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Targeting Pain-evoking Transient Receptor Potential Channels for the Treatment of Pain

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Abstract: Chronic pain affects billions of lives globally and is a major public health problem in the United States. However, pain management is still a challenging task due to a lack of understanding of the fundamental mechanisms of pain. In the past decades transient receptor potential (TRP) channels have been identified as molecular sensors of tissue damage and inflammation. Activation/sensitization of TRP channels in peripheral nociceptors produces neurogenic inflammation and contributes to both somatic and visceral pain. Pharmacological and genetic studies have affirmed the role of TRP channels in multiple forms of inflammatory and neuropathic pain. Thus pain-evoking TRP channels emerge as promising therapeutic targets for a wide variety of pain and inflammatory conditions.

Keywords: Transient receptor potential channels, pain, inflammation, neuropathy, pain management, drug target.

1. PAIN IS A COMPLEX PHENOMENON

According to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is present in multiple forms and is the most common reason for seeking medical assistance in the United States and significantly impacts patients' quality of life. Acute pain usually starts suddenly and resolves quickly. It serves as a warning of tissue damage, injury or a threat to the body. However, chronic pain persists even after an injury has healed and becomes a debilitating condition, imposing both physical and emotional effects on affected individuals. Chronic pain is not a simple extension in time of acute pain; instead, the transition from acute to chronic pain involves neuronal plasticity in both peripheral and central nervous systems [1, 2].

Pain results from complex processing of neural signals at multiple levels. Primary sensory neurons residing in dorsal root, trigeminal and nodose ganglia sense specific environmental cues through peripheral nerve endings in the skin and visceral organs and inform the CNS of thermal, mechanical and chemical conditions *via* action potential firing and release of neurotransmitters that activate postsynaptic neurons in the CNS [3, 4]. Noxious conditions such as extreme temperatures, tissue damage, or noxious chemicals are detected by a subpopulation of sensory neurons, termed nociceptors, which upon excitation can evoke subjective sensations of pain and induce neurogenic inflammation [5]. Although great strides have been made in understanding the molecular mechanisms of pain in the past decade, treatment of pain still remains a major challenge in clinical practice. The most commonly used pain medicines, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and anti-convulsants (for neuropathic pain), produce serious side effects. Therefore, there is an urgent need to develop novel and safer pain medicines to meet the needs of patients.

2. TEMPERATURE-SENSITIVE TRP CHANNELS AND PAIN

Ion channels play critical roles in pain pathways [3, 6]. In the past decades, the transient receptor potential (TRP) channel family members have been identified as molecular sensors in primary sensory neurons [4, 7]. TRP channels are calcium-permeable non-selective cation channels. In mammals, TRP channels comprise six related protein subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP, and TRPML. 28 mammalian TRP channels have been clearly identified so far, with different numbers of splice variants in each group [8]. The widespread expression of TRP channels in both neuronal and non-neuronal tissues suggests that they may play important roles in many cellular and physiological functions. TRP channelopathies are part of important mechanisms in a variety of diseases such as inflammatory bowel diseases, epilepsy, diabetes mellitus, neurodegenerative disorders, and cancer [9]. Several members of the TRP family (TRPV1-4, TRPM3, TRPM8 and TRPA1, "ThermoTRPs") are involved in the detection of temperature changes, thus acting as molecular thermometers of our body [10, 11]. In addition, TRP channels, especially TRPV1 and TRPA1, are polymodal detectors integrating painful stimuli and play central roles in pain sensation under physiological and pathological conditions including inflammation and neuropathy [12].

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2.1. ThermoTRPs Contribute to Nociceptive and Inflammatory Pain

TRPV1 is the first cloned prototypical vanilloid TRP channel expressed primarily in small-diameter primary sensory neurons and by both peptidergic and non-peptidergic primary afferents [13, 14]. TRPV1 is activated by a variety of physical and chemical stimuli including capsaicin, noxious heat (> 43°C under common experimental conditions), low pH (5.2), voltage, bioactive lipids and other pungent natural compounds [14-17]. Several lines of evidence have demonstrated that TRPV1 plays important roles in inflammatory pain: 1) the number of fibers immunoreactive for TRPV1 is increased in inflamed human skin and vulva, correlated with inflammatory hyperalgesia [18, 19]; 2) capsaicin-induced nocifensive behavior and thermal hyperalgesia are markedly enhanced in complete Freund's adjuvant (CFA)- and carrageenan-induced inflammatory pain models [20]; 3) application of selective TRPV1 blockers such as A-425619, SB-705498 and AMG9810 reduces both hyperalgesia and allodynia in rodent models of nociception and inflammatory pain [21-24]; 4) thermal hypersensitivity accompanying inflammation is dramatically decreased in TRPV1 KO mice [25-27]; and 5) many inflammatory mediators potentiate or sensitize TRPV1 responses in primary sensory neurons under inflammatory conditions. For instance, TRPV1 activity is clearly associated with tumor necrosis factor-α (TNF-α)-induced monoarthritis [28, 29]. TRPV1 also co-expresses with protease-activated receptor 2 (PAR2) in dorsal root ganglion (DRG) neurons and mediates the sensitized responses induced by activation of PAR2 receptors in inflamed knee joints [30].

TRPA1 is expressed in a subset of mammalian sensory ganglion neurons that also express TRPV1 [31, 32]. TRPA1 is a molecular integrator of many exogenous and endogenous noxious stimuli, such as the natural pungent compound allyl isothiocynate (AITC), environmental irritant acrolein and oxidative oxygen radicals [33, 34]. The recent finding that a gain-of-function mutation in TRPA1 causes familial episodic pain syndrome in humans provides compelling evidence for the involvement of TRPA1 in pain sensation [35]. Accumulating evidence suggests that TRPA1 is a critical mediator of inflammatory pain: 1) TRPA1 expression is increased in DRG by CFA-induced inflammation [36-38]; 2) TRPA1 KO mice display reduced thermal and mechanical pain responses to intraplantar injection of bradykinin or AITC [39]; and 3) the TRPA1 antagonist AP18 and HC-030031 reduce nocifensive behaviors induced by paw injection of formalin and suppress mechanical hyperalgesia in the CFA model of inflammatory pain [40, 41]. Interestingly, AP18 also attenuates mechanical hyperalgesia produced by intra-articular injection of CFA, suggesting that TRPA1 might directly mediate inflammatory and arthritic pain [28, 29].

TRPM8, activated by innocuous cool to noxious cold temperatures (< 30°C) and cooling agents including icilin and menthol, is expressed in a subset of primary nociceptive sensory neurons (Aδ and C-fibers) [10, 42]. Noxious cooling compounds activate TRPM8 to produce nocifensive responses manifested as avoidance towards noxious cold surfaces in wild-type but not TRPM8 KO mice [43, 44]. The role of TRPM8 in pain sensation has been further confirmed by the fact that pharmacological blockade of TRPM8 attenuates cold pain sensation in mice [45].

The role of TRPV3 in nociception remains controversial in mice where TRPV3 is mainly present in epidermal keratinocytes and its expression in primary sensory neurons is not clear. However, recent studies have demonstrated that specific chemicals can induce pain-producing or antinociceptive effects by activating or inhibiting TRPV3 channels [46, 47]. Accumulative evidence suggests that activation of TRPV3 in skin keratinocytes may release inflammatory mediators including ATP, PGE_2, and nitric oxide (NO), which can act on sensory terminus to initiate pain sensation [48-50]. However, no deficiency of acute heat pain is observed in TRPV3 KO mice [51], suggesting that TRPV3 is unlikely a major contributor to acute thermal pain. On the other hand, TRPV3 is clearly expressed in both epidermal keratinocytes and sensory neurons and might mediate pain sensation in humans [52].

2.2. ThermoTRPs are Involved in Neuropathic Pain

In addition to inflammatory pain, TRPV1 is also involved in the neuropathic pain. Evidence that TRPV1-positive fibers are required for neuropathic pain comes from the analgesic effects of desensitization or ablation of TRPV1-positive sensory nerve endings, which has encouraged their use therapeutically to attenuate neuropathic pain [53, 54]. For example, ablation of TRPV1-positive fibers by resiniferatoxin abolishes spinal ventral root afterdischarges as well as mechanical hyperalgesia in a rat spared nerve injury (SNI) model [55]. Furthermore, spinal nerve ligation (SNL) injury-induced spontaneous neuropathic pain and thermal hyperalgesia but not tactile hypersensitivity can be abolished by desensitization of TRPV1-positive fibers with systemic administration of resiniferatoxin [56].

Nerve injuries promote expression and function of TRPV1 in sensory ganglia. For instance, SNL-induced nerve injury increases the proportion of TRPV1-expressing IB4-positive DRG neurons and up-regulates TRPV1 function, leading to persistent thermal hyperalgesia [57]. In a partial infraorbital nerve ligation-induced trigeminal neuropathic pain model, the number of TRPV1-positive trigeminal neurons is also markedly increased [58]. Consistent with enhanced activity of TRPV1 in neuropathic pain, administration of selective TRPV1 inhibitors alleviates SNL-induced heat hyperalgesia and mechanical allodynia [57-60]. Furthermore, the function of TRPV1 at the central terminals of primary afferent neurons in the spinal cord is also up-regulated after sciatic nerve transection in rats [61]. Up-regulated TRPV1 at the central terminals may contribute to the enhanced release of inflammatory neuropeptides, such as substance P and CGRP (calcitonin gene-related peptide) from the presynaptic central terminals as well as enhanced glutamatergic neurotransmission, participating in the neuropathic pain [62-64].

Although genetic studies show that TRPV1 is selectively expressed by peripheral sensory nociceptors with minimal expression in the CNS [65-67], TRPV1 has also been

reported to be present in GABAergic spinal interneurons, which upon activation results in long-term depression of excitatory inputs. Interestingly, peripheral nerve injury-induced mechanical hypersensitivity is attenuated by pharmacological or genetic ablation of TRPV1 function but not in mice lacking TRPV1-positive sensory nociceptors, indicating that TRPV1 in the spinal interneurons contributes greatly to neuropathic pain [68]. However, the degree of expression of TRPV1 in spinal neurons and the functional significance of TRPV1 in these neurons remain controversial [65, 69].

TRPA1, along with TRPM8 has been proposed to function as a cold transducer and is considered to be a major candidate for mediating cold allodynia, which is a common feature of neuropathic pain [38, 45, 70, 71]. Nerve injury increases TRPA1 mRNA transcripts in DRG neurons [38]. Pharmacological inhibition of TRPA1 function markedly attenuates cold allodynia in a chronic constriction injury (CCI) model of neuropathic pain [72]. Intrathecal administration of TRPA1 antisense oligodeoxynucleotide also suppresses SNL-induced cold allodynia [73]. On the other hand, Caspani *et al*. did not find strong correlations between functional changes of TRPA1 or TRPM8 and cold allodynia induced by chronic constriction of the sciatic nerve [74], even though the TRPM8 protein was found to be increased within two weeks in CCI rats associated with cold hyperalgesia in another study [75]. A case report showing abnormal responses to cold and menthol in C-nociceptors of a patient with a small-fiber neuropathy further confirms the role of TRPM8 in neuropathic pain [76]. However, there is also evidence that activation of TRPM8 has analgesic effects [77]. Therefore, distinct mechanisms may underlie TRPM8-mediated proalgesic and analgesic effects.

Both TRPV1 and TRPA1 are critical players in chemotherapy-induced peripheral neuropathy and neuropathic pain [52, 78]. Genetic or pharmacological ablation of TRPA1 function also abolishes both mechanical and cold allodynia induced by treatments with cisplatin and oxaliplatin, two of the most commonly used chemo-therapeutic agents [79, 80]. Consistent with TRPA1 being a mediator of chemotherapy-induced neuropathy, treatment with oxaliplatin promotes TRPA1 expression and enhance TRPA1 channel function to selective TRPA1 agonists in nociceptors [79]. Interestingly, treatment with paclitaxel, an antimitotic drug, also potentiates cold allodynia in streptozotocin-induced diabetic rats by increasing production of reactive oxygen species that subsequently activate TRPA1 [81].

Chronic oxaliplatin treatment produces a dose-dependent increase of capsaicin response, presumably caused by intra-cellular cAMP in nociceptors [82]. Paclitaxel chemotherapy is also reported to evoke release of mast cell tryptase to activate PAR2, which in turn sensitizes TRPV1, TRPV4 and TRPA1 through PLC, PKCε and PKA signaling to initiate neuropathic pain behaviors [83]. Chronic paclitaxel treatment, in addition to sensitizing TRPV1 channels by intracellular signaling molecules, also increases the TRPV1 mRNA transcripts and amount of TRPV1 protein in small-to-medium-diameter DRG neurons, which likely contributes to neuropathic pain [84].

2.3. TRP Channels Play Critical Roles in Visceral Pain

TRPV1 is extensively expressed in the gastrointestinal tract and serves as an important regulator of gastrointestinal motility and visceral hypersensitivity. In patients suffering from inflammatory bowel diseases the number of TRPV1-positive nerve fibers have increased three times more than that in control subjects [85]. Increased numbers of nerve fibers expressing TRPV1 in muscle, mucosal, and submucosal layers have also been observed in patients with rectal hypersensitivity and faecal urgency, which correlates well with increased hypersensitivity to heat and distension within the gastrointestinal tract [86]. TRPV1 is also involved in acid reflux-induced esophagitis in both humans and rodents [87, 88], and genetic ablation of TRPV1 function markedly suppresses acid-induced esophagitis in mice [88].

Retrograde labeling reveals that TRPV1-expressing peripheral terminals of DRG and nodose ganglion neurons are present in the pancreas [89]. It has long been known that TRPV1 is a key player in neurogenic inflammation and pancreatic pain, especially in both acute and chronic pancreatitis [90-92]. In L-arginine-induced rat pancreatitis model, there is a great increase in spontaneous abdominal contractions and *c-fos* expression in spinal neurons. Increases in TRPV1 function and the proportion of pancreatic DRG neurons have been observed in a chronic rat model of pancreatitis, accompanied by visceral hyperalgesia which can be markedly reduced by a TRPV1 antagonist [91, 92]. It has also been shown that siRNA-mediated knockdown of TRPV1 diminishes spontaneous visceral pain in mice [93]. Furthermore, nerve growth factor (NGF) increases TRPV1 expression and up-regulates TRPV1 function to promote pain in chronic pancreatitis [94].

TRPA1 is also expressed in visceral afferent neurons and plays an important role in visceral sensory transduction, particularly in the context of visceral inflammation and pain in both gastrointestinal and urinary tracts [95-97]. Rodent models of colitis generated by intracolonic infusion of 2, 4, 6-trinitrobenzene-sulfonic-acid (TNBS) and drinking dextran-sulfate-sodium-salt (DSS)-containing water are commonly used to investigate mechanisms of colitis [98, 99]. TRPA1 mediates intestinal inflammation in both models by releasing substance P, an inflammatory sensory neuropeptide, which can initiate and maintain neurogenic inflammation [100, 101]. TNBS is an electrophilic compound that directly activates TRPA1 by covalently modifying cytosolic cysteine residues [101-103]. Furthermore, endogenously released inflammatory mediators, for instance, 4-hydroxynonenal (4-HNE), can activate TRPA1 to initiate a vicious positive feedback cycle [101, 103]. Both TRPV1 and TRPA1 are expressed in visceral sensory neurons and respond to physiological mechanical stimuli. They also contribute to visceral mechanical hypersensitivity in chemically induced rodent models of intestinal inflammation [104-106]. Further studies show that TRPV1 and TRPA1 play a pivotal role in visceral hypersensitivity at the peripheral and spinal cord levels evoked by colon distension during acute TNBS-induced colitis in rats [101, 107].

A recent study suggests that TRPA1 mediates a duodeno-pancreatic neural reflex that can induce acute neurogenic

pancreatitis [108]. TRPA1 not only contributes to pancreatic pain but also mediates pancreatic inflammation in both caerulein- and TNBS-induced mouse models of pancreatitis [109, 110]. Interestingly, activation of TRPV1 and TRPA1 seems to have a synergistic effect in promoting pain and inflammation in caerulein-induced pancreatitis because selective TRPV1 and TRPA1 inhibitors act synergistically to reverse pancreatic inflammation and pain [111]. More importantly, early intervention with TRPA1 and TRPV1 inhibitors seems to effectively attenuate the transition from acute to chronic pancreatitis in a mouse model of chronic pancreatitis generated by repeated episodes of caerulein-induced acute pancreatitis [112]. Although the underlying mechanisms remain unknown, TRPV1 and TRPA1 are expressed by the same subset of nociceptors and exhibit cross desensitization. Therefore, blockade of one receptor might be able to remove the cross desensitization to promote the function of the other, which might explain the synergistic effect between TRPV1 and TRPA1 inhibitors [113, 114]. The other possibility is that TRPV1 and TRPA1 form heteromeric channels which might display novel pharmacological properties [115].

It has been reported that the mechanosensitive TRPV4 is also expressed in visceral sensory DRG neurons, and the TRPV4 agonists evoke visceral hypersensitivity, which is attenuated by TRPV4-targeted gene knockdown or in TRPV4 KO mice [116, 117]. TRPV4-mediated visceral hypersensitivity is enhanced by histamine, serotonin, and activation of PAR2 [118, 119]. In addition to the visceral sensory DRG neurons, TRPV4 is also present in mouse urothelial cells [120] and inhibition of TRPV4 by pharmacological or genetic ablation improves the bladder overactivity [121].

The presence of cooling sensing TRPM8 in colonic DRG neurons has been confirmed by several groups, however, it is proposed that TRPM8 expressed in high threshold sensory neurons may couple to TRPV1 and TRPA1 and inhibit their downstream chemosensory and mechanosensory function. This is based on the findings that activation of TRPM8 blocks TRPV1-mediated CGRP release and attenuates inflammatory response [122, 123].

3. TRP CHANNELS AND PAIN MANAGEMENT

The identification of TRP channels, particularly TRPV1 and TRPA1, in pain pathways has shed light on the molecular basis of pain signaling during inflammatory and neuropathic conditions. TRPV1 and TRPA1 thus are considered promising drug targets for the management of a number of pain conditions because of their ability to be activated by nociceptive signals and sensitized/up-regulated by pro-inflammatory mediators.

3.1. Potent Synthetic TRPV1 and TRPA1 Inhibitors

Intense efforts have been carried out to develop drugs that selectively inhibit TRPV1 for pain relief [124-126]. Over the years a number of potent and selective TRPV1 antagonists have been developed [125]. Amgen has reported several potent competitive TRPV1 antagonists including AMG0347, AMG8163, and AMG9810 [127, 128]. Further optimization of the drug design led to the clinical candidate AMG517 [129]. Along with SB-366791 (GSK) [130], A-425619, A-784168 and A-795614 (Abbott) [22, 131], JNJ-17203212 (Johnson and Johnson) [132] and a nonvanilloid TRPV1-antagonist, BCTC [133], these selective TRPV1 inhibitors have demonstrated efficacy in a range of inflammatory and neuropathic pain conditions in animal models [54]. Besides AMG517, several other TRPV1 inhibitors have been evaluated in clinical trials including ABT102 (Abbott), AZD1386 (AstraZeneca), GRC 6211(Glenmark), JTS-653 (Japan Tobacco), MK 2295 (Merck), SB-705498 (GSK), and PF-4065463 (Pfizer) [54, 124, 125].

Although development of selective inhibitors targeting pain-initiating TRP channels on peripheral nociceptors appears promising, the first generation TRPV1 antagonists carry undesired on-target side effects of hyperthermia and loss of heat pain, evident both in rodents and in humans, making them unsuitable for further development into pain management drugs [124, 125, 134]. Hyperthermia has been induced by different chemical classes of TRPV1 antagonists [124]. For instance, AMG517 [135], ABT-102 [136] and AZD1386 [137] produce hyperthermia in multiple species including humans. The hyperthermia induced by TRPV1 inhibitors results from an on-target side effect in the periphery, rather than direct effects on hypothalamic cells encoding the body's temperature set-point [127, 135]. Interestingly, repeated administration of AMG517 attenuates its hyperthermic action [128]. Furthermore, common antipyretic agents like acetaminophen can also suppress AMG517-induced hyperthermia [128]. Importantly, recent studies reveal that blockade of TRPV1 activation by protons is strongly associated with the hyperthermic side effects while suppression of the heat or capsaicin activation modes has little or no impact on the development of hyperthermia in rodents. These acid-sparing TRPV1 antagonists are reasonably effective in attenuating inflammatory pain without significantly increasing core body temperature [138-140]. It will be interesting to see if these TRPV1 antagonists sparing proton activation provoke no hyperthermia in humans.

Several selective TRPA1 antagonists have been identified using high-throughput screening of chemical compound libraries. AP-18 (GNF) and HC-030031 (Hydra) are the first selective TRPA1 inhibitors displaying promising analgesic effects by inhibiting both inflammatory and neuropathic pain [36, 40, 41, 54, 70, 141, 142]. A-967079 (Abbott) is another selective and potent TRPA1 inhibitor that effectively suppresses spontaneous and mechanically evoked firing of spinal neurons in uninjured, CFA-inflamed, and osteoarthritc rats [143]. A-967079 also shows good bioavailability *in vivo* and exhibits analgesic efficacy in AITC-induced nocifensive responses and osteoarthritic pain in rats. Unlike TRPV1 inhibitors, A-967079 has no reported hyperthermic side effects [72]. Other available potent TRPA1 inhibitors include GRC17536 from Glenmark [144] and a series of TRPA1 inhibitors developed by Janssen Pharmaceutica [145]. However, the bioavailability, efficacy, and safety of these drugs are still waiting to be explored in preclinical studies [52].

The commercially available TRPM8 antagonist AMTB has been shown to act on the bladder afferent pathway to

attenuate the bladder micturition reflex and nociceptive reflex responses. Application of this antagonist leads to the drop of body temperature [146]. Another TRPM8 channel blocker PMBC has been shown to diminish cold hypersensitivity in inflammatory and nerve-injury pain models [45]. Recently, several potent and selective small molecule TRPM8 antagonists from Janssen show promising efficacy in suppressing icilin-evoked "wet dog shakes" (used as a pharmacodynamic model) and CCI-induced cold allodynia in rats [147, 148]. Up to now, selective TRPV3 antagonists are not commercially available. A series of chemicals proposed to be TRPV3 inhibitors from Hydra and Glenmark are still waiting to be tested [52].

3.2. Endogenous Lipid Metabolites are Potent Inhibitors of Pain-initiating TRP Channels

Endogenous bioactive lipids play a critical role in TRP channel signaling [149, 150]. Resolvins are a family of endogenous lipids generated from the omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during inflammation [151]. Recent studies show that resolvins are among the most potent regulators (being effective in the nM range) of thermoTRPs including TRPV1, TRPA1, TRPV3 and TRPV4 [46, 152]. Intraplantar or intrathecal administration of resolvin E1 and D1 markedly attenuates inflammatory pain responses produced by paw injection of formalin, carrageenan, or CFA [153]. Spinal resolvin E1 also inhibits spontaneous pain and inflammatory hyperalgesia induced by intrathecal injection of capsaicin or TNF-α. Resolvins appear to act on both peripheral and central sites since they not only reduce both capsaicin- and TNF-α-evoked release of glutamate from the central terminals of primary nociceptors but also suppress the enhancement of spinal N-methyl-D-aspartate (NMDA) receptor function by TNF-α [153]. Both resolvin E1 and D1 selectively inhibit TRPV1 while resolvin D2 suppresses both TRPA1 and TRPV1, with IC_{50} values around 1 nM [46, 154]. Intrathecal application of resolvin D2 also attenuates inflammatory pain [154] and systemic application of low doses of resolvins reduces inflammatory pain in an adjuvant-induced arthritis model [155]. Besides TRPA1 and TRPV1, resolvin D1 also suppresses two important epidermal thermoTRPs, TRPV3 and TRPV4, both of which are strongly associated with inflammation, barrier function and skin disorders [156-159].

3.3. Inhibition of TRP Channels by Agonist-induced Desensitization

Capsaicin is not only a valuable tool to study pain but also offers a promising analgesic effect through desensitization of TRPV1. For instance, topical creams, injectable preparations and oral compounds containing capsaicin are being used to treat pain [160]. In fact, NGX-4010 (NeurogesX), WN-1001 (Winston Laboratories), and ALGRX-4975 (Anesiva) have reached phase III clinical trials and shown promising therapeutic benefits for both inflammatory and neuropathic pain [54, 161]. Furthermore, repeated or high-dose application of capsaicin can reversibly ablate the TRPV1-positive nerve fibers and produces long-lasting analgesic effects against both mechanical and thermal pain [160]. Degeneration of TRPV1-positive sensory nerves involves an intracellular Ca^{2+}-overload and, with higher doses near the cell bodies, consequent cell death (either through apoptosis or necrosis) [160]. Resiniferatoxin, an ultrapotent analog of capsaicin, seems to be more effective than capsaicin to treat a variety of pain conditions including but not limited to interstitial cystitis, post-herpetic neuralgia, and osteoarthritis [124, 162-165]. Resiniferatoxin can be injected intradermally, intraganglionally, and intrathecally to block different types of localized pain [163]. Low doses of resiniferatoxin can desensitize TRPV1 and suppress pain reversibly, but high doses of resiniferatoxin produce neurotoxicity and permanently degenerate TRPV1-positive nerve endings [163]. Recently, small molecules such as MRS1477 (a 1, 4-dihydropyridine) that serve as positive allosteric modulators of TRPV1 have been used to inactivate the TRPV1-positive sensory nerve endings and produce analgesic effects by the same mechanisms as resiniferatoxin [166]. To enhance these effects, positive allosteric modulators of TRPV1 can be co-applied with a TRPV1 agonist, such as capsaicin or acid, amplifying the activation of TRPV1, which leads to subsequent reversible desensitization or irreversible axonal degeneration of the sensory nerve endings [166].

It should be noted that although both capsaicin and resiniferatoxin ablate sensory nerve endings in a TRPV1-dependent manner, the analgesic effect is mediated by many signaling molecules besides TRPV1 in the TRPV1 positive neurons. For instance, TRPA1 and Nav1.8 are two important nociceptive ion channels colocalized with TRPV1, loss of which will also decrease pain sensitivity [31, 32, 167]. Furthermore, loss of TRPV1-positive neurons and nerve endings will also lead to depletion of sensory neuropeptides such as substance P and CGRP, which are key neurotransmitters for chronic pain [168]. Therefore, the analgesic effect is a reflection of the loss of a specific subset of nociceptors instead of only the TRPV1 channels [66, 67, 164].

A number of prostaglandins are potent inflammatory mediators contributing to pain and inflammation in various animal models by facilitating functions of TRP channels, especially TRPV1 and TRPA1 [169-172]. Paradoxically, 15-Deoxy-Δ12, 14-prostaglandin J2 (15d-PGJ2) can also inhibit TRPA1-mediated pain-related behaviors by a long-lasting desensitization of the activated channel following initial activation [173].

3.4. Inhibition of TRP Channel Activities by Disruption of Inflammation-induced Sensitization

The expression and function of pain-sensing TRP channels are highly regulated by inflammation and tissue damage. Functional regulation of TRP channel function generally is associated with protein phosphorylation mediated by activation of GPCRs (G-protein coupled receptors) and tyrosine kinase receptors, such as receptors for bradykinin and NGF (nerve growth factor), which sensitizes TRP channels [83, 174-177]. Recent studies show that scaffolding proteins such as the AKAP (A kinase anchoring protein) family, serve as important biochemical platforms that are critical to the formation of protein signaling complexes, facilitating gating and membrane trafficking of TRP channels [178-181]. Since sensitization of nociceptive TRP channels is an important mechanism underlying neuronal

hypersensitivity at both peripheral and central nerve endings it would be beneficial to disrupt the protein signaling complexes to interrupt TRP channel sensitization in the peripheral nociceptors [182]. Indeed, short peptides capable of preventing TRPV1–AKAP79 interaction are effective in preventing TRPV1 sensitization *in vivo* and suppressing inflammatory hyperalgesia generated by paw injections of formalin, PMA (phorbol 12-myristate 13-acetate), and carrageneenan. More importantly, these interfering short peptides have no effect on pain thresholds in the absence of inflammation, which suggests that they may offer a promising therapeutic route for novel analgesics by suppressing sensitization of TRPV1 without producing on-target hypothermic side effect generated by small molecule TRPV1 blockers [183, 184].

3.5. TRP Channels and Anesthetics

In contrast to analgesics which relieve pain without compromising other forms of sensation, anesthetics eliminate sensation generally and reversibly by inhibiting voltage-gated Na^+ channels [185, 186]. Interestingly, both local and general anesthetics activate nociceptive ion channels including TRPV1 and TRPA1 to enhance pain and inflammation [187-194]. Lidocaine activates TRPV1 through a mechanism similar to that of capsaicin [187]. Depletion of PIP_2 and a point mutation disrupting the PIP_2 interaction site at the C-terminus of TRPV1 also attenuate the excitatory effect of lidocaine on TRPV1 [187]. For TRPA1, lidocaine has a bimodal action: it not only activates TRPA1 through cytosolic cysteine residues known to be covalently modified by electrophilic agonists [102, 103] but also suppresses TRPA1 in a species-specific manner through interacting with the channel pore region that also determines menthol sensitivity of mammalian TRPA1 [188, 195]. Volatile general anesthetics including isoflurane, sevoflurane, enflurane, desflurane, and propofol sensitize responses to other TRPV1 agonists and modulators [191] and directly activate TRPA1 to increase neurogenic inflammation and pain-related behaviors [190, 193, 194]. These findings strongly suggest that both TRPV1 and TRPA1 might play an important role in postoperative pain and inflammation.

On the other hand, TRP channels can also be used to facilitate the action of anesthetics. Binshtok *et al*. showed that intracellular introduction of a charged, membrane-impermeant lidocaine derivative QX-314 (N-ethyl-lidocaine) specifically into TRPV1-positive nociceptors could be achieved through activated TRPV1 channels. Unlike the use of membrane-permeable local anaesthetics, this novel approach blocks the voltage-gated sodium channels only in the TRPV1-positive neurons and axons without affecting the function of TRPV1-negative neurons that are required for mechanical sensation and motor function [196]. Since lidocaine is a TRPV1 activator, co-application of lidocaine with QX-314 can prolong analgesia without causing the initial burning pain sensation evoked by capsaicin [187, 197]. Activation of TRPV1 by acidic solution can also facilitate QX-314 translocation into nociceptors, which alleviates chronic neuropathic pain in mice [198]. Of note, like other local anesthetics, QX-314 seems to activate TRPV1 at high concentrations, but it suppresses TRPV1 function at low concentrations [199]. Agonist-induced pore dilation following long-term stimulation with high concentrations of agonists has been reported for TRPV1 and TRPA1 but not TRPM8 [200-202], but pore dilation is not required for QX-314 entry into TRPV1-positive neurons [203]. Interestingly, QX-314 does not pass through TRPA1 and TRPM8 channels when activated by AITC or menthol, respectively [204], which raises an interesting question of whether there are specific properties required for QX-314 passing through the TRPV1 channel pore that are absent from TRPA1 and TRPM8.

4. CONCLUSION

Relief of chronic pain is a largely unmet medical need. Ion channels play critical roles in both peripheral and central sensitization, generating and sustaining chronic pain by dynamically increasing neuronal excitability in primary sensory neurons and possibly other neurons in the CNS. TRP channels function as molecular sensors of environmental stimuli and initiate activity in pain pathways when they sense signs of tissue damage and inflammation. Over the past few decades, the sensory and nociceptive roles of TRP channels in the genesis of both acute and chronic pain have become increasingly clear, and TRP channels are emerging as promising drug targets for the management of both inflammatory and neuropathic pain conditions. Although it is challenging to translate basic research findings into clinical tools for better treatments of pain and to overcome deleterious side effects produced by the TRP channel inhibitors, targeting the pain-evoking TRP channels on primary nociceptors remains a promising and rewarding approach to provide pain relief for millions of chronic pain patients.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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