**Abstract:** Dental pulp is densely innervated by sensory afferents that are primarily involved in nociception. Elucidating the type and properties of these afferents and their distribution patterns within the dental pulp is crucial for understanding the mechanisms of acute dental pain and dental hypersensitivity. Recent studies on the release of the transmitter glutamate and the expression of glutamate receptors and vesicular glutamate transporters (VGLUT) in the pulpal axons and trigeminal ganglion (TG) have suggested the possibility of a distinct glutamate signaling mechanism underlying the peripheral processing of dental pain. This review discusses recent findings on the innervation of dental pulp and glutamate signaling by pulpal axons. First, recent findings on the morphological features and types of axons innervating the dental pulp are summarized. Then, glutamate signaling in the dental pulp and changes in the expression of VGLUT1 and VGLUT2 in the pulpal axons and TG neurons following pulpal inflammation are explained. Finally, findings on glutamate release from odontoblasts are briefly described.

**Keywords:** dental pulp, glutamate signaling, pulpal axons, vesicular glutamate transporter

**Introduction**

Dental pulp is a useful organ for studying the peripheral mechanisms of pain. Activation of the pulpal nerve by many types of stimuli, including chemical, mechanical, and thermal stimuli, primarily induces painful sensations even though it is innervated by various types of sensory nerve fibers, including Aβ large myelinated fibers [1-3]. Elucidation of the types and properties of nerve fibers innervating dental pulp and of the sensory receptors and ion channels expressed in each type of pulpal nerve fiber is crucial for understanding the peripheral mechanisms of dental pain. Recently, many studies have reported expressions of glutamate receptors and various molecules involved in the release of glutamate in pulpal axons [4,5] and their upregulation in inflamed pulp [6,7]. This suggests that glutamate signaling, associated with the pulpal nerve may play a crucial role in acute and pathologic dental pain.

This review summarizes recent findings on the innervation of dental pulp and glutamate signaling associated with intrapulpal axons, which may assist understanding of peripheral mechanisms of dental pain.

**Types and morphological features of axons innervating dental pulp**

**Types of axons innervating dental pulp**

Dental pulp contains a unique sensory system that primarily produces painful sensations by various external stimuli [1]. Many electron microscopic (EM) studies have revealed that 70-90% of the axons within the dental pulp are unmyelinated “C” fibers and the remaining small proportion comprises small myelinated “A” fibers [1,8]. Many studies have also shown that intrapulpal axons arise from larger extrapulpal (parent) axons; thus, Thus, the axons innervating the dental pulp: 1) have higher conduction velocity in their extrapulpal segments than in their intrapulpal segments [9,10]; 2) have a higher ratio of myelinated to unmyelinated axons in the extrapulpal segment (e.g. inferior alveolar nerve) than in the intrapulpal segment [11,12]. And 3) although most intrapulpal axons are unmyelinated, most sensory neurons innervating the dental pulp in the trigeminal ganglion (TG) are large- and medium-sized which are usually associated with large myelinated “Aβ” fibers and small myelinated “Aδ” fibers, respectively [11,13].

An EM study employing retrograde tracing indicated that the parent axons innervating the rat molar pulp at the sensory root of the TG consist of 1) mostly (76%) small myelinated Aδ fibers, which are associated with the transduction of sharp, well-localized pain, and 2) many fewer unmyelinated fibers (4%), which are associated with the transduction of diffuse, dull pain, and 3) a significant fraction (20%) of large myelinated Aβ fibers, which are associated with the transduction of mechanical, non-noxious stimuli (Fig. 1) [2]. Some of the large myelinated Aβ fibers innervating dental pulp may evoke pain by low-threshold stimuli and contribute to dentin sensitivity [14] and/or may be nociceptive fibers that respond to noxious stimuli [15]. This assumption is supported by the findings that about 20% of the large myelinated Aβ fibers are nociceptive [15] and that some large myelinated Aβ fibers project to the superficial lamina of the spinal dorsal horn where spinal nociceptive neurons are concentrated [16].

**Morphological features of axons within the dental pulp**

The myelinated axons of the primary sensory neurons usually lose their myelin sheath during their course from neuronal cell bodies to peripheral targets (Fig. 2) [17,18], which exposes several receptors and ion channels on the membrane of the unmyelinated part of the axon: these receptors and ion channels can be activated by various stimuli and extracellular ligands.

Previous EM studies identified both myelinated and unmyelinated axons in dental pulp [19,20], but the authors did not elucidate where and how the morphology of the parent myelinated axons change between their origin in the TG and their target in the dental pulp, or within the dental pulp itself. It was shown that virtually all axons in the sensory roots of the TG that are immunopositive for parvalbumin (PV+) are myelinated [21]. A study using PV as a marker for myelinated axons indicated that the parent myelinated axons innervating human dental pulp undergo significant morphological changes during their peripheral course before and after they enter the dental pulp [3]. Thus, about 66%, 79%, and 99% of the PV+ axons in the radicular pulp, the core of the coronal pulp, and the peripheral pulp, respectively, were unmyelinated (Fig. 3), implying that 66% of the parent axons that are myelinated at the TG lose their myelin before reaching the dental pulp. Also, 40% of the myelinated axons at the apical foramen become unmyelinated before reaching the core of the coronal pulp, and the remaining 60% become unmyelinated in their course from the core of the coronal pulp to the peripheral pulp. This suggests that most unmyelinated fibers in the peripheral pulp come from myelinated parent axons.

**Expression and distribution of receptors and ion channels in the axons of dental pulp**

Many receptors and channels are expressed in the pulpal axons and TG neurons that innervate dental pulp. They are activated by a variety of stimuli and are involved in the generation and signal transduction of acute nociceptive and pathological pain. The number that have been discovered have rapidly increased over the last decade and those that have been studied most extensively are: 1) thermosensitive channels, including the heat-sensing channels transient receptor potential vanilloid (TRPV1) (>43°C), TRPV2 (<2°C), TRPV4 (27-35°C), and transient receptor potential melas-
tatin (TRPM3 (&gt;40°C) and the cold-sensing channels TRPM8 (&lt;26°C) and transient receptor potential ankyrin 1 (TRPA1) (&lt;17°C); 2) mechano-sensitive channels, including TRPV1, TRPV2, TRPV4, TRPM3, TRPA1, epithelial sodium channel (ENaC), acid-sensing ion channel 3 (ASIC3), and Piezo-type mechanosensitive ion channel component 2 (PIEZO2); 3) other channels, including the ATP-binding purinergic receptors P2X2 and P2X3, and the hyperpolarization-activated cyclic nucleotide-gated channels HCN [5].

Recent immunohistochemical studies showed the distribution of cold-sensing channels TRPA1 and TRPM8 in the axons of dental pulp [7,22]: thus, nerve fibers expressing TRPA1 and/or TRPM8 are scant in the radicular pulp and the core of the coronal pulp, but they branch extensively and form a network of fibers in the peripheral pulp: many TRPM8-positive axons were also found to penetrate the dentinal tubules toward the enamel. The latter observation, in particular, may have clinical implications since it indicates that the TRPA1- and TRPM8-mediated pain from noxious cold is primarily perceived at the level of the peripheral pulp and dentin. This suggests that applying TRPA1 or TRPM8 blockers to the peripheral pulp and dentinal tubules may be more effective in relieving dentin cold hypersensitivity and there may be fewer side effects than applying those blockers systemically.

The HCN contributes to hyperpolarization-induced membrane currents and is implicated in pathological pain following nerve injury and inflammation, but not in acute nociceptive pain [23-25]. Two major isoforms of HCN, HCN1 and HCN2, are expressed in pulpal axons. They are primarily in nociceptive pulpal axons in the peripheral pulp that co-express calcitonin gene-related peptide (CGRP) [26]. Conversely, in the TG, HCN is co-expressed with neurofilament 200 (NF200)- or PV-positive, large-sized mechanosensitive neurons, but rarely expressed in small-sized, CGRP- and isolectin B4 (IB4)-positive neurons. They are densely expressed as ring-like structures at the peripheral plasma membrane of the neuronal cell body rather than at the cytoplasm in the TG. The numbers of HCN1+ and HCN2+ neuronal cell bodies in the TG significantly increased throughout the maxillary region of the TG following pulpal inflammation of the maxillary teeth, which are innervated by a small number of neurons. These findings suggested that HCN-mediated inflammatory pain may be controlled by two distinct neuronal types in two distinct sites, that is, the cell bodies of mechanosensitive neurons in the TG and the nociceptive axons in the dental pulp. These findings are also consistent with the existence of intercellular communication, perhaps through a diffusible molecule or molecules, under conditions of pulpal inflammation, between the mechanosensitive neurons innervating the dental pulp and other non-inflamed tissues [27,28].

Peripheral glutamate signaling in nociception
Peripheral release of glutamate and the expression of glutamate receptors are upregulated following inflammation
The transmitter glutamate is produced by deamination of glutamine in the cell bodies of neurons in the dorsal root ganglia (DRG) and TG. It is then transported to the peripheral axons, as evidenced by the existence of glutamate in pulpal axons at a concentration much higher than what would be expected by its metabolic function, and by the accumulation of
glutamate in the sensory root proximal to the site of a crush injury [Fig. 4] [29-31]. Glutamate release from peripheral axons and dental pulp can be triggered by electrical, chemical, and thermal stimuli [32,33]. Receptors for transmitter glutamate (GluR), including a variety of ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-o-aspartate (NMDA), and metabotropic glutamate receptors, are also expressed in peripheral myelinated and unmyelinated axons [34-36]. In addition, their expression is increased following tissue injury and inflammation [31,37-41]. Many reports in the literature have supported the hypothesis that glutamate is released from peripheral axons, which mediates nociception via binding to GluR on the axons themselves (autocrine activation) and/or on adjacent axons (paracrine activation) [30].

Peripheral glutamate signaling mediates normal and pathologic nociception

Several lines of evidence have suggested that peripheral glutamate signaling plays an important role in the transmission of nociception under normal and pathological conditions; thus, 1) application of τ-glutamate to the rat skin excites Aδ and C fibers, but not Aβ fibers, and induces their sensitization to heat (thermal hyperalgesia) [42]; 2) injecting glutamate into the human masseter muscle or temporomandibular joint causes acute pain and/or mechanical allodynia [43-47]; and 3) intraplantar injections of AMPA, kainate, or NMDA receptor agonists cause thermal and mechanical hyperalgesia and mechanical allodynia, which are blocked by the corresponding antagonists [48-50].

Expression of vesicular glutamate transporter 1 (VGLUT1) and VGLUT2 in primary sensory neurons

Vesicular glutamate transporters (VGLUTs), which are integral proteins in the membrane of synaptic vesicles, are involved in the loading of glutamate into synaptic vesicles and its release, and they are widely used as markers for neurons that use glutamate as a neurotransmitter [51,52]. VGLUT1 and VGLUT2, two major isoforms of VGLUT, show neural circuit-specific and complementary expression patterns in the central nervous system, and they are expressed in distinct subsets of primary sensory neurons [52,53]. Thus, VGLUT1 is expressed in neurons that also express markers for low-threshold mechanoreceptive neurons NF200 or PV, and primarily project to laminae III/IV of the spinal dorsal horn. VGLUT2 is expressed in neurons that also express markers for nociceptive neurons substance P (SP), CGRP, and TRPV1, and they primarily project to laminae I/II of the spinal dorsal horn [54-58]. In addition, studies analyzing the effect of experimental deletion of the mouse genes encoding for VGLUT (global and conditional deletion of the mouse genes encoding for VGLUT (global and conditional deletion of the mouse genes encoding for VGLUT1 or VGLUT2-/- mice are not viable) [59,60] have indicated involvement of VGLUT2 in acute and pathologic pain, but no clear evidence for a role for VGLUT1 in nociception (i.e. heterozygous VGLUT1-/- mice showed no change in the response to painful stimuli under normal and pathological conditions) [58,61]. Therefore, accumulating evidence points to the involvement of VGLUT1 primarily in the transmission of mechano-sensation and proprioception and the involvement of VGLUT2 primarily in the transmission of nociception.

Glutamate signaling in dental pulp

Pulpal axons express VGLUT1 and VGLUT2

It has been shown that VGLUT1 and VGLUT2 are expressed in many pulp axons, suggesting that VGLUT1- as well as VGLUT2-mediated glutamate signaling is involved in pulp nociception [4]. Since VGLUT1 is primarily expressed in mechanosensitive neurons (see above) and dental pulp is primarily involved in nociception, it is assumed that VGLUT1 is expressed in a specific subset of sensory afferents (Aβ low-threshold mechanosensitive) in dental pulp that are involved in nociception. This is supported by observations that about 20% of the axons innervating dental pulp are Aβ large myelinated fibers [2] and about 20% of the Aβ large myelinated fibers are involved in nociception [14,15]. If this is correct, then the neural circuitry for nociception and the mechanism for processing pain information in the dental pulp may be different from those in other tissues.

VGLUT and soluble NSF attachment protein receptor (SNARE), which are two classes of proteins associated with synaptic vesicle exocytosis, are densely expressed in the varicosities of pulp axons, suggesting that glutamate may be released from the pulp axons at those varicosities (similar to the terminals of the central axons in the spinal cord, which are the sites for transmitter glutamate release) [4,6,7,62-64]. Reportedly, many axons possessing varicosities expressed VGLUT in the peripheral pulp and many of those axons entered the denta! tubules [4]. Taken together with another observation that metabotropic glutamate receptor 5 (mGluR5) is also expressed in axons in the peripheral pulp [63], it suggests that the primary site of glutamate signaling associated with dental nociception is the peripheral pulp.

VGLUT2 in the pulp axons is upregulated following inflammation

VGLUT2 (but not VGLUT1) is upregulated in TG neurons and peripheral pulp axons following experimental pulp inflammation (using complete Freund’s adjuvant (CFA)) [6]. mGluR5 is upregulated in pulp axons following inflammatory dentin injury [63]. These findings suggest that, following inflammation, the VGLUT2-mediated glutamate release from pulp axons increases, leading to the activation and subsequent heterologous or autologous upregulation of GluRs in pulp nociceptive axons (Aδ and C fibers, but not Aβ fibers), which in turn can contribute to their sensitization and eventually to the development of pathologic pain [42]. The release of glutamate may also evoke the release of neuropeptides (among them, CGRP) from pulp axons, which is known to induce neurogenic inflammation that can further contribute to sensitization of the pulp nociceptive axons [65].

The expression of VGLUT1 in pulpaxons and TG neurons remains virtually unchanged following pulp inflammation, suggesting that the VGLUT1-mediated glutamate signaling by pulp axons may be involved in the mechanisms of acute nociceptive pain but not in the mechanisms of inflammatory pain [6]. The enhanced glutamate release from rat pulp axons following inflammation follows the pattern of increases in glutamate release from peripheral axons following inflammation or tissue injury elsewhere in the body [30]. VGLUT1 and VGLUT2 are also expressed in C6D6+ inflammatory cells that infiltrate pulp following inflammation [6], suggesting that non-neuronal cells may also be related to the increase in VGLUT-mediated glutamate signaling following inflammation of the pulp.

Expression of VGLUT in the TG neurons and pulp axons that express TRPM8

Sensory neurons that innervate pulp express a variety of receptors and ion channels, the activation of which can evoke glutamate release from their central and/or peripheral axons. For example, it was shown that activation of TRPM8 in neurons induces release of glutamate from their central afferents, which plays a crucial role in the transmission of TRPM8-mediated signaling of cold [66,67]. In addition, many TRPM8-expressing TG neurons and pulp axons express VGLUT2 (but not VGLUT1) [7]. Considering that both VGLUT2 and TRPM8 in the primary sensory neurons have been implicated in the mediation of acute nociceptive and pathologic pain [68,69], it seems likely that VGLUT2-mediated glutamate signaling is involved in the transmission of TRPM8-mediated noxious cold. Furthermore, the expression of VGLUT2 in TG neurons is upregulated following pulp inflammation, whereas the expression of TRPM8 is not significantly changed [7]. Since both TRPM8 and VGLUT2 are implicated in cold hypersensitivity following inflammation [69-71], it is reasonable to assume that cold hypersensitivity following pulp inflammation is induced by upregulation of the expression of VGLUT2 in the TRPM8-expressing TG neurons, rather than by the direct effect of TRPM8 upregulation. The activation of TRPM8 following pulp inflammation may further enhance the increase in VGLUT2-mediated glutamate release through an indirect mechanism. Several studies also reported no change in the expression of TRPM8 in DRG neurons following nerve injury and inflammation [72,73]. One study reported the downregulation of TRPM8 in the radicular pulp of the human teeth with irreversible pulpitis [74]. The discrepancy may be due to differences in rats versus humans or in pulp versus TG or DRG.

Glutamate release from odontoblasts

That odontoblasts can also engage in glutamate signaling is supported by the following observations: 1) odontoblasts contain levels of glutamate that are far too high to be explained by their metabolic needs, 2) the levels of glutamate in the odontoblasts (and the expression of the mGluR5 receptor in pulp axons that are adjacent to them) are increased following pulp inflammation, and 3) glutamate release from odontoblasts is increased by...
experimentally raising the intracellular Ca\(^{2+}\) [31]. Additionally, mechan- 
al stimulation of the odontoblasts in a coculture of odontoblasts and TG 
neurons was shown to induce Ca\(^{2+}\) influx in adjacent odontoblasts and TG 
neurons, which is inhibited by the application of mGlur antagonists [75]. 
These findings provided morphological and electrophysiological evidence 
supporting the notion that odontoblasts, when activated, release glutamate, 
which then activates GluR expressed on adjacent pulp nociceptive axons, 
thus playing a role in the mechanisms of acute dental pain and hypersensit- 
ivity following inflammation.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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