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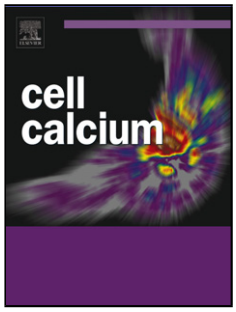

I scream for ice cream – TRPC5 as cold sensor in teeth

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I scream for ice cream -

TRPC5 as cold sensor in teeth

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Graphical Abstract

Not needed for N&V

Highlights

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"My curse upon your venom'd stang,

That shoots my tortur'd gums alang"

In his famous poem "*Address To The Toothache"* (1786), Robert Burns describes toothache as the "hell o' a' diseases", and those of us who have experienced a bout of severe dental pain will likely agree. The tooth, a three-layered system consisting of enamel, dentin and the pulp chamber, is a remarkable physiological ecosystem. On the one hand, it is extremely hard and strong due to hydroxyapatite microcrystals forming the outer layer of the tooth, the enamel. On the other hand, it is very sensitive to environmental factors such as pH, mechanical stress and cold temperatures. These stimuli evoke pain via activation of nociceptors that belong to the trigeminal nerve, the largest and most complex nerve in the face carrying sensory information and controlling motor functions, with nerve endings in the pulp chamber and dentin. Particularly, teeth with enamel decay or inflammation of the pulp chamber (pulpitis) display very high sensitivity to such external stimuli, eliciting sharp, severe and long-lasting pain sensations.

Odontoblasts are specialized cells situated at the interface between the pulp chamber and the dentinal layer and play a key role in dentin formation through the secretion of collagen. Recently, they emerge as important sensors of the dentin environment, implicated in signal transduction in response to environmental triggers. Notably, there is mounting evidence that odontoblasts and neighboring sensory nerve endings express distinct sets of ion channels that may be involved in pain signaling [1, 2].

Bernal et al. now report that the canonical transient receptor potential channel TRPC5, located in the dentin-protruding processes of odontoblasts, may serve as one of the key cold sensors in teeth [3]; see **Figure 1**. TRPC5 is a receptor-operated, Ca^{2+}-permeable, non-selective cation channel activated downstream of phospholipase C-coupled receptors [4]. Earlier work also reported activation of TRPC5 by cold temperatures, but a contribution to peripheral cold sensing remained unclear [5]. Now, Bernal et al. show that $TRPC5^{-/-}$ mice are severely impaired in sensing inflammatory tooth pain provoked by dental pulp injury, while mice lacking TRPM8 or TRPA1, two major cold-sensing TRP channels in the peripheral nervous system, are not affected. Elegantly, the authors used an intact whole jaw-nerve preparation to directly monitor nerve responses to cold temperatures from intact teeth-innervating nerve endings. Exposing the intact jaw to cold triggered high-frequency action potentials in ~10% of all nociceptor fibers, a number that was diminished by about half upon treatment with TRPC5 inhibitors or in $TRPC5^{-/-}$ mice. Surprisingly, only few isolated cold-sensitive dental primary afferent neurons (DPANs) responded to riluzole (TRPC5 agonist) and the TRPC5 expression in DPANs appeared extremely low. Instead, immunofluorescent labelling in murine molars revealed high TRPC5 expression in the odontoblast cell layer, in close contact with the nerve endings. Unfortunately, TRPC5 activity in odontoblasts was not directly demonstrated, possibly due to inevitable changes in gene expression upon odontoblast culturing. TRPC5 was also detected in the odontoblastic layer of human teeth, but it remains uncertain whether TRPC5 is expressed in human odontoblasts or solely in sensory nerves innervating this layer. Notably, TRPC5 expression appeared elevated in human teeth with pulpitis, resulting in an increased number of TRPC5-positive nerve fibers.

Intriguingly, the authors show that eugenol, a major compound present in cloves, inhibits TRPC5 channels. This provides a plausible explanation why cloves have been used for ages to treat dentin hypersensitivity and inflammatory tooth pain. Further research is warranted to determine whether inhibiting TRPC5 by more specific antagonists represents a viable new route to tooth pain relief.

Bernal et al. provide novel insights in dental cold sensation, putting TRPC5 channels and odontoblasts as the focal point for transducing cold into electrical activity in sensory neurons. Excessive activation of TRPC5 channels in response to cold stimuli might serve as an early warning system for enamel decay and dentin exposure. Based on these findings, we may revisit the mechanisms whereby cold evokes tooth pain. Indeed, it has been hypothesized that cold temperatures induce fluid movement within the dental tubules, thereby opening mechanosensitive channels leading to pain [6]. In contrast, the findings of Bernal et al. suggest a direct activation of TRPC5 by cold. Of course, it cannot be excluded that other mechanosensitive ion channels contribute or modulate cold-elicited pain. For instance, the highly mechanosensitive Piezo channels are expressed in both odontoblasts and DPANs [7]. Of note, teeth with pulpitis also display increased sensitivity to mechanical stress, and thus upregulation of such mechanosensitive channels may contribute to cold-induced pain sensation.

To pinpoint the role of TRPC5 and other ion channels in cold-induced toothache, further pain models should be employed to evaluate cold-sensitivity during dental injury, preferably using odontoblast-specific knockout animals to exclude potential alterations within the central nervous system that could confound the behavioral readouts. Moreover, further research is warranted to understand the mechanisms downstream TRPC5-induced Ca^{2+} signaling/depolarization in odontoblasts. For instance, mechanical stimulation of odontoblasts triggers ATP release through Pannexin-1 channels, eliciting electrical signaling in the trigeminal nerve by opening ionotropic ATP (P2X3) receptors [8]. In addition to ATP, odontoblasts can also release glutamate and expression of glutamate receptors on odontoblasts and trigeminal nerves has been reported [9]. The contribution of these intercellular signaling events in response to cold stimulation represent intriguing fields of further research.

In conclusion, this work suggests that TRPC5 may serve as a biosensor that monitors dental health and acts as an early alarm system to warn for dental problems.

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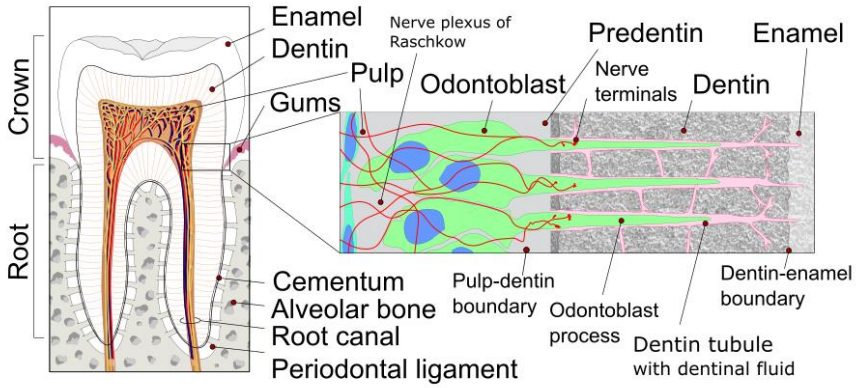
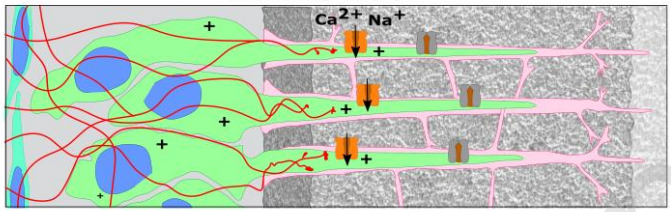
Legend for figure

Teeth can be subdivided into three compartments: i. the outer hard shell, the enamel, mainly consisting of hydroxyapatite microcrystals, ii. the middle part made of dentin (50% hydroxyapatite, 25% water, 25% collagen), and iii. the pulp chamber, where blood capillaries and nerve terminals are located. Odontoblasts reside at the boundary between the pulp chamber and the dentin layer. These cells are not only responsible for producing dentin, but are also important sensors of the dentin environment through their processes that protrude the dentin layer and that are connected to dentinal tubules. Odontoblasts further establish pseudo-synaptic connections with nerve terminals from the trigeminal nerve. Ca^{2+} influx into or depolarization of odontoblasts may be transduced into nociceptive responses through paracrine signaling, such as via the release of adenosine triphosphate (ATP); the exact mechanisms in the case of cold-induced signaling must be further resolved. Odontoblasts express several ion channels that open in response to cold, heat or mechanical stress. Bernal et al. identified TRPC5 channels in odontoblasts as critical sensors for transducing cold-evoked responses in healthy teeth. In teeth with damaged enamel, cold stimuli may hyperactivate TRPC5 channels due to a more direct exposure of the odontoblast TRPC5 channels to thermal stimuli. In teeth with inflamed pulp chambers, expression of TRPC5 channels can become upregulated, further exacerbating cold-induced pain. The figure was taken from Bernal et al, Sci Adv, 2021 (DOI: 10.1126/sciadv.abf5567) and further amended.



Healthy tooth

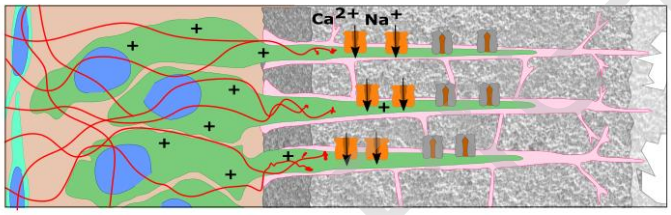
Moderate nerve activity (in response to cold)



Cold sensitivity: normal
Pain threshold: high

Tooth with enamel decay

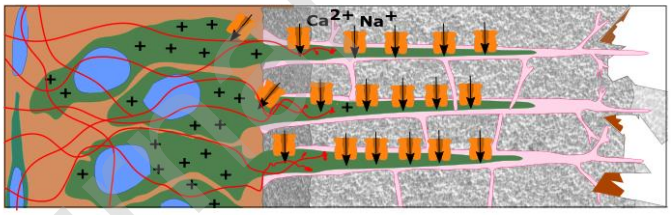
High nerve activity (in response to cold)



Cold sensitivity: high
Pain threshold: low

Tooth with dentin damage and inflammation

Very high nerve activity (in response to cold)



Cold sensitivity: very high
Pain threshold: very low