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TRANSIENT RECEPTOR POTENTIAL (TRP) CHANNEL: AN EMERGING TARGET FOR PAIN

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ABSTRACT: Pain perception begins with the activation of primary sensory nociceptors. Over the past decade, flourishing research has revealed that members of the Transient Receptor Potential (TRP) ion channel family are fundamental molecules that detect noxious stimuli and transduce a diverse range of physical and chemical energy into action potentials in somatosensory nociceptors. Here we highlight the roles of TRP ankyrin 1 (TRPA1), TRP melastatin 8 (TRPM8), TRP vanilloid 3 (TRPV3) and TRP vanilloid 4 (TRPV4) in the activation of nociceptors by heat and cold environmental stimuli, mechanical force and by chemicals including exogenous plant and environmental compounds as well as endogenous inflammatory molecules. The contribution of these channels to pain and somatosensation is discussed at levels ranging from whole animal behavior to molecular modulation by intracellular signaling proteins. An emerging theme is that TRP channels are not simple ion channel transducers of one or two stimuli, but instead serve as promising drug targets for the management of pain. As a result, major efforts are put into the development of selective TRP channel agonists and antagonists and the assessment of their therapeutic potential. This review focuses on summarizing the evidence that modulation of selected TRP channels may have beneficial effects in pain management.

INTRODUCTION: Transient receptor potential (TRP) channels comprise a large family of nonselective cation channels that contribute to a range of sensory processes, including thermo sensation, photo transduction, chemo sensation, and nociception [1].

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In keeping with such varied physiological roles, TRP channels are activated by diverse stimuli that include exogenous chemical agonists (such as capsaicin and menthol), changes in ambient temperature, and neurotransmitters or growth factors that stimulate phospholipase C signaling systems [2].

A number of TRP channels respond to combinations of stimuli and function as polymodal signal detectors that assess changes in the chemical and physical environment of the cell. While the sphere of TRP channel function and physiology has received intensive study, little is presently known about TRP channel structure.

TRP channels are members of the cation channel superfamily that includes voltage-gated channels for calcium, potassium and sodium as well as cyclic nucleotide-gated channels Mammalian Transient Receptor Potential (TRP) family consist of 28 known members and can be subdivided into six subfamilies based on sequence homology (**figure 1**): TRPC (canonical subfamily, 7 members), TRPV (vanilloid, 6), TRPM (melastatin, 8), TRPA (ankyrin, 1), TRPP (polycystin, 3) and TRPML (mucolipin, 3) [3].

In common with other superfamily members, TRP channels are complexes consisting of four pore-forming subunits [4]. Each subunit is thought to contain six transmembrane regions (S1–S6) in which the loop between transmembrane segments S5 and S6 constitutes the selectivity filter. The N- and C-terminal domains are thought to be intracellular, where they may engage in subunit-subunit interactions, associate with other cellular proteins, and interact with cytoplasmic factors.

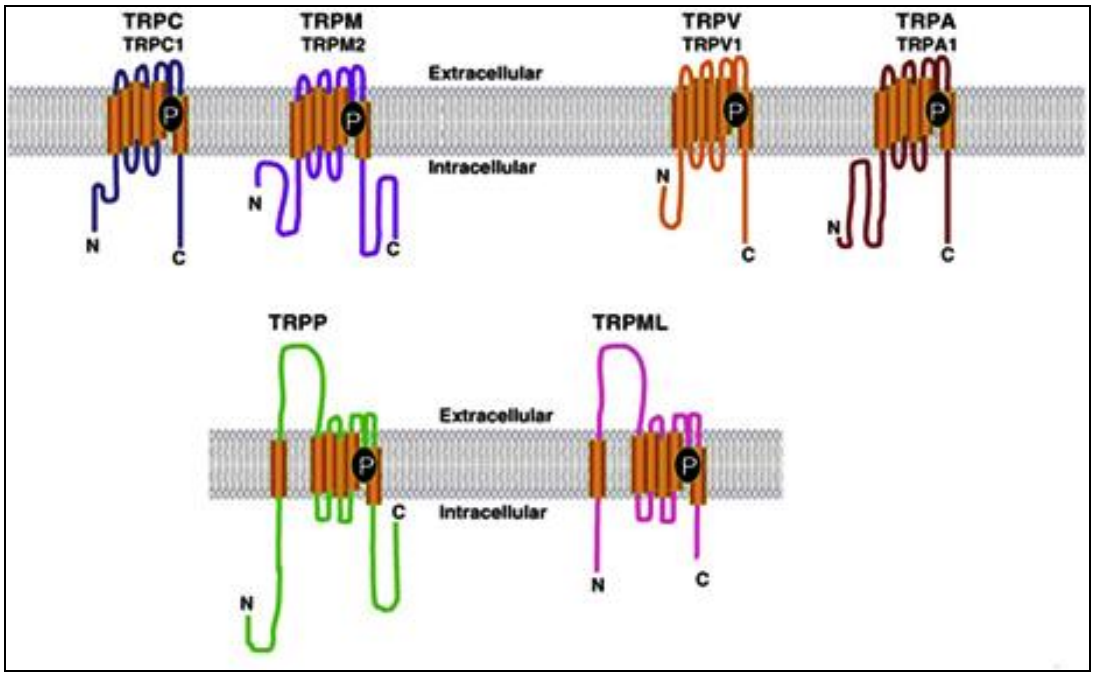

FIGURE 1: TRP SUPERFAMILY EXPRESSED IN MAMMALIAN CELLS

Each TRP channel comprises six putative transmembrane domains (vertical rectangles in the figure) and a cation-permeable pore (was indicated by 'P' between transmembrane domain 5 and transmembrane domain 6). The major differences between TRP channel subfamilies is demonstrated by their intracellular N-terminal and C-terminal cytosolic domains as illustrated. The extracellular domain inserted between transmembrane domain 1 and 2 is also indicated for TRPP and TRPML [5, 6].

The animal nervous system has evolved complex neural pathways to respond to a wide variety of stimuli, including chemical and physical pain, as well a range of harmless or noxious temperatures, but the mechanism behind these actions is poorly understood. The inability to perceive these sensations would make species survival impossible. Therefore, many laboratories explore the molecular mechanisms involved that determine whether an organism will feel pain or a change in the intensity of heat or cold. It is discovered that different families of the transient receptor potential channel (TRP) mediate the responses to these stimuli by opening or closing their pores to extracellular calcium.

Detailed mechanistic models that serve to explain the reasoning to how and why animals can sense pain and changes in temperature and the mechanisms of how TRP channels also serve as mediators to injury by causing inflammation was studied using household ingredients such as chili peppers, mustard oil and menthol by Flaksman (Department of Biology Lake Forest College) (**figure 2**).

With this knowledge, TRP channels can serve as useful targets for novel analgesic drugs that treat a wide variety of tissue injury and degenerative conditions that promote inflammation and chronic pain.

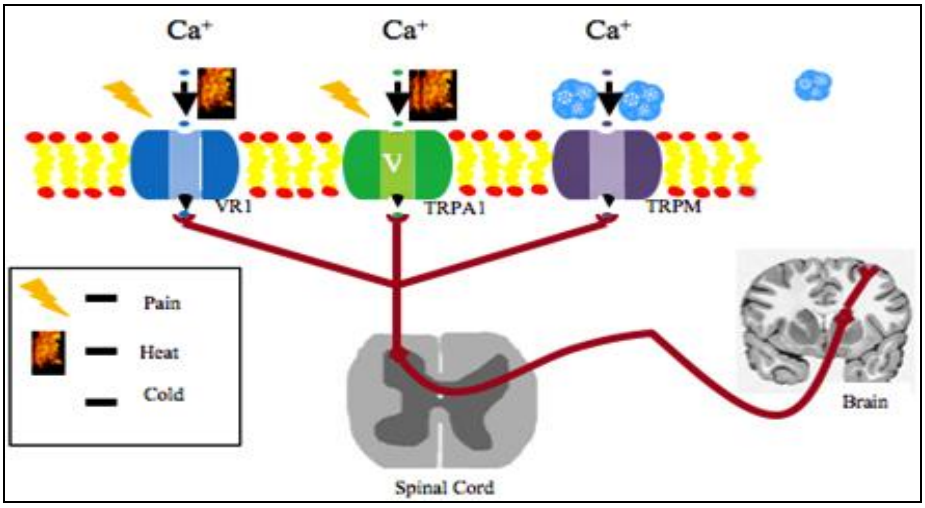

FIGURE 2: THE GENERALIZED PAIN AND THERMOSENSATION PATHWAY

Within animal cells, three different channels of the receptor family, transient receptor potential channel (TRP), are shown. When there is an environmental stimulus such as heat, cold, or pain, the respective channel for each stimulus will open in response, creating a pathway that allows for the influx of calcium ions. When calcium rushes into the cell membrane, action potentials are generated that get transmitted to the brain via sensory neurons in the spinal cord. When the relayed message arrives in the somatosensory cortex of the brain, the specific sensation can be felt by the animal [7]. The majority of sensory TRP channels studies and research efforts in drug discovery have focused on TRPV1, which acts as a receptor for noxious heat; capsaicin, acidic solutions and some endogenous lipid-derived agents. Antagonists of TRPV1 are effective in reversing established thermal and mechanical hypersensitivities in a range of animal models of chronic neuropathic and inflammatory pain [8]. The finding that one TRPV1 antagonist (AMG-517) caused hyperthermia in early clinical trials and the demonstration of hyperthermia in rodents treated with some, but not all, TRPV1 antagonists has raised concerns about the safety of inhibiting TRPV1 [9]. This potential safety concern has led to increased interest in other sensory TRP channels as possible targets for pain relief (**figure 3**).

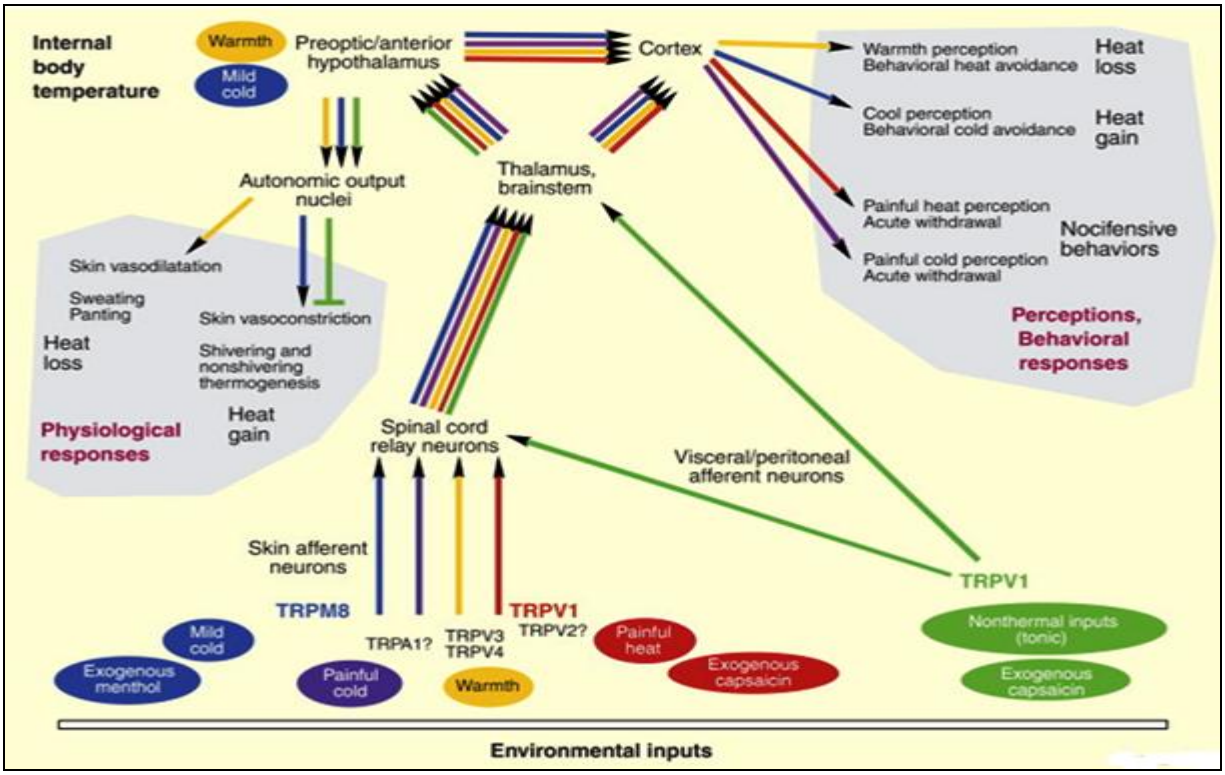

FIGURE 3: SCHEMATIC OVERVIEW OF MAMMALIAN TEMPERATURE-EVOKED RESPONSES

Intrinsic and extrinsic thermal and nonthermal inputs are represented by ovals. Colored arrows indicate pathways related to detection of painful heat (red), nonpainful warmth (gold), painful cold (purple), nonpainful mild cold (blue), and nonthermal visceral inputs to thermoregulatory centers (green). Arrows represent stimulatory pathways. Green T-bar represents inhibition [10].

Primary afferent sensory neurons express other thermosensitive TRP channels in addition to TRPV1. TRPV3 [11-13] and TRPV4 act as receptors for warm temperatures, TRPM8 acts as a receptor for cool temperatures and TRPA1 has been reported to be activated by noxious cold temperatures [14-16], although this property is disputed. Various other TRP channels are also expressed on afferent neurons, but the possible roles of these channels in sensory transduction has attracted little attention [17, 18]. This review summarizes the properties of sensory TRP channels and their possible functions in mediating or modulating the transduction or transmission of painful stimuli. Most of the studies have used RNAi techniques or genetically modified mice to investigate the function of TRP channels but, in a few cases, low molecular weight agonists or antagonists also have been used.

1. **TRPA1**: TRPA1 is expressed in approximately 25% of the sensory neurons located in the dorsal root ganglia (DRG). These are small-diameter neurons that also express TRPV1. In the DRG, TRPA1 is found in approximately 50% of TRPV1-positive neurons [14].

   TRPA1 can be activated by an increase in the concentration of intracellular calcium (Ca^{2+}), caused by an influx of (Ca^{2+}) ions into the neuron or by the release of Ca^{2+} from intracellular stores [19-21]. TRPA1 channels can also be activated by the stimulation of Gq/α11-linked G-protein-coupled receptors (GPCRs) [22, 23]. The activation of these receptors stimulates the activity of phospholipase C and leads to the hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP2). PIP2 has been proposed to bind to and inhibit some TRP channels, including TRPA1 and TRPV1. The hydrolysis of PIP2 halts this inhibition and opens the channel. A direct relationship between Gq/α11-linked GPCRs, including protease-activated receptor 2 (PAR2), and the activation of TRPA1 has been suggested [22]. Another study suggests that TRPA1 is indirectly activated by bradykinin GPCRs in a process involving an initial activation of TRPV1 and a consequent increase in [Ca^{2+}] [23]. Irrespective of the detailed mechanisms, the available evidence demonstrates that TRPA1 plays a role in mediating the effects of several mediators produced during inflammation on Gq/α11-linked GPCRs.

   TRPA1 is a sensor for a range of noxious or irritant chemicals. These chemicals include some pungent food ingredients such as allyl isothiocyanate [24, 25] and allicin [26] (from mustard and raw garlic, respectively), and aldehydes such as cinnamaldehyde [25] and formaldehyde [27]. Formaldehyde is of interest because the modulation of pain behaviors evoked by the injection of formaldehyde (formalin) into the paw of rodents has been used as an experimental test for analgesic drugs. Acrolein, an environmental pollutant in vehicle exhaust fumes, and the active components in tear gas (eg, phenacyl chloride and 2-chlorobenzal malononitrile) also exert their irritating effects by activating TRPA1 [28, 29].

   All of these exogenous compounds are electrophilic, and site-directed mutagenesis studies have demonstrated that these compounds act by covalently binding to cysteine residues located in the N-terminal segment of TRPA1 [30, 31]. Behavioral experiments have demonstrated that most of the noxious effects of these electrophilic compounds can be attributed to the activation of TRPA1. These agents elicit pain-related behaviors when injected into the paws of wild-type mice, but not when injected into genetically modified mice lacking TRPA1 [23].

   TRPA1 is also activated by several endogenous electrophilic chemicals that are generated during pathophysiological conditions such as inflammation and reperfusion after ischemia. These include hydrogen peroxide, probably acting via the production of hydroxyl radicals, and some bioactive lipids [32]. Two major types of lipids activate TRPA1: cyclopentenone prostaglandins (15d-PGJ2) [33] and products of lipid peroxidation (eg, 4-hydroxynonenal and 4-oxononenal).

Hypochlorite, which is generated with hydrogen peroxide under conditions of neutrophil accumulation, has also been demonstrated to be a TRPA1 agonist [34]. The pain-related behavioral effects of all of these agents are also largely mediated by TRPA1, as responses to their experimental administration are greatly reduced or ablated in mice lacking TRPA1 [35].

TRPA1 is also activated by a range of non-electrophilic compounds, including some dihydropyridine calcium-channel ligands [36], high concentrations of Δ9-tetrahydrocannabinol [24], the fatty acid amide hydrolase inhibitor Org-231295 (URB-597; Schering-Plough Corp) [37] and icilin. Menthol, which was originally thought to be a selective activator of TRPM8 (see the TRPM8 section), is a TRPA1 agonist at lower concentrations (tens of micromolar) at the mouse and human channels, but an antagonist of mouse TRPA1 at higher concentrations [28,38,39]. Caffeine is also an activator of murine TRPA1, but this agonist activity is species-dependent, and caffeine acts as an antagonist when tested on human TRPA1 [40].

The finding that both electrophilic and non-electrophilic chemicals can be agonists of TRPA1 has been incorporated into screening strategies to identify antagonists of TRPA1. Species selectivity has also proven to be a potential problem, as some compounds identified in chemical screens act as antagonists at TRPA1 in humans, but agonists at channels in rodents [41, 42]. This latter property has prevented the use of these compounds as research tools in animal studies to elucidate the roles of TRPA1 antagonists in pain.

TRPA1 was first described in sensory nerves as a cold-activated channel that was triggered by temperatures below approximately 17°C [14], although this property has been disputed [43]. Several research groups have presented data for a lack of cold activation of TRPA1 [44], but some recent publications have provided results that support this function [15, 16, 41, 45]. The amino-acid sequence in the N-terminal region of TRPA1 contains many (~ 14) ankyrin-like repeat domains, which are usually considered to be involved in interactions with structural proteins [46].

This architecture, together with the knowledge that some invertebrate TRP channels are involved in mechanosensation, led to the hypothesis that TRPA1 is a mechanosensor. The finding that mammalian TRPA1 channels can be activated by deformation of the cellular membrane by chemicals [47] and by exposure to hyperosmotic solutions [48] is consistent with this hypothesis.

The observations that TRPA1 is expressed in mechanosensitive cells in the vertebrate auditory system and that TRPA1 orthologs are expressed in the lateral line canal of fish (an organ that senses water vibration) also suggested a link between this channel and mechanosensation [49]. However, available evidence does not support a role for TRPA1 as a primary mechano-transduction channel in vertebrate neurons. No report of a clear correlation between TRPA1 expression and mechanosensitivity has been published. Furthermore, mice lacking TRPA1 have normal hearing [23, 50, 51] and mutations in zebrafish TRPA1 orthologs do not affect mechanosensation, although the chemo-sensitivity to irritant chemicals is lost [52].

Some experiments in mice lacking TRPA1 and with the available TRPA1 antagonists support the hypothesis that the inhibition of TRPA1 reduces mechanosensitivity, although this effect may not be by direct inhibition of the primary step in sensory transduction.

2. **TRPM8**: TRPM8 was identified as a sensor for cool temperatures and the cooling compound menthol [53, 54], which opens TRPM8 channels by raising the temperature for channel activation toward normal body temperature. The temperature threshold for TRPM8 activation is approximately 25°C, although this can vary [55].

The ability to modulate the temperature for TRPM8 activation is shared by endogenous lysophospholipids generated by the action of one subtype of phospholipase A2 (PLA2), namely iPLA2. The modulation of the activation temperature probably explains the variation in TRPM8 thermal thresholds reported in different studies. The activity of TRPM8 is also regulated by the activation of phospholipase C and the consequent hydrolysis of PIP2 but, unlike

TRPV1 and TRPA1 channels, TRPM8 is inhibited by PIP2 depletion [56]. These findings suggest that TRPM8 activity is reduced in inflammatory conditions that produce a variety of GPCR agonist mediators. The thermal sensitivity of TRPM8 is also modulated by polyunsaturated fatty acids and pH level. A reduction in pH, which occurs in inflammatory conditions, inhibits cold activation of TRPM8 [57].

TRPM8 is expressed in a subpopulation (~ 10%) of small-diameter sensory neurons. Using mice expressing green fluorescent protein (GFP) under the control of the TRPM8 promoter, detailed studies of the phenotype, morphology and connectivity of TRPM8 expressing nerve fibers have been performed [58, 59]. *In vivo*, the GFP-expressing neurons constitute a unique population of DRG neurons that terminate in the most superficial layers of the skin. Most of the TRPM8-expressing neurons are non-peptidergic, isolectin B4 (IB4)-negative neurons. Some co-expression of TRPM8 with TRPV1 has been observed in 10 to 20% of TRPM8 neurons, and this percentage is increased after inflammation, which induces the increased expression of TRPV1 [58]. These findings suggest that TRPM8 is expressed in neurons that can encode signals for both cooling and noxious cold.

Cold allodynia is a frequent finding following nerve lesions, but also in cold injury patients. The exact physiologic role of various cold transducing receptors and the mechanisms of cold allodynia in the different patients groups are still unclear. The molecular basis of cold transduction in primary afferent neurons has been expanded by cloning and characterization of two cold sensitive receptors, TRPM8 and TRPA1. TRPM8 is activated by moderate cold between 25 and 28°C and can also be activated and sensitized chemically by menthol [54].

TRPM8 seems to play a different role in cold hyperalgesia: stimulation of TRPM8 with icilin evoked analgesia in different animal models of neuropathic and inflammation pain and TRPM8 antisense oligonucleotides prevent this analgesia in CCl nerve injury [60]. Proalgesic involvement of TRPM8 in neuropathy-induced cold allodynia has not been proven so far.

To clarify the relative contributions of signaling pathways to regulation of TRPM8 in various conditions will require more work. Further questions include the molecular identity of additional cold sensors, and the apparent paradox that activation of cold fibers could lead both to analgesic effects and painful sensation.

3. **TRPV4:** TRPV4 was first identified as an osmotically activated channel that is sensitive to reduced osmolarity. The channel is expressed in primary afferent neurons and expression levels appear to be significantly higher in colonic sensory neurons compared with other visceral and somatic sensory neurons [61]. The expression of TRPV4 in cochlear hair cells and Merkel cells, in addition to sensory neurons, suggests a role in mechano-sensation beyond osmosensation [62].

   TRPV4 is also activated by innocuously warm temperatures and by the synthetic phorbol ester 4α-phorbol 12, 13-didecanoate (4α-PDD) [63], bisandrographolide A [64] and 5', 6'-epoxyeico-satrienoic acid [65]. Because TRPV4 is expressed in a wide range of tissues, including skin keratinocytes, it is possible that some of the reported sensory effects of TRPV4 activation *in vivo* may be indirect and may be mediated by actions on TRPV4 in non-neuronal cells.

4. **TRPV3:** TRPV3 is expressed in human DRG and trigeminal ganglion neurons, although lower levels of sensory neuron expression have been reported for rodents, in which TRPV3 is expressed more abundantly in skin keratinocytes [11-13,66]. TRPV3 is activated by innocuous warm temperatures and thus is likely to be partly activated at body temperature, but not necessarily skin temperature. TRPV3 is also sensitized by arachidonic acid [67], consistent with sensitization in inflammatory conditions. TRPV3 expression in human sensory nerves is increased after nerve injury [68], although the functional significance of this finding is unclear.

   Gullapalli *et al.*, reported two TRPV3 antagonist compounds (GRC-15133 and GRC-17173; structures unknown) with IC50 values of approximately 200 to 250 nM and greater than 35-fold selectivity over other TRP channels.

The *intraperitoneal* administration of these compounds reversed thermal and mechanical hyperalgesia in a model of CFA-induced inflammation and reversed mechanical hyperalgesia in the chronic constriction injury model of neuropathic pain [69]. TRPV3 is also expressed in other tissues, including the gastrointestinal tract, lungs, kidneys, moto-neurons and dopaminergic neurons in the substantia nigra [12, 68, 70], and plays a role in regulating hair growth [71]. These findings indicate potential areas for investigation when studying the analgesic effects of TRPV3 antagonists *in vivo*.

5. **TRPV2:** TRPV2 is expressed in medium-to-large diameter (Aδ and Aβ) rodent sensory neurons [72, 73] and when expressed hetero-logously, is activated by high (>52°C) temperatures [74]. This temperature sensitivity has led to the suggestion that TRPV2 is involved in the processing of noxious thermal pain[75]. However, while rodent TRPV2 channels are heat sensitive, heterologously expressed human TRPV2 channels are not activated by these temperatures [76], casting doubt on the role of this channel as a high-threshold thermoreceptor. TRPV1 and TRPV2 can form heteromultimers in heterologous expression systems and in native (DRG) cells, and this may increase the functional diversity of these channels [77].

   The functions of TRPV2 have been difficult to determine; however, the availability of genetically modified mice lacking TRPV2 may help to determine the function of this channel. Preliminary data indicate that these mice demonstrate sensory deficits in mechanical and thermal pain in behavioral assays under normal conditions and after inflammation or partial nerve damage, suggesting that TRPV2 influences pain behaviors [78].

   TRPV2 is expressed in intrinsic neurons including motoneurons in the spinal cord and brainstem [79] and intrinsic neurons in the intestine [80]. TRPV2 is also expressed in non-neuronal cells, such as urothelial cells [81], mast cells [82], myocytes in the heart and vasculature [83], and in skeletal muscle [84]. Currently, there is no reported selective antagonist of TRPV2, and this hampers the further investigation of the possible roles of this channel in nociception. The expression of TRPV2 in other tissues necessitates careful study for any non-sensory neuron actions of TRPV2 antagonists.

CONCLUSION AND FUTURE DIRECTIONS: Until recently, TRPV1 has been the focus of the majority of efforts to discover and develop novel TRP channel ligands for the treatment of pain. However, sensory neurons express several other TRP channels that can be activated either directly or indirectly by stimuli that are known to evoke pain in normal or pathological conditions. Furthermore, behavioral studies in mice lacking individual TRP channels or using TRP channel antagonists have demonstrated that the activity of these sensory TRP channels influences pain behaviors in animal models of neuropathic or inflammatory pain. These channels therefore offer additional targets for the development of novel analgesic and anti-hyperalgesic agents.

At present, there are few specific investigational compounds available, but the increasing research activity in this area is likely to identify compounds that can be used to further investigate the potential uses and liabilities of these antagonists. The importance of these sensory TRP channels for chronic pain in humans will only be revealed with the discovery and development of compounds suitable for clinical testing.

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