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TRP Channels in Dental Pain

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Abstract: Despite the high incidence of dental pain, the mechanism underlying its generation is mostly unknown. Functional expression of temperature-sensitive transient receptor potential (thermo-TRP) channels, such as TRPV1, TRPV2, TRPM8, and TRPA1 in dental primary afferent neurons and TRPV1, TRPV2, TRPV3, TRPV4, and TRPM3 in odontoblasts, has been demonstrated and suggested as responsible for dental pain elicited by hot and cold food. However, dental pain induced by light touch or sweet substance cannot be explained by the role of thermo-TRP channels. Most of current therapeutics of dentin hypersensitivity is based on hydrodynamic theory, which argues that light stimuli such as air puff and temperature changes cause fluid movement within dentinal tubule, which is then transduced as pain. To test this theory, various TRP channels as candidates of cellular mechanotransducers were studied for expression in dental primary afferents and odontoblasts. The expression of TRPV1, TRPV2, TRPA1, TRPV4, and TRPM3 in trigeminal neurons and TRPV1, TRPV2, TRPV3, TRPV4 and TRPM3 in odontoblasts has been revealed. However, their roles as cellular mechanotransducers are controversial and contribution to generation of dental pain is still elusive. This review discusses recent advances in understanding of molecular mechanism underlying development of dental pain.

Keywords: TRP, Dental Pain, Odontoblast, Mechanosensation, Thermosensation.

1. INTRODUCTION

The tooth is a unique tissue in that its surrounding temperature is subject to change in extreme ranges. The temperature within oral cavity can change from ice-cold to burning-hot within a few seconds depending on the food consumed. Unlike other tissues in the body, noxious hot or cold temperature does not elicit nociception in the teeth under normal circumstances, because of the thermal insulating capacity of the outer shell of the tooth, the enamel. When enamel is decayed or abraded and dentin is exposed, small changes in temperature and light touches such as air puff or water spray can evoke sudden and intense pain in the tooth.

A number of hypotheses were proposed to elucidate the mechanism underlying generation of dental pain [1]. Among them three hypotheses have received particular attention. The first hypothesis, the so called neural theory, focuses on direct transduction of temperatures by nerve innervating the dentin and pulp. The second hypothesis postulates the sensory role of odontoblasts. And the third, hydrodynamic, theory describes that the detection of the movement of tissue fluid within dentinal tubules is the cause of dental nociception.

The transient receptor potential (TRP) channels are widely accepted as cellular transducers of various physical and chemical stimuli [2]. The expression of several members of TRP channels has been studied in dental primary afferent neurons and odontoblasts for their functional roles as transducers of noxious temperature or mechanical stress. This review discusses the possible involvement of the temperature-sensitive or mechanosensitive TRP channels in generation of tooth pain.

2. NEUROANATOMY OF A TOOTH

The tooth is composed of tooth pulp and surrounding mineralized tissues. The tooth pulp is densely innervated by primary sensory neurons branched from the largest cranial nerves, namely the trigeminal nerve. Both myelinated and unmyelinated nerve fibers are present in the pulp. 70-90% of intrapulpal axons consist of unmyelinated C-fibers, which might be involved in slow, dull, drawling dental pain [3-5]. The remaining myelinated intrapulpal fibers are mostly Aδ fibers that are responsible for the rapid, sharp, lancinating, well-localized nociception [4, 6]. These observations are consistent with traditional view that human tooth pulp produces only pain in response to noxious and non-noxious physical stimuli [7], and that dental primary afferent neurons are composed entirely of nociceptive neurons [8-12].

However, this concept is challenged by the observation of non-nociceptive sensory perception in response to subthreshold electrical stimulation of human teeth [13]. In addition, electromicroscopic studies and measurement of conduction velocities suggest that most of the parental axon of pulpal neurons are medium to large myelinated neurons [14, 15]. More recent literature has proposed that majority of dental afferent neurons are non-nociceptive low-threshold mechanoreceptors [16].

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Between the dentin and tooth pulp is the odontoblast cell layer. Odontoblasts are cells that deposit a calcium matrix to form dentin during tooth development and throughout the lifetime for dentin repair. However, because odontoblasts constitute the outermost cell layer of the dental pulp where temperature of oral cavity is first transmitted, the sensory role of odontoblasts is proposed by several lines of independent studies [17-21].

3. TEMPERATURE SENSITIVE TRP CHANNELS IN DENTAL PAIN

3.1. TRP Channels that Respond to Hot Temperature

Since the tooth is frequently exposed to extreme temperatures, detection of noxious temperature is crucial in order to avoid the severe tissue damage. Pioneered by the discovery of TRPV1 [22], a receptor channel activated by capsaicin and noxious temperature above 42 ℃, responsiveness to capsaicin was studied in an attempt to elucidate the transduction mechanism of noxious temperature. Electrophysiological recording in trigeminal ganglion neurons in slice preparation or in cultured cells revealed capsaicin responses in 14.3 or 38.8% of neurons [23]. Subsequently, TRPV2, a homologue receptor to TRPV1 with a higher threshold (52 ℃) for noxious heat [24], was shown in 14 % of neurons in rat trigeminal ganglion sections [25]. Interestingly, the immunoreactivity to TRPV2 was detected mostly in medium to large size neuron and small TRPV2-immunoreactive neurons were very rare [24, 25]. This result suggests that nociceptive pathway of trigeminal area may be different from that of rest of body innervated by dorsal root ganglion.

In order to address the role of thermo-TRP channels in detection of noxious temperature in the tooth, retrograde labeling technique was used to isolate dental primary afferent neurons. After placing a fluorescent dye in teeth, labeled trigeminal ganglion neurons were considered to innervate tooth pulp and used for analysis. Single-cell RT-PCR and immunocytochemical analysis revealed that 45~85 % of labeled dental afferent neurons expressed TRPV1 [26, 27]. Whole-cell patch clamp recording revealed that 65~71 % of labeled dental afferents responded to application of capsaicin [26-28]. Capsaicin-responding neurons were diverse in size although smaller neurons exhibited higher expression level. The role of dental primary afferents in detection of noxious heat was more directly shown by elevated intracellular calcium concentration in response to noxious heat [26].

Expression of TRPV2 was also shown by immunohistochemical analysis of labeled dental afferent neurons in culture [25]. It is interesting that the expression level of TRPV2 is higher in labeled dental afferent neurons than in unlabeled trigeminal ganglion neurons. While only 14% of trigeminal ganglion neurons showed immunoreactivity to TRPV2, 37% of labeled dental afferents exhibited TRPV2-immunoreactivity [25]. Immunohisto-chemical analysis of retrogradely labeled trigeminal ganglion slice further supported the preferential expression of TRPV2 in dental primary afferents. The expression of TRPV2 was higher in the dental primary afferents than in neurons in overall trigeminal ganglion or in neurons that innervate periodontal ligament (PDL) (50% vs. 15% and 40%, respectively) [29].

Differential expression level of TRPV1 between trigeminal ganglion neurons and dental primary afferents is controversial. Single cell RT-PCR analysis reported that TRPV1 was detected in 60% of dental primary afferent neurons and 45 % of trigeminal ganglion neurons [26]. However, immunohistochemical analysis of trigeminal ganglion slice from another group suggested that the expression of TRPV1 in dental primary afferents was less than the expression in trigeminal ganglion neurons in general or PDL neurons (17% vs. 26% and 26%, respectively) [25]. The discrepancy between the expression levels of TRPV1 appeared in immunohistochemical analysis of the sectioned tissue and the isolated neurons might be due to preferential expression of TRPV1 channels in small-sized neurons and differential survival rate between large and small neurons during acute isolation procedures. This should not be an issue in investigating the expression level of TRPV2, which is preferentially expressed in large neurons [25].

TRPV1 contributes to the development of pain not only as a receptor of hot temperature, but also as an integrator of numerous factors and inflammatory mediators [30]. It was recently shown that TRPV1 in trigeminal ganglion was up-regulated in experimental pulpitis induced by lipopolysaccharide (LPS), a product of Gram-negative bacteria [31]. The increased expression of TRPV1 might contribute to the hyperexcitability to warm stimuli in chronic pulpitis patients.

3.2. TRP Channels that Respond to Cold Temperature

Considering that cold stimuli evoke toothache more often than hot stimuli, it is reasonable to assume that dental afferents express TRP channels that are activated by cold temperatures. Single cell RT-PCR and immunocyto-chemistry investigation of retrogradely labeled rat dental afferent neurons revealed expression of TRPM8 and TRPA1 [26]. The application of noxious temperatures and appropriate chemical ligands further confirmed the functional expression of thermo-TRP channels. Surprisingly, the expression of both TRPM8 and TRPA1 was lower than that of TRPV1 [26]. Since tooth pain is often confused with cold sensation, it was expected that cold receptors were expressed in majority of the dental afferent neurons. Some of the dental afferents showed co-expression of TRPM8 or TRPA1 with TRPV1. In such neurons, it may be difficult to discern cold temperature from hot temperature by nerve impulses. These ambiguities suggest that other mechanism might be involved in detection of noxious temperature in teeth, while the thermo-TRP channels expressed in dental afferents may contribute to some extent. It was recently found by Western blotting analysis that expression of TRPA1 in trigeminal ganglion was increased by an experimental injury applied to rodent teeth [32].

3.3. Thermo-TRP Channels Expressed in Odontoblasts

The main function of odontoblasts is to secrete mineralized calcium matrix to form dentin in the junction of pulp and dentin. The strategic location of odontoblasts prompted the investigation that odontoblasts might play a sensory role as well. Evidence supporting that odontoblasts

are excitable cells include expression of voltage-gated Na^+ channels [18], voltage-gated K^+ channels [33], calcium-activated K^+ channels [21], store-operated calcium channels [34], Na^+/Ca^{2+} exchanger [35] and TREK-1 channels [19].

Multiple research groups investigated the expression of TRP channels in odontoblasts. The results, however, remain controversial. Son *et al*. used odontoblasts obtained by *in vitro* differentiation of pulpal cells of neonatal rats and found that odontoblasts expressed TRPV1, TRPV2, TRPV3, TRPV4, and TRPM3 by patch clamp recording and RT-PCR analysis [17]. Yeon *et al*. used acutely isolated odontoblasts from adult rat incisors and reported that they could not find any evidence for the expression of TRPV1, TRPV2 by single cell RT-PCR, immunohistochemistry and functional analysis using calcium imaging [36]. Possible explanations for this discrepancy include: (1) the differentiated pulp cells might not be identical to the actual odontoblasts, (2) acutely isolation procedures damage the odontoblasts with TRPV1 or TRPV2, and (3) developmental difference in TRP expression between adult and neonatal rats.

Both group agreed, however, that odontoblasts do not express TRPM8 and TRPA1. Therefore, it is likely that sensory role of odontoblasts does not involve TRPM8 or TRPA1. However, this might not be the case in humans. Expression of TRPV1, TRPA1 and TRPM8 was recently confirmed by PCR, Western blotting and immunohistochemistry of odontoblasts differentiated from pulp extract of human third molars [37]. Functional channels were also shown by calcium imaging experiments with application of appropriate ligands or actual noxious low and high temperatures [37]. The same group also reported expression of TRPM8 and TRPA1 in human dental pulp fibroblasts [38]. Thus, it is possible that odontoblast and pulpal fibroblasts might play a role in detection of noxious temperature in human. Recent studies demonstrating cooperation of TRP channels with TRAAK and TREK-1 channels in perception of warm and cold sensation [39] also support the role of odontoblasts as sensory cells [40]. However, in order to fully address this possibility, the signaling mechanism between odontoblasts and dental primary afferents must be elucidated.

4. MECHANOSENSITIVE TRP CHANNELS IN DENTAL PAIN

4.1. Hydrodynamic Theory

It is complicated to explain dental pain strictly based on transduction of noxious temperature by thermo-TRP channels. Temperature transduction alone cannot explain sudden and intense pain in teeth induced by normally innocuous stimuli such as air puff, water spray or sweet substances. Chronic pulpitis patients often describe pulsating pain, which might be induced by hydrostatic pressure applied to inflamed swollen pulp tissue contained within hard tissue [41, 42]. The light touch-induced intense pain and pulsating chronic pain implies that etiology of dental pain might involve detection of physical force. These speculations led to hydrodynamic theory, which ascribes the cause of dental pain to be mechanical forces generated by movement of tissue fluid within dentinal tubules [43, 44]. The movement of dentinal fluid is limited when both ends of dentinal tubule are obstructed by pulp and enamel layer [45]. When dentin is exposed by dental caries, tooth crack or tooth erosion, the dentinal fluid movement can be exaggerated by mild temperature changes [13], evaporation from light air puff or by hyperosmotic substance [9]. The hydrodynamic theory is the foundation of therapeutic procedures aimed at blocking the dentinal tubules by physical and chemical means in order to relieve odontogenic hypersensitivity.

Unfortunately, this theory remains to be a theory because the mechanical transduction mechanism of dental afferent neurons, which is the central part of the theory, is yet to be discovered. A number of studies investigated the mechano-sensitive nature of dental primary afferent neurons. However, the mechanical transduction mechanism has not been fully explained. In fact, investigation of mechanical transduction mechanism has begun only recently, and there is no single entity that gathers consensus among researchers [46].

4.2. Mechanosensitive TRP Channels in Neurons

TRP channels that exhibit mechanosensitivity include TRPC1, TRPC6, TRPV1, TRPV2, TRPV4, TRPM3, TRPM4, TRPM7, TRPA1 and TRPP2 [46]. Of these channels, the expression of TRPV1, TRPV2 and TRPA1 has been shown in retrogradely labeled dental afferent neurons [25-29], whereas expression of TRPV4 and TRPM3 was reported in trigeminal ganglion neurons [47, 48]. As yet, no evidence for expression of TRPC1, TRPC6, TRPM4, TRPM7 and TRPP2 has been published.

TRPA1 is of particular interest in relation to tooth pain. TRPA1 is found at the tip of the hair bundles of inner ear receptor cells, where mechanotransduction of fluid movement is crucial in function [49]. Functional expression of TRPA1 in dental primary afferent neurons [26] suggests that TRPA1 might play an important role in detection of fluid movements within dentinal tubule. The dual role of TRPA1 in dental afferents as a mechanotransducer and a cold receptor might explain why dental pain is often confused with cold hyperalgesia. However, phenotypes of TRPA1-deleted mice questioned the role of TRPA1 as cellular mechanical transducer. While two independent lines of TRPA1-deleted mice developed by Kwan *et al.* and Bautista *et al*. showed discrepancy in response to cold, both lines showed normal response to loud noise [50, 51]. It is possible that another cellular machinery for mechanotransduction exists and compensate for the function of TRPA1 in these transgenic mice. The role of TRPA1 in mechanotransduction and in generation of dental pain needs to be verified. A recent report on up-regulation of TRPA1 in experimental tooth injury suggests that TRPA1 is still a promising candidate molecule [32].

Although controversial, TRPV1 has been proposed to have mechanosensitivity. The bladder and urothelial epithelial cells from TRPV1-deleted mice showed markedly diminished response to stretch [52]. Single unit analysis of afferent fibers of jejunum from $TRPV1^{-/-}$ mice showed reduced response to pressure [53]. Reduced secretion of antidiuretic hormone (ADH) in systemic hypertonicity in $TRPV1^{-/-}$ mice suggests that TRPV1 might play a role in detection of hypertonicity [54], thereby contributing generation of dental pain elicited by hyperosmotic substances.

Recent publications strongly suggest that IB4-positive non-peptidergic afferents play a important role in transduction of mechanical stimuli in skin [55, 56]. Since TRPA1 and TRPV1 channels are expressed only in a peptidergic fraction of unmyelinated C fibers [57, 58], key mechanical transducer of dental primary afferents are likely to be other than TRPA1 and TRPV1. A more recent paper showed non-peptidergic mechanosensitive subpopulation in trigeminal ganglion neurons, which might be responsible for detection of dentinal fluid [59]. Mechanical transducer molecule responsible for dental pain in non-peptidergic polymodal nociceptors remains to be elucidated in future research.

In vivo recording from single nerve fibers in beagle dogs revealed that 75 % of mandibular pulpal nerves responded to direct mechanical stimulation of exposed pulp. It is interesting that all of the mechanosensitive nerve fibers were myelinated A fibers according to conduction velocities [60]. In addition, it was proposed that majority of dental afferent neurons are non-nociceptive low-threshold mechanoreceptors [16], based on observation that most of dental afferents are medium to large myelinated Aβ fibers [14, 15, 61, 62]. It is possible that TRPV2 is the key transducer molecule since TRPV2 was preferentially detected in medium to large neurons [24, 25], and stretch-induced activation of TRPV2 was reported in vascular smooth muscle [63]. TRPM3 and TRPV4 are cation channels that are important in volume-regulation [64]. Mechanosensitivity of TRPM3 was shown by modulation of the spontaneous Ca^{2+} influx by changes of osmolarity in heterologously expressed TRPM3 [65]. TRPV4 is also well known for osmolarity-dependent gating, but not by direct membrane stretch [66]. More detailed investigation on these TRP channels might provide a plausible explanation of mechanism underlying dental pain.

4.3. Mechanosensitive TRP Channels in Odontoblasts

An odontoblast has an ovoidal cell body and a process that extends to dentinal tubules. This morphological characteristic together with spatial advantage led to investigation of mechanosensitivity of odontoblasts. Interestingly, most of thermo-TRP channels reported in odontoblasts (TRPV1, TRPV2, TRPV4 and TRPM3) show mechanosensitivity, as well [40]. In addition to the TRP channels, odontoblasts also express mechanosensitive K^+ channels and N-type Ca^{2+} channels [40], that could contribute to the role as mechanotransducer of dentinal fluid. Excitability of odontoblasts was shown by functional expression of voltage-gated Na^+ channels and action potentials evoked by electrical stimulation *in vitro* [18]. However, the activation of odontoblasts by direct stretching of cell membrane and the crosstalk between odontoblasts and pulpal neurons needs to be demonstrated in future studies.

Dentin formed before the tooth eruption is called primary dentin, in contrast to the secondary dentin that is formed in response to bacterial infection and thought to have a protective role. However, dentin formation continues without bacterial infection throughout the lifetime. This type of dentin is called tertiary dentin, and the mechanism underlying its formation is unknown. Recent investigation that argues differentiation of human dental pulp stem cells into odontoblastic cells by hydrodynamic pressure suggests that mechanical force applied to dentin or pulp might contribute to the formation of tertiary dentin [67]. Mechanosensitive TRP channels expressed in odontoblasts might play a central role in detection of hydrostatic pressure within pulp.

SUMMARY

Dental pulp is a highly innervated tissue and pain originating from dental pulp is severe and exacerbating. Despite its high prevalence, the mechanism underlying transduction of dental pain is not fully understood. Considering that teeth are subjected to frequent and extreme temperature changes, it is not surprising that dental afferent neurons and odontoblasts express a variety of thermo-TRP channels. However, dental pain can also be induced by light mechanical stimuli or increased hydrostatic pressure. The hydrodynamic theory provides a plausible explanation for the etiology of sudden intense dental pain when dentin is exposed. Although the nature of the key mechanical transducer molecule remains unknown, dental afferent neurons and odontoblasts have been shown to express various mechanosensitive TRP channels, which could play a central role in dental pain. Development of pharmacologic intervention targeting these thermosensitive or mechanosensitive TRP channels might provide a novel therapeutic strategy against dental pain.

CONFLICT OF INTEREST

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

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