Heliyon 11 (2025) e41730

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Transient receptor potential channels in dental inflammation and pain perception: A comprehensive review

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ARTICLE INFO

Keywords:
Transient receptor potential (TRP) channels
Ion channels
Sensory transduction
Nociception
Therapeutic strategies

ABSTRACT

Transient Receptor Potential (TRP) channels are a family of ion channels that play pivotal roles in various physiological processes, including sensory transduction, temperature regulation, and inflammation. In the context of dentistry, recent research has highlighted the involvement of TRP channels in mediating sensory responses and inflammation in dental tissues and temporomandibular joint (TMJ) structure. TRP channels have emerged as major contributors in the development of inflammatory conditions and pain affecting the oral cavity and related structures, such as periodontitis, dental erosion cause hypersensitivity, pulpitis, and TMJ disorders. These inflammatory conditions notably contribute to oral health challenges, often leading to sharp pain, dull aches, and compromised functionality. Pharmacological interventions and emerging strategies aimed at modulating TRP channel activity are critically evaluated. The therapeutic potential of targeting TRP channels in the management within dental practice is a focal point of view to alleviate pain and inflammation. In conclusion, this comprehensive review provides a valuable synthesis of current knowledge regarding the involvement of TRP channels in inflammatory conditions of dentistry underscoring the potential of TRP channels as promising targets for therapeutic intervention, and then paving the way for innovative strategies to address the complexities of inflammatory dental conditions.

The transient receptor potential (TRP) channels constitute a versatile family of ion channels that make substantial contributions to sensory transduction and inflammation [1]. The modular structure of TRP channels allows them to respond to a wide array of physical and chemical stimuli, rendering them crucial in processes like thermosensation, chemosensation, and mechanosensation [2]. The current understanding of TRP channels, which includes their structural attributes and various functions in cellular physiology, highlights their participation in sensory perception, notably in temperature and pain detection. Moreover, it explores their broader relevance in cellular signaling and oral-facial conditions within dentistry. Furthermore, the review investigates recent progress in TRP channel studies and potential therapeutic approaches aimed at these channels.

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https://doi.org/10.1016/j.heliyon.2025.e41730
Received 21 August 2024; Received in revised form 9 December 2024; Accepted 4 January 2025
Available online 7 January 2025

1. Brief overview of Ion channels, cellular signaling, and their functions

Ion channels are integral membrane proteins that play a fundamental role in cellular physiology by facilitating the selective movement of ions across cell membranes [1]. This regulated ion flux is crucial for maintaining cellular homeostasis, signal transduction, and various physiological processes. Ion channels exhibit remarkable diversity in structure, function, and specificity, allowing them to respond to a myriad of environmental cues and contribute to the intricate balance of ion concentrations within and between cells [3]. Preclinical studies categorize channels according to their selectivity for specific ions, including calcium, potassium, sodium, and chloride. They can be further categorized into mechanically-gated, voltage-gated, and ligand-gated channels. Mechanically-gated channels are triggered by the mechanical stimuli while voltage-gated channels react in response to alterations in membrane potential. In addition, ligand-gated channels, on the other hand, become activated through the binding of specific molecules [4].

TRP channels have a rich history dating back over 50 years. In 1960, Cosens et al. made a pivotal discovery by identifying a visual mutant in Drosophila [5]. This mutant exhibited a transient response, rather than a sustained one, to bright light stimuli [6]. Subsequently, in 1975, Minke et al. coined the name "transient receptor potential" for this mutant based on its distinctive electrophysiological behavior [7]. The turning point arrived in 1989 when Montell et al. and Wong et al. independently cloned the TRP gene, identifying it as a transmembrane protein. This groundbreaking accomplishment marked the beginning of a focused research effort aimed at broadening our understanding of TRP [8]. Since these seminal discoveries, scientists have been dedicated to unraveling the intricate functions and physiological roles of TRP channels. This ongoing exploration has led to significant advancements in our comprehension of these channels and their involvement in various biological processes.

All TRP (Transient Receptor Potential) gene products are intrinsic membrane proteins characterized by six transmembrane helices (S1-S6) and a cation-permeable pore located between the S5 and S6 helices, forming a voltage-sensor-like domain (VSLD). The intracellular amino (N) and carboxy (C) termini vary in length across different TRP channel subfamilies (Fig. 1). These cytoplasmic domains play a crucial role in regulating channel function and modulating their trafficking within the cell (Table 1).

TRPA (Transient Receptor Potential Ankyrin) channels are characterized by an abundance of N-terminal ankyrin repeats and function as receptors for a diverse array of harmful external stimuli, encompassing extreme cold, irritating substances, mechanical pressures, reactive chemicals, and endogenous signals associated with cellular injury. TRPA1 activates the nuclear factor kappa-B (NF-κB) and AMP-activated protein kinase (AMPK) signaling pathways [23,24] (Table 2), which in turn stimulate the production of inflammatory factors such as TNF-α and members of the IL family. Activation of TRPA1 channels also triggers an influx of sodium and calcium ions, leading to depolarization of nociceptive nerve endings—essential for generating centrally propagating nociceptive signals. The broad roles and distribution of TRPA1 across nociceptive nerve fibers, epithelial cells, and various other cell types underscore its involvement in a wide range of diseases, including neurogenic inflammation, osteoarthritis, allergic dermatitis, asthma, inflammatory bowel disease, migraine, cancer pain, and gout. These characteristics make TRPA1 an attractive target for therapeutic interventions [9,10].

Like TRPA channels, TRPC channels also feature N-terminal ankyrin repeats and function as nonselective cation channels. The C-terminus is involved in protein-protein interactions, influencing channel trafficking, assembly into complexes, and regulation by intracellular signaling pathways. The structure of TRPC channels shares similarities with the voltage sensor domains of voltage-gated K+, Na+, and Ca2+ channels, with the S5–S6 regions forming a conserved ion conductance or pore domain common to all TRP channels, as well as voltage-gated channels, inwardly rectifying K+ channels, and bacterial K+ and Na + channels [11,12]. TRPC4 has been implicated in skin inflammation, such as erythema and desquamation. Inflammation in an imiquimod (IMQ)-induced psoriasis model can be inhibited by TRPC4 antagonists [25]. TRPC channels play a significant role in vasospasm following hemorrhagic stroke, neuronal death and survival in ischemic stroke, and thrombin-induced pathological changes in astrocytes. They also contribute to stroke risk by influencing blood pressure and atherosclerosis [26]. In Ca2+ imaging experiments, Ca2+ influx through TRPC6 activates MAPK signaling, promoting the neuroprotective chemokine CXCL1 [27], which helps protect nerves after a stroke.

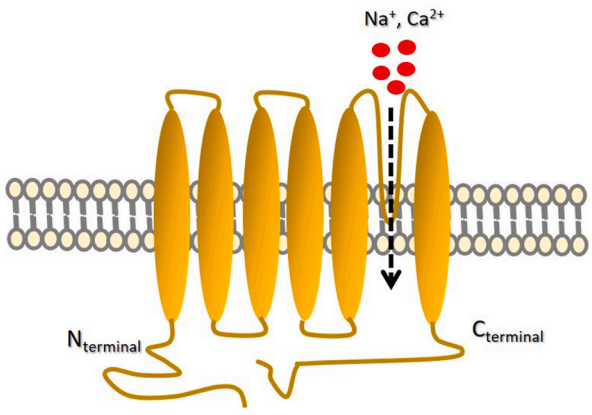

Fig. 1. The overall architecture of mammalian transient receptor potential (TRP) channels consists of a tetrameric arrangement, where each subunit is composed of six transmembrane domains (S1-S6). The N- and C-terminal domains are situated in the cytoplasmic regions.

Table 1
Provides a detailed overview of the N- and C-terminal domains, highlighting the specific functions associated with each TRP subfamily.

	N-terminal	C-terminal	Function	Ref
TRPA	Ankyrin binding domain	–	Thermosensitivity, Nociception	9, 10
TRPC	Ankyrin binding domain	TRP box, Homer, calmodulin, IP3R, PDZ domain	Blood pressure regulation, angiogenesis	11, 12
TRPM	TRPM homology region (MHR) domain	TRP box, calmodulin, IP3R, α-kinase, ADP-ribose hydrolase	Core body temperature sensation, inflammatory pain, cold sensation	13, 14, 15
TRPML	Nuclear localization domain	EF-hand, Late endosomal/lysosomal targeting signal	Immune response, cell depolarization	16, 17
TRPP	GSK3 phosphorylation site, Cilial transport motif	EF-hand, ER retention signal, coiled-coil domain	Calcium signaling	18, 19
TRPV	Ankyrin binding domain	PIP2, PDZ domain, calmodulin	Neurodepolarization, Thermosensitivity, Mechanosensitivity	20, 21, 22

Table 2
TRP channels involve on various signaling pathways.

	MAPK	TGF-β	NF-KB	AMPK
TRPA1	Activation [23]	–	Activation [24]	–
TRPC4	Activation [25]	–	–	–
TRPV1	Activation [34,35]	Modulation [36]	–	Activation [34,35]
TRPV4	Activation [37,38]	–	Activation [39]	–
TRPM8	Activation [29]	–	Modulation [30]	–
TRPML1	Activation [32]	–	–	–

TRPM channels, specifically, belong to the melastatin subfamily. The structures of TRPM channels have been elucidated through various techniques, including X-ray crystallography and cryo-electron microscopy (cryo-EM), providing insights into their gating mechanisms and regulation. They are involved in various physiological functions such as sensing temperature, osmolarity, pH, and other environmental stimuli. TRPM4 and TRPM7, participate in the regulation of sodium and potassium homeostasis. TRPM4, for instance, acts as a calcium-activated non-selective cation channel, influencing cellular excitability and ion balance. TRPM7 has been implicated in magnesium and divalent cation homeostasis, affecting cell viability and function [28]. TRPM channels are associated with the regulation of various cations, including K+, Na+, Mg2+, and Ca2+, and are activated and modulated by MAPK and NF-κB signaling pathways [29,30]. They also play a role in regulating respiratory conditions such as cough by modulating oxidative stress in the cough center [31]. Furthermore, TRPM channels are crucial in mediating cell death triggered by oxidative stress-related pathological factors, including ischemia-reperfusion injury, neurotoxic amyloid β-peptide, and MPTP/MPP+, all of which contribute to neuronal death in the brain [13–15].

TRPML stands for Transient Receptor Potential Mucolipin. The structure of TRPML channels consists of six transmembrane segments (S1-S6), with both the N- and C-termini located intracellularly. TRPML channels form tetrameric complexes, where each subunit contributes to the formation of the ion-conducting pore. These channels are permeable to a variety of cations, including K+, Na+, and Ca2+. TRPML channels are particularly interesting because of their involvement in lysosomal function and membrane trafficking. They are primarily located in the membranes of lysosomes, which are cellular organelles responsible for degradation and recycling of cellular waste [16,17]. The TRPML signaling pathway is activated through calcium-dependent kinases and AMPK. TRPML is associated with oxidative stress, and its upregulation or downregulation is linked to the emergence of a tumor phenotype. This strongly suggests that changes in TRPML protein expression may represent an early event in the tumorigenesis of glioblastoma (GBM) [32].

Polycystin proteins, which are encoded by the PKD1 and PKD2 genes in humans, are essential components of TRPP channels. Mutations in these genes are associated with polycystic kidney disease (PKD), a genetic disorder characterized by the formation of fluid-filled cysts in the kidneys and other organs. TRPP channels have been implicated in various physiological processes, including calcium signaling, mechanosensation, and regulation of cell proliferation and differentiation. They are particularly important in the kidney, where they are involved in sensing fluid flow and maintaining proper renal function [33]. The exact structures and functions of TRPP channels are still being elucidated, as research in this area is ongoing. However, they are known to form complex multi-protein complexes and play critical roles in cellular signaling pathways [18,19].

The general architecture of TRPV (Transient Receptor Potential Vanilloid) channels bears resemblance to voltage-gated potassium channels and encompasses six subfamilies. Each family exhibits unique characteristics and responds to various endogenous ligands, along with distinct gating stimuli like heat, pH, mechanical stress, or osmotic shifts. Activation of the TRPV family regulates MAPK signaling, which induces neuronal cell death and is associated with neuronal dysfunction [34–38]. TRPV modulation of the TGF-β signaling pathway has been linked to renal and liver fibrosis [36]. Additionally, TRPV activation via the NF-κB pathway leads to the production of proinflammatory cytokines, contributing to tissue inflammation [39]. Their physiological roles are remarkably diverse and are often specific to particular subtypes and tissues. Across numerous tissues, they function as detectors of diverse pain stimuli, including heat, pressure, and pH fluctuations, while also contributing to electrolyte homeostasis, barrier integrity, and macrophage development [20–22].

Activating TRP channels induces ionic alterations both inside and outside the cell, initiating downstream pathways. TRPs impact

various signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, transforming growth factor (TGF)-β signaling pathway, nuclear factor kappa-B (NF-κB) pathway, and AMP-activated protein kinase (AMPK) pathway. Table 2 shows the specific TRP channels affecting several downstream pathways.

2. Role of TRP channel in inflammatory diseases of orofacial structure

A key aspect of TRP channels is their role in sensory transduction. TRP channels act as molecular sensors, converting physical or chemical stimuli into electrical signals that are then transmitted to the central nervous system. This sensory transduction is evident in processes such as the detection of temperature changes, the perception of noxious stimuli (nociception), and the recognition of specific tastes [40–42].

Temperature sensation refers to the ability of organisms to detect and interpret temperature changes in their environment or within their bodies [43]. It's a fundamental aspect of physiology that allows organisms to respond appropriately to temperature variations, whether warmth or cold, avoiding extreme temperatures, or regulating internal body temperature. TRP channels are a diverse group of ion channels found in various organisms, including mammals, and play a crucial role in detecting temperature changes. Some TRP channels are specifically sensitive to temperature alterations, hence termed thermosensitive TRP channels. These channels act as molecular sensors, responding to different temperature ranges, including both hot and cold stimuli. The role of thermosensitive TRP channels involves their ability to sense temperature and convert these temperature cues into electrical signals that can be transmitted to the nervous system [44]. Upon activation by specific temperature ranges, these channels allow ions to flow across the cell membrane, triggering nerve impulses that convey temperature in-formation to the somatosensory cortex [45]. Dysfunction or alterations in these channels can lead to various sensory disorders related to temperature perception, such as hypersensitivity to temperature extremes, impaired thermoregulation, or conditions like chronic pain syndromes.

The perception of pain is a critical physiological response that serves as a protective mechanism in response to harmful stimuli. Nociception, the neural process of encoding noxious stimuli, involves complex mechanisms, with TRP channels playing a pivotal role [46]. TRP channels, a diverse family of ion channels, serve as molecular sensors for various pain-inducing stimuli, including thermal, chemical, and mechanical stimuli. Specific subtypes of TRP channels, such as TRPV1, TRPA1, and TRPM8, are extensively involved in nociceptive signaling pathways, contributing to the detection and transmission of painful stimuli [47]. The identification of TRP channels in the orofacial structure is presented in Table 3.

This section comprehensively explores the TRP channel function in pathological orofacial inflammatory conditions including pulpitis, dentin hypersensitivity, periodontitis, and temporomandibular joint (Fig. 2).

2.1. Pulpitis

Pulpitis is an inflammatory condition affecting the dental pulp, which is the soft tissue at the center of a tooth containing blood vessels, nerves, and connective tissue. This inflammation is commonly caused by bacterial infection, often resulting from untreated tooth decay or dental cavities.

In caries-induced pulpitis, bacterial toxins have the potential to directly activate pulpal nerve fibers, preceding the onset of neurogenic inflammation triggered by the immune response to infection and contributing to the manifestation of pain [57]. These toxins can, in turn, activate TRPV4 expressed on odontoblasts, leading to elevated intracellular $Ca2+$ levels of odontoblasts and subsequent activation of intra-dental sensory neurons.

The TRPV2 receptor is notably more highly expressed in pulpal sensory neurons compared to its expression in the trigeminal ganglia (TG) as a whole [58]. Conversely, TRPV1 appears to be underrepresented in pulpal sensory neurons relative to its expression in the broader TG [59]. These findings suggest that the dental pulp possesses a distinctive nociceptive innervation pattern and may have a limited ability to perceive heat through TRPV1, especially in uninjured conditions. This observation might relate to the clinical unreliability of heat as a stimulus for testing pulp vitality [60]. Considering that TRPV2 is no longer considered a primary transducer of noxious heat stimuli, it can be implied that either a sparse number of TRPV1 afferents are adequate to convey heat sensitivity in the dental pulp, or alternative yet undiscovered heat transducers or mechanisms might be involved in this process [61]. Inflammatory conditions can lower the activation threshold of TRP channels in odontoblasts and sensory neurons, leading to nerve hyperexcitability. The upregulation of TRPV1 [62] and TRPA1 [63] in the nerve fibers of the dental pulp is associated with the pain experienced in dental pulpitis. Lipopolysaccharide (LPS), a bacterial toxin, has been found to activate cultured TG neurons and sensitize TRPV1 channels via

Table 3
The discovery of TRP channels in orofacial structures.

Year	Discovery/Key Event in Dental & TMJ Related to TRP Channels
2005	The involvement of TRPV1 in both dental pulp and odontoblasts related to inflammation [48,49]
2013	Study indicating TRPV1 activation in dental pulp inflammation [50]
2015	Research linking TRPV4 to odontoblast function and dentin sensitivity [51]
2015	Role of TRPM8 in dental afferent neuron caused hypersensitivity and cold-induced pain [52]
2016	Implications of TRPA1 in odontoblast induced dental nociception and pain signaling [53]
2020	Exploration of TRPV1 and TRPA1 In afferent signaling from muscle induced temporomandibular joint pain and inflammation [54]
2021	Investigating the involvement of TRPV1 and TRPV4 in trigeminal afferent neurons in crucial for understanding their role in temporomandibular disorders and pain [55,56]

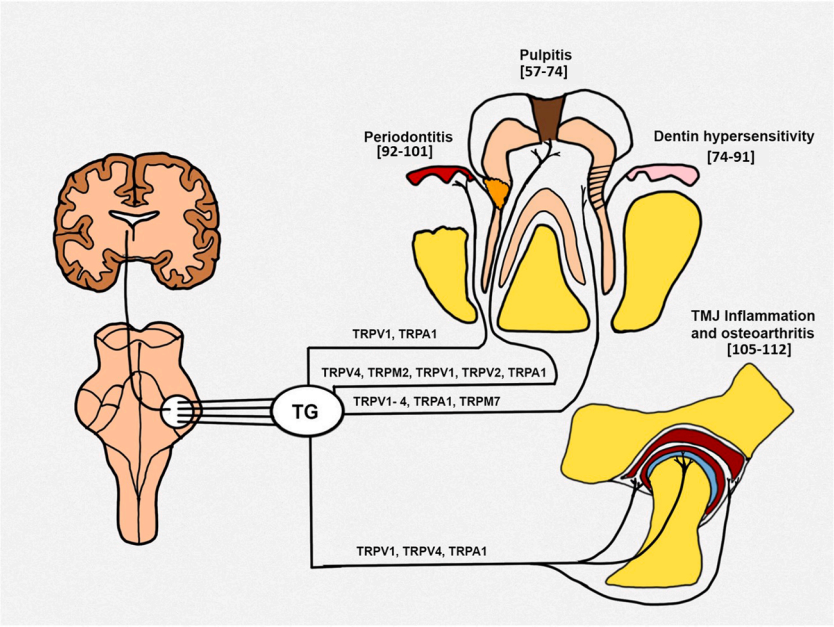

Fig. 2. The diagram representative transient receptor potential (TRP) channels involved in orofacial inflammatory conditions. TG; trigeminal ganglion, TMJ; temporomandibular joint.

a toll-like receptor 4 (TLR4)-mediated mechanism [64], while sensitizing TRPA1 channels in a TLR4-independent manner [65].

Therefore, TRP Channels in dental tissue are included.

1. Thermal Sensation: TRPV1 and TRPA1 channels contribute to thermal sensation in dental pulp, impacting responses to hot and cold stimuli.
2. Nociception: TRPV1 and TRPA1 are implicated in dental pain perception, responding to noxious stimuli and contributing to nociceptive signaling.

TRP channels such as TRPV1 or TRPM2 are also expressed on pulpal fibroblasts, playing a significant role in pulpitis. Abundantly present in the dental pulp, fibroblasts are responsible for synthesizing the extracellular matrix and maintaining the structural integrity of the dental pulp [66,67]. The activation of the TRPV1 channel leads to the release of IL-6, a pro-inflammatory cytokine, in response to bacterial stimulation, suggesting a role in the development of pulpitis [68]. Furthermore, the overexpression of TRPM2 in the pulpal fibroblasts of teeth exhibiting signs of irreversible pulpitis has been observed [69].

Moreover, studies have reported that during inflammation, pulpal pressure can increase from 15 to 40–50 cm H_2O [70,71]. This elevation is attributed to the release of fluid from blood vessels within the pulp, which is encased by hard tissues [70]. Such an increase in intra-pulpal pressure can activate mechanosensitive TRP channels on the nerve fibers within the pulp, thereby resulting in spontaneous pain.

Members of the TRP family are expressed in various cells of orofacial structures, such as vascular cells, immune cells, odontoblasts, fibroblasts, neurons, including mesenchymal stem cells [72]. Notably, TRPV1 has garnered significant attention due to its expression in a substantial subset of nociceptive afferent neurons. Antagonists such as SB366791, which target this receptor, have demonstrated efficacy in preclinical models of both inflammatory and neuropathic pain [73]. The extensive innervation of human dental pulp by neurons expressing both calcitonin gene-related peptide (CGRP) and the TRPV1 receptor. Moreover, applying capsaicin to human dental pulp leads to a concentration-dependent release of CGRP, a response that is effectively inhibited by pretreatment with Capsazepine, a TRPV1 antagonist [74]. These findings collectively support the hypothesis that orofacial tissues can engage in inflammatory responses mediated via transduction processes facilitated by TRP channels.

2.2. Dentin hypersensitivity

Dentin hypersensitivity, often characterized by sharp pain or discomfort in response to various stimuli (such as hot, cold, sweet, or acidic substances), is a common dental condition that can significantly affect an individual's quality of life. The involvement of TRP channels, particularly those expressed in sensory nerve fibers within the dentin-pulp complex, has gained attention in understanding the mechanisms underlying dentin hypersensitivity [74].

Among TRP channels, several subtypes have been implicated in dentin sensitivity, including TRPV1, TRPV3, TRPV4, and TRPA1 [75]. These channels are expressed in the nerve endings of odontoblasts, which are specialized cells forming the dentin-pulp interface.

Their activation, triggered by various stimuli, can lead to the generation of action potentials and the transmission of pain signals [76]. Specifically, TRPV1 has been associated with its responsiveness to heat, acidic pH, and capsaicin. TRPV1 activation in dentin hypersensitivity might occur due to the exposure of dentinal tubules to thermal changes or acidic conditions resulting from dietary factors or dental erosion [77]. TRPV3 and TRPV4 are sensitive to warmth and mechanical stimulation. Their involvement in dentin sensitivity might be linked to temperature changes and mechanical stimuli that cause dentinal fluid movement and subsequent nerve excitation [78]. TRPA1 is another TRP channel activated by cold, mechanical stimuli, and certain chemicals. Its role in dentin hypersensitivity could be associated with responses to cold stimuli or other triggers that activate the channel in dentinal tubules [79]. The exact mechanisms and contributions of these TRP channels in dentin sensitivity are still under investigation. However, their presence and responsiveness in odontoblasts and nerve endings within the dentin-pulp complex suggest their involvement in the transmission of nociceptive signals related to dentin hypersensitivity.

Intense thermal stimulation on the tooth surface can gradually alter the temperature at the dentine-pulp junction, potentially activating thermosensitive TRP channels found on odontoblasts and sensory neurons in the TG [80,81]. These TRP channels, acting as thermoreceptors, trigger inward currents in afferent neurons within the TG [78]. Furthermore, external stimuli activating TRP channels and other receptors on odontoblasts can increase the concentration of intracellular Ca2+ [72,82–84]. Consequently, odontoblasts may release ATP and glutamate, which can signal adjacent nerve fibers of afferent neurons in the TG in a paracrine manner [82–85]. Notably, ATP activates purinergic receptors on peripheral sensory nerve fibers, which is significant for pain signaling [86], and glutamate may also function as a communicating molecule between odontoblasts and TG neurons [87].

Applying a thermal stimulus to a tooth surface generates the thermal gradient between the enamel and dentine, leading to mechanical stress [87], and, in turn, inducing expansion of the dentinal wall, resulting in fluid movement within the dentinal tubules [88]. This suggests that intense thermal stimulation causes mechanical deformation of the dentine, potentially activating mechanosensitive TRP channels and other mechanoreceptors found in odontoblasts and pulpal nerve fibers. Moreover, mechanical stretching of the cell membrane, induced by hypotonic solutions, increases intracellular Ca^{2+} levels in cultured odontoblast-like cells [75,82–84,89,90]. This response is inhibited by antagonists of TRPV1 (capsazepine), TRPV2 (tranilast), TRPV4 (RN-1734) [75,83,84], TRPA1 (HC030031) [89], and TRPM7 (FTY720, extracellular Mg^{2+}, and Gd^{3+}) [90], suggesting their potential roles as mechanoreceptors and/or osmoreceptors. Both mechanosensitive and thermo-sensitive TRP channels expressed in odontoblasts and sensory neurons in the TG can be activated by thermal stimuli applied to an intact tooth. The dentin hypersensitivity experienced after thermal stimulation of the tooth surface may be partially due to the activation of mechanoreceptors on odontoblasts and sensory neurons in the TG induced by mechanical stress.

2.3. Periodontitis

In the context of periodontitis, the hypoxic environment of subgingival region in-duces abnormal apoptosis, which play a pivotal role in disease development by promoting ongoing infection and exacerbating immune reaction. This imbalance between the destruction of resorption and the reconstruction of mineralization in periodontal tissue perpetuates the disease [91]. Of particular interest is the transient receptor potential ankyrin 1 (TRPA1), which is the nonselective permeable Ca2+ channel within the transient receptor potential cation channels superfamily. TRPA1 is expressed in periodontal ligament cells (PDLCs) [92] and contributes to inflammatory pain and mechanical hyperalgesia [93]. The increase in cytosolic Ca2+ triggered by TRPA1 activation during inflammation consistently correlates with heightened levels of reactive oxygen species (ROS), cellular apoptosis, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction. These mechanisms collectively contribute to additional cytosolic Ca2+ elevation by regulating Ca2+ gates and promoting Ca2+ leakage from the ER or plasma membrane [94]. Previous research indicates that oxidative stress (OS), characterized by the activation of reactive oxygen species (ROS), and apoptosis occur prior to the onset of periodontitis [91] The overproduction of ROS and irregular apoptosis are implicated in the loss of alveolar bone during the progression of periodontitis [95]. Hence, protecting periodontal tissues or cells from various factors that induce oxidative stress and apoptosis becomes a potential approach to delay the start and progression of periodontitis. Moderately pre-venting or eliminating excessive ROS or apoptosis is crucial in managing the microenvironment of periodontitis and establishing favorable conditions for periodontal homeostasis [96–98].

Moreover, the upregulation of TRPV1 has been linked to numerous inflammatory conditions, including periodontitis [99]. Studies by Sooampon S et al. demonstrated that the activation of TRPV1, a nociceptive ion channel receptor, by capsaicin, resulted in the increased expression of osteoprotegerin (OPG) in periodontal ligament cells [100]. They found that thermal stimulation induced TRPV1 activation in these cells, leading to calcium influx, which served as a secondary messenger, ultimately promoting the expression of TNF-α [101]. Moreover, inhibiting TRPV1 ion channels by capsazepine was observed to disrupt the differentiation process of periodontal osteoclasts and osteoblasts in vitro [102].

Orthodontic force also causes mechanical irritation and, in turn, induced localized inflammation in the periodontium, often resulting in pain for many patients. In mice, nocifensive behaviors triggered by orthodontic force can be significantly reduced by intraganglionic injection of resiniferatoxin (RTX), a neurotoxin specifically targeting a subset of neurons expressing TRPV1 [103]. Nociceptive inputs via TRPV1 expressing afferents seem to initiate subsequent alterations in gene expression, not only evident in TRPV1-positive neurons but also present in TRPV1-negative neurons and non-neuronal cells throughout the ganglia [103]. The transcriptomic changes triggered by orthodontic force may signify an active regenerative program within the TG in response to axonal injury resulting from orthodontic force application [59].

2.4. Temporomandibular joint

TRP channels have been identified in various tissues and structures within the orofacial region, including the temporomandibular joint (TMJ). These channels play a role in sensory perception, nociception, and inflammatory processes, making their presence in the TMJ significant for understanding its physiology and potential involvement in TMJ-related disorders [104]. Several studies have indicated the expression of different TRP channel subtypes in the TMJ. TRPV1, TRPV4, TRPA1, and other TRP channels have been detected in sensory nerve fibers, chondrocytes, and synovial cells within the TMJ. TRPV1, known for its sensitivity to heat, capsaicin, and inflammatory mediators, has been found in sensory nerve fibers in the TMJ region. Activation of TRPV1 in these nerve endings might contribute to pain sensation associated with TMJ disorders.

Acute temporomandibular disorder typically come from muscle injury. This injury may lead to altered biomechanics and increased stress on the joint. The heightened mechanical load can trigger a local inflammatory response within the synovium. This process is characterized by the release of pro-inflammatory mediators and an increased production of synovial fluid, resulting in synovitis. Prolonged activation of the inflammatory response can contribute to the transition from the acute phase to a chronic stage of synovitis. if left the synovitis untreated or unmanaged, may ultimately lead to the development of joint osteoarthritis. The synovium, a thin membrane lining the inner surface of the joint capsule, contains a rich supply of nerve endings. These nerve endings are primarily composed of free nerve endings, and they play a crucial role in conveying pain signals.

TRPV4, responsive to osmotic changes, mechanical stimuli, and temperature, has also been identified in chondrocytes and synovial cells within the TMJ [105]. Its involvement in mechanosensation and cellular responses to mechanical stress in the TMJ suggests a role in joint function. The findings from a prior study suggested that TMJ pain is triggered by increased bite force, leading to the upregulation of TRPV4 through phosphorylated extracellular-signal-regulated kinase (ERK). Conversely, TRPV4 likely operates downstream of MEK/ERK phosphorylation during the inflammation stage [106,107]. TRPA1, sensitive to chemical irritants and cold stimuli, has been detected in sensory nerves and synovial tissue of the TMJ. Its activation might contribute to nociceptive responses and inflammatory processes within the joint [108]. The co-expression of TRPV1-TRPA1 is present in masseter muscles. The activation of TRPV1 through the p38 MAPK pathway simultaneously induces the upregulation of TRPA1 [109]. Inhibiting this pathway could be a viable option to halt the progressive advancement toward the degenerative stage of TMJ. The recent study was revealed that the expression of TRPV1 in the TMJ exhibited an increase in mice subjected to a model of complete Freund's adjuvant (CFA) injection by day 21 [110]. The induction of synaptic plasticity by glutamate in sensory nerves is a pivotal factor in the peripheral sensitization of TRPV1, given its modulation through the activation of protein kinase C [54]. Preserving the adaptability of sensory nerves becomes imperative to preclude the development of hypersensitivity sensations that could progress into chronic pain.

Generally, TRPV1 and TRPA1 are predominantly present in orofacial tissue, as depicted in Fig. 2. Following injury and inflammation, there is an upregulation of these channels, resulting in peripheral sensitization. This subsequently leads to heightened regulation of neurogenic inflammation and cytokine release through various signaling pathways, as detailed in Table 2. This progression initiates apoptosis in various tissues, signifying the shift to the chronic phase of inflammation. Ultimately, structural integrity diminishes, leading to deformities. Highlighting the potential effectiveness of targeted interventions aimed at selectively modulating these primary channels underscores promise for managing inflammatory conditions and their associated symptoms.

3. Implications and future therapeutic potential of TRP channel in orofacial regions

The implications and future directions of TRP channels encompass a wide array of areas in both basic science and clinical applications. Here are some significant implications and potential avenues for future research concerning TRP channels TRP channels represent potential therapeutic targets for orofacial inflammatory conditions. Further research into developing selective modulators (agonists or antagonists) with improved specificity and reduced side effects holds promise for clinical interventions [111] Table 4 represents the TRP channels involved in pain and inflammation along with agonists and antagonists.

A previous study indicated that TRPV1 (Capsazepine) and TRPA1 (HC-030031) antagonists effectively mitigated oxidative stress in the periodontal ligament (PDL) and dental pulp [92] leading to a reduction in calcium influx associated with nociceptive pain behavior [112]. Additionally, the antagonists such as HC030031, AP18, and HC067047 were found to diminish ATP release in human odontoblasts [113]. Furthermore, the TRPV4 antagonist (HC 067047) exhibited inhibitory effects on hypotonic stress-induced RANKL expression in human PDL cells [114]. In addition, the TRPM8 antagonist (Cannabidivarin) exhibited the capacity to modulate IL-1β-induced inflammation in human gingival fibroblasts [115].

Continued exploration and development of TRP channel modulators, especially subtype-specific drugs, using innovative

Table 4
Agonists and antagonists of TRP channels.

	agonists	antagonists	Applications	Ref
TRPA1	Mustard oil, Cinnamaldehyde	HC-030031, A-967079	Pain, inflammation	79
TRPV1	Capsaicin, Heat, Resiniferatoxin	Capsazepine, Capsaicin (high dose)	Pain	80
TRPV4	4α-PDD, GSK1016790A	HC-067047, RN-1734	Inflammation	81
TRPM8	Menthol, Eucalyptol, Cubebol	AMG-333, Cannabidivarin, PF-05105679	Pain	15

pharmacological approaches, including high-throughput screening, structure-based drug design, and novel compound discovery, are crucial for translating TRP channel research into effective pharmaceuticals. Pharmacological interventions and emerging strategies targeting the modulation of TRP channels represent a focal point for alleviating pain and inflammation. These approaches are under critical evaluation due to the pivotal roles TRP channels play in sensory perception and the transmission of nociceptive signals. Several pharmacological interventions have been developed to modulate TRP channel activity. Antagonists targeting specific TRP channel subtypes, such as TRPV1 or TRPA1, have shown promise in preclinical studies and some clinical trials for managing pain and inflammation. For instance, Capsazepine have been explored for their potential in mitigating neuropathic pain, while HC-030031 have demonstrated efficacy in addressing inflammatory pain conditions [116,117]. Moreover, compounds that can selectively activate certain TRP channels have been investigated. For instance, capsaicin, an activator of TRPV1, has been employed topically for pain relief, particularly in conditions like arthritis or neuropathy. Similarly, menthol, an activator of TRPM8, has been utilized for its cooling effects in pain management [15].

Recent research has unveiled novel strategies for modulating TRP channels, including the development of small molecules, antibodies, natural compounds, and gene therapy approaches. These strategies aim to fine-tune TRP channel activity, either by blocking or enhancing their function, to alleviate pain and dampen inflammatory responses. However, challenges persist in developing TRP channel modulators with high specificity and minimal off-target effects. The dual roles of TRP channels in physiological and pathological processes necessitate careful consideration to avoid unwanted side effects when targeting these channels for therapeutic purposes. Emerging technologies and approaches, such as structure-based drug design, high-throughput screening, and CRISPR-based gene editing, offer promising avenues for the development of more precise and effective TRP channel modulators.

Understanding the roles of specific TRP channels in pain sensation and nociception is essential for developing targeted therapies for pain management. Investigating TRP channel interactions with other pain-related receptors and signaling pathways could unveil novel strategies for pain relief. Elucidating the involvement of TRP channels in inflammatory processes and immune responses may provide insights into modulating these channels to regulate inflammatory conditions. Targeting TRP channels might offer therapeutic opportunities for conditions such as asthma, arthritis, and inflammatory bowel disease. Exploring the diverse functions of TRP channels in sensory physiology, including temperature sensation, taste, vision, and olfaction, could provide deeper insights into sensory perception mechanisms. Understanding the interplay between different TRP channel subtypes in sensory systems is an intriguing area for future investigation. Translating basic TRP channel research findings into clinical applications, such as developing diagnostic tools, prognostic markers, and personalized therapies, remains a critical direction for future investigations.

4. Conclusion

TRP channels have gained attention in the field of dentistry due to their presence and involvement in various oral tissues, including dental pulp, periodontal tissues, and sensory nerves within the oral cavity. These channels, acting as molecular sensors, play pivotal roles in sensory perception, nociception, and the response to various stimuli in dental structures. In dentistry, TRP channels, particularly subtypes such as TRPV1, TRPV4, TRPA1, and TRPM8, are implicated in several aspects. TRP channels, especially TRPV1 and TRPA1, are expressed in sensory nerve fibers within dental pulp and periodontal tissues. They play a role in detecting temperature changes, chemical stimuli, and mechanical stress, contributing to dental pain perception and sensitivity. TRP channels have been identified in odontoblasts and nerve endings within dentin. They are involved in dentin hypersensitivity, where stimuli like cold, hot, sweet, or acidic substances elicit pain responses due to the activation of these channels. TRP channels, when activated, contribute to the release of inflammatory mediators and participate in the modulation of immune responses in periodontal tissues. They are involved in the regulation of inflammatory processes associated with periodontitis and other oral inflammatory conditions. Understanding TRP channel involvement may offer insights into the mechanisms underlying dental treatments and their effects on sensory perception and pain management in dental procedures. TRP channels represent potential targets for developing novel therapeutic interventions aimed at managing dental pain, dentin sensitivity, and inflammatory conditions in the oral cavity. Efforts to modulate these channels selectively might lead to improved treatments for oral health-related discomfort and diseases.

Continued research into the roles and mechanisms of TRP channels in dental physiology and pathology could pave the way for innovative diagnostic tools and targeted therapies to address various dental conditions, ultimately contributing to improved oral health care and patient comfort during dental procedures. Further research into TRP channels is poised to have substantial implications across diverse fields, ranging from fundamental biology to clinical therapeutics, offering potential solutions for various health conditions and improving our understanding of sensory perception and cellular signaling mechanisms.

CRediT authorship contribution statement

Varunya Chantadul: Writing – original draft, Supervision, Investigation, Formal analysis, Data curation. **Nattapon Rotpenpian:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Tawepong Arayapisit:** Writing – review & editing, Writing – original draft, Formal analysis. **Aree Wanasuntronwong:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

Not applicable.

Clinical trial registration

Not applicable.

Funding

Not applicable.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Aree Wanasuntronwong reports financial support was provided by Mahidol University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

References

[1] D.E. Clapham, TRP channels as cellular sensors, Nature 426 (2003) 517–524.
[2] H. Li, TRP channel classification, Adv. Exp. Med. Biol. 976 (2017) 1–8.
[3] X. Tao, C. Zhao, R. MacKinnon, Membrane protein isolation and structure determination in cell-derived membrane vesicles, Proc Natl Acad Sci U S A 120 (2023) e2302325120.
[4] M. Kashio, Thermosensation involving thermo-TRPs, Mol. Cell. Endocrinol. 520 (2021) 111089.
[5] Y. Chen, J. Mu, M. Zhu, A. Mukherjee, H. Zhang, Transient receptor potential channels and inflammatory bowel disease, Front. Immunol. 11 (2020) 180.
[6] T. Hof, S. Chaigne, A. Récalde, L. Sallé, F. Brette, R. Guinamard, Transient receptor potential channels in cardiac health and disease, Nat. Rev. Cardiol. 16 (2019) 344–360.
[7] B. Minke, C. Wu, W.L. Pak, Induction of photoreceptor voltage noise in the dark in Drosophila mutant, Nature 258 (1975) 84–87.
[8] C. Montell, G.M. Rubin, Molecular characterization of the Drosophila trp locus: a putative integral membrane protein required for phototransduction, Neuron 2 (1989) 1313–1323.
[9] G.M. Story, A.M. Peier, A.J. Reeve, S.R. Eid, J. Mosbacher, T.R. Hricik, T.J. Earley, A.C. Hergarden, D.A. Andersson, S.W. Hwang, P. McIntyre, T. Jegla, S. Bevan, A. Patapoutian, ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures, Cell 112 (2003) 819–829.
[10] F. Fujita, T. Moriyama, T. Higashi, A. Shima, M. Tominaga, Methyl p-hydroxybenzoate causes pain sensation through activation of TRPA1 channels, Br. J. Pharmacol. 151 (2007) 153–160.
[11] Y. Zhu, Q. Pan, H. Meng, Y. Jiang, A. Mao, T. Wang, D. Hua, X. Yao, J. Jin, X. Ma, Enhancement of vascular endothelial growth factor release in long-term drug-treated breast cancer via transient receptor potential channel 5-Ca(2+)-hypoxia-inducible factor 1α pathway, Pharmacol. Res. 93 (2015) 36–42.
[12] O.C. Lau, B. Shen, C.O. Wong, Y.W. Tjong, C.Y. Lo, H.C. Wang, Y. Huang, W.H. Yung, Y.C. Chen, M.L. Fung, J.A. Rudd, X. Yao, Author Correction: TRPC5 channels participate in pressure-sensing in aortic baroreceptors, Nat. Commun. 9 (2018) 16184.
[13] M. Behrendt, Transient receptor potential channels in the context of nociception and pain - recent insights into TRPM3 properties and function, Biol. Chem. 400 (2019) 917–926.
[14] I. Hirschler-Laszkiewicz, S.J. Chen, L. Bao, J. Wang, X.Q. Zhang, S. Shanmughapriya, K. Keefer, M. Madesh, J.Y. Cheung, B.A. Miller, The human ion channel TRPM2 modulates neuroblastoma cell survival and mitochondrial function through Pyk2, CREB, and MCU activation, Am J Physiol Cell Physiol 315 (2018) C571–c586.
[15] R. González-Muñiz, M.A. Bonache, C. Martín-Escura, I. Gómez-Monterrey, Recent progress in TRPM8 modulation: an update, Int. J. Mol. Sci. 20 (2019).
[16] Y. Song, R. Dayalu, S.A. Matthews, A.M. Scharenberg, TRPML cation channels regulate the specialized lysosomal compartment of vertebrate B-lymphocytes, Eur. J. Cell Biol. 85 (2006) 1253–1264.
[17] K. Nagata, L. Zheng, T. Madathany, A.J. Castiglioni, J.R. Bartles, J. García-Añoveros, The varitint-waddler (Va) deafness mutation in TRPML3 generates constitutive, inward rectifying currents and causes cell degeneration, Proc Natl Acad Sci U S A 105 (2008) 353–358.
[18] Y. Chen, Z. Zhang, X.Y. Lv, Y.D. Wang, Z.G. Hu, H. Sun, R.Z. Tan, Y.H. Liu, G.H. Bian, Y. Xiao, Q.W. Li, Q.T. Yang, J.Z. Ai, L. Feng, Y. Yang, Y.Q. Wei, Q. Zhou, Expression of Pkd2l2 in testis is implicated in spermatogenesis, Biol. Pharm. Bull. 31 (2008) 1496–1500.
[19] H.F. Cantiello, Regulation of calcium signaling by polycystin-2, Am J Physiol Renal Physiol 286 (2004) F1012–F1029.
[20] M.J. Caterina, M.A. Schumacher, M. Tominaga, T.A. Rosen, J.D. Levine, D. Julius, The capsaicin receptor: a heat-activated ion channel in the pain pathway, Nature 389 (1997) 816–824.
[21] T. Voets, G. Droogmans, U. Wissenbach, A. Janssens, V. Flockerzi, B. Nilius, The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels, Nature 430 (2004) 748–754.
[22] D. Becker, C. Blase, J. Bereiter-Hahn, M. Jendrach, TRPV4 exhibits a functional role in cell-volume regulation, J. Cell Sci. 118 (2005) 2435–2440.
[23] T. Kondo, J. Sakurai, H. Miwa, K. Noguchi, Activation of p38 MAPK through transient receptor potential A1 in a rat model of gastric distension-induced visceral pain, Neuroreport 24 (2013) 68–72.
[24] C.K. Wu, C.L. Wu, T.S. Lee, Y.R. Kou, D.C. Tarng, Renal tubular epithelial TRPA1 acts as an oxidative stress sensor to mediate ischemia-reperfusion-induced kidney injury through MAPKs/NF-κB signaling, Int. J. Mol. Sci. 22 (2021).

[25] S.H. Lee, R. Tonello, Y. Choi, S.J. Jung, T. Berta, Sensory neuron-expressed TRPC4 is a target for the relief of psoriasiform itch and skin inflammation in mice, J. Invest. Dermatol. 140 (2020) 2221–2229.e2226.
[26] J. Huang, TRPC channels and stroke, Adv. Exp. Med. Biol. 976 (2017) 61–71.
[27] H. Shirakawa, R. Katsumoto, S. Iida, T. Miyake, T. Higuchi, T. Nagashima, K. Nagayasu, T. Nakagawa, S. Kaneko, Sphingosine-1-phosphate induces Ca(2+) signaling and CXCL1 release via TRPC6 channel in astrocytes, Glia 65 (2017) 1005–1016.
[28] B. Nilius, T. Voets, TRP channels: a TR(I)P through a world of multifunctional cation channels, Pflugers Arch 451 (2005) 1–10.
[29] S. Cai, L. Wu, S. Yuan, G. Liu, Y. Wang, L. Fang, D. Xu, Carvacrol alleviates liver fibrosis by inhibiting TRPM7 and modulating the MAPK signaling pathway, Eur. J. Pharmacol. 898 (2021) 173982.
[30] S. Cao, Q. Li, J. Hou, Z. Li, X. Cao, X. Liu, B. Qin, Intrathecal TRPM8 blocking attenuates cold hyperalgesia via PKC and NF-κB signaling in the dorsal root ganglion of rats with neuropathic pain, J. Pain Res. 12 (2019) 1287–1296.
[31] Z. Ji, Z. Wang, Z. Chen, H. Jin, C. Chen, S. Chai, H. Lv, L. Yang, Y. Hu, R. Dong, K. Lai, Melatonin attenuates chronic cough mediated by oxidative stress via transient receptor potential melastatin-2 in Guinea pigs exposed to particulate matter 2.5, Physiol. Res. 67 (2018) 293–305.
[32] J. Coblentz, C. St Croix, K. Kiselyov, Loss of TRPML1 promotes production of reactive oxygen species: is oxidative damage a factor in mucolipidosis type IV? Biochem. J. 457 (2014) 361–368.
[33] J. Ren, Q. Yuan, J. Liu, L. Zhong, H. Li, G. Wu, F. Chen, Q. Tang, Identifying the role of transient receptor potential channels (TRPs) in kidney renal clear cell carcinoma and their potential therapeutic significances using genomic and transcriptome analyses, BMC Med Genomics 15 (2022) 156.
[34] G.H. Lee, C.Y. Kim, C. Zheng, S.W. Jin, J.Y. Kim, S.Y. Lee, M.Y. Kim, E.H. Han, Y.P. Hwang, H.G. Jeong, Rutaecarpine increases nitric oxide synthesis via eNOS phosphorylation by TRPV1-dependent CaMKII and CaMKKβ/AMPK signaling pathway in human endothelial cells, Int. J. Mol. Sci. 22 (2021).
[35] M. Chen, X. Dong, H. Deng, F. Ye, Y. Zhao, J. Cheng, G. Dan, J. Zhao, Y. Sai, X. Bian, Z. Zou, Targeting TRPV1-mediated autophagy attenuates nitrogen mustard-induced dermal toxicity, Signal Transduct Target Ther 6 (2021) 29.
[36] Y. Wang, D.H. Wang, Protective effect of TRPV1 against renal fibrosis via inhibition of TGF-β/Smad signaling in DOCA-salt hypertension, Mol Med 17 (2011) 1204–1212.
[37] Z. Zhu, R. Li, R. Stricker, G. Reiser, Extracellular α-crystallin protects astrocytes from cell death through activation of MAPK, PI3K/Akt signaling pathway and blockade of ROS release from mitochondria, Brain Res. 1620 (2015) 17–28.
[38] P. Jie, Z. Hong, Y. Tian, Y. Li, L. Lin, L. Zhou, Y. Du, L. Chen, L. Chen, Activation of transient receptor potential vanilloid 4 induces apoptosis in hippocampus through downregulating PI3K/Akt and upregulating p38 MAPK signaling pathways, Cell Death Dis. 6 (2015) e1775.
[39] D. An, X. Qi, K. Li, W. Xu, Y. Wang, X. Chen, S. Sha, C. Wu, Y. Du, L. Chen, Blockage of TRPV4 downregulates the nuclear factor-kappa B signaling pathway to inhibit inflammatory responses and neuronal death in mice with pilocarpine-induced status epilepticus, Cell. Mol. Neurobiol. 43 (2023) 1283–1300.
[40] M. Tominaga, Frontiers in neuroscience, the role of TRP channels in thermosensation, in: W.B. Liedtke, S. Heller (Eds.), TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades, CRC Press/Taylor & Francis, Boca Raton (FL), 2007. Copyright © 2007, Taylor & Francis Group, LLC.
[41] T. Rosenbaum, S.A. Simon, Frontiers in neuroscience, TRPV1 receptors and signal transduction, in: W.B. Liedtke, S. Heller (Eds.), TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades, CRC Press/Taylor & Francis, Boca Raton (FL), 2007. Copyright © 2007, Taylor & Francis Group, LLC.
[42] H. Wang, J. Siemens, TRP ion channels in thermosensation, thermoregulation and metabolism, Temperature (Austin) 2 (2015) 178–187.
[43] R. Yadav, A.K. Jaryal, H.N. Mallick, Participation of preoptic area TRPV4 ion channel in regulation of body temperature, J. Therm. Biol. 66 (2017) 81–86.
[44] A.D. Güler, H. Lee, T. Iida, I. Shimizu, M. Tominaga, M. Caterina, Heat-evoked activation of the ion channel, TRPV4, J. Neurosci. 22 (2002) 6408–6414.
[45] C.D.S. Scarpellini, C. Cristina-Silva, V. Biancardi, L.H. Gargaglioni, M.C. Almeida, K.C. Bícego, Hypothalamic TRPV4 channels participate in the medial preoptic activation of warmth-defence responses in Wistar male rats, Pflugers Arch 471 (2019) 1191–1203.
[46] C. Moore, R. Gupta, S.E. Jordt, Y. Chen, W.B. Liedtke, Regulation of pain and itch by TRP channels, Neurosci. Bull. 34 (2018) 120–142.
[47] Y. Dai, TRPs and pain, Semin. Immunopathol. 38 (2016) 277–291.
[48] C.R. Morgan, H.D. Rodd, N. Clayton, J.B. Davis, F.M. Boissonade, Vanilloid receptor 1 expression in human tooth pulp in relation to caries and pain, J. Orofac. Pain 19 (2005) 248–260.
[49] R. Okumura, K. Shima, T. Muramatsu, K. Nakagawa, M. Shimono, T. Suzuki, H. Magloire, Y. Shibukawa, The odontoblast as a sensory receptor cell? The expression of TRPV1 (VR-1) channels, Arch. Histol. Cytol. 68 (2005) 251–257.
[50] S. Matsuura, K. Shimizu, M. Shinoda, K. Ohara, B. Ogiso, K. Honda, A. Katagiri, B.J. Sessle, K. Urata, K. Iwata, Mechanisms underlying ectopic persistent tooth-pulp pain following pulpal inflammation, PLoS One 8 (2013) e52840.
[51] Y. Shibukawa, M. Sato, M. Kimura, U. Sobhan, M. Shimada, A. Nishiyama, A. Kawaguchi, M. Soya, H. Kuroda, A. Katakura, T. Ichinohe, M. Tazaki, Odontoblasts as sensory receptors: transient receptor potential channels, pannexin-1, and ionotropic ATP receptors mediate intercellular odontoblast-neuron signal transduction, Pflugers Arch 467 (2015) 843–863.
[52] Y.S. Kim, T.H. Kim, D.D. McKemy, Y.C. Bae, Expression of vesicular glutamate transporters in transient receptor potential melastatin 8 (TRPM8)-positive dental afferents in the mouse, Neuroscience 303 (2015) 378–388.
[53] Y.S. Cho, C.H. Ryu, J.H. Won, H. Vang, S.B. Oh, J.Y. Ro, Y.C. Bae, Rat odontoblasts may use glutamate to signal dentin injury, Neuroscience 335 (2016) 54–63.
[54] M.K. Chung, J.Y. Ro, Peripheral glutamate receptor and transient receptor potential channel mechanisms of craniofacial muscle pain, Mol. Pain 16 (2020) 1744806920914204.
[55] Y. Luo, A. Suttle, Q. Zhang, P. Wang, Y. Chen, Transient receptor potential (TRP) ion channels in orofacial pain, Mol. Neurobiol. 58 (2021) 2836–2850.
[56] A. Wanasuntronwong, V. Punyawattananon, N. Rotpenpian, R. Meepong, A. Srikiatkhachorn, Nociceptive receptors are expressed differently in trigeminal nociception after lingual nerve injury and unilateral external carotid artery occlusion in rats, Arch. Oral Biol. 126 (2021) 105128.
[57] B. Boonen, Y.A. Alpizar, V.M. Meseguer, K. Talavera, TRP channels as sensors of bacterial endotoxins, Toxins (2018) 10.
[58] T. Sasase, F. Fatchiyah, T. Ohta, Transient receptor potential vanilloid (TRPV) channels: basal properties and physiological potential, Gen. Physiol. Biophys. 41 (2022) 165–190.
[59] S. Wang, M.K. Chung, Orthodontic force induces nerve injury-like transcriptomic changes driven by TRPV1-expressing afferents in mouse trigeminal ganglia, Mol. Pain 16 (2020) 1744806920973141.
[60] K. Petersson, C. Söderström, M. Kiani-Anaraki, G. Lévy, Evaluation of the ability of thermal and electrical tests to register pulp vitality, Endod. Dent. Traumatol. 15 (1999) 127–131.
[61] J.L. Gibbs, J.L. Melnyk, A.I. Basbaum, Differential TRPV1 and TRPV2 channel expression in dental pulp, J. Dent. Res. 90 (2011) 765–770.
[62] J.J. Lin, Y. Du, W.K. Cai, R. Kuang, T. Chang, Z. Zhang, Y.X. Yang, C. Sun, Z.Y. Li, F. Kuang, Toll-like receptor 4 signaling in neurons of trigeminal ganglion contributes to nociception induced by acute pulpitis in rats, Sci. Rep. 5 (2015) 12549.
[63] Y.S. Kim, H.K. Jung, T.K. Kwon, C.S. Kim, J.H. Cho, D.K. Ahn, Y.C. Bae, Expression of transient receptor potential ankyrin 1 in human dental pulp, J. Endod. 38 (2012) 1087–1092.
[64] A. Diogenes, C.C. Ferraz, A.N. Akopian, M.A. Henry, K.M. Hargreaves, LPS sensitizes TRPV1 via activation of TLR4 in trigeminal sensory neurons, J. Dent. Res. 90 (2011) 759–764.
[65] V. Meseguer, Y.A. Alpizar, E. Luis, S. Tajada, B. Denlinger, O. Fajardo, J.A. Manenschijn, C. Fernández-Peña, A. Talavera, T. Kichko, B. Navia, A. Sánchez, R. Señarís, P. Reeh, M.T. Pérez-García, J.R. López-López, T. Voets, C. Belmonte, K. Talavera, F. Viana, TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins, Nat. Commun. 5 (2014) 3125.
[66] M.Z. Hossain, S. Daud, P. Nambiar, F.A. Razak, N. Ab-Murat, R. Saub, M.M. Bakri, Correlation between numbers of cells in human dental pulp and age: implications for age estimation, Arch. Oral Biol. 80 (2017) 51–55.
[67] S. Daud, P. Nambiar, M.Z. Hossain, M.R. Rahman, M.M. Bakri, Changes in cell density and morphology of selected cells of the ageing human dental pulp, Gerodontology 33 (2016) 315–321.
[68] R. Miyamoto, M. Tokuda, T. Sakuta, S. Nagaoka, M. Torii, Expression and characterization of vanilloid receptor subtype 1 in human dental pulp cell cultures, J. Endod. 31 (2005) 652–658.

[69] K.C. Rowland, C.B. Kanive, J.E. Wells, J.F. Hatton, TRPM2 immunoreactivity is increased in fibroblasts, but not nerves, of symptomatic human dental pulp, J. Endod. 33 (2007) 245–248.
[70] D.H. Pashley, How can sensitive dentine become hypersensitive and can it be reversed? J. Dent. 41 (Suppl 4) (2013) S49–S55.
[71] A. Stenvik, J. Iversen, I.A. Mjör, Tissue pressure and histology of normal and inflamed tooth pulps in macaque monkeys, Arch. Oral Biol. 17 (1972) 1501–1511.
[72] A. Parenti, F. De Logu, P. Geppetti, S. Benemei, What is the evidence for the role of TRP channels in inflammatory and immune cells? Br. J. Pharmacol. 173 (2016) 953–969.
[73] E. Uchytilova, D. Spicarova, J. Palecek, TRPV1 antagonist attenuates postoperative hypersensitivity by central and peripheral mechanisms, Mol. Pain 10 (2014) 67.
[74] J.C. Fehrenbacher, X.X. Sun, E.E. Locke, M.A. Henry, K.M. Hargreaves, Capsaicin-evoked iCGRP release from human dental pulp: a model system for the study of peripheral neuropeptide secretion in normal healthy tissue, Pain 144 (2009) 253–261.
[75] I.A. El Karim, G.J. Linden, T.M. Curtis, I. About, M.K. McGahon, C.R. Irwin, F.T. Lundy, Human odontoblasts express functional thermo-sensitive TRP channels: implications for dentin sensitivity, Pain 152 (2011) 2211–2223.
[76] M.Z. Hossain, M.M. Bakri, F. Yahya, H. Ando, S. Unno, J. Kitagawa, The role of transient receptor potential (TRP) channels in the transduction of dental pain, Int. J. Mol. Sci. 20 (2019).
[77] R. Ramli, S.N. Mohd Nafi, N.A. Ahmad Tarmidzi, N. Hasbullah, N. Ghani, Immunohistochemistry as a detection tool for ion channels involved in dental pain signaling, Saudi Dent J 34 (2022) 155–166.
[78] C.K. Park, M.S. Kim, Z. Fang, H.Y. Li, S.J. Jung, S.Y. Choi, S.J. Lee, K. Park, J.S. Kim, S.B. Oh, Functional expression of thermo-transient receptor potential channels in dental primary afferent neurons: implication for tooth pain, J. Biol. Chem. 281 (2006) 17304–17311.
[79] P. Sotelo-Hitschfeld, L. Bernal, K. Zimmermann, , Odontoblasts are cold sensory cells in teeth: Comment on, L. Bernal, P. Sotelo-Hitschfeld, C. König, V. Sinica, A. Wyatt, Z. Winter, A. Hein, F. Touska, S. Reinhardt, A. Tragl, R. Kusuda, P. Wartenberg, A. Sclaroff, J.D. Pfeifer, F. Ectors, A. Dahl, M. Freichel, V. Vlachova, S. Brauchi, C. Roza, U. Boehm, D.E. Clapham, J.K. Lennerz, K. Zimmermann, Odontoblast TRPC5 channels signal cold pain in teeth, Sci. Adv. 10 (2023) 9–12, 7, eabf5567 (2021), Temperature (Austin).
[80] E. Jyväsjärvi, K.D. Kniffki, Cold stimulation of teeth: a comparison between the responses of cat intradental A delta and C fibres and human sensation, J Physiol 391 (1987) 193–207.
[81] M. Närhi, E. Jyväsjärvi, A. Virtanen, T. Huopaniemi, D. Ngassapa, T. Hirvonen, Role of intradental A- and C-type nerve fibres in dental pain mechanisms, Proc. Finn. Dent. Soc. 88 (Suppl 1) (1992) 507–516.
[82] M. Tsumura, U. Sobhan, T. Muramatsu, M. Sato, H. Ichikawa, Y. Sahara, M. Tazaki, Y. Shibukawa, TRPV1-mediated calcium signal couples with cannabinoid receptors and sodium-calcium exchangers in rat odontoblasts, Cell Calcium 52 (2012) 124–136.
[83] A.R. Son, Y.M. Yang, J.H. Hong, S.I. Lee, Y. Shibukawa, D.M. Shin, Odontoblast TRP channels and thermo/mechanical transmission, J. Dent. Res. 88 (2009) 1014–1019.
[84] M. Sato, U. Sobhan, M. Tsumura, H. Kuroda, M. Soya, A. Masamura, A. Nishiyama, A. Katakura, T. Ichinohe, M. Tazaki, Y. Shibukawa, Hypotonic-induced stretching of plasma membrane activates transient receptor potential vanilloid channels and sodium-calcium exchangers in mouse odontoblasts, J. Endod. 39 (2013) 779–787.
[85] A. Nishiyama, M. Sato, M. Kimura, A. Katakura, M. Tazaki, Y. Shibukawa, Intercellular signal communication among odontoblasts and trigeminal ganglion neurons via glutamate, Cell Calcium 60 (2016) 341–355.
[86] S.G. Hamilton, ATP and pain, Pain Pract. 2 (2002) 289–294.
[87] P. Linsuwanont, J.E. Palamara, H.H. Messer, An investigation of thermal stimulation in intact teeth, Arch. Oral Biol. 52 (2007) 218–227.
[88] M. Hashimoto, S. Ito, F.R. Tay, N.R. Svizero, H. Sano, M. Kaga, D.H. Pashley, Fluid movement across the resin-dentin interface during and after bonding, J. Dent. Res. 83 (2004) 843–848.
[89] M. Tsumura, U. Sobhan, M. Sato, M. Shimada, A. Nishiyama, A. Kawaguchi, M. Soya, H. Kuroda, M. Tazaki, Y. Shibukawa, Functional expression of TRPM8 and TRPA1 channels in rat odontoblasts, PLoS One 8 (2013) e82233.
[90] J. Won, H. Vang, J.H. Kim, P.R. Lee, Y. Kang, S.B. Oh, TRPM7 mediates mechanosensitivity in adult rat odontoblasts, J. Dent. Res. 97 (2018) 1039–1046.
[91] J.L. Ebersole, S.S. Kirakodu, O.A. Gonzalez, Oral microbiome interactions with gingival gene expression patterns for apoptosis, autophagy and hypoxia pathways in progressing periodontitis, Immunology 162 (2021) 405–417.
[92] A. Morii, Y. Miyamura, M.I. Sago, M. Mizuhara, T. Shikayama, M. Naniwa, S. Hitomi, I. Ujihara, K.N. Kuroishi, K.K. Gunjigake, M. Shiga, Y. Morimoto, T. Kawamoto, K. Ono, Orthodontic force-induced oxidative stress in the periodontal tissue and dental pulp elicits nociception via activation/sensitization of TRPA1 on nociceptive fibers, Free Radic. Biol. Med. 147 (2020) 175–186.
[93] T. Tsutsumi, H. Kajiya, T. Fukawa, M. Sasaki, T. Nemoto, T. Tsuzuki, Y. Takahashi, S. Fujii, H. Maeda, K. Okabe, The potential role of transient receptor potential type A1 as a mechanoreceptor in human periodontal ligament cells, Eur. J. Oral Sci. 121 (2013) 538–544.
[94] R. Martinez-Carrasco, P. Argüeso, M.E. Fini, Dynasore protects ocular surface mucosal epithelia subjected to oxidative stress by maintaining UPR and calcium homeostasis, Free Radic. Biol. Med. 160 (2020) 57–66.
[95] X. Zhang, Y. Jiang, J. Mao, X. Ren, Y. Ji, Y. Mao, Y. Chen, X. Sun, Y. Pan, J. Ma, S. Huang, Hydroxytyrosol prevents periodontitis-induced bone loss by regulating mitochondrial function and mitogen-activated protein kinase signaling of bone cells, Free Radic. Biol. Med. 176 (2021) 298–311.
[96] M.M. Taskan, H. Balci Yuce, O. Karatas, F. Gevrek, H. Toker, Evaluation of the effect of oleuropein on alveolar bone loss, inflammation, and apoptosis in experimental periodontitis, J. Periodontal. Res. 54 (2019) 624–632.
[97] X. Qiu, Y. Yu, H. Liu, X. Li, W. Sun, W. Wu, C. Liu, L. Miao, Remodeling the periodontitis microenvironment for osteogenesis by using a reactive oxygen species-cleavable nanoplatform, Acta Biomater. 135 (2021) 593–605.
[98] C.A. Aral, K. Aral, A. Yay, Ö. Özçoban, A. Berdeli, R. Saraymen, Effects of colchicine on gingival inflammation, apoptosis, and alveolar bone loss in experimental periodontitis, J. Periodontol. 89 (2018) 577–585.
[99] S. Ying, M. Tan, G. Feng, Y. Kuang, D. Chen, J. Li, J. Song, Low-intensity Pulsed Ultrasound regulates alveolar bone homeostasis in experimental Periodontitis by diminishing Oxidative Stress, Theranostics 10 (2020) 9789–9807.
[100] S. Sooampon, W. Phoolcharoen, P. Pavasant, Thermal stimulation of TRPV1 up-regulates TNFα expression in human periodontal ligament cells, Arch. Oral Biol. 58 (2013) 887–895.
[101] N. Takahashi, T. Tsuzuno, S. Mineo, M. Yamada-Hara, Y. Aoki-Nonaka, K. Tabeta, Epithelial TRPV1 channels: expression, function, and pathogenicity in the oral cavity, J. Oral Biosci. 62 (2020) 235–241.
[102] C.A. Ossola, N.B. Balcarcel, J.I. Astrauskas, C. Bozzini, J.C. Elverdin, J. Fernández-Solari, A new target to ameliorate the damage of periodontal disease: the role of transient receptor potential vanilloid type-1 in contrast to that of specific cannabinoid receptors in rats, J. Periodontol. 90 (2019) 1325–1335.
[103] S. Wang, M. Kim, Z. Ali, K. Ong, E.K. Pae, M.K. Chung, TRPV1 and TRPV1-expressing nociceptors mediate orofacial pain behaviors in a mouse model of orthodontic tooth movement, Front. Physiol. 10 (2019) 1207.
[104] Y. Luo, A. Suttle, Q. Zhang, P. Wang, Y. Chen, Transient receptor potential (TRP) ion channels in orofacial pain, Mol. Neurobiol. 58 (2021) 2836–2850.
[105] F.C. Dias, Z. Wang, G. Scapellato, Y. Chen, Silencing of TRPV4-expressing sensory neurons attenuates temporomandibular disorders pain, Mol. Pain 19 (2023) 17448069231185696.
[106] A. Suttle, P. Wang, F.C. Dias, Q. Zhang, Y. Luo, L. Simmons, A. Bortsov, I.E. Tchivileva, A.G. Nackley, Y. Chen, Sensory neuron-TRPV4 modulates temporomandibular disorder pain via CGRP in mice, J. Pain 24 (2023) 782–795.
[107] Y. Chen, S.H. Williams, A.L. McNulty, J.H. Hong, S.H. Lee, N.E. Rothfusz, P.K. Parekh, C. Moore, R.W.t. Gereau, A.B. Taylor, F. Wang, F. Guilak, W. Liedtke, Temporomandibular joint pain: a critical role for Trpv4 in the trigeminal ganglion, Pain 154 (2013) 1295–1304.
[108] X. Kodji, Z. Kee, R. McKenna, J. de Sousa Valente, H. Ravenscroft, H. McMillan, J. Gamble, Y. Dombrowski, P. Moynagh, D. Brough, F.T. Lundy, S.D. Brain, I. A. El Karim, Evidence that a TRPA1-mediated murine model of temporomandibular joint pain involves NLRP3 inflammasome activation, Pharmaceuticals 14 (2021).

[109] P. Wang, Q. Zhang, F.C. Dias, A. Suttle, X. Dong, Y. Chen, TMEM100, a regulator of TRPV1-TRPA1 interaction, contributes to temporomandibular disorder pain, Front. Mol. Neurosci. 16 (2023) 1160206.
[110] N. Rotpenpian, T. Arayapisit, A. Roumwong, N. Pakaprot, M. Tantisira, A. Wanasuntronwong, A standardized extract of Centella asiatica (ECa 233) prevents temporomandibular joint osteoarthritis by modulating the expression of local inflammatory mediators in mice, J. Appl. Oral Sci. 29 (2021) e20210329.
[111] H.A. Silverman, A. Chen, N.L. Kravatz, S.S. Chavan, E.H. Chang, Involvement of neural transient receptor potential channels in peripheral inflammation, Front. Immunol. 11 (2020) 590261.
[112] E.M. Rita Pereira, J.M. Souza, N.V. Carobin, J.F. Silva, D.C. Santos, C.A. Silva Júnior, N.S. Binda, M.H. Borges, R.A. Pinto Nagem, C. Kushmerick, J. Ferreira, C. J. Castro Junior, F.M. Ribeiro, M.V. Gomez, Phoneutria toxin PnTx3-5 inhibits TRPV1 channel with antinociceptive action in an orofacial pain model, Neuropharmacology 162 (2020) 107826.
[113] O. Egbuniwe, S. Grover, A.K. Duggal, A. Mavroudis, M. Yazdi, T. Renton, L. Di Silvio, A.D. Grant, TRPA1 and TRPV4 activation in human odontoblasts stimulates ATP release, J. Dent. Res. 93 (2014) 911–917.
[114] G.Y. Son, Y.M. Yang, W.S. Park, I. Chang, D.M. Shin, Hypotonic stress induces RANKL via transient receptor potential melastatin 3 (TRPM3) and vaniloid 4 (TRPV4) in human PDL cells, J. Dent. Res. 94 (2015) 473–481.
[115] A.H. Abidi, V. Abhyankar, S.S. Alghamdi, D.A. Tipton, M. Dabbous, Phytocannabinoids regulate inflammation in IL-1β-stimulated human gingival fibroblasts, J. Periodontal. Res. 57 (6) (2022) 1127–1138.
[116] J.P. Kukkonen, A ménage à trois made in heaven: G-protein-coupled receptors, lipids and TRP channels, Cell Calcium 50 (2011) 9–26.
[117] T. Rosenbaum, S.L. Morales-Lázaro, Regulation of ThermoTRP channels by PIP2 and cholesterol, Adv. Exp. Med. Biol. 1422 (2023) 245–277.