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Changes in TRP Channels Expression in Painful Conditions

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Abstract: Over the last fifteen years after the successful cloning of the first nociceptive Transient Receptor Potential (TRP) channel, TRP Vanilloid 1, other members of the TRP channel family have been cloned, characterized and implicated in different modalities of pain. Tremendous progress has been made with regard to the specific role of these TRP channels in nociception using electrophysiological and molecular methods, along with behavioral models combined with gene disruption techniques. This review summarizes the evidence supporting the role of TRP channels (TRP Vanilloid 1, TRP Vanilloid 2, TRP Vanilloid 3, TRP Vanilloid 4, TRP Ankyrin 1, TRP Melastatin 2, TRP Melastatin 3, TRP Melastatin 8, TRP Mucolipin 3 and TRP Canonical 1, 6) involved in nociception. The review also highlights the current status and future avenues for developing TRP channel modulators as analgesic agents.

Keyword: Analgesia, Inflammation, nociception, pain, TRP channels.

INTRODUCTION

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is a major symptom in many medical conditions and is the most common reason for consultation with physicians in the United States. It can significantly interfere with day to day activities and affect the quality of life.

Based on the duration, pain can be classified as acute or chronic. Acute pain has a short duration, identifiable pathology, and the pain is alleviated with over the counter analgesics. Whereas, chronic pain has an unpredictable prognosis, unclear pathology, and requires polypharmacy approach; some of which are prescription medications. Pathophysiological classification of pain include: acute/nociceptive, inflammatory and chronic/neuropathic. Acute/nociceptive pain is detected and transmitted by nociceptors and is resolved within seconds or minutes; inflammatory pain is associated with inflammation and persists as long as the inflammation lasts; chronic/neuropathic pain may or may not have a peripheral component and persists for months to years, even after the initial injury has healed.

Nociceptors are of two types: 1) small diameter cell bodies with unmyelinated C fibers; 2) medium diameter cell bodies with thinly myelinated A-δ fibers. The management of chronic pain is a major unmet medical need in our society because of inadequate responsiveness to currently available pain therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anti-epileptics and tricyclic antidepressants. Chronic pain is associated with certain diseases and the occurrence of which is steadily increasing (e.g., arthritis, diabetes, viral infections, cancer and AIDS). There has been growing interest in pursuing novel pharmacological approaches targeting newly identified receptors that include the family of ion channels called Transient Receptor Potential (TRP) channels. Here we will describe the expression and function of nociceptive TRP channels that may be targets for next generation analgesics.

TRANSIENT RECEPTOR POTENTIAL CHANNELS

To date, more than 30 mammalian Transient Receptor Potential (TRP) channels have been cloned and characterized. They are grouped into six subfamilies on the basis of their amino acid sequence homology: TRPC ("canonical"), TRPM ("melastatin"), TRPV ("vanilloid"), TRPA ("ankyrin"), TRPML ("mucolipin"), and TRPP (or PKD) ("polycystin"). Most of TRP channels are non-selective cation channels expressed at the plasma membrane with a high permeability to Ca^{2+}. They are responsible for several physiological and pathophysiological functions, ranging from sensory functions (such as vision, nociception, taste transduction, temperature sensation and pheromone signaling) to homeostatic functions (such as Ca^{2+} and Mg^{2+} flux and osmoregulation). TRP channels are associated with several pathophysiological conditions involving the disciplines of neurology, dermatology, pulmonology, cardiology, urology, oncology and heritable diseases. The role of TRP channels in pain is reasonably well understood. TRPV1, TRPV3 and TRPA1 channel antagonists have already advanced to clinical trials, whereas other TRP channel antagonists are in preclinical development. Ever increasing number of animal models and gene-disrupted animals has unraveled the role of other TRP channels

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(TRPV2, TRPV4, TRPM2, TRPM3, TRPM8, TRPML3 and TRPC) in painful conditions. In the following sections we will summarize the expression and function of different TRP channels involved in nociception.

TRANSIENT RECEPTOR POTENTIAL VANILLOID 1 (TRPV1)

TRPV1, a nonselective cation channel that has high permeability to Ca^{2+} ions was cloned and characterized by David Julius and colleagues in 1997 [1]. TRPV1 consists of a long intracellular N-terminus with three ankyrin-repeat domains and the intracellular C-terminus that consists of a TRP domain. Given the co-expression of other TRP channels in the same nociceptor, the possibility of forming heteromultimers with TRPV2 or TRPV3 has been suggested [2-4].

TRPV1, a polymodal receptor is expressed at the peripheral terminals of a subset of neurons in dorsal root ganglia (DRG), trigeminal ganglia (TG), nodose ganglia (NG) and jugular ganglia (JG, superior ganglion of glossopharyngeal nerve) [5, 6]. They are also present at the central terminals where they form synapses with the second order neuron in the substantia gelatinosa (SG), cadual spinal trigeminal nucleus (CSTN) and nucleus tractus solitarius (NTS) [7-15]. They are expressed in the areas that are involved in ascending and descending pain pathway such as hypothalamus, thalamus, ventral medulla and periaqueductal gray [16]. TRPV1 has been shown to be distributed in other nonsensory regions of the brain such as raphe nucleus, locus coeruleus, hippocampus, ventral tegmental area, cerebellum, substania nigra and somatosensory cortex [17-22]. A Number of single-nucleotide polymorphisms have been described in the TRPV1 gene; the "G" allele (rs222747) has been found to increase channel activity and in human enhance cortical excitability as compared to "non-G" allele (rs222749) [23]. Recently, genetic reporter mice approach has indicated very sparse distribution of TRPV1 in the CNS [24, 25].

TRPV1 is predominantly expressed in C-and Aδ type nociceptors and has been shown to be involved in the transmission of inflammatory thermal hypersensitivity. In consensus with this idea, TRPV1 knock-out mice are able to sense pain associated with acute temperature, but inflammation-induced thermal hypersensitivity is significantly reduced [1, 26, 27]. TRPV1 expressed at the peripheral terminals of nociceptors and is activated by heat (>42^{o}C) and responsible for transmitting acute noxious thermal sensation and inflammatory thermal hypersensitivity.

Capsaicin (pungent ingredient of hot chili peppers) is a potent exogenous ligand for TRPV1 that has been extensively used in the field to characterize TRPV1 properties; this included functional cloning of TRPV1 where cells that responded to capsaicin-induced Ca^{2+} influx were isolated and propagated [1]. Resiniferatoxin (RTX), (obtained from the cactus, *Euphorbia resinifera*) is a high affinity agonist, which has been very useful to delineate the expression and functions of TRPV1 [1, 28, 29]. TRPV1 is also activated by spider and jellyfish toxin [30, 31].

TRPV1 is activated by several endogenous agonists that include protons [1], anandamide [32], Arachidonic Acid (AA) metabolites, N-arachidonyl dopamine (NADA), oleoylethanolamide (OEA), N-oleyldopaine (NODA), polyamines [33, 34] and adenosine [35]. TRPV1 is robustly potentiated by pro-inflammatory agents and trophic factors. The activation temperature threshold is reduced below the body temperature when the receptor is in the phosphorylated state [10, 36]. TRPV1 is sensitized by activin [37], adenosine triphosphate (ATP) [38-40], bradykinin (BK) [36, 41, 42], glutamate [43], histamine [44], proteinase-activated receptor-2 [45], serotonin [46], trypsin [45, 47], nerve growth factor (NGF) [48-50], glial cell derived neurotrophic factor [50], and insulin/insulin like growth factor 1 (IGF-1) [51, 52].

Both TRPV1 agonists and antagonists are capable of inducing pain relief. Antagonism of TRPV1 receptor prevents the generation of receptor potential in response to temperature and endogenous ligands. However, while using potent endogenous agonists the generation of receptor potential and subsequent action potential is prevented by either desensitization of the receptor or by depolarization block of the nerve terminal [11, 53]. Desensitization of TRPV1 receptor is dependent on the concentration of the agonist and the Ca^{2+} influx through the receptor [11, 53]. Persistent activation of TRPV1 by low concentrations of agonists can cause nerve terminal depolarization by maintaining the sodium channels in an inactivated state, thereby preventing nociceptive transmission in the short-term and enhancing Ca^{2+} influx into the nerve terminal causing nerve terminal ablation in the long-term [11]. Therefore, both peripheral and central nerve terminals at the spinal cord can be targeted to induce pain relief by TRPV1 agonists [11]. Administration of capsaicin and RTX increases the frequency of sEPSCs without altering the amplitude, suggesting a presynaptic locus of action. Capsaicin induces a desensitizing response, whereas RTX induces a sustained response [10, 11]. Interestingly, while recording evoked synaptic currents, synaptic failures were observed [11]. Intrathecal administration of RTX reduces inflammatory thermal hypersensitivity, without altering acute thermal pain sensitivity [11, 54]. Furthermore, it has been found in immunostaining studies that following intrathecal administration of RTX TRPV1 staining in the central sensory nerve terminals was completely abolished, whereas the staining of the cell bodies in the DRG and the peripheral terminals in the skin remained intact [11, 54]. Based on these findings, it is proposed that sensory efferent functions that are dependent on CGRP and substance P (SP) release from the peripheral nerve terminals would not be affected following intrathecal administration of RTX [11, 54]. To test the effectiveness of intrathecal administration of RTX in treating cancer pain, a clinical trial has been initiated (Study NCT008041; Sponsor: National Institute of Dental and Craniofacial Research (NIDCR).

Several newer TRPV1 antagonists have been synthesized and characterized. SB-366791 is a competitive inhibitor of TRPV1 that blocks all modes of TRPV1 activation (capsaicin, acid and heat) [55, 56]. Spontaneous and miniature excitatory synaptic currents recorded from the substantia gelatinosa neurons following administration of complete Freund's adjuvant (CFA)-injected animals were decreased following administration of SB-366791 [56]. SB-

782443 showed excellent potency in human, guinea pig, and rat TRPV1 and exhibited a favorable pharmacokinetics profile while testing in inflammatory pain models [57, 58]. Further research has led to the development of two other TRPV1 antagonists, SB-705498 and SB-452533.

A-425619, a competitive antagonist inhibits Ca^{2+} influx and membrane currents elicited by capsaicin, NADA, anandamide or protons. A-425619 blocks TRPV1-mediated current at lower concentrations, when the receptor is in the phosphorylated state [59]. It reduces pain associated with inflammation and tissue injury in rats [60]. A-784168 is able to penetrate the CNS significantly, but not A-795614. Both of these compounds exhibit equal efficacy when given intrathecally, however when administered orally, A-784168 shows higher efficacy [61].

Amgen has developed several potent TRPV1 antagonists (AMG517, AMG0347, AMG8163, and AMG9810) and some of them had entered phase I clinical trials [61]. Neurogen/Merck has launched NDG-8243/MK-2295 in Phase II clinical trials. Other TRPV1 antagonists that have been developed include GRC-6211 (Glenmark/Eli Lilly), ABT-102 (Abbott), JNJ-17203212 (Johnson and Johnson), SAR115740 (Sanofi Aventis), and JYL1421 (Pacific corp.) [62-64]. Recently, endogenous substances known as resolvins have been found to be potent inhibitors of TRPV1 and TRPA1 and are able alleviate inflammatory pain when administered intrathecally [65, 66].

TRPV1 agonists/antagonists have been demonstrated to be beneficial in pain induced by arthritis, bone cancer, diabetic peripheral neuropathy, herpes zoster, inflammatory bowel disease and migraine [67-72]. Several TRPV1 antagonists are in clinical trials for these conditions [62-64, 73, 74]. A major side effect encountered in clinical trials while using TRPV1 antagonists was hyperthermia [75-77]. This unexpected side effect has led major pharmaceutical companies to halt their efforts of pursuing TRPV1 antagonists as analgesics and has prompted the search for novel targets.

TRANSIENT RECEPTOR POTENTIAL VANILLOID 2 (TRPV2)

TRPV2 was cloned soon after the cloning of TRPV1 and has a 50% sequence homology to TRPV1 and transmits noxious heat sensation [78, 79]. It is activated by temperature (>52 °C), mechanical stretch, osmotic stimuli, chemicals such as cannabinoids [80], probenecid [81] and 2-aminoethoxydiphenyl borate (2-APB) [82, 83].

TRPV2 is abundantly expressed in nociceptors, the cell bodies of which are located in DRG, TG, and NG. TRPV2 is expressed all through the spinal cord, including laminae III and IV, suggesting a broader role than TRPV1, which is expressed only in laminae I and II [78, 84-87]. TRPV2 is expressed in tyrosine kinase C (trkC) and neurotrophin 3 (NT3) receptor expressing neurons in the spinal cord suggesting a role in trkC and NT3 receptor-mediated thermal and mechanical hypersensitivity [88, 89]. The expression of TRPV2 in neurons innervating the larynx, bladder and intestine suggests its role in sensory functions of the internal organs [90-93].

Translocation of channels from the intracellular pools to the plasma membrane is an effective way of enhancing the function of a channel. Stimulation of its receptor by insulin like growth factor I (IGF-I) has been shown to enhance the plasma membrane content of TRPV2 [94]. Other intracellular regulators such as Ca^{2+}/calmodulin- dependent protein kinase (CAMK) [95], phosphatidylinositol 3-kinase (PI3-K) [96], A-kinase anchor protein (AKAP)/cAMP/protein kinase A (PKA)-mediated phosphorylation [97] have been shown to modulate TRPV2 functions. Although it is not clear as to the extent of TRPV1 expression in non-sensory neurons in the brain, heteromerization of TRPV1 and TRPV2 has been demonstrated in the central neurons [2, 98, 99].

In primates, some of the Aδ-fiber nociceptors exhibit a much higher threshold (~53°C) that can be sensitized by repetitive applications of heat as demonstrated in recombinant TRPV2. Heat-sensitive, capsaicin-insensitive DRG neurons with an activation thresholds of >50°C have also been observed in rat and mouse DRG cultures [84, 100]. In order to understand the exact role of TRPV2, electrophysiological and behavioral studies using TRPV2 knock-out mice have been performed, which show normal responses to noxious heat and mechanical stimuli both in the basal state and under inflammatory conditions [100].

Individuals with Norrbottnian congenital insensitivity to pain show loss of TRPV2 nerve fibers in their skin, suggesting their role in nociception [101]. TRPV2 expression in dental pulp may play a role in odontogenic pain [102, 103]. In a recent study, it has been reported that TRPV2 plays a role in mechanically-evoked neurite outgrowth [104]. The role of TRPV2 in nociception is far from clear.

TRANSIENT RECEPTOR POTENTIAL VANILLOID 3 (TRPV3)

TRPV3 has a high sequence homology with TRPV1 and is located on the same chromosome [105]. TRPV3 is found to be expressed in DRG, TG and NG neurons, keratinocytes, CNS neurons, nasal mucosa, tongue and testis and may play a role in thermoregulation [106].

The warmth produced by camphor when applied on the skin is due to activation of TRPV3, which has been shown to be a potent activator of TRPV3 in *in vitro* studies. The channel is also activated by menthol (in mint), carvacrol (in oregano), eugenol (in clove), insensol, 2-APB [107] and moderate heat (between 30-35^{o}C) [108]. A possibility of TRPV1 and TRPV3 subunit stoichiometry in the same channel has been suggested because of their co-expression in the same neuron [108].

The endogenous ligand for TRPV3 has not been identified. During inflammation Arachidonic Acid (AA) is produced and the active metabolites of AA (such as prostaglandins) can modulate TRPV3 channel activity. In TRPV3 over-expressing mice, keratinocytes can release prostaglandins and nerve growth factor (NGF) in response to activation of TRPV3 [109]. In several skin conditions, AA levels are increased [110, 111]. Further, AA has been shown to activate and sensitize PKC [112]. A possible role of PIP2 in modulating TRPV3 channel has been suggested by agonists that activate PLC [113]. It is possible that IP3-

mediated Ca^{2+} release can have a modulatory role, because both extracellular and intracellular Ca^{2+} inhibit TRPV3 [114].

Since free nerve endings of sensory neurons that carry nociceptive information are tightly surrounded by keratinocytes, it is possible that substances released from keratinocytes such as ATP and prostaglandins can excite TRP channels at the peripheral sensory nerve terminals. This was confirmed by TRPV3 knock-out animals that lacked ATP release from peripheral terminals [115]. In several painful conditions, TRPV3 expression is enhanced such as following mastectomy, in chronic constriction injury, and in avulsed DRG after a nerve injury [108, 116-118].

From the expression pattern and functional characteristics of TRPV3, it is apparent that TRPV3 can be targeted to induce analgesia. TRPV3 knock-out animals have revealed more clearly its role in nociception [119, 120]. Glenmark Pharmaceuticals involved in developing TRP channel antagonists has developed GRC 15300, which is in phase I Clinical trials [121]. Hydra Biosciences has developed TRPV3 antagonists, which show effectiveness in animal models of pain [122, 123]. TRPV3 over-expressing animals exhibit a 'hair-less' phenotype indicating the involvement in functions other than nociception [124, 125]. Since TRPV3 is involved in temperature sensation (30-35^{o}C), its role in regulating body temperature has to be clarified [109]. Unexpected hyperthermia caused by TRPV1 antagonists in human studies warrants detailed pharmacological profiling of TRPV3 antagonists.

TRANSIENT RECEPTOR POTENTIAL VANILLOID 4 (TRPV4)

TRPV4, a putative mammalian mechanosensitive channel, is a homologue of the *Caenorhabditis elegans* osmosensory channel (OSM-9) that is expressed in sensory neurons, hypothalamus, trachea, cochlear hair cells, vascular smooth muscle cells, endothelial cells, kidney and keratinocytes [126-130]. TRPV4 is activated by hypotonicity as a result of cell swelling and by shear stress [129-133]. Other activators of TRPV4 include heat (>27^{o}C), diacyl glycerol (DAG), PKC activating (phorbol 12-myristate 13-acetate, PMA) and non-activating (4α-phorbol 12,13-didecanoate, 4α-PDD) phorbol esters, and 5',6'-epoxyeicosatrienoic acid (5',6'-EET) derived from anandamide and AA [127, 134, 135]. It appears that TRPV4 is involved in sensing sustained mechanical sensation that occurs during vasodilation and cell swelling. It was proposed that second messengers produced during cell swelling can activate the channel [129, 136]. A direct mechanosensitivity of TRPV4 has been demonstrated recently by its activation by hypotonic solution in a system, independent of polyunsaturated fatty acids [137] and by direct mechanical force in excised membrane patches [138, 139].

TRPV4 is expressed in primary afferent nociceptors and transduces subtle changes in osmolarity, which occurs during inflammation and extravasation. Following injection of the simplified "inflammatory soup" (prostaglandin E2 and serotonin), the percentage of C-fibers responding to a hypotonic stimulus and the magnitude of response is significantly weaker in $TRPV4^{-/-}$ mice as compared to $TRPV4^{+/+}$ mice [140]. Osmotransduction was studied using hypotonic or hypertonic solutions, which caused significant nocifensive behavior [140, 141]. This behavior is further enhanced by the inflammatory mediator, PGE2. Using antisense-oligodeoxynucleotides, the role of TRPV4 has been implicated in both hypotonic and hypertonic stimulus-induced nociception [140, 141]. Further, it has been suggested that TRPV4-mediated nocifensive behavior induced by osmotransduction is dependent on Src tyrosine kinase [142].

Using electrophysiological, molecular and behavioral techniques, it has been shown that TRPV4 plays a role in pancreatitis [143]. Immunoreactivity of TRPV4 along with TRPA1 has been detected in pancreatic nerve fibers and in DRG neurons innervating the pancreas. DRG neurons from TRPV4 knock-out mice exhibit significantly attenuated Ca^{2+} influx in response to TRPV4 agonists. They also exhibit reduced pain and inflammatory response. Therefore, TRPV4 channel antagonists can be effective in the treatment of pain associated with pancreatitis [143]. There are several lines of evidence that TRPV4 is involved in other pain-related conditions. TRPV4 plays a crucial role in painful peripheral neuropathy. Spinal administration of antisense oligodeoxynucleotides to TRPV4 attenuated taxol-induced mechanical hyperalgesia and hypotoniciy-induced hyperalgesia [144]. TRPV4 appears to be in a sensitized state after paclitaxel-induced neuropathy [145]. TRPV4 also plays a critical role in chronic compression of DRG-mediated mechanical allodynia and thermal hyperalgesia. Nitric oxide-mediated cGMP or NF-κB pathways could be involved [146-148]. Activation of TRPV4 within the meninges initiates afferent nociceptive signaling that may contribute to migraine-type headaches [148]. TNF-α differentially induces TRPV4 expression in synoviocytes [149] which can affect inflammatory pain states. Anti-nociceptive effects of agents such as butamben and dimethylallyl pyrophosphate have been shown to be mediated by TRPV4 [150, 151]. TRPV4 along with TRPV1 and TRPA1 is a potential integrator of nociception during inflammation. TRPV4 can be an attractive pharmacological target for the development of novel analgesics [152].

TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 (TRPA1)

A channel with overlapping sequence homology to TRPA1 was first isolated from human fibroblasts [153]. When TRPA1 was cloned, it was initially named as ANKTM1 [154]. TRPA1 is a non-selective Ca^{2+} permeable cation channel; it is unique in its structure among TRP channel for having a large number (17) of ankyrin repeat domains, which impart a spring-like action to proteins [155]. TRPA1 is expressed in hair cells, superior cervical ganglion (SCG) neurons, geniculate ganglion, GI tract, heart, brain, urinary bladder and immune cells [156-159]. Its involvement in cold allodynia and mechanical hyperalgesia has been demonstrated using behavioral models [160-164]. TRPA1 is co-expressed with TRPV1 in C and Aδ nociceptors in DRG and TG neurons raising the issue of the functional specificity. Recently, it has been shown that TRPA1 is expressed in rat pancreatic beta cells and involved in insulin release [165].

TRPA1 is activated by allicin, diallyldisulfide (in garlic extract), allyl isothiocyanate (AITC, in mustard oil, horseradish and wasabi), cinnamaldehyde (in cinnamon oil), icilin (a synthetic compound that produces a sensation of extreme cold), acrolein (in tear gas and car exhaust) and N-methyl maleimide (NMM, an oxidizing agent) [166-169]. It is also activated by bradykinin (BK), tetrahydrocannabinoid (THC) and WIN55,212-2 [161, 170-172]. TRPA1 is selectively activated by reactive chemicals produced endogenously, which include H_2O_2/hydroxyl radicals, aldehydes, such as 4-hydroxynonenal (4-HNE), cyclopentenone prostaglandins, such as 15d-PGJ2, methylglyoxal (MG), hypochlorite and hydrogen sulfide [165, 173-175]. In Drosophila, TRPA1 appears to suggest origin of chemical nociception [176]. Finally, noxious cold temperatures and mechanical force have been proposed to activate TRPA1 [161, 164]. The *Drosophila* TRP homologue of TRPA1, *painless*, participates in mechanical nociception, therefore it has been proposed that TRPA1 may respond to mechanical force [176]. However, the role of TRPA1 in sensing cold and mechanical force is still controversial [161, 164, 177, 178].

TRPA1 agonists, cinnamaldehyde, acrolein and mustard oil, when applied topically induce pain in humans [179-181]. Several endogenous activators of TRPA1 (for example, 4-hydroxy-nonenal, A- and J-series prostaglandins, BK and H_2O_2 that are released following tissue damage and inflammation induce pain behaviors in mice [177-182]. Resolvins have been found to be potent endogenous inhibitors of TRPA1 [65, 66]. TRPA1 antagonists (e.g.HC-030031 and CHEM-5861528) reduce acute and chronic inflammatory pain and diabetes-induced neuropathic pain [183, 184]. In rats, intrathecal administration of TRPA1-targeted antisense oligonucleotides or TRPA1 antagonists can also dramatically reduce cold hypersensitivity after nerve injury or inflammation [159, 162]. A-967079, a TRPA1 antagonist structurally similar to AP-18, reduces cold hypersensitivity after nerve injury without affecting acute responses to environmental cold [185]. Thus, TRPA1 appears to selectively mediate cold hypersensitivity in pathological conditions, where other activators of the channel are also present. Preclinical animal studies and more recently human studies highlight that TRPA1 as a promising new target for the treatment of acute and chronic pain [186]. TRPA1 antagonists by Glenmark Pharmaceuticals, Abbott Laboratories and Hydra Biosciences are in pre-clinical trials [186]. In humans, a gain-of-function TRPA1 mutant has been shown to be involved in familial episodic pain syndrome [187].

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 2 (TRPM2)

TRPM2 has been cloned from human brain, lymphocytes, and monocytes [188, 189]. The subunits are assembled as homomultimers to form the ion channel pore [190]. The distal C-terminal of TRPM2 channels has strong homology to the NUDT9 proteins and exhibit adenosine 5'-diphophoribose (ADPR) pyrophosphatase activity [189]. These channels are permeable to cations including Ca^{2+}. Ca^{2+} activates these channels either directly or facilitates the activation via ADPR [189-191]. In addition to ADPR, nicotinamide adenine dinucleotide and their metabolites are capable of activating TRPM2 [192]. TRPM2 can also be activated by molecules produced during oxidative stress such as H_2O_2, tumor necrosis factor-α (TNF-α) and amyloid β-peptide [182]. The expression of TRPM2 channel has been shown in brain, bone marrow, spleen, heart, liver, lung, pancreatic β-cells, endothelial cells, immune cells, blood cells and microglia [182].

TRPM2 has been shown to be involved in insulin release, cytokine/chemokine production and apoptotic/necrotic cell death. TRPM2-mediated insulin release is via a K_{ATP} channel-independent mechanism [193]. It has been reported that pancreatic β-cells respond to warm temperatures with increased cytosolic Ca^{2+} and resultant insulin release through activating TRPM2 channels [193]. Several cellular functions of TRPM2 are related to oxidative stress and generation of reactive oxygen species in numerous cell types [182]. It is involved in the production of chemokine (CXCL8/CXCL2 in monocytes), induction of Ca^{2+} influx, mediation of cell death (in neurons, monocytes, lymphocytes, insulin secreting cells and cardiomyocytes) [182]. These channels can be non-specifically inhibited by several compounds such as 8-BrcADPR, flufenamic acid (FFA), imidazole anti-fungal agents (clotrimazole and econazole), N-(p-amylcinnamoyl) anthranilic acid (ACA), and 2-APB [182]. There are no specific inhibitors to elucidate the functional role to exploit their therapeutic potential, although TRPM2 knock-out animals have revealed its fundamental functions. TRPM2 is involved in insulin secretion from pancreatic β-cells, chemokine/cytokine production, cardiovascular diseases (induces endothelial hyper-permeability) and neurodegenerative disorders [182, 193-195]. Ablation of *Trpm2* gene reduces chemokine production, neutrophil infiltration, and ulceration in a colitis animal model [196]. Activation of the TRPM2 channel by oxidative stress, TNF-α and Aβ42 and the resultant loss of neuronal cells strongly suggest a role of these channels in the pathophysiology of Alzheimer's disease [197-199]. Altered TRPM2 channel expression and/or function are also reported in several neurological diseases such as stroke, Western Pacific amyotrophic lateral sclerosis and Parkinsonism-dementia [200].

One of the recent studies has suggested the role of TRPM2 channels in inflammatory and neuropathic pain but not in spontaneous pain [201]. TRPM2 expressed in macrophages and microglia aggravates peripheral and spinal pro-nociceptive inflammatory responses and contributes to the pathogenesis of inflammatory and neuropathic pain [201]. Wild-type and TRPM2 knock-out mice showed no difference in their basal thermal and mechanical sensitivities [201]. However, TRPM2 knock-out mice showed significant reduction in formalin-induced nocifensive behavior, carrageenan-induced inflammatory pain and sciatic nerve injury-induced neuropathic pain [201]. Carrageenan-induced inflammation and sciatic nerve injury increased the expression of TRPM2 mRNA in the inflamed paw and around the injured sciatic nerve. Microglial activation, production of CXCL2 and induction of nitric oxide synthase after nerve injury are also suppressed in the spinal cord, cultured macrophages and microglia obtained from TRPM2 knock-out mice [201]. Oxidative stress and depletion of thiol

groups are implicated in the neuropathology of pain particularly neuropathic pain [201]. TRPM2 is activated by oxidative stress and pro-inflammatory mediators, which is suggestive of its involvement in neuropathic and inflammatory pain conditions [202]. Modulation of TRPM2 channels using N-Acetyl cysteine, 2-APB and flufenamic acid paves the way for understanding the role of TRPM2 in nociception [203-205].

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 3 (TRPM3)

TRPM3 is a voltage-dependent, nonselective cation channel permeable to Ca^{2+} ions. Using Ca^{2+} imaging and patch clamp techniques, two TRPM3 (1555-AA and 1325-AA containing variants) isoforms have been identified. In the longer variant, intracellular Ca^{2+} is significantly increased following inclusion of extracellular Ca^{2+} [206]. Removal of extracellular Ca^{2+} or application of gadolinium (Gd^{3+}) reduces the increases in intracellular Ca^{2+} confirming the Ca^{2+} permeability of this channel [207]. From cells expressing shorter TRPM3 variants, whole-cell recordings have revealed Ca^{2+} and Mg^{2+} permeability of this isoform as well. Activity of the shorter variant of TRPM3 was suppressed by Gd^{3+} and La^{3+}, but increased by cell swelling [206]. TRPM3 is expressed in several neuronal and non-neuronal tissues including kidney, brain, endocrine pancreas, vascular smooth muscle, and sensory neurons [207, 208-214]. Using Northern blot analyses of mouse brain, at least three transcripts coding for TRPM3 have been detected [206].

TRPM3 has been found to be activated by the endogenous sphingolipid D-erythro-sphingosine (sphingosine) and its precursor, dihydrosphingosine [215]. This activation may be due to the stimulation of the sphingomyelinase/ceramidase pathway, which results in the release and intracellular accumulation of sphingosine [215]. The activation by sphingosine is selective for TRPM3 because other TRP superfamily members did not respond to this lipid compound [206]. Exogenously, pregnenolone sulphate is the most potent activator of TRPM3 channel [212].

Recent reports have implicated the TRPM3 channel as a heat sensor [216]. TRPM3 is functionally expressed in a subset of sensory neurons in DRG and TG. Intraplantar administration of pregnenolone caused nocifensive behavior in wild-type mice but not in TRPM3 knock-out animals [216, 217]. TRPM3-deficient mice exhibit deficits in their avoidance response to noxious heat, but not to noxious cold or mechanical stimuli. TRPM3-deficient mice also failed to develop inflammatory thermal hypersensitivity [216]. Fenamates and N-phenyl-substituted anthranilic acid derivatives, which are clinically used as non-steroid anti-inflammatory drugs, act through TRP channels [204]. One of the potent fenamates, mefenamic acid is a selective and potent TRPM3 blocker, whereas other fenamates also blocked TRPM3, TRPV4, TRPC6 and TRPM2 [204]. All these studies suggest that TRPM3 can be a target for developing analgesics.

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 8 (TRPM8)

TRPM8 was isolated by expression cloning as a menthol receptor from trigeminal neurons by David Julius group, and from sequence homology from genomic database by Ardem Potapoutian group [218, 219]. A channel with a similar sequence homology had already been cloned from prostate cancer cells [220]. TRPM8 is expressed in a subset of C and Aδ nociceptors in DRG and TG. TRPM8 is expressed in peripheral terminals that sense sensory information. TRPM8 is also expressed in the central terminals, the role of which is not clear [9, 221].

TRPM8 could be activated by cold temperatures (10–28 °C) and 'cooling' compounds such as menthol and icilin. It is also activated by peppermint oil, cornmint oil, eucalyptus oil etc. Lysophospholipids that are produced by the activation of PLA2 has been shown to be an endogenous agonist of TRPM8 [222]. There are no known selective antagonists for TRPM8. Of note, the TRPA1 antagonist HC030031, the TRPV1 antagonist BCTC, and the non-selective agonist of TRPV1, TRPV2 and TRPV3. 2-APB, all block TRPM8 [223-227]. TRPM8 knock-out animals exhibit lack of cold sensitivity, implying an analgesic potential for TRPM8 antagonists. However, the low temperature-induced cold pain was intact in these animals [164, 228, 229]. This is not unexpected since TRPA1, potassium channels and a sodium channel are also involved in cold sensation [230-233].

Activation of PKC reciprocally modulates TRPV1 and TRPM8 in that it up-regulates TRPV1 and down-regulates TRPM8 [9]. Differential modulation of PKC and PKA may determine the broader implication of sustained increase in TRPV1-mediated intracellular Ca^{2+}, which could mediate Ca^{2+} dependent processes such as neurotransmitter/neuropeptide release and transcriptional regulation of proteins. TRPM8 is modulated by PIP2. Depletion of PIP2 by activation of PLC decrease channel activity of TRPM8, but increase the channel activity of TRPV1 [234-236].

The implication of the reciprocal modulation is that thermal hyperalgesia caused by PKC-induced sensitization of TRPV1 by inflammatory mediators could be further aggravated by PKC-mediated down-regulation of TRPM8. Paradoxically, when needed during TRPV1-induced hypersensitivity, TRPM8 is down-regulated. In fact, intraplantar capsaicin-induced nocifensive behavior was alleviated by intraplantar administration of menthol [9]. Therefore, soothing sensation induced by activation of TRPM8 could be useful to alleviate hyperalgesia. The TRPM8 agonist menthol decreases nociceptive responses in inflammatory and neuropathic pain models [237, 238]. On the other hand, TRPM8 antagonism or deletion may also provide pain relief [186, 238].

TRANSIENT RECEPTOR POTENTIAL MUCOLIPIN 3 (TRPML3)

TRPML3 is a cation-selective channel regulated by changes in pH [239-241]. TRPML3 expression has been reported in hair cells (distributed in intracellular vesicular compartments and plasma membrane) of the

cochlea/vestibulum and melanocytes [242]. Deletion of TRPML3 causes abnormalities in mitochondrial functioning and lysosomal storage [243]. TRPML3 was discovered in varitint-waddler mice by positional cloning as a result of a mutated channel (gain-of-function mutation (A419P) in the S6 segment. The mutant mice exhibit hearing loss, vestibular defects, pigmentation abnormalities and perinatal lethality [240, 244]. TRPML3 can be activated by pre-incubation in low sodium medium [241]. Gain-of-function mutants exhibit increased Ca^{2+} influx and cell death [240]; the loss of melanocytes in the cochlea and the vestibule probably underlies the deafness and the circling behavior of varitint-waddler mice [240, 244].

TRPML3 is significantly down-regulated in the adults but reappears following nerve injury, which has been demonstrated in three different nerve injury models (axotomy, sciatic nerve ligation, spared and partial nerve injury model) [214]. Further, *in situ* hybridization revealed a significant increase and widespread expression of TRPML3 in both small sized non-peptidergic and peptidergic nociceptors as well as large NF200-positive mechanoreceptors after spinal nerve ligation [214]. A recent report claims the identification of TRPML3 ligand through chemoinformatic analysis that will hopefully serve as useful tools to understand the role of these channels in pain transmission [245].

TRANSIENT RECEPTOR POTENTIAL CANONICAL (TRPC)

Seven mammalian transient receptor potential canonical (TRPC) proteins (TRPC1–7) have been identified. These channels can be divided into three subgroups by sequence homology: C1/C4/C5, C3/C6/C7, and C2. All mammalian TRPC proteins seem to be associated with G-protein-coupled receptors and receptor tyrosine kinases [246]. Of these channels, TRPC1 and TRPC6 have been studied for their expression and function in DRG and TG following inflammatory conditions [214].

Stretch activated channels (SACs) are expressed in DRG neurons including TRPC1, TRPC6 and TRPV4 [247]. TRPC1 and TRPC6 along with TRPV4 mediate mechanical hyperalgesia and primary afferent nociceptors sensitization. TRPC1 and TRPC6 channels do not contribute to baseline mechanical nociceptive threshold [248]. Using the selective SAC inhibitor, GsMTx-4, the role of these channels in mechanical hyperalgesia has been implicated [248]. Furthermore, similar to TRPV4, spinal intrathecal administration of antisense oligodeoxynucleotides to TRPC1 and TRPC6 reversed hyperalgesia to mechanical/hypotonic stimuli induced by inflammation [248]. Antisense to TRPC6, but not to TRPC1, reversed the mechanical hyperalgesia induced by a thermal injury or the TRPV4-selective agonist 4δ-PDD suggesting different roles of these channels [248]. We suggest that TRPV4, TRPC6 and TRPC1 participate in mechanical hyperalgesia and primary afferent nociceptors sensitization. Moreover, TRPC6 emerges as an attractive candidate to transduce mechanical stimuli in the setting of inflammation or nerve injury.

TRPCs are involved in mediating the melittin-induced activation of different subpopulations of primary nociceptors [249]. TRPC channels are also involved in melittin-induced inflammatory nociceptive responses as studied using several behavioral models [249]. Pre- and post-administration of the TRPC antagonist SKF-96365 prevented and suppressed the nociceptive behavior. In addition, SKF-96365 had no effect on baseline threshold for either thermal or mechanical sensitivities [250]. TRPC channels, which are known as store-operated channels, are expressed in human osteoblasts cell lines and SaM-1 cells that may mediate nociceptive transmission in bone pain [251].

CONCLUDING REMARKS

Members of the TRP channel family are constantly being added to the list of nociceptive TRP channels as their relevance is revealed by their expression pattern, gene disruption studies and specific antagonists. Furthermore, in disease conditions over-expression of nociceptive TRP channels suggests the specific role of a TRP channel in a specific modality of pain. It is not well understood whether the type of TRP channel or its expression pattern is responsible for carrying a specific type of pain. But it appears that targeting a specific type of TRP channel can alleviate a specific type of pain. This idea has been elegantly demonstrated by targeting TRPV1, which selectively alleviates inflammatory thermal hypersensitivity without affecting mechanical hypersensitivity.

Several TRP channels have been suggested to play a role in mechanical pain sensitivity. Mechanical pain sensitivity involves allodynia and hyperalgesia, but the receptors that sense these modalities have not been clarified. Further, several TRP channels are expressed in the same nociceptor. This raises the question how does the interplay between TRP cannels in the same neuron come into picture during nociceptive transmission? It is also intriguing that interfering with any one of these TRP channels results in pain relief. Some of the nociceptive TRP channels are only expressed in primary afferent neurons, but neurotransmitters/neuro-peptides released during neuronal activity in the spinal cord may alter the expression and function of receptors in higher order neurons and glia that could participate in nociceptive transmission as proposed in central sensitization. The role of the descending pathway as a result of enhanced primary afferent excitability has to be taken into consideration as well. It is likely that nociceptive and non-nociceptive receptors in primary afferent and higher order neurons function in concert, thereby when the threshold is crossed, painful sensation is perceived. As experimentally demonstrated, interfering with any one of these components that maintains the system below the threshold can induce pain relief. Therefore, it is not certain whether it can be claimed that the targeted receptor is the key component or one of many inter-related components that maintains the system under the threshold. Hence, the strategy is to affect multiple targets that may include other than nociceptive TRP channels by a single molecule or by multiple molecules or by non-drug strategies that maintains the system well below the threshold, so that subtle changes are not capable of initiating and maintaining nociceptive transmission resulting in painful episodes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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