhibition of TRPM8 expression levels in DRG significantly inhibited stz-induced mechanical and cold pain, but not thermal nociceptive sensitization	L4-6 DRGs	male SD rat	[102]
DNP	TRPM2/ TRPV1	/	TRPM2 and TRPV1 channels modulate diabetes-induced oxidative stress, apoptosis, and calcium ion concentration in dorsal root ganglia and hippocampus	T13–L5 DRGs	female Wistar rat	[106]
DNP	TRPC6/TRPV1/ TRPA1	up	Peripheral TRPV1, TRPA1 and TRPC6 channels are involved in streptozotocin-induced nociceptive hypersensitivity and peripheral nerve fiber loss	L4-6 DRGs	female Wistar rat	[107]

Table 2 (continued)

Model	TRPs	Regulation	Biological function	Tissue	Species	References
DNP	TRPC6	up	TRPC6-AS reverses increased calcium in-flow in DRG neurons and attenuates mechanical abnormal pain in DNP rats	L4-6 DRGs	male SD rat	[108]
DNP	TRPV1	up	a-lipoic acid attenuated hypersensitivity and neuronal excitability neurons were attenuated by suppressing p65 signaling and TRPV1 expression	L4-6 DRGs	female SD rat	[101]
CIPN	TRPA1 TRPV1	up	Chemotherapeutic agents induce increased cytoplasmic calcium concentrations in TRPA1/TRPV1-positive DRG neurons, leading to mitochondrial dysfunction and increased reactive oxygen species concentrations	DRGs	Wistar rat	[110]
CIPN	TRPA1 TRPV1	/	Inhibition of TRPV1 and TRPA1 attenuates abnormal tactile and thermal sensitization induced by chemotherapeutic agents	/	male CD-1 mice	[111]
CIPN	TRPA1 TRPV1 TRPM8	up	TRPA1, TRPM8 and TRPV1 play an important role in oxaliplatin-induced painful neuropathies, especially cold sensitization	L4-6 DRGs	male Wistar rat	[112]
CIPN	TRPV1	up	Inhibition of TRPV1 and spinal astrocyte activation to suppress oxaliplatin-induced neuropathic pain	L4-6 DRGs	male SD rat	[113]
CIPN	TRPM3		TRPM3 participates in the development of cold and mechano hypersensitivity by regulating the ERK pathway	DRGs	male C57 mcie	[61]
CIPN	TRPM8	/	Compound 14 inhibited TRPM8-mediated cold hypersensitivity and significantly reduced cold abnormal pain in vivo	/	Male C57 mice	[114]
CIPN	TRPM8	/	Targeting TRPM8 for initial drive and/or membrane depolarization may prevent oxaliplatin-induced neuropathic pain	DRGs	male C57 mice	[115]
CIPN	TRPM8	up	L-type calcium channel blockers inhibit TRPM8 expression and alleviate oxaliplatin-induced cold sensory hypersensitivity	L4-6 DRGs	male SD rat	[116]
CIPN	TRPV4	up	Paclitaxel-induced trpv4-mediated nociceptive hypersensitivity and enhanced osmotransduction in cultured nociceptors depend on integrin/Src tyrosine kinase signaling	L2-6 DRGs	male SD rat	[54]

Table 2 (continued)

Model	TRPs	Regulation	Biological function	Tissue	Species	References
CIPN	TRPV4/ TRPC1/ TRPC6	up	TRPV4, TRPC1 and TRPC6 antagonists can reverse nociceptive hypersensitivity to mechanical and hypotonic stimuli induced by inflammatory mediators	L4-6 DRGs	male SD rat	[50]
CIPN	TRPV1	up	TRPV1 upregulation in small- and medium-diameter DRG neurons is involved in paclitaxel-induced neuropathic pain	L4-6 DRGs	male Wistar rat	[117]
CIPN	TRPV1	up	Warfarin inhibits TRPV1up and spinal astrocyte activation to relieve nociceptive hypersensitivity	L4-6 spinal cord	male SD rat	[118]
CIPN	TRPV1 TRPV4 TRPA1	/	PAR2 signaling regulates paclitaxel-induced mechanical allodynia and thermal nociceptive hypersensitivity through TRPV1, TRPV4, and TRPA1 signaling pathways	spinal cord	male ICR mice	[72]
CIPN	TRPC6	up	PAX6 gene hypomethylation is involved in chemotherapeutic drug-induced mechanical allodynia through upregulation of TRPC6	L4-6 DRGs	male SD rat	[119]
CIPN	TRPV1	up	TRPV1 upregulation in small diameter DRG neurons is involved in vincristine-induced nociceptive hypersensitivity	L4-6 DRGs	male Wistar rat	[120]
CIPN	TRPV1/ TRPM8	up	White mandrake can alleviate vincristine-induced neuropathic pain by inhibiting TRPV1/TRPM8 and ERK/ JNK/p38MAPK pathways	brain/ spinal cord/ sciatic nerve	male mice	[121]
CIPN	TRPV1	up	Niflumic acid relieves neuropathic pain symptoms by directly antagonizing TRPV1 channels and indirectly inhibiting TRP channels by blocking oxidative and inflammatory responses	brain/ sciatic nerve	male SD rat	[122]

"/" means not mentioned in the article; "up" means up-regulation and "down" means down-regulation in the article.

in different neuropathic pain models. (Table 2) Here, we briefly review the recent advancements regarding TRP receptors in these described neuropathic pain models.

TRPs in Different Neuropathic Pain Models

CCI Model

In studies exploring nociception within the CCI model, multiple TRP receptors have demonstrated significant involvement. TRPM8, crucial for cold sensation post-injury, exhibits increased expression in the dorsal root ganglion, contributing to the generation of cold

sensory hypersensitivity [95]. Both TRPM8 antagonist and TRPM8 knockout models significantly alleviate mechanical and thermal sensitization [77, 95]. TRPM2 and TRPM3 have also shown sensitization to these stimuli [75, 76]. Similarly, Wang et al. investigated the mechanism of TRPA1-induced stimulation of the progression of neuropathic pain via Mas-related GPCR D (MrgprD) regulation, revealing that TRPA1 can activate MrgprD via the PKA pathway to amplify sensitivity [96]. Notably, the pain hypersensitivity induced by alanine injection into the plantar surface of TRPA1 knockout mice was significantly attenuated. Traditional Chinese medicine studies involving baicalin exhibited analgesic effects via a dose-dependent reduction in mechanical and thermal injury reactions [70]. The potential mechanism may be related to the inhibition of TRPV1 overexpression in the dorsal root ganglion and the phosphorylation of ERK, thus ameliorating peripheral neuroinflammation [70]. TRP channels have been observed to influence the oxidative stress response in the CCI model. Elevated ROS expression and TRPV1/TRPA1 overexpression in dorsal root ganglion neurons suggest oxidative stress injury in local tissues triggered by the CCI model [71]. Notably, the inhibition of TRPV1/TRPA1 expression significantly reduced thermal and mechanical sensitization. Additionally, TRPM2 was associated with iNOS expression, NO, and ROS generation [75]. A previous study [69] showed increased TRPC6 expression in the dorsal root ganglion in the CCI model. Continuous intraperitoneal dexmedetomidine injection significantly reduced TRPC6 and inflammatory cytokine expression, alleviating mechanical nociception and thermal sensitization.

SNI Model

The SNI model closely mimics clinical neuropathic pain features. Staaf et al. [97]. explored the differential regulation of TRP channels in an SNI rat model. Among the members of the TRP channel, TRPML3 showed significant changes between the surgical and control groups [97]. In situ hybridization revealed increased TRPML3 expression across neurons of different sizes. Additionally, mRNA levels of TRPM6, TRPM8, TRPV1, TRPA1, TRPC3, TRPC4, and TRPC5 were decreased in the SNI model [97]. Thus, these observations suggest that TRPML3 is associated with the development of neuropathic pain. Similarly, Poulson et al. [78]. Discovered that normal mice and nude mice have comparable sensitivity to mechanical stimuli, but showed variation in their reaction to cold. Compared to normal mice, naked mole rats showed increased TRPA1 mRNA expression and decreased TRPM8. Moreover, TRPM2 knockout mice, compared to wild-type mice, demonstrated no basal sensitivity differences to mechanical and thermal stimulation but played a key role in injurious stimuli [60]. Elevated TRPC6 expression in the dorsal horn of SNI model rats correlated with microglial proliferation and increased inflammatory factors [68]. It is worth noting that TRPC6 co-localized with microglia. The administration of larixyl acetate, a TRPC6 inhibitor, significantly inhibited microglial activation and p38 phosphorylation in the spinal cord dorsal horn, alleviating inflammatory response and pain behavior [68]. Furthermore, TRPV1 receptors in SNI rats have been studied for their role in regulating neural activity and neuropathic pain following nerve injury. Yamamoto et al. demonstrated the role of TRPV1 receptor-expressing fibers in spinal ventral root discharges and mechanical pain in a rat model of SNI [98]. Discharges were observed in the ventral roots of the spinal cord on the first day after surgery, which persisted for two weeks. These discharges were positively correlated with the development of mechanical pain. In rats with selective ablation of TRPV1-positive fibers with resiniferatoxin, mechanical hyperalgesia was abolished together with the discharges, while allodynia was unaffected, suggesting different nerve fibers contribute to the two processes [98]. Overall, TRPV1 is speculated to play a crucial role in regulating neural activity and neuropathic pain post-nerve injury.

SNL Model

In the SNL model, TRPM8 and TRPA1 receptors take center stage. Ji et al. [73]. Highlighted the role of TRPA1 in primary sensory neurons, correlating increased sensitivity to cold stimuli post-surgery with elevated TRPA1 expression in the dorsal root ganglia. This receptor, transported from the dorsal root ganglion to peripheral axons, localizes in unmyelinated and finely myelinated cutaneous axons, impacting physiological functions. TRPA1 antagonists significantly reduced the electrical activity of Aδ fibers and alleviated nociceptive hypersensitivity. In another study, ICLIN, an agonist of TRPM8 and TRPA1, increased calcium ion concentration in the dorsal root ganglia [99]. Suppression of those expression lessened abnormal neuronal firing and reduced sensitivity to mechanical and cold stimuli. Moreover, neuroinflammation and nerve injury-induced cold sensory hypersensitivity were suppressed by the intrathecal administration of an anti-nerve growth factor, p38MAPK inhibitor, and TRPA1 antagonist [74], indicating that NGF induces TRPA1 overexpression in sensory neurons through p38 activating, serving as an essential factor in cold nociceptive hypersensitivity. However, Hagenacker et al. [100]. Found no significant difference in the effect of ICLIN on voltage-gated calcium channels in uninjured and SNL-injured DRG neurons using the whole-cell membrane clamp

technique. Neither local nor intrathecal application of ICLIN had an effect on tactile hypersensitivity or thermal hyperalgesia after SNL in vivo. Therefore, they concluded that ICLIN, an agonist of TRPM8 and TRPA1, does not regulate voltage-gated calcium channels in DRG neurons or mediate the pathogenesis of cold hypersensitivity. Collectively, these studies imply that TRPM8 and TRPA1 are strongly associated with mechanical pain and cold sensitization; however, further studies are warranted in the SNL model.

DNP Model

The complex pathogenesis of DNP involves ion channel activation leading to neuronal hyperexcitability under hyperglycemic conditions [101]. In the DNP model, the expression level of TRPM8 increased in DRG neurons, while the expression level of TRPA1 showed no significant changes [102]. Nefopam pretreatment effectively reduced TRPM8 expression and inhibited STZ-induced mechanical and cold sensory hypersensitivity. However, painful neuropathy associated with diabetes has been linked to TRPA1 in animal studies [103, 104]. TRPA1 knockout diabetic neuropathic rats exhibited hyperglycemia and mechanical allodynia, suggesting TRPA1 gene deletion's crucial role in diabetic neuropathy development [105]. Additionally, TRPM2 and TRPV1-mediated calcium influx and oxidative stress contribute to peripheral neuralgia. Kahya et al. [106]. Found that TRPM2 and TRPV1 were involved in neuronal death induced by Ca^{2+} efflux. Melatonin and selenium mitigate diabetes-induced oxidative stress, apoptosis, and calcium ion concentration by modulating TRPM2 and TRPV1 in the dorsal root ganglia and hippocampus. Similarly, on intrathecal injection of Alpha-lipoic acid, TRPV1 expression can be inhibited through the NF-κB pathway, which effectively relieves pain hypersensitivity and neuronal excitability [101]. The role of TRPC6 also has been closely scrutinized. It is increased within the dorsal root ganglion in the DNP model. Hydrogen sulfide (H_2S) synthesized by cystathionine beta-synthase (CBS) enzymes activates/sensitizes TRPV1, TRPA1, and TRPC channels, leading to nociceptive hypersensitivity and peripheral nerve fiber loss [107]. Inhibitors of CBS enzymes or TRP channel blockers present potential treatments for diabetic peripheral neuropathic pain. Furthermore, Miao et al. [108] reported a time-dependent expression of BDNF and TRPC6 in the dorsal root ganglia and spinal cord of DNP rats, which was closely related to the generation of mechanical abnormality. Moreover, the inhibition of TRPC6 expression attenuated intraneuronal calcium influx and reversed anaphylaxis.

CIPN Model

CIPN is a prevalent side effect of various chemotherapy drugs like cisplatin, oxaliplatin, and paclitaxel, causing symptoms such as numbness, aching, burning, or tingling in the affected limb [109].

Using models of cisplatin/oxaliplatin-induced painful neuropathy, Leo et al. [110]. Demonstrated that TRPA1/TRPV1 expression was increased within dorsal root ganglion neurons, promoting calcium ion concentrations in the cytoplasm and mitochondria. This results in mitochondrial dysfunction and reduced antioxidant capacity, contributing significantly to neuropathic pain following chemotherapy. Similarly, compounds like LPP1 and pregabalin can inhibit TRPV1 and TRPA1 expression, reducing abnormal tactile and thermal sensitization induced by oxaliplatin/paclitaxel chemotherapeutic agents. However, their effects on cold sensitization are limited [111]. In other models of neuropathic pain induced by oxaliplatin, acute cold sensory hypersensitivity arises after four days of treatment, and increased TRPA1 and TRPV1 expression in small DRG neurons and increased TRPM8 expression in medium-sized DRG neurons was reported [112]. The alteration in the expression of TRP channels emerges as a potential therapeutic target for treating oxaliplatin-induced peripheral neuropathic pain. The herbal medicine Cinobufacini demonstrated the inhibition of oxaliplatin-induced TRPV1 upregulation in the dorsal root ganglion and spinal astrocyte activation, thereby reducing mechanical pain and thermal hypersensitivity in rats [113]. Additionally, the significance of TRPM8 cannot be understated. Bertamino et al. [114]. Screened the tryptophan derivative 14 and demonstrated through in vivo studies its potential analgesic effects by alleviating TRPM8-mediated hypersensitive response to cold perception. Moreover, oxaliplatin may contribute to the development of neuropathic pain by depolarizing IB4 neurons through the TRPM8 channel [115]. Membrane depolarization can be blocked by utilizing TRPM8 antagonists, preventing oxaliplatin-induced neuropathic pain. Accordingly, TRPM8 expression increases within the dorsal root ganglion in oxaliplatin-induced nociceptive hypersensitivity, and the administration of an L-type calcium channel antagonist effectively alleviates cold nociceptive hypersensitivity via the NFAT/TRPM8 pathway [116].

In the model of paclitaxel-induced peripheral neuralgia, increased TRPV4 expression in sensory nerve fibers [54] contributes to nociceptive hypersensitivity, while enhanced osmotic conductance in nociceptors depends on integrin/Src tyrosine kinase signaling. Administering TRPV4 antisense helps mitigate mechanical hypersensitivity [54]. Additionally, there appears to be an association between TRPV4 and stretch-activated ion channels that contribute to mechanical pain transmission mechanisms

[50]. TRPV4 collaborates with TRPC1/TRPC6 to facilitate mechanical hypersensitivity and enhance the sensitivity of primary afferent nociceptors to alleviate neuropathic pain caused by paclitaxel [50]. TRPV1 has been established as a critical receptor in paclitaxel-induced hypersensitivity to pain. It was increased in small and medium DRG neurons after paclitaxel treatment, revealing a potential role of TRPV1 in thermal nociceptive hypersensitivity [117]. Ba et al. [118] used warfarin to mitigate the mechanical and thermo-sensory hypersensitivity caused by paclitaxel, which was achieved by inhibiting TRPV1 upregulation, spinal astrocyte activation, and reducing the production of inflammatory factors such as TNF-α and IL-1β. Moreover, Chen et al. [72] also observed an increasing activity of mast cell trypsin in the spinal cord, dorsal root ganglia, and peripheral tissues of mice during paclitaxel treatment. The protease receptor triggered the activation of phospholipase C, protein kinase A, and protein kinase C, along with the activation of downstream TRPV1, TRPV4, and TRPA1 signaling pathways [72]. Targeting this signaling molecule may provide novel avenues for the treatment of paclitaxel-induced neuropathy. PAX6/TRPC6 in DRG neurons may be considered a common signaling pathway for mechanical nociceptive hypersensitivity after oxaliplatin, paclitaxel, or bortezomib application [119]. Notably, epigenetic mechanisms, specifically DNA hypomethylation of the PAX6 gene, facilitate the upregulation of the TRPC6 pathway implicated in peripheral neuropathic pain.

In peripheral neuropathy induced by vincristine, increased TRPV1 expression was observed in the dorsal root ganglion and was mainly concentrated in small B^{4+} neurons. TRPV1 antagonists significantly inhibited nociceptive hypersensitivity [120]. Khan et al. [121] reported that substances like white mandrake exhibit neuroprotective effects by attenuating the levels of inflammatory cytokines and oxidative stress via the downregulation of TRPV1 and TRPM8 expression. This effect mitigates vincristine-induced mechanical pain, as well as cold and heat sensory sensitization. Similarly, in a stavudine-induced neuropathic pain model, niflumic acid alleviated nociceptive hypersensitivity in rats by directly antagonizing the TRPV1 pathway and blocking oxidative stress and inflammatory responses [122]. Studies across various chemotherapeutic drug-induced peripheral neuropathic pain models underscore the important role of TRP channels, establishing them as potential therapeutic targets for alleviating peripheral neuropathic pain.

Conclusions and Perspectives

In this review, we have described various models of neuropathic pain and elucidated the analgesic mechanism orchestrated by TRP channels (Fig. 2). Chronic neuropathic pain, often associated with damage or dysfunction in the somatosensory nervous system, [16, 123] poses challenges in obtaining clinical samples due to its specific neural nature. Animal models provide a simplified representation of human neuropathic pain, inclusive of the spatial, temporal, and biological complexity of human neuropathic pain, making them a valuable tool in pain research. However, caution is imperative when translating findings from animals to humans, considering factors like genetic heterogeneity, treatment interventions, disease progression, and pharmacokinetics. Despite these limitations, rodent pain models remain invaluable, with peripheral nerve injury-induced neuropathic pain currently being the most prevalent. Models like SNL, SNI, and CCI induce regional pain associated with single-branch neuropathy. Additionally, STZ-induced neuropathic pain in diabetes mellitus and chemotherapeutic drug-induced neuropathic pain models causing peripheral neuropathy are widely employed.

The development and maintenance of neuropathic pain involve multifaceted factors within the peripheral and central nervous systems, encompassing altered ion channel activity [44, 124], immune cell activation [29, 125], and immune regulation imbalances [126]. TRP channels play a key role as sensors and modulators in neuropathic pain, influencing pain signal generation and transmission by modulating neuronal excitability, plasticity, and neuroinflammatory responses [127, 128] (Fig. 3). Different TRP subfamilies and subtypes exhibit varying sensitivities and functional characteristics, potentially interacting to form complex signaling networks.

This review presents novel insights into the molecular mechanisms by which TRP channels contribute to chronic neuropathic pain, establishing them as potential therapeutic

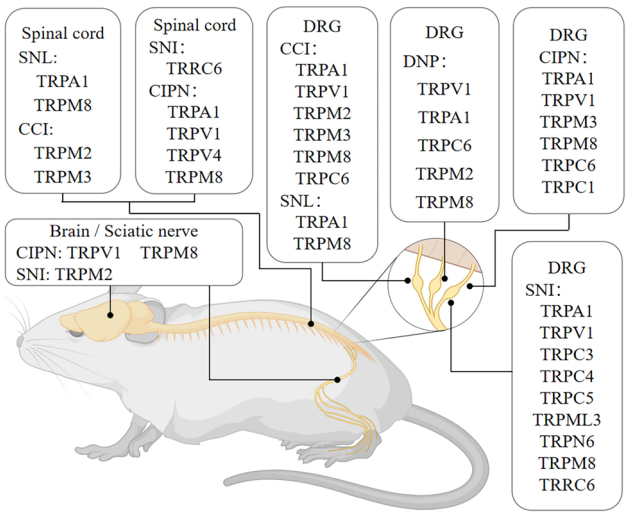

Fig. 2 Overview TRP channels that have been implicated in different models of chronic neuropathic pain. The black dots represent the source of the tissue

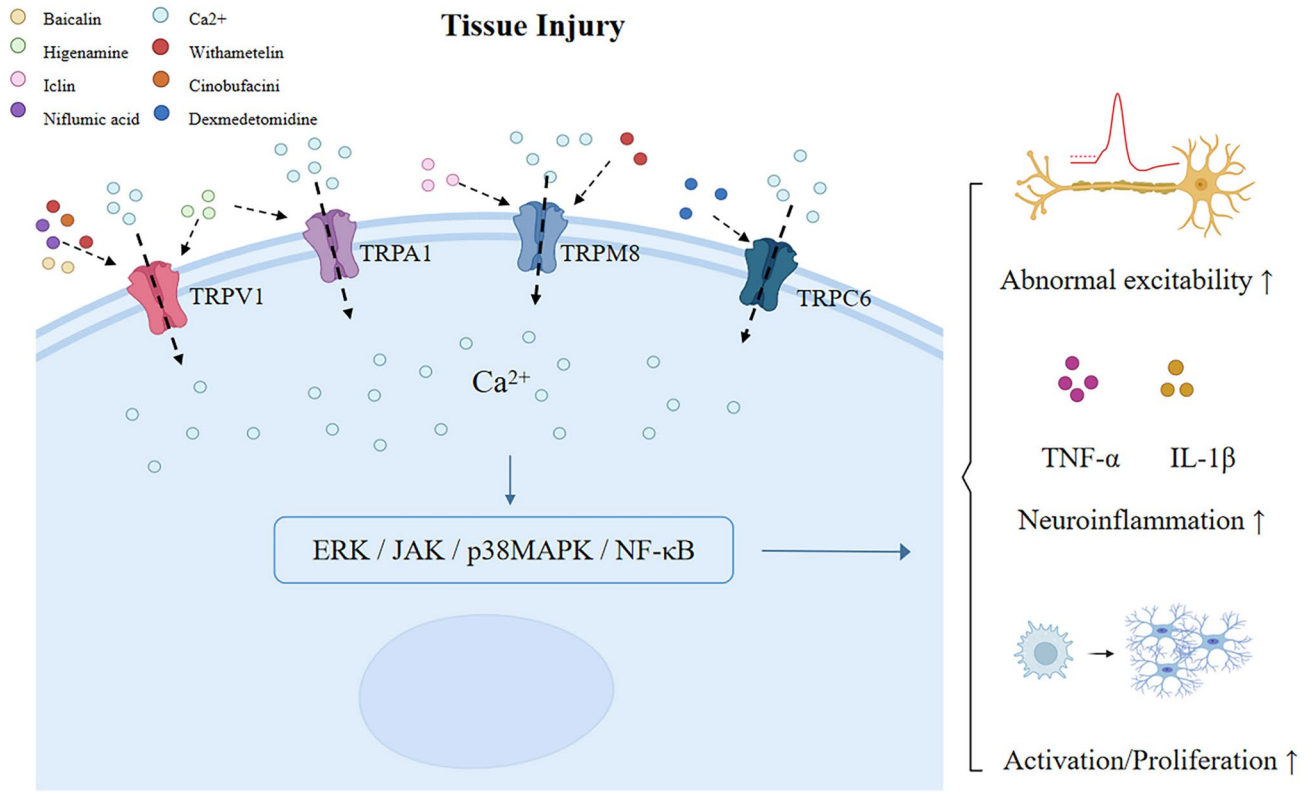

Fig. 3 Potential mechanisms of TRP receptors in neuropathic pain. TRP, as transmembrane entities, are widely distributed in the nervous system. Here we take microglia as an example (not limited to this type of cell). Tissue damage leads to receptor activation. They can affect intracellular ion concentrations and abnormal excitability. Similarly, they will interfere with immune cell activation and proliferation, as well as neuroinflammatory responses via downstream pathways (such as ERK/ JAK p38MAPK/ NF-κB). Inhibitors (shown in the figure, Baicalin, etc.) suppress TRP expression and attenuate pain sensitization. Only some of the TRP receptors are listed here

targets. Given the important and diverse roles of TRP channels in neuropathic pain, they provide opportunities and approaches for the development of novel analgesics [129]. Receptors such as TRPA1, TRPV1, TRPM8, and TRPC6 have demonstrated unique roles in neuropathic pain, and several agonists or antagonists targeting these TRP channels have entered clinical trials or the market for treating various pain conditions, dermatologic diseases, and respiratory disorders [80, 130, 131]. However, challenges such as TRP channel selectivity and side effects remain, necessitating highly selective drug development to avoid interference with other stimuli [132]. TRPV1 has also been demonstrated to be sensitive to high temperature, low pH, and capsaicin treatment [133]. Meanwhile, TRPA1 activity exhibits significant species-related differences, which impede the efficacy of preclinical studies in predicting clinical efficacy [134]. Furthermore, in clinical trials, TRPV1 inhibitors elevated body temperature in participants and reduced their ability to perceive harmful heat [135]. Nonetheless, the study of TRP channels is of clinical significance from both basic research and drug discovery perspectives, necessitating continued in-depth exploration.

Central mechanisms underlying neuropathic pain, especially TRP-related studies in the central nervous system, are less explored. Understanding altered neuronal excitability, neural-immune cell interactions, and relevant brain nuclei activation remains an area for further investigation [136–138]. Gene editing technologies, such as knockout animals, allow one to study the role of specific genes in the development and maintenance of pain, as well as identify novel therapeutic targets. It can inactivate or replace the function of a target gene within an experimental animal, thus helping researchers to understand the normal function of the gene and the effect of gene deletion or mutation on pain perception. In conclusion, we highlight recent advances in understanding TRPs in various rodent models of neuropathic pain, and future research should explore TRP channels in lesser-utilized models of neuropathic pain, particularly those stemming from CNS disease, while also focusing on developing safer and more effective TRP channel modulators.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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