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TRP Channels and Analgesia

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Abstract

Since cloning and characterizing the first nociceptive ion channel Transient Receptor Potential (TRP) Vanilloid 1 (TRPV1), other TRP channels involved in nociception have been cloned and characterized, which include TRP Vanilloid 2 (TRPV2), TRP Vanilloid 3 (TRPV3), TRP Vanilloid 4 (TRPV4), TRP Ankyrin 1 (TRPA1) and TRP Melastatin 8 (TRPM8), more recently TRP Canonical 1, 5, 6 (TRPC1, 5, 6), TRP Melastatin 2 (TRPM2) and TRP Melastatin 3 (TRPM3). These channels are predominantly expressed in C and A δ nociceptors and transmit noxious thermal, mechanical and chemical sensitivities. TRP channels are modulated by pro-inflammatory mediators, neuropeptides and cytokines. Significant advances have been made targeting these receptors either by antagonists or agonists to treat painful conditions. In this review, we will discuss TRP channels as targets for next generation analgesics and the side effects that may ensue as a result of blocking/activating these receptors, because they are also involved in physiological functions such as release of vasoactive neuropeptides and regulation of vascular tone, maintenance of the body temperature, gastrointestinal motility, urinary bladder control etc.

Keywords

TRP channels nociceptors; inflammatory mediators; pain; nociceptive ion channels

Introduction

Cloning of the first heat sensitive receptor in 1997, aided by an ingenious methodology of functional cloning by Julius and colleagues (Caterina et al, 1997) demarks the time period that significantly advanced our understanding of molecular mechanisms underlying

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nociception. It was considered as a TRP channel based on the sequence homology and similarity in hydropathy profile to a mutant channel that responded transiently to a light stimulus in *Drosophila*, which was cloned by Montell and Rubin in 1989 (Montell and Rubin, 1989). This channel was heat sensitive ($>42^{\circ}\text{C}$) and was activated by capsaicin, an active ingredient in hot chili peppers, a vanillyl moiety containing chemical; hence it was named TRP Vanilloid 1 (TRPV1). TRPV1 was found to be specifically involved in inflammatory thermal hypersensitivity by *TRPV1* gene deletion by two independent groups (Caterina et al, 2000; Davis et al, 2000). Within a year of cloning TRPV1, Julius and colleagues cloned another heat sensitive ($>55^{\circ}\text{C}$) receptor and because of the sequence homology with TRPV1, named it TRPV2 (Caterina et al, 1999). Since the heat sensitive receptors have been identified, a race for identifying cold sensitive receptors began. It was thought that there was no specific cold sensitive receptor, because neurons exposed to cold temperatures ($<15^{\circ}\text{C}$) depolarized and generated action potentials by closing a set of potassium channels (Reid and Flonta, 2001; Viana et al, 2002). However, cloning of a cold sensitive channel was announced in 2002 by Julius and colleagues again by functional cloning and called it cold- and menthol- sensitive receptor 1 (CMR1) (McKemy et al, 2002) and by Patapoutian and colleagues by genomic sequence homology (Peier et al, 2002a). Since it had sequence homology to TRPM channels, it was named TRP Melastatin 8 (TRPM8), which was similar to a channel already cloned from prostate cancer cells (Tsavaler et al, 2001). Another pungent chemicals and cold sensitive TRP channel TRP Ankyrin 1 (TRPA1) was cloned, which was initially named as ANKTM1 (Story et al, 2003), that had sequence homology to a channel cloned from human lung fibroblast (Jaquemar et al, 1999). During this time, two other likely nociceptive TRP channels TRP Vanilloid 3 (TRPV3) (Peier et al, 2002b; Smith et al, 2002; Xu H et al, 2002) and TRP Vanilloid 4 (TRPV4) (Strotmann et al, 2000) were cloned. Although they are activated by moderate temperatures (between 23 and 35°C), their role in nociception has not been fully elucidated. In spite of identifying receptors that responded to noxious thermal and chemical stimuli, the receptor/s carrying nociceptive mechanical sensitivity is/are still elusive. Although, TRPA1 was thought to be a mechanosensor of the inner ear hair cells, TRPA1 knockout animals had normal hearing, this was a disappointment (Corey et al., 2004; Bautista et al, 2006). TRPV4 has been shown to be involved as an osmosensor and a mechanosensor (Watanabe et al, 2002a,b; Watanabe et al, 2003; Alessandri-Haber et al, 2005, 2006; Loukin et al, 2009). Since heightened mechanosensitivity is a key component of several modalities of pain, it is surprising that a bonafide mechanosensitive TRP channel has not yet been identified. It is important to note that channels other than TRP channels may be involved in carrying mechanosensitivity (Drew et al, 2004; Gottlieb et al, 2008; Coste et al, 2010; Gottlieb and Sachs, 2012). Recently, TRPC1,5,6, TRPM2 and TRPM3 have been implicated in nociception (Gomis et al, 2008; Alessandri-Haber et al, 2009; Vriens et al, 2011; Ding et al, 2011; Haraguchi et al, 2012)

Transient Receptor Potential Vanilloid 1 (TRPV1)

The Transient Receptor Potential Vanilloid (TRPV) family consists of six members and was first cloned from *C.elegans* by Colbert et al. in 1997 and from vertebrates by Caterina et al, in 1997. Transient receptor potential vanilloid 1 (TRPV1), a nonselective cation channel

with high Ca^{2+} permeability is expressed in the peripheral and central terminals of small diameter sensory neurons (Caterina et al, 1997; Tominaga et al, 1998; Clapham, 2003; Dinh et al, 2004; Lazzeri et al, 2004; Venkatachalam and Montell, 2007). It functions as a polymodal receptor at the peripheral nerve terminals and modulates synaptic transmission at the first sensory synapse between dorsal root ganglion (DRG)/trigeminal ganglion (TG)/nodose ganglion (NG) neurons and dorsal horn (DH)/caudal spinal trigeminal nucleus (CSTN)/nucleus tractus solitarius (NTS) neurons (Nakatsuka et al, 2002; Baccei et al, 2003; Premkumar et al, 2005; Sikand and Premkumar, 2007; Jeffry et al, 2009). TRPV1 has also been shown to modulate synaptic transmission in certain regions of the brain (Doyle et al, 2002; Marinelli et al, 2002; Marinelli et al, 2003; Gibson et al, 2008; Chavez et al, 2010; Grueter et al, 2010). However, genetically modified reporter mice revealed restricted expression of TRPV1 in the central nervous system (Cavanaugh et al, 2011; Mishra et al, 2011). TRPV1 is activated by heat ($> 42^{\circ}\text{C}$), protons (Caterina et al, 1997), anandamide (Zygmunt et al, 1999; Premkumar and Ahern, 2000), arachidonic acid (AA) metabolites (Hwang et al, 2000) N-arachidonyl dopamine (NADA) (Huang et al, 2002), oleoylethanolamide (OEA), N-oleoyldopamine (NODA) (Ahern, 2003; Chu et al, 2003), polyamines (Ahern et al, 2006), adenosine (Puntambekar et al, 2004), capsaicin (a pungent ingredient of hot chili peppers), resiniferatoxin (RTX), (obtained from the cactus, *Euphorbia resinifera*) (Szallasi and Blumberg, 1990a,b; Caterina et al, 1997; Premkumar and Ahern, 2000; Raisinghani et al 2005). TRPV1 is also activated by spider and jellyfish toxin (Cuypers et al, 2006; Siemens et al, 2006).

TRPV1 is robustly potentiated by pro-inflammatory agents and trophic factors. The activation temperature threshold is reduced to body temperature when the receptor is in the phosphorylated state (Sugiura et al, 2002; Sikand and Premkumar, 2007). TRPV1 is sensitized by activin (Zhu et al, 2007), adenosine triphosphate (ATP) (Kress and Guenther, 1999; Kwak et al, 2000; Tominaga et al, 2001), bradykinin (BK) (Premkumar and Ahern, 2000; Sugiura et al, 2002), glutamate (Hu et al, 2002), histamine (Kim et al, 2004), protease-activated receptor-2 (Dai et al, 2004), serotonin (Sugiuar et al, 2004), trypsin (Amadesi et al, 2004; Dai et al, 2004), nerve growth factor (NGF) (Shu and Mendell, 1999; Donnerer et al, 2005; Stein et al, 2006), glial cell derived neurotrophic factor (Amaya et al, 2004), and insulin/insulin like growth factor 1 (IGF-I) (Sathianathan et al, 2003; Van Buren et al, 2005).

Activation of Protein kinase C (PKC) by phorbol ester was found to depolarize sensory neurons (Dray et al, 1988; Dray et al, 1992). Phorbol ester potentiated TRPV1 responses in oocytes 5-15 fold (Premkumar and Ahern, 2000; Premkumar et al, 2004). PKC activation also profoundly sensitized heat-mediated responses in sensory neurons, which could be mimicked by BK and attenuated by PKC inhibitors (Cesare and McNaughton, 1996; Premkumar and Ahern, 2000; Premkumar et al, 2004). Mutations of S502 and S800 almost completely abolished PKC induced TRPV1 potentiation (Numazaki et al, 2002). Phosphorylation not only sensitizes TRPV1, but also promotes its translocation from cytosol to plasma membrane (Morenilla-Palao et al, 2004; Van Buren et al, 2005). PKC plays a pivotal role in pathological somatic pain. PKC ϵ gene disruption in mice dramatically reduced thermal and inflammatory pain (Khasar et al, 1999). In mice lacking PKC γ , acute pain was preserved, but neuropathic pain was reduced (Malmberg et al, 1997).

During inflammation prostaglandins (PGs) are released and increase intracellular cyclic adenosine monophosphate (cAMP) in sensory neurons (Hingtgen et al, 1995). This effect can be mimicked by membrane permeable cAMP analogs (Cui and Nicol, 1995). Nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates decrease cAMP levels. There is substantial evidence that cAMP and Protein kinase A (PKA) sensitize TRP channels, indicating that analgesics may work through reducing TRP channel sensitization. NSAIDs relieve pain by blocking cyclooxygenases and reducing the production of PGs. PGE₂ and forskolin enhance capsaicin-evoked currents (Lopshire and Nicol, 1997; Lopshire and Nicol, 1998). TRPV1 channel mutations at S116, T370, T144, S502 reversed forskolin-induced potentiation (Bhave et al, 2002; Rathee et al, 2002; Mohapatra and Nau, 2003; Mohapatra et al, 2003). There is also a link between cAMP and PKC. cAMP has been shown to activate PKC ϵ in a PKA-independent mechanism via Epac, a cAMP-activated guanine exchange factor (Hucho et al, 2005).

In addition to PKC and PKA, other kinases also modulate TRP channels. Ca²⁺-dependent kinases may mediate desensitization and tachyphylaxis (Docherty et al, 1996; Mohapatra and Nau, 2003; Mohapatra et al, 2003). Ca²⁺-calmodulin dependent protein kinase (CAMK) has been shown to modulate TRPV1 function and capsaicin binding (Jung et al, 2004; Rosenbaum et al, 2004). It has also been shown that direct binding of calmodulin and phosphatidylinositol 4-5, biphosphate (PIP2) to TRPV1 regulates the channel (Prescott and Julius, 2003; Rosenbaum et al, 2004). An increase in extracellular cationic strength potentiates TRPV1 and regulates the physiological function by inducing thermal hyperalgesia and mechanical allodynia (Ahern et al, 2005).

TRPV1 knockout mice are able to sense normal temperature with some deficiency, but lack thermal hypersensitivity following inflammation (Caterina et al, 2000; Davis et al, 2000). Results from knockout mice studies reveal several non-sensory functions of TRPV1. TRPV1 knockout mice showed reduced anxiety-related behavior and exhibited deficits in developing long-term potentiation (Marsch et al, 2007). TRPV1 has been shown to be involved in a form of synaptic depression in the hippocampus and nucleus accumbens, which was absent in knockout animals (Gibson et al, 2008; Grueter et al, 2010). TRPV1-expressing pancreatic sensory neurons control islet inflammation and insulin resistance in diabetes (Gram et al, 2005; Razavi et al, 2006; Gram et al, 2007).

There are several conditions in which TRPV1 is tonically activated and can manifest as different modalities of pain. In inflammatory conditions, the activation temperature threshold is reduced causing the channel to be active at normal body temperatures. The pain conditions that can be associated with TRPV1 activation are acute thermal pain, inflammatory thermal hypersensitivity, trigeminal neuralgia, post-herpetic neuralgia, diabetic peripheral neuropathy, constriction type nerve injury, cancer pain, cardiac pain, pain arising from GI diseases, lung diseases, vulvodynia, cluster headache and migraine (Cortright and Szallasi, 2004; Szallasi and Appendino, 2004; Hicks, 2006; Szallasi, 2006, 2007; Premkumar and Sikand, 2008; Premkumar and Bishnoi, 2011). It is not clear whether TRPV1 antagonists will be useful in neuropathic pain conditions, where there is a lack of a peripheral component.

TRPV1 is considered as a target for next generation analgesics. Several clinically useful TRPV1 antagonists have been synthesized and evaluated. SB-366791 (GlaxoSmithKline) and (N-(4-tertiarybutylphenyl)-4-(3-cholorphyrudin-2-yl) tetrahydropyrazine-1(2H)-carboxamide (BCTC) blocked both capsaicin and acid-mediated TRPV1 responses (Urban and Dray, 1991; Rigoni et al, 2003; Valenzano et al, 2003; Lappin et al, 2006). A series of compounds from Amgen showed great promise to treat certain modalities of pain (El Kouhen et al, 2005; Cui et al, 2006; Lehto et al, 2008; Garami et al, 2010). But in human subjects, in phase I clinical trials, TRPV1 antagonist (AMG517), caused hyperthermia, which is a major adverse effect and some of the pharmaceutical industries have abandoned their efforts to pursue TRPV1 as a target for pain conditions (Gavva et al, 2008). Currently, SB-705498 (GlaxoSmithKline) a TRPV1 antagonist is in phase II clinical trials for treatment of chronic cough, allergic rhinitis and non-allergic rhinitis (Szallasi et al, 2007; Wong and Gavva 2009; <http://www.clinicaltrials.gov>). ABT-102 (Abbot), a TRPV1 antagonist is in Phase I clinical trials in three different doses and formulations (Othman et al, 2012). Other TRPV1 antagonists have been synthesized and evaluated which include NDG-8243/MK-2295 (Neurogen/Merck), GRC-6211 (Glenmark/Eli Lilly) JNJ 17203212 (Johnson and Johnson) and JYL1421 (Pacific corp.) (Szallasi et al, 2007). In animal models and phase I clinical trials, TRPV1 antagonists were effective in alleviating inflammatory thermal hypersensitivity and proven to be effective in several other pain conditions (Szallasi et al, 2007; Gavva et al, 2008).

Although it is counterintuitive, TRPV1 agonists have been successfully used to treat certain modalities of pain. The basis for their usefulness comes from their ability to cause desensitization of the channel at higher concentrations and/or induce depolarization block that can prevent the initiation of an action potential by maintaining the Na⁺ channels in their inactivated state at lower concentrations. However, continued exposure to a lower concentration of agonists can cause nerve terminal ablation (Jeffry et al, 2009; Bishnoi et al, 2011). This may be the reason for the delayed onset of effect following topical application of capsaicin containing ointments. An ultrapotent TRPV1 agonist, RTX has shown promise in alleviating pain following intrathecal administration (Brown et al, 2005; Jeffry et al, 2009). Since TRPV1 is expressed both in the peripheral and central terminals, targeting central terminals has shown promise of relieving inflammatory thermal hypersensitivity without affecting acute pain (Jeffry et al, 2009; Bishnoi et al, 2011). Further, the DRG neuronal cell bodies and the peripheral nerve terminals are intact following intrathecal administration of RTX that can maintain peripheral functions of TRPV1 such as release of CGRP that can maintain microvascular circulation. A clinical trial is underway to determine the role of RTX to treat chronic debilitating pain condition arising from malignancies of internal organs and bone (NCT00804154). Adlea, an ultrapure capsaicin (liquid form) developed by Anesiva successfully passed the phase III clinical trials, and a promising candidate for treatment of neuropathic pain (<http://www.medicalnewstoday.com>). Qutenza (NeurogesX) is a rapid delivery patch application, which showed success in the phase III clinical trial. Qutenza contains 8% synthetic form of trans capsaicin, which is indicated for the management of neuropathic pain (Wong and Gavva 2009). NeurogesX is also developing capsaicin liquid formulation NGX-1998, which is currently in the Phase I clinical trial (<http://www.neurogesx.com>).

Transient Receptor Potential Vanilloid 2 (TRPV2)

Following cloning of TRPV1, a vanilloid receptor like protein (VRL-1) was cloned and later renamed as TRPV2. TRPV2 has 50% sequence homology to TRPV1 and mediates noxious heat sensation (Caterina et al, 1999; Montell et al, 2002). It has been shown to be activated by temperature ($>52^{\circ}\text{C}$), osmotic stimuli and mechanical stretch (Caterina et al, 1999; Iwata et al, 2003; Muraki et al, 2003). There are no known specific endogenous or exogenous agonists for TRPV2. It is activated by a nonspecific TRP channel agonist such as 2-APB. The likely involvement of TRPV2 in sensory modalities is apparent as shown with TRPV1; they are abundantly expressed in A δ and A β fibers of DRG, TG, and NG. The expression of TRPV2 in neurons innervating the larynx, bladder and intestine suggests its role in sensory functions of the internal organs (Schroder, 1984; McKenna and Nadelhaft, 1986; Ichikawa and Sugimoto, 2002; Kashiba et al, 2004; Okano et al, 2006). Enhanced expression of TRPV2 was found in sympathetic ganglia following peripheral axotomy suggesting a role in sympathetic reflex pain (Gaudet et al, 2004). As compared to TRPV1, the expression of which is restricted to nerve terminals in laminae I and laminae II, TRPV2 is expressed throughout the spinal cord, including laminae III and IV suggesting a role other than nociception (Caterina et al, 1999; Ahluwalia et al, 2002; Ichikawa and Sugimoto, 2002; Lewinter et al, 2004; Zhang et al, 2004). In the spinal cord, TRPV2 expression in tyrosine kinase C (TrkC) and neurotrophin 3 (NT3) receptor expressing neurons suggests its role in NT3 receptor-mediated thermal and mechanical hypersensitivity (Malcangio et al, 1997; Shu et al, 1999). TRPV2 expression is also seen in ependymal cells lining the central canal that may play a role in circulation of cerebrospinal fluid (Lewinter et al, 2004).

As shown with TRPV1, TRPV2 has been found in several areas of the CNS such as supraoptic, suprachiasmatic and paraventricular nuclei and cerebral cortex (Liapi and Wood, 2005) and may be involved in CNS functions (Wainwright et al, 2004). The methodologies used to determine the expression have to be cautiously evaluated because although TRPV1 expression was considered to be throughout the neuroaxis, recent experiments using genetic reporter mice have shown highly restricted expression (Cavanaugh et al, 2011; Mishra et al, 2011).

TRPV2 has been shown to translocate from intracellular pools upon IGF-I stimulation in transfected cells (Kanzaki et al, 1999). It is also regulated by CAMK (Boels et al, 2001), phosphatidylinositol 3-kinase (PI3-K) and A-kinase anchor proteins (AKAP)/cAMP/PKA-mediated phosphorylation (Stokes et al, 2004). Heteromerization of TRPV1 and TRPV2 has been demonstrated in the CNS (Rutter et al, 2005). Although TRPV2 is expressed in nociceptors and involved in sensory transduction, targeting TRPV2 for developing analgesics has not been a priority. The attention and the enthusiasm to study the channel properties have been hampered by lack of specific agonists and antagonists.

Transient Receptor Potential Vanilloid 3 (TRPV3)

TRPV3, a channel that has high sequence homology and located in the same chromosome as TRPV1 was identified using expressed sequence tags (EST) clones by three different groups simultaneously (Peier et al, 2002b; Smith et al, 2002; Xu H et al, 2002). TRPV3 was

initially shown to be expressed only in keratinocytes, but later studies have shown its expression in sensory neurons (Facer et al, 2007; Frederick et al, 2007). TRPV3 is found in DRG, TG and NG neurons, keratinocytes and certain regions of the brain that may play a role in thermoregulation (Moqrich et al, 2005). The channel is activated by camphor (Sherkheli et al, 2009), menthol (Sherkheli et al, 2009), carvacrol (Xu H et al, 2006), eugenol (Xu H et al, 2006), insensol (Moussaieff et al, 2008) or temperature (between 30-35°C) (Smith et al, 2002). A non-selective TRP channel agonist 2-APB also activates TRPV3. Application of camphor on the skin induces a sense of warmth by activating TRPV3 (Sherkheli et al, 2009). Since TRPV1 and TRPV3 are co-expressed in the same neuron, it has been suggested that they can form heterooligomers (Smith et al, 2002). Studies have proposed that TRPV1 and TRPV3 receptors can act as a potential therapeutic target for the treatment of pain and inflammation (Steenland et al, 2006; Szallasi, 2006). TRPV3 is expressed in nasal mucosa and tongue, which may be responsible for sensing the active ingredients of oregano (carvacrol) and clove (eugenol) (Xu H et al, 2006).

TRPV3 knockout animals have more clearly revealed its role in nociception (Moqrich et al, 2005). Keratinocytes obtained from TRPV3 overexpressing mice can release PGE2 and NGF in response to activation of TRPV3 (Huang et al, 2008). Subsequently, PGE2 can sensitize other TRP channels expressed in the nerve terminals including TRPV1.

Although activated by several plant derived compounds, there are no known endogenous activators of TRPV3 that may play a role in normal and/or disease conditions. It is indirectly activated by substances that are produced during inflammation such as AA and by substances that phosphorylate and modulate TRPV3 such as prostaglandins (Mandadi et al, 2009). In several skin conditions, AA levels are increased (Hammarstrom et al, 1975; Brash, 2001). A possible role of PIP2 in modulating TRPV3 channel has been suggested by agonists that activate phospholipase C (PLC) (Xu H et al, 2006). It is possible that subsequent to activation of PLC, IP3-mediated Ca^{2+} release can have a modulatory role, because both extracellular and intracellular Ca^{2+} inhibits TRPV3 (Xiao et al, 2008).

Although it is implicated in pain transmission, the role of its predominant expression in keratinocyte is far from clear. The free nerve endings of sensory neurons that carry nociceptive information are tightly surrounded by keratinocytes; there is a possibility that substances released from keratinocytes can excite sensory nerve terminals. One such molecule that has been shown to play a role is ATP. The absence of ATP release from keratinocytes in TRPV3 knockout animals suggests a role of TRPV3 in releasing ATP (Mandadi et al, 2009). ATP can act on a variety of targets including P2X and P2Y receptors and activation of TRPV1 by binding the Walker domain (Kwak et al, 2000).

In several pain conditions TRPV3 expression levels have been altered such as chronic constriction injury (Frederick et al, 2007). In breast cancer pain following mastectomy, TRPV3 expression is enhanced (Gopinath et al, 2005). It is not clear whether the role of TRPV3 in nociception is direct or indirect by modulating other TRP channels following TRPV3-mediated release of PG, AA and ATP. Increased TRPV3 expression in avulsed DRG (Smith et al, 2002) and after nerve injury has been shown (Facer et al, 2007).

TRPV3 antagonists are being developed. Hydra Biosciences has developed TRPV3 antagonists that showed effectiveness in formalin-, thermal-, inflammation-induced hypersensitivity (Chong et al, 2006, 2007). Glenmark Pharmaceuticals has developed TRPV3 antagonists with the potential of pain relief in animal models (Gullapalli, 2008). One of the Glenmark compounds (GRC 15300) is in Phase I Clinical Trials. Given the expression in keratinocytes, blockade of TRPV3 is expected to induce undesirable effects. TRPV3 over expressing animal exhibited a 'hair-less' phenotype (Asakawa et al, 2006; Imura et al, 2007). The lesson learnt from human studies that TRPV1 antagonism can cause hyperthermia, cautions that the blockade of TRPV3 leading to hyperthermia has to be considered as a potential adverse effect (Huang et al, 2008).

Transient receptor potential vanilloid 4 (TRPV4)

Transient receptor potential vanilloid 4 (TRPV4) is a putative mechano/osmosensitive channel expressed in many cell types including sensory neurons. It is a homologue of the *C. elegans* osmosensory channel, OSM-9 that is expressed in sensory neurons, hypothalamus, vascular smooth muscle cells, kidney, trachea, cochlear hair cells, endothelial cells, and keratinocytes (Strotmann et al, 2000; Watanabe et al, 2002b; Nilius et al, 2003a; Suzuki et al, 2003; Cohen, 2005). TRPV4 is sensitive to cell swelling and shear stress, thus functioning as a putative mechanosensor (Gao et al, 2003; Nilius et al, 2003a,b; Alessandri-Haber et al, 2005; O'Neil and Heller, 2005; Alessandri-Haber et al, 2006; Kohler et al, 2006; Loukin et al, 2010). TRPV4 is activated by hypotonicity, heat (>27°C), diacylglycerol (DAG), PKC activating (phorbol 12-myristate 13-acetate, PMA) and nonactivating phorbol esters (4 α -phorbol 12,13-didecanoate, 4 α -PDD), and 5',6'-epoxyeicosatrienoic acid (5',6'-EET) derived from anandamide and AA (Watanabe et al., 2002a,b; Watanabe et al, 2003), and is involved in nociception (Alessandri-Haber et al, 2005; Alessandri-Haber et al, 2006). In general, direct mechanosensitivity occurs during punctate mechanical stimulation and the receptors tend to desensitize readily to this type of stimulus (Drew et al, 2004). In contrast, vasodilation and swelling exert a sustained mechanical stimulation, which may be mediated through generation of second messengers (Nilius et al, 2003a, b). Recently, it has been shown that TRPV4 can be activated by hypotonic solution in a system, independent of poly unsaturated fatty acids (PUFAs) (Loukin et al, 2009) and by mechanical force in excised membrane patches (Cao et al, 2009; Loukin et al, 2009).

Vascular endothelial cells (Watanabe et al, 2002a), renal collecting duct cells (Strotmann et al, 2000) and vascular smooth muscle cells (Jia et al, 2004; Yang et al, 2006) expressing TRPV4 are particularly susceptible to cell swelling-induced Ca²⁺ influx. Cell swelling also activates phospholipase A2 (PLA2) and produces AA. AA and its cytochrome P450 metabolite 5',6'-EET activates TRPV4. Further, evidence for the involvement of this pathway is shown by the ability of PLA2 blockers to inhibit hypotonicity-induced Ca²⁺ influx and TRPV4 channel current (Watanabe et al, 2003). It is likely that TRPV4 is sensitive to membrane stress both directly as well as indirectly through the generation of intracellular second messengers. It has been shown that TRPV4 is physically associated with several Src kinases and can be activated by cell swelling (Xu F et al, 2003; Xu H et al, 2003).

In TRPV4 knockout mice, the sensitivity of the tail to pressure and acidic nociception is reduced as compared to wild type mice (Suzuki et al, 2003). It was surprising that there was no change in von Frey hair test between TRPV4 knockout and wild type mice (Suzuki et al, 2003). However, TRPV4 is necessary for the normal response to changes in osmotic pressure and functions as an osmosensor (Liedtke and Friedman, 2003). Ca^{2+} influx through endothelial TRPV4 channels may contribute significantly to vasodilation. Lack of TRPV4-mediated shear stress-induced vasodilation in TRPV4 knockout mice shows the importance of TRPV4 (Hartmannsgruber et al, 2007). Studies have shown that TRPV4 is also involved in hearing (Tabuchi et al, 2005). Presently, selective TRPV4 antagonists have not been developed, which delays the advancement in this field.

Transient Receptor Potential Ankyrin 1 (TRPA1)

TRPA1 is a non-selective, Ca^{2+} permeable cation channel which was cloned in 2003 and was initially named as ANKTM1 (Story et al, 2003). A similar channel with identical sequence homology had been already isolated from human lung fibroblasts (Jaquemar et al, 1999). It is unique in its structure among TRP channel for having a large number (17) of ankyrin repeat domains, which imparts a spring-like action to proteins, therefore a potential channel that could be activated by mechanical force (Sotomayor et al, 2005). It is activated by allyl isothiocyanate (AITC, in mustard, horseradish and wasabi), allicin, diallyldisulfide (in garlic extract), cinnamaldehyde (in cinnamon oil), acrolein (in tear gas, car exhaust and a metabolite of certain chemotherapeutic agents such as cyclophosphamide and ifosfamide) and N-methyl maleimide (NMM, an oxidizing agent) through modification of cysteine residues. It is also activated by tetrahydrocannabinoid (THC), WIN 55,212-2 (WIN) and BK (Fleming et al, 1997; Nicol, 2002; Peier et al, 2002a; Story et al, 2003; Bandell et al, 2004; Corey et al, 2004; Jordt et al, 2004; Bautista et al, 2005; Macpherson et al, 2005; Nagata et al, 2005; Hinman et al, 2006). TRPA1 is also activated by endogenous chemicals produced during oxidative stress including H_2O_2 /hydroxyl radicals, aldehydes, such as 4-hydroxynonenal (4-HNE), cyclopentenone prostaglandins such as 15d-PGJ2 and hypochlorite (Andersson et al, 2008; Bessac et al, 2008). The activation mechanism of TRPA1 has been shown to be by covalent modification of cysteine residues, yet the responses are readily reversible during washout in electrophysiological experiments (Hinman et al, 2006; Raisinghani et al, 2011).

Finally, physical stimuli like noxious cold ($<18^\circ\text{C}$) temperatures and mechanical force are proposed to activate the TRPA1 channel (Peier et al, 2002b; Story et al, 2003). TRPA1 has been suggested to be a sensor for mechanical stimuli because its *Drosophila* homolog, *painless* is involved in mechanical nociception and belongs to the TRP channel family (Tracey et al, 2003; Corey et al, 2004).

TRPA1 is expressed in lung fibroblasts and hair cells of the inner ear (Corey et al, 2004; Nagata et al, 2005). Neuronal expression of TRPA1 has been shown in DRG (Story et al, 2003) in superior cervical ganglion (Smith et al, 2004) and geniculate ganglion (Katsura et al, 2006). Most of the TRPA1 expressing C and A δ nociceptors also express TRPV1, raising the issue of functional specificity. TRPA1 is expressed in GI tract, urinary bladder, heart, brain and immune cells (Andrade et al, 2006).

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Involvement of TRPA1 in cold allodynia and mechanical hyperalgesia has been shown using behavioral models (Bandell et al, 2004; Allchorne et al, 2005; Obata et al, 2005; Katsura et al, 2006; Bautista et al, 2007). Behavioral studies in mice lacking TRPA1 (TRPA1^{-/-}) have confirmed its role in nociception to pungent substances (Bautista et al, 2006; Kwan et al, 2006). The role of TRPA1 in noxious cold and mechanical sensation is still controversial. Treatment with TRPA1 antisense oligodeoxynucleotides reduced behavioral hypersensitivity to cold after Complete Freund's Adjuvant (CFA)-induced inflammation or sciatic nerve injury and decreased cold hyperalgesia following L5 spinal nerve ligation (Obata et al, 2005; Katsura et al, 2006). TRPA1 knockout mice exhibited impaired behavioral responses to a cold plate maintained at 0 °C. However, Bautista, et al (2006), and Nagata, et al (2005) failed to demonstrate this effect. Further, Kwan et al (2006) reported that TRPA1^{-/-} mice showed a deficiency in sensing noxious punctate cutaneous mechanical stimuli; these mice had higher mechanical thresholds and reduced response to a series of suprathreshold stimuli when compared to wild-type mice, suggesting a potential role in the transduction of high-threshold mechanical stimuli. On the other hand, Bautista et al (2006) reported no difference in mechanical thresholds between TRPA1 knockout and wild-type mice. It has been shown using pharmacological blockade and TRPA1 knockout animals that low threshold Aδ and D-hair mechanoreceptive fiber have altered characteristics (Kerstein et al, 2009; Kwan et al, 2009). Further, mice with ablation of channels that are linked to TRPV1 lineage, which include TRPA1, exhibited a complete loss of thermal sensitivity but the mechanical sensitivity was intact (Mishra et al, 2011). These results suggest the complexity of receptors involved and the assessment of mechanosensitivity.

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The modulation of TRPA1 by phosphorylation may depend on its activation mode. Since it is proposed to be activated by covalent modification, the receptor sensitivity may not be enhanced and the agonist binding affinity may not be altered (Raisinghani et al, 2011). However, if phosphorylation facilitates receptor translocation from cytosol to plasma membrane and/or enhances its expression, a change in receptor density can be observed. For this reason, PKC- and PKA-mediated phosphorylation had no effect on the TRPA1-mediated currents (Raisinghani et al, 2011). But, Wang et al (2008) (Wang et al, 2008) have shown a potentiation following PKA-activation, may be as a result of receptor translocation. BK has been shown to activate/modulate TRPA1 currents possibly as a result of BK2 receptor activation, which is coupled to PLC (Bandell et al, 2004; Jordt et al, 2004). Glial-derived neurotrophic factor has been shown to increase TRPA1 expression (Elitt et al, 2006). NGF-induced MAPK activation plays a role in the potentiation of TRPA1 (Obata et al, 2005; Mizushima et al, 2006). Extracellular-regulated protein kinase (ERK) and PIP2 metabolism by PLC activation have been shown to modulate TRPA1 to alter thermal hypersensitivity (Dai et al, 2007; Katsura et al, 2007; Mizushima et al, 2007). Opioid receptor activation antagonizes icilin-induced wet-dog shaking behavior that may be mediated via TRPA1 and/or TRPM8 (Werkheiser et al, 2007). In certain conditions, TRPA1 may be ubiquitinated that may play a role in cancer (Stokes et al, 2006).

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The challenge is to delineate the functional neuronal effects that are distinct from that of TRPV1, since most neurons express TRPA1 also express TRPV1. Identification of TRPA1 antagonists would be the choice as an analgesic. The activation mechanism and the sensitization and desensitization characteristics are different from those of TRPV1, therefore

use of agonists of TRPA1 to treat painful conditions has not been explored. Hydra Biosciences and Glenmark Pharmaceuticals have developed TRPA1 antagonists, which have entered clinical trials (Moran et al, 2011). From these developments, it is inferred that hyperthermia may not be a serious issue with TRPA1 antagonists as compared to TRPV1 antagonists.

Transient Receptor Potential Melastatin 8, 2 and 3

After cloning of heat sensitive channels TRPV1 and TRPV2, the cloning of cold sensitive channels was undertaken. Its sensory role was recognized when it was isolated by expression cloning by Julius and colleagues from trigeminal neuronal cDNA library (McKemy et al, 2002). At the same time Potaputian and colleagues cloned TRPM8 by sequence homology from genomic data base while looking for TRP like proteins (Peier et al, 2002a). It was revealed that TRPM8 had sequence homology to an already identified TRP-like channel that was found in prostate cancer cells (Tsavaler et al, 2001). When expressed in heterologous expression systems, TRPM8 could be activated by cold temperatures ($<15^{\circ}\text{C}$) and 'cooling' compounds such as menthol and icilin (Chuang et al, 2004; Andersson et al, 2008). TRPM8 is activated by peppermint oil, cornmint oil, eucalyptus oil etc (McKemy et al, 2002; Peier et al, 2002a).

TRPM8 is expressed in a subset of C and A δ nociceptors in DRG, TG and NG. TRPM8 is expressed in peripheral terminals that sense sensory information; it is also expressed in the central terminals of the sensory neurons and modulates synaptic transmission (Tsuzuki et al, 2004; Premkumar et al, 2005).

TRPM8 knockout animals exhibit lack of cold sensitivity ($10-25^{\circ}\text{C}$) and reduced pain sensitivity. However, low temperature ($<5^{\circ}\text{C}$) induced cold pain was intact in these animals (Bautista et al, 2007; Colburn et al, 2007; Dhaka et al, 2007). There are other channels that may underlie cold sensitivity, which include TRPA1, two pore potassium channels, and a sodium channel that does not inactivate at cold temperatures (Reid and Flonta, 2001; Viana et al, 2002; Munns et al, 2007; Zimmermann et al, 2007).

Modulation of TRPV1 by PKC and PKA has been studied extensively (Premkumar and Bishnoi, 2011). Activation of PKC potentiates and prolongs TRPV1-mediated responses as compared to activation of PKA, which potentiates the response transiently and reverses tachyphylaxis (Mohapatra and Nau, 2003). However, stimulation of PKC results in downregulation of TRPM8 function (Premkumar et al, 2005; Abe et al, 2006). From these studies it is clear that PKC reciprocally modulates TRPV1 and TRPM8, in that stimulation of which upregulates TRPV1, but downregulates TRPM8. The importance of differential modulation of TRPV1 and TRPM8 and its broader implication in pain perception has to be elucidated.

As shown with TRPV1, TRPM8 is modulated by PIP2, but in an opposite manner. Depletion of PIP2 by activation of PLC decreased TRPM8 channel activity (Liu and Qin, 2005; Rohacs et al, 2005; Benedikt et al, 2007), whereas PIP2 depletion relieved its block of TRPV1 and enhanced channel activity (Chuang et al, 2001). Identification of endogenous

ligands for TRPM8 has been a challenge, lysophospholipids that are produced by the activation of PLA2 has been shown to be an agonist of TRPM8 (Vanden Abeele et al, 2006).

PLC-mediated downregulation of TRPM8 by PKC-dependent and independent mechanisms and upregulation of TRPV1 is detrimental during inflammatory conditions (Premkumar et al, 2005). It is paradoxical, when needed during TRPV1-induced hypersensitivity, TRPM8 is downregulated. Intradermal capsaicin-induced nocifensive behavior was alleviated by intradermal administration of menthol suggesting in acute pain conditions menthol is still effective (Premkumar et al, 2005). Therefore, soothing sensation induced by activation of TRPM8 could be useful to alleviate hyperalgesia. Ideally, a TRPV1 and TRPA1 antagonists with TRPM8 agonistic activity would be a useful agent to treat certain modalities of pain. There are no selective antagonists for TRPM8. TRPV1 antagonist BCTC also blocks TRPM8 (Behrendt et al, 2004; Weil et al, 2005). 2-APB, an agonist of TRPV1, TRPV2 and TRPV3 has been shown to block TRPM8 (Hu et al, 2004). Some of the agonists of TRPA1 such as URB597 blocks TRPM8, while menthol agonist of TRPM8 blocks TRPA1 (Macpherson et al, 2006; Niforatos et al, 2007).

TRP Melastatin 2 (TRPM2) is a Ca^{2+} permeable nonselective cation channel, which is expressed in several tissues particularly in immune cells, glial cells and DRG neurons (Nagamine et al, 1998; Sano et al, 2001; McHugh et al, 2003; Grimm et al, 2005; Kaneko et al, 2006). TRPM2 is considered as a sensor of reactive oxygen species and activated by adenosine diphosphate ribose (ADPR) (Nagamine et al, 1998). The contribution of TRPM2 to inflammatory and neuropathic pain has been revealed by TRPM2 knockout mice (Haraguchi et al, 2012). TRPM2 knockout animals exhibited reduced nocifensive behavior to intraplantar formalin administration. Mechanical allodynia and thermal hyperalgesia were reduced in carrageenan-induced inflammatory model and sciatic nerve injury-induced neuropathic pain (Haraguchi et al, 2012).

TRP Melastatin 3 (TRPM3) is a cationic channel that has high Ca^{2+} permeability is expressed widely in a variety of tissues (Lee et al, 2003). TRPM3 has been found to be expressed in pancreatic beta cells and has been shown to be involved in insulin release, when activated by pregnenolone sulfate and nifedipine (Wagner et al, 2008). It is expressed in small-diameter DRG and TG neurons. TRPM3 knockout animals are devoid of noxious heat sensation and do not develop inflammatory thermal hypersensitivity to administration of CFA (Vriens et al, 2011). A non-steroidal anti-inflammatory agent mefenamic acid is able to block TRPV3-mediated Ca^{2+} entry as well as insulin release (Klose et al, 2011).

Transient receptor potential canonical (TRPC)

TRPC1 was the first mammalian homolog of drosophila TRP channels to be identified (Wes et al, 1995). Since then, seven mammalian transient receptor potential canonical channels (TRPC1–7) have been cloned and characterized. TRPC proteins in mammals are associated with G-protein coupled receptors and receptor tyrosine kinases (Montel, 1999). These channels are divided into three subgroups according to sequence homology: C1/C4/C5, C3/C6/C7, and C2.

Previous studies have shown that TRPC1, TRPC5 and TRPC6 are expressed in DRG and TG. Antisense oligodeoxynucleotide treatment revealed that both TRPC1 and TRPC6 are involved in inflammation induced hyperalgesia to thermal/mechanical/hypotonic stimuli (Alessandri-Haber et al, 2009). GsMTx-4, a peptide obtained from tarantula spider venom suppresses mechanical pain by blocking TRPC1 and TRPC6 channels (Alessandri-Haber et al, 2009). Similarly, studies have shown that TRPC5 is activated by hypo-osmotic stimulus, which is dependent on PIP2 (Gomis et al, 2008). SKF-96365, a non-specific TRPC antagonist has been shown to suppress inflammatory pain induced by melittin, a component of bee venom (Ding et al, 2011), suggesting that TRPC channels also mediate inflammatory pain response. These studies suggest that TRPC1, TRPC5 and TRPC6 can be attractive targets for treating both mechanical and inflammatory pain. Hydra Biosciences has been developing drugs targeting TRPC5 along with TRPA1, TRPV3 and TRPV4 antagonists (<http://www.hydrabiosciences.com>). GsMTx-4 peptide can also be further developed in treating mechanical and inflammatory pain.

Concluding remarks

The promise of adding nociceptive TRP channel antagonists into the therapeutic armamentarium as next generation analgesics has encountered a road block by TRPV1 antagonists-induced hyperthermia. Hopefully, antagonists that are devoid of this adverse effect could be identified, unless TRPV1-mediated regulation of body temperature is an inherent mechanism that is required for the maintenance of body temperature. Further, TRPV1 expressing peripheral and central nerve terminals release vasoactive peptides, one such peptide, CGRP is a potent vasodilator. Blocking TRPV1 may interfere with the process of CGRP release and impact the microvascular circulation leading to untoward effects such as worsening of coronary artery and peripheral vascular disease have not been considered seriously. TRPA1 antagonists are being pursued as analgesics. Since, all the TRPA1 expressing neurons are also expressing TRPV1; inhibiting TRPA1 may also manifest the same untoward effects associated with TRPV1 antagonists. However, TRPA1 antagonists do not appear to cause hyperthermia and have entered clinical trials. TRPV3 is predominately expressed in keratinocytes, but their involvement in pain signaling is far from clear. TRPV3 antagonists are under consideration for pain relief. TRPV4 has been shown to be involved in mechanosensitivity, however, the lack of specific TRPV4 antagonists has been an impediment for progress. TRPM8 agonists can induce cool soothing sensation; however, its downregulation in phosphorylated state is not beneficial during inflammation-induced hyperalgesia. More recently, TRPC1, 5, 6, TRPM2 and TRPM3 have been shown to be involved in pain transduction. Therefore, instead of focusing efforts to develop selective antagonists for one type of TRP channel, the possibility of developing nonselective antagonist has to be considered seriously. This is a pragmatic approach, since all the nociceptive TRP channels described here have been shown to play some role in painful conditions.

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