# Chapter 2
# TRP Channels in Nociception and Pathological Pain


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**Abstract** Thermal and noxious stimuli are detected by specialized nerve endings, which transform the stimuli into electrical signals and transmit the signals into central nervous system to facilitate the perception of temperature and pain. Several members within the transient receptor potential (TRP) channel family serve as the sensors for temperature and noxious stimuli and are involved in the development of pathological pain, especially inflammatory pain. Various inflammatory mediators can sensitize and modulate the activation threshold of TRP channels and result in the development of inflammatory pain behaviors. A brief review of the role of TRP channels in nociception and the modulatory mechanisms of TRP channels by inflammatory mediators, focusing on TRPV1, TRPA1, and TRPM2, will be presented. Recent advances in the development of therapeutic strategies targeting against TRP channels will also be reviewed.

**Keywords** Nociception · Pain · TRP · TRPV1 · TRPA1 · TRPM2

## 2.1 Introduction

"Pain," the word that comes from Greek goddess of revenge, Poine, describes an unpleasant experience that is elicited by noxious stimuli. Such experience often serves as a warning flag and reminds an individual of avoiding or eliminating the encountered threats. Pain can be divided into three categories including nociceptive

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pain, inflammatory pain, and neuropathic pain [66]. Nociceptive pain is generated by specialized nerve endings (nociceptors) with a relatively high activation threshold compared with those responsible for the sensation of light, sound, smell, and taste. Nociceptors serve as sensors for strong mechanical stimuli, chemical irritants, and noxious thermal stimuli, and only stimuli that are potentially capable of causing tissue injuries can reach the threshold to activate nociceptive nerve terminals and generate actions potentials, which are then transmitted and perceived as pain signals [21]. Transformation of these stimuli into electrical signals and transduction of the action potentials involve the participation of multiple receptors and channels located on free nerve endings and synaptic terminals. As a group of multimodal cation-permeable channels that depolarize the cells, TRP channels are involved in various aspects of physiological function, including nociception [70].

TRP channels were first discovered in *Drosophila melanogaster* and viewed as mutant structures exhibiting only a transient receptor potential (TRP) rather than normal sustained potential in response to light [16]. Later on, mammalian homologs of TRP channels were discovered [89], which then opens the opportunity for further investigation on the functional roles of TRP channels. To date, 28 mammalian TRP channels have been identified and are divided into 6 subfamilies according to their sequence homology: canonical or classic (TRPC), vanilloid (TRPV), melastatin (TRPM), polycystin (TRPP), mucolipin (TRPML), and ankyrin (TRPA) [77]. Among them, several types of TRP channels have been found to be involved in the generation of pain, including TRPV1 [13], TRPV2 [93], TRPV3 [58], TRPV4 [80], TRPA1 [60, 91], TRPM2 [30], and TRPM8 [27]. Each channel has its unique characteristics and contributes to the generation of various pain behaviors including heat hyperalgesia, mechanical hyperalgesia, cold allodynia, and inflammatory hyperalgesia.

As for the roles of TRP channels in inflammatory pain, inflammatory mediators can sensitize or alter the threshold of TRP channels, leading to pain behaviors including thermal hyperalgesia, mechanical allodynia, and spontaneous pain [41]. In this review, we will focus on the molecular mechanisms of TRP channel modulation in the generation of nociception and the development of inflammatory pain, focusing on TRPV1, TRPA1, and TRPM2.

## 2.2 TRPV1

Among the members within the TRP channel family, TRPV1 is the one that has been most thoroughly investigated, and its pivotal role in sensing noxious stimuli and generating pain in primary afferent nociceptors has also been demonstrated across different studies [41]. Since the successful cloning of TRPV1 in 1997, follow-up studies have identified TRPV1 as a cation-permeable channel which is responsive to thermal stimuli in the range of noxious heat (over 43 °C) [82] and changes in pH [19]. As a polymodal channel, TRPV1 can also be activated by vanilloids (e.g., capsaicin from chili peppers or anandamide from inflammation process)

[72], vanillotoxins [73], and protons [3]. The finding of TRPV1 being expressed almost exclusively in C-fibers indicates its role as a sensor for noxious stimuli [46]. Furthermore, the activity of TRPV1 can be enhanced by a variety of inflammatory mediators, including bradykinin, ATP, and nerve growth factor (NGF), through second messenger-signaling pathways such as phospholipase C (PLC) and protein kinase A (PKA) [56]. The sensitization and activation of TRPV1 in peripheral nociceptors lead to the transmission of the noxious signals to the central nervous system and, hence, the production of unpleasant and painful sensation warning the body of potentially harmful threat [41, 66].

The success in the application of cryo-microscopy to understand the molecular structure of TRPV1 has enabled us to gain deeper understanding in the gating mechanism of TRP channels [12]. TRPV1 is composed of four identical protein subunits assembled into a functional and cation-permeable channel [12]. Each subunit contains six transmembrane segments, a loop constructing pore helix between segment five and six, and intracellular N- and C-termini with two restriction points in the pore helix defined as the selectivity filter and the lower gate [12, 28]. During inactive state, both the selectivity filter and the lower gate are constricted, and the pathway for ion conduction is blocked. An intracellularly located hydrophobic pocket, the so-called vanilloid pocket, is composed of the external surface of the S3–S4 helices, S4–S5 linkers, and S6 helix [12, 32]. It allows small vanilloid molecules, such as resiniferatoxin (RTX) and capsaicin, to cross the plasma membrane to bind and allosterically modulate the pore, more precisely, expanding the lower gate of the pore domain. As for the extracellular outer pore region, the binding of chemicals, such as double-knot toxin (DkTx), or stimulation with thermal stimuli cause substantial conformational changes of TRPV1, resulting in marked change in the relative position of the pore helix in the outer pore region. The change of the relative position of the pore helix may also break down the potential hydrogen bonding formed between the amino acids on the chains within the outer pore region in resting state resulting in the widening of the selectivity filter. It is rather remarkable that the upper and lower gates could be allosterically coupled and regulate the activation of the channel. Such synergy between different levels of gates could contribute to the coordination of disparate physiologic signals [12].

Under physiological condition, TRPV1 has been shown to be co-expressed with PKCβII in a subset of sensory neurons. In these neurons, TRPV1 binds directly to PKCβII, which in return markedly enhances the responses of TRPV1 by phosphorylating TRPV1 at T705 [52]. The differences in the basal phosphorylation of TRPV1 at T705 may explain the differences in the threshold of TRPV1-expressing neurons to heat stimuli [45]. In addition, TRPV1-PKCβII complex-containing neurons have been suggested to represent a subset of hypersensitive nociceptive neurons [95]. Not only does TRPV1 play a pivotal role in generating proportionate pain under physiological condition, it also contributes to the generation of action potentials during inflammation, leading to pathological pain behaviors such as thermal hyperalgesia, spontaneous pain, and mechanical allodynia [7, 13, 56]. In response to tissue damages, numerous inflammatory mediators such as eicosanoids (e.g., prostaglandin E2), neuropeptides (e.g., substance P and bradykinin), excitatory amino acids (e.g.,

glutamate), leukotrienes, and cytokines (e.g., TNF-α, IL-6and INF-γ) [90] are released, and the inflammatory mediators lower the mechanical and thermal thresholds of the exposed sensory neurons, a process called "sensitization" [41]. Besides acting as a downstream target of proalgesic factors, TRPV1 itself can also trigger the secretion of neuropeptides, including substance P and calcitonin gene-related peptide (CGRP) upon activation [39, 91]. The neuropeptides secreted then bind to specific receptors expressed on the surrounding cells, such as lymphocytes, dendritic cells, mast cells, and macrophages, which then trigger a series of reactions involved in immune responses [4]. This process is known as neurogenic inflammation, and the involvement of TRPV1 in the development of inflammatory pain is clearly demonstrated by the significantly reduced thermal hyperalgesia in TRPV1 knockout mice after tissue injury [13, 18].

The mechanisms responsible for the exaggerated response of TRPV1 during inflammatory state are associated with protein kinases [8], which modulate the activities of proteins through phosphorylation. Phosphorylation of TRPV1 can be facilitated by inflammatory mediators through multiple protein kinases including cyclic AMP-dependent protein kinase (PKA) and protein kinase C (PKC), phosphatidylinositol-3 kinase (PI3K), $Ca^{2+}$/calmodulin-dependent kinase II (CaMKII), and extracellular signal-regulated protein kinase/mitogen-activated protein kinase (ERK/MAPK) [56]. Receptors of several inflammatory mediators, including prostaglandin receptors (e.g., prostaglandin E2 receptor 2, prostaglandin E2 receptor 4, I prostanoid receptor, and prostaglandin D2 receptor 1), 5-hydroxytryptamine(5-HT) receptors and endothelin $ET_A$ receptors, are G protein-coupled receptors (GPCRs) which are coupled to the Gs type of Gα subunit [54]. When these inflammatory mediators bind to GPCRs, adenylyl cyclases are activated and cause increase of intracellularly cAMP level and full activation of PKA [78].

Another mechanism modulating the function of TRPV1 is through the PLC/PKC pathway. Receptors for inflammatory mediators such as histamine H1, bradykinin B2, protease-activated receptor-2 (PAR2), prostaglandin E2 receptor 1, substance P, neurokinin 1 (NK1), and purinergic P2Y are also GPCRs. Instead of being coupled to Gs type of Gα subunit, they are coupled to Gαq type of Gα subunit which then initiate the activation of phospholipase C (PLC). The activation of PLC leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate ($PIP_2$) and results in the production of two second messengers: 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) [25]. Some studies showed results suggesting that $PIP_2$ causes inactivation or desensitization of TRPV1, and the hydrolysis of $PIP_2$ by PLC results in the activation of TRPV1 [25, 69]. However, there are conflicting results showing that direct application of $PIP_2$ causes TRPV1 activation and absence of $PIP_2$ results inTRPV1 inactivation [71]. Another study showed that TRPV1 can be fully functional in the absence of $PIP_2$, suggesting that $PIP_2$ contributes to the sensitization of TRPV1 by disinhibiting the channel [11]. In addition, $PIP_2$ was shown to activate TRPV1 even in the absence of capsaicin, though the current intensity was much smaller than that elicited by capsaicin. The result suggests that $PIP_2$ is a positive regulator of TRPV1 and the difference of amplitude caused by the presence of capsaicin may

indicate that $PIP_2$ serves as a cofactor rather than pure agonist of TRPV1 [44]. The lack of conclusion for the role of $PIP_2$ on the regulation of TRPV1 indicates the sophisticated modulation of TRPV1. Meanwhile, DAG stimulates PKC and subsequently leads to the activation of TRPV1 [25, 35]. However, one study showed that 1-oleoyl-2-acetyl-sn-glycerol (OAG), an analog of DAG, causes TRPV1 activation in rat dorsal root ganglion neurons in the presence of chelerythrine, a PKC inhibitor, suggesting that DAG is a direct endogenous ligand of TRPV1 and the TRPV1 activation induced by OAG is independent of PKC. In addition, the study also showed that the binding site of DAG is similar to that of capsaicin, though the effect of DAG on TRPV1 is much smaller than that of capsaicin [92]. All these results indicate the involvement of Gαq-PLC pathway in the modulation of TRPV1 by inflammatory mediators.

The TRPV1 modulatory mechanisms mentioned above are basically at post-translational level, which includes phosphorylation and proteolysis of protein subunits, resulting in the change of the activity of TRPV1. However, inflammatory mediators have a more comprehensive effect on TRPV1. For example, NGF, a neurotrophic factor that binds to tropomyosin receptor kinase A (trkA) [74], modulate TRPV1 through several different aspects, including level of transcription, translation, and posttranslation, and such interactions are also suggested to be responsible for the development of thermal hyperalgesia during inflammation [51]. One study showed an increased level of NGF and higher percentage of neurons expressing TRPV1 following inflammation induced by intraplantar injection of Freund's complete adjuvant, and inhibiting the effect of NGF with anti-NGF was shown to prevent the increased TRPV1 expression within trk-A positive neurons and lessen the thermal hyperalgesia induced by inflammation [1]. These results indicate the mechanisms modulating TRPV1 at transcription or translation level.

## 2.3 TRPA1

As a member of TRP channel family, TRPA1 and TRPV1 share some common features, including the similarity in the structures consisting of six transmembrane domains with intracellular N- and C-termini and ion permeability to cation nonselectively. Within vertebrate TRP channel family, TRPA1 is characterized by a long N-terminus with multiple ankyrin repeats along with three critical cysteine residues. These three cysteine residues are located in the linker region connecting the ankyrin-rich domain to the transmembrane domain and are involved in the channel activation by electrophiles [34, 41, 67]. In addition, TRPV1 and TRPA1 are co-expressed in a specific subgroup of dorsal root ganglion neurons that is responsible for the detection and transduction of noxious stimuli [23]. Interestingly, TRPA1 was shown recently, to work together with TRPV1 and TRPM3 for acute noxious heat sensing in mice [84].

Like TRPV1, TRPA1 is also a polymodal receptor and has been shown to be activated by numerous natural pungent chemicals, including allyl isothiocyanate

(AITC), cinnamaldehyde, and allicin, which are all electrophiles [85]. One intriguing question is the mechanism by which these structurally diverse electrophiles serve as specific agonists for TRPA1 activation and modulation. Instead of structural specificity, the activation of TRPA1 by the pungent chemicals depends on the covalent modification of cysteine residues on the N-terminal of the channel. The covalent modification causes conformational change in protein structure and modulates the channel permeability [34, 57].

Furthermore, presence of calcium ions may also play a pivotal role in TRPA1 modulation. TRPA1 currents evoked by some agonists, such as AITC and cinnamaldehyde, were shown to be potentiated in the presence of extracellular $Ca^{2+}$ [40, 63]. Meanwhile, TRPA1 activation by icilin requires the presence of calcium, and adding BAPTA (an intracellular calcium chelator) to the pipette solution significantly reduces icilin-evoked currents. This indicates that intracellular calcium serves as a co-agonist of TRPA1 [20, 87]. Modulation of intracellular calcium on TRPA1 through direct binding to an EF-hand-like motif within intracellular N-terminus has been suggested by several studies [20, 96]. However, some other studies suggest that the activation might be contributed by $Ca^{2+}$-binding protein calmodulin [31]. Both suggestions have been demonstrated in genetic deletion model with both positive and negative results [20, 31, 87]. These divergent results implie that the underlying mechanism is complicated and further revaluation is needed.

Besides pungent chemicals, TRPA1 can also be activated by environmental irritants, such as acrolein [5], formalin [60], and metabolic by-products of chemotherapeutic agents. The activation of the TRPA1-expressing C-fibers in the respiratory tract and bladder was proposed to be associated with the development of airway and urinary tract symptoms, as evidenced by the findings showing that TRPA1 agonists evoke coughing in both guinea pig and human volunteers and TRPA1 antagonists attenuate symptoms of cyclophosphamide-induced hemorrhagic cystitis [9, 61].

Apart from the activation by the chemicals mentioned above, TRPA1 is activated or potentiated during inflammatory state as well. During tissue injury, the reactive oxygen species generated cause superoxidation of membrane phospholipids and result in the production of 4-hydroxy-2-nonenal (HNE), which then causes activation of TRPA1 [2, 83]. The inhibition of the pain-related behaviors elicited by 4-HNE injection with TRPA1 antagonists and the absence of the pain-related behaviors in TRPA1-deficient mice demonstrate the importance of TRPA1 in mediating the effect of 4-HNE in the development inflammatory pain [2, 83]. In addition, the binding of bradykinin to bradykinin receptor B2 causes activation of PLC and PKA, and results in the enhancement of the TRPA1 current activated by AITC or cinnamaldehyde [86]. All the results above indicate the involvement of TRPA1 in the induction of acute pain and hyperalgesia during inflammation.

## 2.4 TRPM2

Interactions between neurons and immune cells contribute substantially to the initiation of pathological pain, in which neurogenic inflammation and generation of reactive oxygen species and reactive nitrogen species (ROS/RNS) are of fundamental importance. TRPM2 is a member within TRP channel family that plays a crucial role in serving as the downstream target of ROS/RNS [42] and can be activated by micromolar levels of $H_2O_2$ and agents producing ROS/RNS [29, 88]. TRPM2 is a cation channel characterized by a nudix hydrolase (NUDT9) homology region in the intracellular C-terminus, which was suggested to be responsible for channel activation and modulation by intracellular adenosine diphosphate ribose (ADPR) [48, 68]. In addition, cADPR and NAADP have synergistic effect with ADPR, as evidenced by the finding showing that the $EC_{50}$ for cADPR and NAADP decrease significantly from 44 to 3 μM and from 95 to 1 μM, respectively, in the presence of subthreshold levels of ADPR (100 nM) [49]. However, whether they bind directly to the Nudix box motif as ADPR or to distinct synergetic sites or had been converted to ADPR beforehand remains unclear. ADPR can also be produced extracellularly. Extracellular $NAD^+$ can be catalyzed into ADPR, cADPR, and NAADP with the enzymatic activity of nicotinamide adenine dinucleotide nucleosidase, such as CD38 [64] and CD157 [38] that are extensively expressed on hematopoietic and non-hematopoietic cells [55, 77]. However, as the binding site of ADPR for the activation of TRPM2 seems to be located inside the plasma membrane, whether and how these extracellularly formed ADPR crosses the membrane and activates TRPM2 channels is not entirely known. Nevertheless, extracellular ADPR has been reported to modulate the activity of TRPM2 indirectly from the extracellular area through activation of P2Y receptors [50] and PLC [36]. In either pathways, the activation of P2Y receptors and PLC results in an increase in intracellular calcium concentration and leads to the enhancement of TRPM2 channel sensitivity toward ADPR. Intracellular $Ca^{2+}$ has also been shown to serve as a coactivator of TRPM2, and a minimum of 30 nM intracellular calcium concentration is required to cause partial TRPM2 activation with ADPR in the absence of extracellular $Ca^{2+}$ [17, 76]. In addition to the metabolites and ROS/RNS mentioned above, TRPM2 can also be activated by thermal stimuli with an activation threshold at temperature above 35 °C [81]. Meanwhile, the temperature threshold for TRPM2 activation has also been shown to be lowered in the presence of $H_2O_2$, a phenomenon termed “sensitization” [43].

TRPM2 is ubiquitously expressed among various tissues (e.g., central nervous system, peripheral nervous system, bone marrow, and heart) and in different cell types (e.g., pancreatic β-cells, endothelial cells, microglial cells, neurons, and immune cells) [33, 37, 47, 65]. Importantly, the expression of TRPM2 in the phagocytic lineages (e.g., neutrophils and monocytes/macrophages) of immune cells enables the cells to respond to signals of ROS/RNS [49, 94].

The TRPM2 expressed in sensory neurons in dorsal root ganglion plays an important role in thermosensation and nociception. In the experiment investigating

the effect of TRPM2 on thermal preference, wild-type male mice showed preference for a 33 °C plate over a 38 °C plate, while TRPM2 knockout male mice showed no such preference. The results indicate that the genetic deletion of TRPM2 causes a remarkable behavioral change in the thermal preference [79]. In addition to the crucial role of TRPM2 in the warmth sensation, TRPM2 has also been shown to be involved in the pathogenesis of various chronic pain in several studies. When tested with von Frey filament test for mechanical sensitivity and Hargreaves and hot plate test at 52 °C and 55 °C for noxious heat sensitivity, wild-type and TRPM2 knockout mice showed no difference in their basal sensitivity. However, TRPM2 knockout mice showed attenuated nocifensive responses when injected intraplantarly with formalin. In carrageenan-induced inflammatory pain and sciatic nerve injury-induced neuropathic pain models, in which the expression of TRPM2 mRNA in the inflamed paw and the area around the injured sciatic nerve were found to be increased, mechanical allodynia and thermal hyperalgesia were attenuated in TRPM2 knockout mice [30]. In addition, the mechanical allodynia in the monosodium iodoacetate-induced osteoarthritis pain model, the mechanical allodynia in paclitaxel-induced peripheral neuropathy and streptozotocin-induced painful diabetic neuropathy models have all been shown to be significantly attenuated in TRPM2 knockout mice [75]. In addition, econazole, a TRPM2 inhibitor, was shown to reduce the visceromotor response to noxious colorectal distention in rats in both baseline condition and trinitrobenzene sulfonic acid-induced colitis model. Furthermore, TRPM2 knockout mice showed significantly reduced visceral hypersensitivity induced by trinitrobenzene sulfonic acid. The results mentioned above all demonstrate the crucial role of the TRPM2 expressed in both sensory neurons and immune cells for the development of various types of pain.

## 2.5 TRP Channel and Analgesic Drug Development

TRP channels have attracted much attention for the development of analgesic agents. Huge effort has been attempted in the development of antagonists of TRPV1 to treat inflammatory pain and cancer-related pain since the results demonstrating the attenuation of thermal hyperalgesia in inflammatory pain model in TRPV1 knockout mice [13, 18]. A TRPV1 antagonist, AMG 9810, was shown to be effective at preventing capsaicin-induced eye wiping and reversed thermal and mechanical hyperalgesia induced by intraplantar injection of complete Freund's adjuvant [26]. One study evaluated the effects of a TRPV1 antagonists, SB-705498, in humans and showed that SB-705498 reduced the area of capsaicin-evoked flare, increased the heat pain threshold on non-sensitized skin, and increased heat pain tolerance at the site of UVB-evoked inflammation [15]. The results all demonstrate the great potentials of TRPV1 as a therapeutic target for treating chronic pain. However, most previous TRPV1 antagonist programs have now been put on hold, due to the unwanted on-target side effects. One side effect was the development of marked hyperthermia after TRPV1 blockade, which caused the early termination of

phase I clinical trials with AMG 517 for dental pain in humans [15]. Furthermore, TRPV1 antagonists also elevate noxious heat sensation threshold and cause higher risk of burn injuries in individuals receiving TRPV1 antagonists. Several TRPV1 antagonists (e.g., MK-2295 [62], SB-705498 [15] and JNJ-39439335 [59]) have been reported to have such adverse effect in human studies. Although direct blockade of TRPV1 causes the adverse effects mentioned above, an alternative strategy of developing therapeutic agents disrupting the sensitization of TRPV1 is showing promising effect. By disrupting the interactions between TRPV1 and AKAP79, the sensitization of TRPV1 under pathological conditions can be inhibited without changing the normal physiological function of TRPV1 [10]. An effective cell permeable peptide capable of preventing TRPV1-AKAP79 interaction was shown to be analgesic in three mouse models of inflammatory hyperalgesia without causing hyperthermia or decreased sensitivity to noxious heat [24]. The approach demonstrates the potentials for developing therapeutic agents targeting against TRPV1.

Meanwhile, TRPA1 antagonists also show some promising results in treating pathological pain. When applying TRPA1 selective antagonists, attenuation in mechanical hypersensitivity was shown in animal inflammatory and neuropathic pain models [14, 22]. Adverse effect regarding body temperature regulation (such as hyperthermia) is not common after TRPA1 antagonist application. However, another concern that has been brought up is whether TRPA1 antagonism will compromise the ability to elicit protective actions against harmful hazards, such as coughing, sneezing, and generation of nociception to eliminate foreign irritants. These protective responses were reported to be absent in TRPA1 knockout mice [6]. Whether TRPA1 antagonists will cause the loss of such protective reflexes will be challenges for the development of therapeutic agents targeting against TRPA1. Furthermore, TRPM2 channel has been proposed to be a therapeutic target for a wide variety of oxidative stress-related diseases including cardiovascular and cerebrovascular diseases. However, effects of therapeutic strategies targeting against TRPM2 selectively have not been reported, and future efforts are needed for the development of such therapeutic agents for clinical use [53].

## 2.6 Conclusions

We have gained much deeper understanding in the functions of TRP channels in nociception and chronic pain in the last two decades. However, the modulatory mechanisms of TRP channels are still not entirely known, which can have enormous effects on the chronic pain state. However, it is also due to this sophisticated and complex design that provides us the chance to develop therapeutic strategies for pain relief without affecting the physiological functions of TRP channels. Meanwhile, analgesic agents targeting against TRP channels without side effects are still under development. Hopefully, in the future, medication targeting against TRP channels and related pathways will be brought into clinical use with fewer side effects to fight against refractory pain and other associated disorders.

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