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Thermo-TRP Channels in Pain Sensation

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Important conceptual changes concerning human thermoregulation have revealed in the last decade. Recent investigations in central and peripheral thermosensitivity have emphasized the importance of temperature-activated transient receptor potential (TRP) cation channels and they are being ardently pursued as targets for analgesic drug discovery. They are the largest group of sensory detectors expressed in nerve terminals and pain receptors activated by temperature and provide information about thermal changes in the environment. Thermo-TRP channels are capable of initiating sensory nerve impulses following the detection of thermal, as well as mechanical and chemical irritant stimuli. At least, a family of six thermo-TRP channels has been characterized to date (TRPA1, TRPM8, TRPV1, TRPV2, TRPV3, and TRPV4) that exhibit sensitivity to increases or decreases in temperature as well as to chemical substances that elicit similar hot or cold sensations. Such irritants include menthol, cinnamaldehyde, gingerol, capsaicin, mustard oil, camphor, eugenol, and others. The thermal thresholds of many thermo-TRP channels are known to be modulated by extracellular mediators, released by tissue damage or inflammation, such as bradykinin, prostaglandins, and growth factors. Antagonists or blockers of these channels are likely as promising targets for new analgesic drugs at the periphery and central levels and thus, controlling the modulation of thermo-TRP channels by inflammatory mediators and ligands may be a useful alternative strategy in developing novel analgesics.

Keywords: Cold pain; heat pain; hyperalgesia; sensory neurons; nociception.

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ABBREVIATIONS

AITC: allyl isothiocyanate; CGRP: calcitonin gene related peptide; CNS: central nervous system; CA: cinnamaldehyde; DRG: dorsal root ganglion; NSAIDs: non-steroidal anti-inflammatory drugs; MO: mustard oil; TG: trigeminal ganglion; TRP: transient receptor potential.

1. INTRODUCTION

Transient receptor potential (TRP) cation channels, which are a large family of receptor channel proteins, are one of the most extensively studied in modern neuroscience and pharmacology. They serve as cellular sensors for a wide spectrum of physical and chemical stimuli such as temperature, pressure, pH, voltage, chemicals, lipids, proteins, osmotic pressure, as well as beneficial or harmful environmental inputs [1-10].

Recent studies have established the role of temperature-sensitive TRP (thermo-TRP) channels as molecular thermometers in the peripheral and central nervous system (CNS) and provided the molecular insight into the mechanisms underlying the exquisite cold and heat sensitivity of these channels. Environment temperature changes too much from the normal level initiate a variety action in mammals required to maintain the core body temperature around 36-37°C. Probably members of the thermo-TRP superfamily are involved in the processes of adaptation of the organisms to their respective habitat environments as they have been identified as highly temperature-sensitive non-selective cation channels acting as primary temperature sensors. The neurons sensing temperature are located in the spinal dorsal root ganglion (DRG) and within cranial nerve ganglia such as the trigeminal ganglion (TG) [7-15]. Their periphery nerve endings are located in the skin and oral mucosa. Particularly, cutaneous pain receptor (nociceptor) endings, a mucous membrane of the mouth and free nerve endings of the tooth pulp detect temperature, chemicals, mechanical and other physical stimuli by means of TRP ion channels responsive to these stimuli [7,11,16-20].

Recent findings in the field of pain have established a subset of thermo-TRP channels that is capable of initiating sensory nerve impulses following the detection of thermal, as well as mechanical and chemical irritant stimuli. Such irritants include menthol from mint, capsaicin from chili peppers, eugenol from cloves, cinnamaldehyde (CA), gingerol, mustard oil (MO), camphor, and others. These substances are previously known to cause pain or pain-like sensations [21-32].

Chronic pain state is still medical and social problems for a large number of populations in our globe. Although the use of new agents for pain has risen in the past few decades (for example, the cyclo-oxygenase inhibitors) the main stay of therapy remains agents such as opiates and non-steroidal anti-inflammatory drugs (NSAIDs) [33-35]. Recent preclinical studies have uncovered new molecular mechanisms underlying the generation and transduction of pain signals for pharmacological intervention. Particularly, manipulating thermo-TRP cation channels on nociceptive neurons is an attractive strategy as targets for a new generation of analgesics [29-31,36-40].

The TRP channel superfamily is mostly classified into six related subfamilies: TRP cation channel subfamily A (ankyrin, TRPA), TRP cation channel subfamily C (canonical, TRPC), TRP cation channel subfamily M (melastatin, TRPM), TRP cation channel subfamily V (vanilloid, TRPV), TRP cation channel polycystin subfamily (TRPP), and TRP cation channel mucolipin subfamily (TRPML). As stated above at least six thermo-TRP channels TRPA1, TRPM8, TRPV1, TRPV2, TRPV3 TRPV4, are involved in the detection of temperature changes, thus acting as the molecular thermometers of the body. They are also polymodal nociceptors that integrate painful stimuli such as noxious temperatures and chemical irritants (Fig. 1).

2. THERMO-TRP CHANNELS

Since thermo-TRP channels are involved in thermosensation as well as other kinds of sensory detection, variability of repertoires may be associated with adaptation of the organisms to their respective habitat environments. The thermo-TRPs are activated by distinct physiological temperatures, and are involved in converting thermal information into chemical and electrical signals within the sensory nervous system.

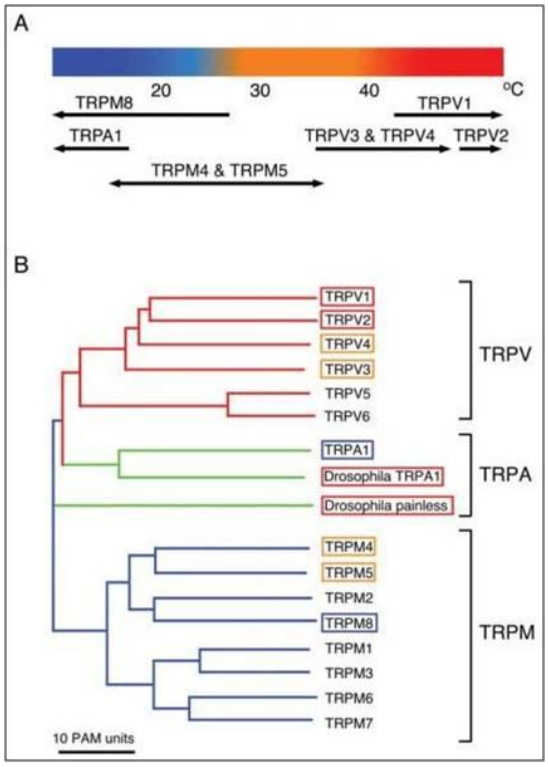

Fig. 1. Phylogenies of three families of TRP cation channels: TRPV, TRPA and TRPM

(A)Temperature ranges activating thermosensitive TRP channels. (B) Phylogenetic relationship among the mammalian TRPV and TRPM channels with two Drosophila TRPA channels. Red, orange, and blue squares indicate channels activated by high heat, warm stimuli, and cold stimuli, respectively (Reproduced from Tominaga [40] with permission)

2.1 Heat Receptors

2.1.1 TRPV1

Exposure to capsaicin evokes a painful burning sensation through the vanilloid TRPV1 receptor that is also activated by noxious thermal stimuli above 43°C or by an acidic environment of pH 5.4. In addition to its sensitivity to various pain-inducing stimuli such as capsaicin, heat, and protons, the TRPV1 ion channel has many features that a receptor related to nociception is supposed to have, such as its preferential distribution in the nervous system within small to medium-sized DRG and TG neurons, which are believed to serve as nociceptive nerve cells [1,7,41]. The first patch-clamp recordings revealed that TRPV1 is a nonselective cation channel with high Ca^{2+} permeability [42,43]. TRPV1 is also expressed by various chemical stimulants including resiniferatoxin, vanillotoxins, olvanil, anandamide, camphor, allicin, eicosanoids, eugenol and others [44,45]. It has been found that the modulation of the thermal threshold of TRPV1 channels is due to their phosphorylation. In particular, TRPV1 activation could trigger the sensation of pain at normal body temperature in the presence of ATP. ATP-induced thermal hyperalgesia was abolished in mice lacking TRPV1, suggesting the functional interaction between ATP and TRPV1 at a behavioral level [46]. But the most important aspect of TRPV1 is that it can integrate all of these noxious stimuli and inflammatory mediators to modulate its threshold of activation [47-50]. Thus capsaicin and other chemical agents acting on TRPV1 receptors will still generate plenty of interest in the future and will shed light on pain mechanisms [51].

In our behavioral experiments we have recently found that the hind paw injected with capsaicin exhibited a concentration-dependent decrease in paw withdrawal latency. Two temperature preference tests have revealed that when exposed to 30° *vs* 15°C plates, rats treated with the higher concentration of capsaicin exhibited a significant preference for the colder 15°C plate compared to vehicle-treated rats, i.e., they significantly avoided the warmer 30°C plate. Another group of rats treated with the highest capsaicin exhibited an opposite effect, a significant preference for the warmer 30° plate. Our data provide an additional view of the effects of intraplantar injections of capsaicin on thermal sensitivity. They showed a dose-dependent heat hyperalgesia lasting >2 hours; also different concentrations of capsaicin exhibited different effects in thermal preference test [8,52].

2.1.2 TRPV2

TRPV2 is widely expressed in sensory neuronal cells (mostly fast Aδ fibers and a small portion of slow C fibers) and non-neuronal cells. It is activated by temperature above 52°C and has a higher threshold than that of TRPV1. However, its role in nociception has been debated because it is not sensitive to capsaicin or protons, and nociceptors lacking both TRPV1 and TRPV2 channels showed normal heat responses in *ex vivo* recordings, suggesting that mechanisms other than TRPV1 and TRPV2 might be more important in the intact physiological environment [53-57]. Recently, the neuroanatomical distribution of TRPV2 in the adult male rat brain has been reported, focusing on the

hypothalamus, hindbrain and forebrain regions. Based on their immune-staining results, the authors concluded that TRPV2 may play an important role in several CNS networks that regulate body fluid homeostasis, autonomic function, and metabolism [58].

2.2 Warm Receptors

2.2.1 TRPV3 and TRPV4

These two TRPV3 and TRPV4 channels can be activated at warm temperatures, which can hardly be perceived as nociceptive. TRPV3 is activated at 32-39°C and shows an increased response to higher temperature or repetitive stimuli. It shares 40-50% homology with TRPV1 and has certain common features such as activation and sensitization by camphor and 2-amino-ethoxy-diphenyl borate (2-APB). The latter is a reliable blocker by IP_3-induced Ca^{2+} release mechanism. Other agonists of TRPV3 include carvacrol, eugenol and thymol. TRPV4 has an even lower threshold of 27-34°C and has a variety of chemical ligands, such as phorbol esters, low pH, citrate, endocannabinoids, arachidonic acid metabolites, and nitric oxide [53,59-61]. Both TRPV3 and TRPV4 are expressed most extensively in skin keratinocytes, indicating that keratinocytes may signal to sensory neurons, instead of thermal stimuli acting directly on neurons. Furthermore, TRPV3-deleted mice lack camphor-induced activation of keratinocytes and exhibit strong deficits in response to innocuous and noxious heat. Thus, TRPV3 expressed in skin keratinocytes may have an important role in mammalian thermosensation [62].

In addition, TRPV4, a Ca^{2+}-permeable nonselective cation channel appears to play a mechano-sensory or osmo-sensory role in several musculoskeletal tissues. TRPV4 is expressed in both osteoblasts and osteoclasts, and the absence of TRPV4 prevents disuse-induced bone loss, suggesting a critical role in skeletal development [63].

2.3 Cold Receptors

2.3.1 TRPM8

The search for the cold receptor began with menthol, the chemical derived from the plants of the mint family. Two independent research groups cloned and characterized a menthol sensitive TRP channel, TRPM8 [64-66]. TRPM8 is mostly expressed in small DRG and TG neurons. It is activated by temperature below 25°C and by various chemicals including menthol, eucalyptol, and icilin [67-71]. Whole-cell recording in HEK293 cells (human embryonic kidney 293 cells) expressing TRPM8 revealed that TRPM8 is a nonselective cation channel with relatively high Ca^{2+} permeability and also it is interesting that TRPM8 is not co-expressed with TRPV1 [7].

By behavioral methods we have recently investigated the effects of topical menthol on thermal (hot and cold) pain and innocuous cold and mechanical sensitivity in rats [8,72]. Menthol dose-dependently increased the latency for noxious heat-evoked withdrawal of the treated hindpaw with a weak mirror-image effect for untreated hindpaw, indicating antinociception. Menthol at the highest concentration reduced mechanical withdrawal thresholds, with no effect at lower concentrations. It was interesting that menthol had a biphasic effect on cold avoidance (thermal preference test). At high concentrations menthol reduced avoidance of colder temperatures (15°C and 20°C) compared to 30°C, while at lower concentrations menthol enhanced cold avoidance. In a –5°C cold plate test, highest menthol concentration significantly increased the nocifensive response latency (cold hypoalgesia) while lower concentrations were not different from vehicle controls [72].

The behavioral effects of topical menthol application seen in our study are consistent with effects on TRPM8 channels. An important role for TRPM8 becomes apparent when this channel is missing. TRPM8 null mice exhibit a deficit in cold avoidance and in general, deficient response behaviors to moderately cool temperatures [64,67]. McKemy has recently presented a molecular model for cold sensation (Fig. 2). According to his suggestion, the core of the model is TRPM8 channel which, unlike the other molecular candidates for cold transduction, appears to be exclusively involved in cold signaling and not mediating other modalities of somatosensation [73].

2.3.2 TRPA1

TRPA1 cation channel is activated by cold temperature of about 17°C, which is close to the reported noxious cold sensation and a lower threshold as compared with TRPM8. As most of the expression of TRPA1 overlaps with that of TRPV1, it seemed reasonable to link TRPA1 to

cold nociception [7,74,75]. Several chemical irritants can activate TRPA1 channel, among them is icilin, a synthetic compound that induces intense cold sensation when applied to human mucous membrane [76]. Other pungent cysteine-reactive chemicals, such as isothiocyanates (from horseradish and mustard), cinnamaldehyde (cinnamon), and allicin (garlic), activate TRPA1 through covalent modification of cysteine, regardless of their overall structures [77]. However, the role of TRPA1 channel in thermal transduction is controversial. In heterologous expression systems, TRPA1 was activated by cold stimuli with an activation temperature of about 17°C, which is close to the reported noxious cold threshold. This finding led to the suggestion that TRPA1 is involved in cold nociception [7]. A study from another group failed to reproduce cold responsiveness in TRPA1 [77]. The reason for this apparent discrepancy is unclear. Both groups have demonstrated that TRPA1 can be activated by pungent isothiocyanate compounds such as those found in wasabi, horseradish, cinnamon, and mustard oil [7,41,74,78]. Thus, several of the thermosensitive TRP channels likely to be involved in nociception can be activated by stimuli other than temperature [7].

Unlike TRPM8, TRPA1 channel is specifically activated in a subset of sensory neurons that express the nociceptive markers as c*alcitonin gene related peptide* (CGRP) and substance P [74]. Furthermore, TRPA1 is frequently co-expressed with TRPV1, raising the possibility that TRPA1 and TRPV1 mediate the function of a class of polymodal nociceptors. Such co-expression might also explain the paradoxical hot sensation experienced when one is exposed to a very cold stimulus [7].

We carried out extensive studies on TRPA1 channel by some behavioral tests to see whether CA and MO affect sensitivity to thermal stimuli in rats [8,24,32]. Unilateral intraplantar injection of CA induced a significant, concentration-dependent reduction in latency for ipsilateral paw withdrawal from a noxious heat stimulus, peaking by 30 min with partial recovery at 120 min. In the thermal preference test CA did not increase cold avoidance when compared to control group. However in other experiments with allyl isothiocyanate (AITC), chemical compound of MO, we have found that in the 30° *vs.* 15°C plates, rats treated with the higher concentrations of AITC exhibited a significant preference for the colder 15°C plate compared to vehicle-treated rats, i.e., they significantly avoided the warmer 30°C plate [51]. We suppose that these findings are consistent with roles for TRPA1 in hot hyperalgesia and cold hypoalgesia [8,24,32,52,79].

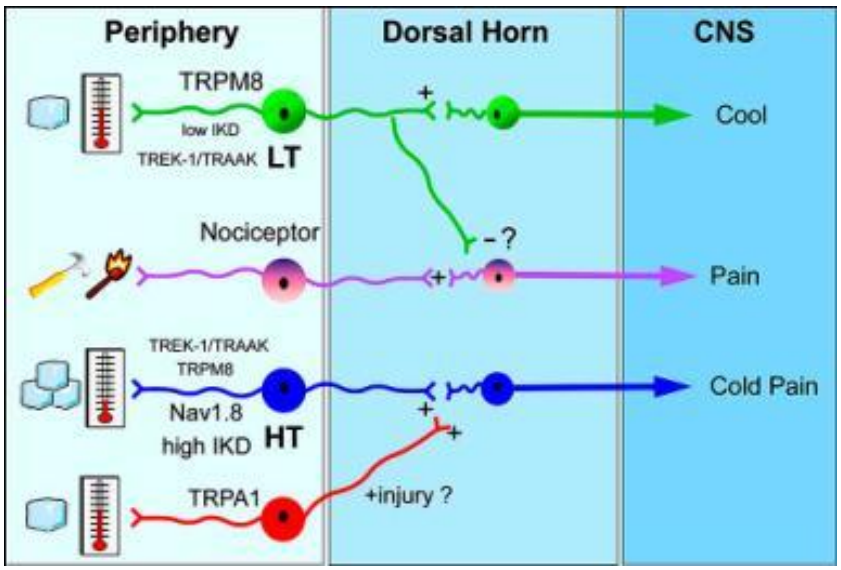

Fig. 2. Model for cold sensation

The differential perception of innocuous cool and noxious cold temperatures in the low-threshold and high threshold neuronal populations, respectively. Abbreviations: HT, high threshold; LH, low threshold; TREK-1/TRAAK, K^+-channels; IKD, inactivation delayed K^+-current; Nav1.8, Na^+-channel. (Reproduced from McKemy [72] with permission)

It has recently reported about bimodal action of CA on the TRPA1 channel. Whole-cell patch clamp experiments in TRPA1-expressing Chinese hamster ovary (CHO) cells revealed that extracellular application of CA strongly stimulates TRPA1 currents. However, subsequent application of CA induced fast and reversible current inhibition. Application of CA in basal conditions induced a rather small current increase, followed by current inhibition and a dramatic rebound of current amplitude upon washout. These observations are reminiscent of the effects of TRPA1 modulators having bimodal effects, e.g., menthol and nicotine [80].

3. CONCLUSION

The recent expansion of investigation into thermo-TRP ion channels has yielded rich information on their molecular mechanisms for identification potential drug targets. Interest is mounting as a result of emerging data from animal models, human genetic disorders and, in some cases, compounds entering clinical trials. At this early stage, much remains to be learned about this important super family of ion channels that serve as temperature cellular sensors. Understanding their activation mechanisms will undoubtedly help revealing the multifaceted roles thermo-TRP channels play in normal and pathological conditions including pain, neurology, oncology, visceral organs and genetic diseases.

The answers to the above questions will help to determine the answer to the most pressing question in the TRP channel-related field: will blocking or modulating TRP channels ameliorate established human disease? This problem will only be resolved after long-term clinical studies have been carried out in patients. However, the broad and pronounced links to patho-physiological processes that have been revealed by extensive preclinical target validation and human genetic studies provide strong cause for optimism [37].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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