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Update on dentin hypersensitivity: with the focus on hydrodynamic theory and mechanosensitive ion channels

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Dentin hypersensitivity is an abrupt intense pain caused by innocuous stimuli to exposed dentinal tubules. Mechanosensitive ion channels have been assessed in dental primary afferent neurons and odontoblasts to explain dentin hypersensitivity. Dentinal fluid dynamics evoked by various stimuli to exposed dentin cause mechanical stress to the structures underlying dentin. This review briefly discusses three hypotheses regarding dentin hypersensitivity and introduces recent findings on mechanosensitive ion channels expressed in the dental sensory system and discusses how the activation of these ion channels is involved in dentin hypersensitivity.

Keywords: Dentin hypersensitivity, Mechanoreceptor, Dental physiology, Hydrodynamic theory

Dentin Hypersensitivity

Pulp tissue inside the intact teeth is densely innervated. However, teeth in normal condition is not considered sensitive, when compared to other highly sensitive areas of the body such as tip of the fingers or vermilion of the lip, as the nerve terminals in the pulp tissue are insulated from external stimuli by mineralized teeth structures such as enamel and dentin. Temperature changes in the noxious ranges or mechanical stimulations such as brushing or probing which may damage the surrounding soft tissue do not elicit recognizable sensation from sound teeth. Only upon the removal of enamel or cementum with dentin exposure often seen in lesions of dental caries or abrasion, patients suffer from sudden and shooting pain by subtle stimulation such as changes in temperature (cold or hot substances), mechanical stimulation (air puff, teeth brushing, probing on dentin) or osmotic stimuli. This exaggerated pain evoked by innocuous stimuli is commonly referred as dentin hypersensitivity. To explain the unique characteristics of dentin hypersensitivity, three hypotheses have been suggested: 1) Neural theory, 2) Odontoblast transducer theory, 3) Hydrodynamic theory [1,2]. In this review, these hypotheses of dentin hypersensitivity are briefly introduced, and among them, the hydrodynamic theory is mainly discussed with a focus on the mechanosensitive ion channels as the possible mediator for dentin hypersensitivity.

1. Neural theory

Up to date, various nociceptive sensory transducers for temperature, tissue damage, or inflammatory substances have been investigated in dental primary afferent neurons, as

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stimulation of dental pulp have been found to elicit pure pain [3]. Molecular screening with single cell reverse transcription polymerase chain reaction (RT-PCR) combined with calcium imaging or patch clamp has successfully revealed the expression of classical nociceptive transducers such as thermosensitive transient receptor potential (TRP) channels and adenosine triphosphate (ATP)-sensitive P2X channels, especially in small-sized lightly myelinated Aδ-fibers or unmyelinated C-fibers [3,4]. Nociceptive TRP channels such as TRP vanilloid receptor 1 (TRPV1) or TRP ankyrin 1 (TRPA1) which respond to noxious heat or cold, respectively, have been detected in dental primary afferent neurons innervating the pulp identified with fluorescent tracers, as calcium transients or excitatory currents were evoked during application of respective selective agonist (TRPV1; capsaicin, TRPA1; icilin) or thermal stimulation (TRPV1; > 43℃, TRPA1; < 17℃) [4]. Nociceptive P2X channels, which respond to extracellular ATP released by tissue damage, have also been found to excitatory currents and action potentials in dental primary afferent neurons [3]. The functional expression of nociceptive receptor ion channels in small-sized dental primary afferent neurons indicate that noxious stimuli on teeth can directly activate nerve terminals of nociceptive neurons innervating the pulp to evoke dental pain. However, the contribution of nociceptive receptor ion channels to dentin hypersensitivity may be less significant as teeth do not discriminate well between hot and cold in response to noxious thermal stimuli, while the discrete hot or cold sensation is evoked by thermal stimuli on other somatic areas.

2. Odontoblast transducer theory

Odontoblasts, originating from the ectomesenchyme cells of the neural crest, serve its primary role in dentin formation [5]. In addition to their role in dentin formation, odontoblasts have been suggested to mediate dental sensation as they consist the outermost compartment of the dentin-pulp complex with their processes projecting through the dentinal tubules, which leads to propose 'odontoblast transducer theory' [1,6,7]. A variety of sensory transducers for noxious stimuli such as heat (TRPV1), cold (TRP melastatin 8 [TRPM8]), or ATP (P2X) have been reported to be expressed in odontoblasts, implying the possible contribution of odontoblasts to dental sensory transduction [8-12]. The possibilities of cellular excitability in odontoblasts and ATP or glutamate-dependent neurotransmission from odontoblasts to adjacent nerve terminals have been also demonstrated [13-15]. However, it is still under debate whether fully differentiated odontoblasts in mature teeth is capable of sensing noxious stimuli as TRPV1, TRPA1, and TRPM8 were not detected in acutely dissociated primary odontoblasts from adult rodents and thus were not responsive to nociceptive temperatures [16].

3. Hydrodynamic theory

Originally proposed by Brännstrom and Åström [17,18] who found that drying the dentinal fluid by air puff or absorbent paper pellets causes dentin hypersensitivity, hydrodynamic theory focuses on the possibility of sensory components in the dentin-pulp border to be activated by dentinal fluid movement caused by various stimuli onto the surface of exposed dentin [19-21]. Previous studies based on the hydrodynamic theory suggest that the external stimulation on dentin such as probing, brushing, or air puff results in movement of dentinal fluid in the dentin-pulp complex or cause deformation of tubule contents [21,22]. In order to respond to such fluid movement or deformation of cellular components, sensory receptor ion channels for mechanical transduction are required, especially those which can also mediate light mechanical stimuli [1,23]. Therefore, the functional expression of mechanosensitive ion channels that can be activated by light stimuli (i.e. low-threshold mechanosensitive ion channels, LTMs), rather than those activated by noxious mechanical forces (i.e. high-threshold mechanosensitive ion channels [HTMs]), have been gaining interest in dental sensory components. Among the putative mechanosensitive ion channels such as acid-sensing ion channels (ASICs), TRPs, Piezos, K^+ channel subfamily K (KCNKs) and transmembrane channel-like proteins (TMCs) [24,25], several candidate ion channels expressed by dental primary afferent neurons and odontoblasts have been suggested to be involved in dental sensation.

Expression of Mechanosensitive Ion Channels in Dental Sensory System

1. Mechanosensitive ion channel expression in dental primary afferent neurons

Molecular screening in dental primary afferent neurons by single cell RT-PCR have revealed the expression of ASIC3, TRPA1, TRPV1, TRPV2, TWIK-related K^+ channel 1 (TREK-1), TREK-2, Piezo2, whereas TRPV4, TRPM3, TWIK-related arachidonic acid-stimulated K^+ channel (TRAAK) and Piezo1 were

reported to be undetected in these cells [4,26,27]. ASIC3 has been suggested to participate in noxious mechanical transduction but whether ASIC3 plays a critical role as a mechanosensitive ion channel is controversial as demonstration of mechanical activity of ASIC3 has been unsuccessful in heterologous expression system, and dorsal root ganglion neurons of transgenic animals lacking ASIC3 did not show alterations in electrophysiological activity under mechanical stimulation [24]. The functional expression of TRP channels have been demonstrated in dental primary afferent neurons by pharmacological or thermal stimulation of the respective channels [4], although whether these channels mediate mechanosensitivity has not been identified yet. Among the TRP channels expressed in dental primary afferent neurons, it is possible that TRPA1 mediate pulpitis-related pain as TRPA1 has been found to participate in mechanical hyperalgesia under inflammation [28]. TREK channels are suggested to modulate rather than directly mediate mechanical transduction in small-sized nociceptive neurons which remain in the pulp rather than innervating the dentin-pulp border [29-31]. Piezo2, in contrast to the other putative mechanosensitive ion channels mentioned above, has been found to mediate tactile sensation by light touch by generating mechanically-sensitive rapidly inactivating non-selective inward currents [32]. In a recent study, the functional expression of Piezo2 has been demonstrated by patch clamp recording in the majority of mechanosensitive dental primary afferent neurons [27]. These neurons were mostly medium- to large-sized but also contained calcitonin gene related peptide (CGRP) and Nav1.8, which seem paradoxical as these are nociceptive neurotransmitter and sodium channels expressed in nociceptive neurons, respectively [27]. This paradoxical character of Piezo2 positive-dental primary afferent neurons also showing nociceptive markers seem to reflect 'algoneurons', a putative population of dental primary afferent neurons which mediate dentin hypersensitivity by transducing innocuous hydrodynamic mechanical stimulation into nociceptive signaling [23]. Transcriptome analysis on dental primary afferent neurons with low threshold mechanosensitive ion channels may shed light on understanding the involvement of 'algoneurons' or Piezo2-positive populations in dentin hypersensitivity [33].

2. Mechanosensitive ion channels in odontoblasts

The expression of mechanosensitive ion channels in odontoblasts has also been investigated in scope of hydrodynamic theory as stimulation on exposed dentin results in movement of dentinal fluid and causes displacement of odontoblasts and their processes [21,22]. Therefore, the functional expression of nociceptive TRP channels with mechanosensitive properties such as TRPV1, TRPV2, TRPV4 or TRPA1 were investigated in odontoblasts and the activation of these channels has been demonstrated in odontoblasts derived from neonatal rats by calcium imaging studies [12]. Mechanical deformation of odontoblasts evoked intracellular calcium transients which were partially blocked by TRPV1, TRPV2, TRPV4, and TRPA1 antagonist, indicating the possible involvement of these channels in dental nociception [12]. As these nociceptive TRP channels are high-threshold mechanosensitive ion channels which mediate injurious mechanical stimuli, these channels may be less involved in transducing subtle mechanical perturbations caused by dentinal fluid movement when expressed in mature odontoblasts. In addition, mechanosensitive K^+-permeable channels such as Ca^{2+}-activated K^+ channels and TREK-1 channels have also been detected in odontoblast-like cells by immunohistochemical methods, but their functional expression in odontoblasts have not been demonstrated yet [34,35]. When considering the nature of K^+-permeable channels, the activation of these channels would rather result in membrane hyperpolarization than to have an excitatory effect. In odontoblasts from adult rats, TRPM7 has been detected in the majority of odontoblasts by single cell RT-PCR and immunohistochemical methods [36-39]. Furthermore, mechanosensitive calcium transients mediated by TRPM7 activation were detected in odontoblasts during hypotonic solution-induced membrane stretch by calcium imaging studies [39]. Interestingly, TRPM7 was mostly localized in the odontoblastic process, emphasizing its possible role in detecting alterations in dentinal tubules [39]. However, interpreting these results to deduce the primary role of TRPM7 in mechanical transduction for dentin hypersensitivity should be done with caution as TRPM7 has also been found to be crucial in dentin mineralization by regulating alkaline phosphatase activity [40]. Whether the ubiquitous expression of TRPM7 is mainly involved in mechanical transduction or dentin mineralization is to be answered in future studies.

Conclusions

The mechanism of dentin hypersensitivity, the abrupt intense pain caused by innocuous stimuli on exposed dentinal tubules, have been attempted to be explained by the cellular components underlying dentin, the dental primary afferent neurons and odontoblasts. Among the dental primary afferent neurons,

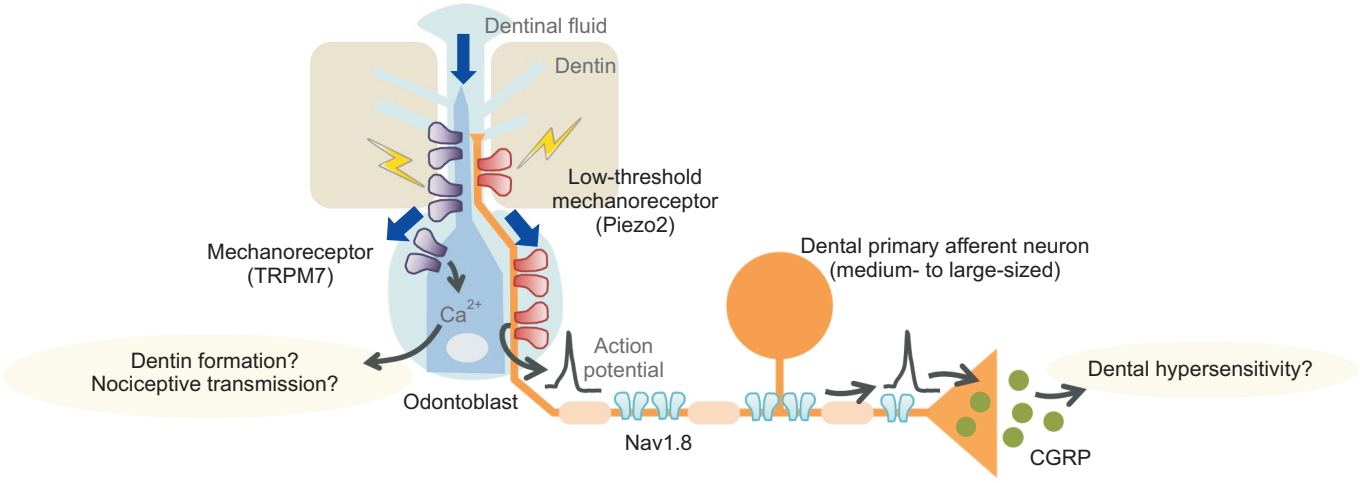

Fig. 1. Mechanosensitive ion channels expressed in dental sensory system. A schematic figure depicting how the activation of mechanosensitive ion channels by dentinal fluid dynamics can participate in dentin hypersensitivity. In dental primary afferent neurons, the activation of low-threshold mechanoreceptor in medium- to large- sized neurons with nociceptive characteristics is suggested to mediate dentin hypersensitivity. The activation of mechanoreceptors expressed in odontoblasts may not only result in nociceptive transmission but may also be involved in tertiary dentin formation after dentin injury.
TRPM7, transient receptor potential melastatin 7; CGRP, calcitonin gene-related peptide.

the subpopulation expressing low-threshold mechanosensitive ion channels may be a candidate for nociceptive signalling regarding dentin hypersensitivity in terms of hydrodynamic theory as large, myelinated neurons which are involved in light touch sensation when expressed in somatic sensory neurons paradoxically exhibit nociceptive characteristics. On the other hand, traditional nociceptive neurons representing neural theory may mediate dental pain evoked by noxious stimuli rather than dentin hypersensitivity. Lastly, the mechanosensitive ion channels expressed in odontoblasts indicate the possibility of odontoblasts to participate not only in dentin hypersensitivity explained by hydrodynamic theory but also in dentin formation under dentinal fluid dynamics following dentin exposure (Fig. 1). Further investigation on the expression of mechanosensitive ion channels and their modulatory mechanism will greatly help in advancing clinical strategies to treat dentin hypersensitivity.

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Conlficts of Interest

No potential conflict of interest relevant to this article was reported.

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