Journal Endo Sapiens

Narrative Review

Ion Channel Regulation of Aδ- and C-Fiber Signaling in Endodontic Pain

Michelle Tang[1,*]

Abstract

Background: Endodontic pain reflects altered signaling in pulpal and periapical afferents. However, conventional diagnostic categories do not fully explain differences in pain quality, persistence, localization, or anesthetic response. Ion channels link inflammatory tissue changes to Aδ- and C-fiber activity.
Objective: To synthesize how stimulus-gated and voltage-gated ion channels regulate Aδ- and C-fiber signaling in pulpal inflammation, apical disease, and pain following endodontic treatment.
Methods: A narrative review evaluated human tissue studies, experimental pulpitis models, electrophysiologic and molecular investigations, and channel-targeted intervention studies. Evidence was appraised according to its relevance to endodontic disease, functional demonstration of channel activity, identification of afferent phenotype, and level of clinical translation.
Results: TRPV1, TRPA1, TRPV4, ASIC3, P2X3, and Piezo2 convert thermal, chemical, acidic, purinergic, osmotic, and mechanical signals into graded receptor potentials. NaV1.7 amplifies threshold responses, NaV1.8 sustains action-potential upstrokes and repetitive firing, and NaV1.9 promotes subthreshold excitability. Kv, CaV, and HCN channels further regulate repolarization, transmitter release, and recurrent firing. Aδ fibers contribute predominantly to rapid, sharp, stimulus-evoked pain, whereas polymodal C fibers contribute more strongly to lingering, spontaneous, throbbing, and poorly localized pain. Inflammation produces overlapping channel expression and recruitment, so these fiber associations are not exclusive. Local anesthetics provide established nonselective NaV blockade; selective NaV1.7, NaV1.8, P2X3, and TRP interventions are promising but are supported mainly by preclinical evidence.
Conclusions: Ion channels organize the initiation, transmission, and persistence of endodontic pain. Translation requires standardized pain phenotyping, functional human tissue studies, and clinical trials linking selective channel modulation to defined Aδ- and C-fiber outcomes.

Keywords: Aδ fibers; C fibers; dental pulp; endodontic pain; ion channels; nociception

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Received for publication Jun 24, 2026; accepted for publication Jul 19, 2026.
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https://doi.org/10.71347/j7u8vb3b

1. Introduction

Endodontic pain often changes as disease progresses: a brief, sharp response to cold may become lingering or spontaneous pain and later tenderness to biting or percussion when inflammation reaches the apical tissues (Yu & Abbott, 2018; Kumar et al., 2025). These changes reflect altered neural activity in the pulp and apical periodontium, not inflammation alone (Fried & Gibbs, 2014; Rechenberg et al., 2016; Zhan et al., 2021). Ion channels are membrane proteins that control ionic movement and determine whether tissue stimuli are ignored, generate a brief warning, or evoke repeated impulses perceived as pain (Linley et al., 2010; McEntire et al., 2016; Lee et al., 2019; Waxman & Zamponi, 2014).

The dental pulp contains two principal groups of pain-conducting fibers. Thinly myelinated Aδ fibers conduct impulses relatively quickly and are associated predominantly with sharp, brief, stimulus-evoked pain that can be localized reasonably well. Unmyelinated C fibers conduct more slowly and contribute more strongly to aching, throbbing, lingering, spontaneous, and poorly localized pain (Jyväsjärvi & Kniffki, 1992; Ahlquist & Franzén, 1994; Kumar et al., 2025). This distinction is clinically useful but not absolute: both populations express overlapping ion channels and become sensitized during pulpitis. Progression from an early sharp response to lingering or spontaneous pain therefore reflects recruitment and sensitization of overlapping afferents, not a simple switch from Aδ to C fibers (Ramli et al., 2022; Chung et al., 2026).

This review focuses on inflammatory pain arising from reversible pulpitis, symptomatic irreversible pulpitis, residual vital tissue in a partially necrotic pulp, symptomatic apical periodontitis, acute apical abscess, and endodontic procedures (Alelyani et al., 2020; Kumar et al., 2025; Chung et al., 2026). It addresses brief thermal pain, lingering pain, spontaneous toothache, throbbing, referred pain, pain on biting or percussion, and postoperative pain (Cha et al., 2020; Kwon et al., 2021). Dentin hypersensitivity is excluded because it usually begins with exposed dentin and movement of fluid within open dentinal tubules, a clinical setting that differs from inflammatory pulpal or apical disease (Aminoshariae & Kulild, 2021; Sun et al., 2025). Cervical sensitivity, exposed-root sensitivity, bleaching sensitivity, and routine restorative sensitivity are therefore outside the scope of this review, although a study may be cited when it clarifies the location or function of an ion channel in pulpal nerves (Han et al., 2022; Sun et al., 2025). Primary neuropathic and nonodontogenic disorders, including trigeminal neuralgia, painful post-traumatic trigeminal neuropathy, persistent idiopathic dentoalveolar pain, temporomandibular disorders, and referred myofascial pain, are also excluded except when a mechanism is directly relevant to endodontic pain (De Laat, 2020). The aim is to explain ion channel biology in terms that help the clinician understand what the patient feels, why the pain pattern changes, why inflamed teeth can be difficult to anesthetize, and where new treatment may act (Lee et al., 2019; Chung et al., 2026).

A structured literature search identified studies relevant to ion channel regulation of Aδ- and C-fiber signaling in endodontic pain. PubMed/MEDLINE, Scopus, and Web of Science were searched from inception through July 5, 2026, using terms for dental pulp, pulpitis, apical periodontitis, endodontic pain, Aδ and C fibers, trigeminal neurons, and TRP, ASIC, P2X, Piezo, NaV, Kv, CaV, and HCN channels. Priority was given to human pulpal or periapical tissue, functional dental-afferent studies, experimental pulpitis, electrophysiology, and channel-targeted interventions. Dentin hypersensitivity, nonodontogenic pain, and neuropathic disorders were excluded unless directly informative. Evidence was interpreted by endodontic relevance, functional demonstration,

afferent identification, and clinical translation.

2. How Pulpal Inflammation Changes the Behavior of Pain Fibers

2.1 Why inflammation is especially painful inside a tooth

The pulp cannot swell freely because it is enclosed by a rigid dentin cage. When inflammation increases blood flow and makes small vessels leak, tissue pressure rises within a space that has little room to expand (Heyeraas & Kvinnsland, 1992). Compression of thin-walled veins can slow blood outflow, reduce local perfusion, and create areas of low oxygen beside still-vital nerve fibers (Yu & Abbott, 2018; Zhan et al., 2021). Recent human studies found that symptomatic pulpitis is associated with lower pulpal blood pH and, in more severe inflammation, lower oxygen saturation (Hosseinzadehfard et al., 2024, 2026). An inflamed pulp is therefore not one uniform tissue: relatively normal, highly inflamed, ischemic, and necrotic areas may exist within the same tooth. Nerves in these areas are exposed to changing pressure, acidity, reduced oxygen, bacterial products, adenosine triphosphate (ATP) released from damaged cells, and inflammatory chemicals. These conditions help explain why symptoms may fluctuate and why clinical findings do not always match a single histologic stage (Walsh et al., 2026).

2.2 How inflammation lowers the nerve's alarm threshold

Cells in the injured pulp release prostaglandins, bradykinin, ATP, protons, nerve growth factor, cytokines, proteases, and reactive oxygen species; recruited immune cells add further mediators (Fischer et al., 2010; Linley et al., 2010; Zhan et al., 2021). These mediators gate ion channels directly or alter their behavior through intracellular relay systems, including cyclic adenosine monophosphate–protein kinase A, phospholipase C–protein kinase C, and phosphoinositide 3-kinase–Src family tyrosine kinase–mitogen-activated protein kinase pathways (Fischer et al., 2010; Linley et al., 2010). Prostaglandin E2 illustrates how several changes cooperate: it enhances sodium currents that favor firing and suppresses potassium currents that normally stabilize the membrane (England et al., 1996; Nicol et al., 1997; Meves, 2006). Interleukin-1β can likewise enhance sodium currents in nociceptors (Binshtok et al., 2008). The resulting lower firing threshold allows cold, heat, pressure, or chemicals that previously caused little response to provoke intense or lingering pain (Jain et al., 2013). Longer-term changes in channel abundance and trafficking are considered in Section 2.5.

2.3 Why a brief response becomes lingering or spontaneous pain

A useful clinical way to understand sensitization is to divide ion channels into sensors, accelerators, and brakes. Transient receptor potential (TRP), acid-sensing ion channel (ASIC), and ATP-gated P2X purinergic receptor channels act mainly as sensors for heat, acidity, and extracellular ATP, respectively. Sodium and calcium channels help start, repeat, and transmit the electrical impulse; and potassium channels help restore the resting state and limit repeated firing (Linley et al., 2010; Waxman & Zamponi, 2014). In a healthy or mildly irritated pulp, a stimulus may open the sensors briefly, produce a few impulses, and stop when the stimulus is removed (Fried & Gibbs, 2014). During more advanced inflammation, the sensors respond more strongly, sodium and calcium channels amplify the signal, and reduced potassium channel activity removes part of the braking effect (Fischer et al., 2010; Linley et al., 2010; Waxman & Zamponi, 2014). Normal fluctuations in pulpal temperature, pressure, acidity, or mediator concentration may then be enough to trigger continued firing without a

new external stimulus. This phenomenon provides a practical explanation for lingering and spontaneous toothache (Linley et al., 2010; Yu & Abbott, 2018). Pacemaker-like hyperpolarization-activated cyclic nucleotide-gated (HCN) currents may further sustain firing in inflamed C fibers. This effect has been reported in experimental inflammatory pain but has not yet been proven as a major cause of human pulpal pain (Weng et al., 2012; Ciotu et al., 2019).

Human painful pulps show increased NaV1.7 expression and focal accumulation around intact and remodeling nodal regions; experimental inhibition of trigeminal NaV1.7 also reduces pulpitis-related neuronal activity (Luo et al., 2008; Kwon et al., 2021). These findings illustrate that sensitization reflects the combined behavior of several channel systems rather than one molecular switch (Lee et al., 2019; Chung et al., 2026). Pain on biting or percussion involves a different sensory territory, principally sensitized mechanosensitive and nociceptive afferents in the periodontal ligament and apical tissues after inflammation extends beyond the pulp (Trulsson, 2006; Alelyani et al., 2020). Figure 1 summarizes this progression from pulpal injury to changing clinical pain.

2.4 Pulpal nerves also help shape the inflammatory response

Pain fibers do more than carry information to the brain. When activated, pulpal afferents release calcitonin gene-related peptide (CGRP) and substance P (Caviedes-Bucheli et al., 2021). These proinflammatory neuropeptides can dilate vessels, increase vascular leakage, attract immune cells, and alter the activity of pulpal cells (Fehrenbacher et al., 2009; Sattari et al., 2010; Zhan et al., 2021), resulting in neurogenic inflammation (Chiu et al., 2012). In an experimental pulp-injury model, CGRP contributed to spontaneous pain-related behavior and to the early arrival of neutrophils and monocytes (Erdogan et al., 2024). Removing these immune cells reduced subsequent mechanical hypersensitivity, but it also allowed greater bacterial

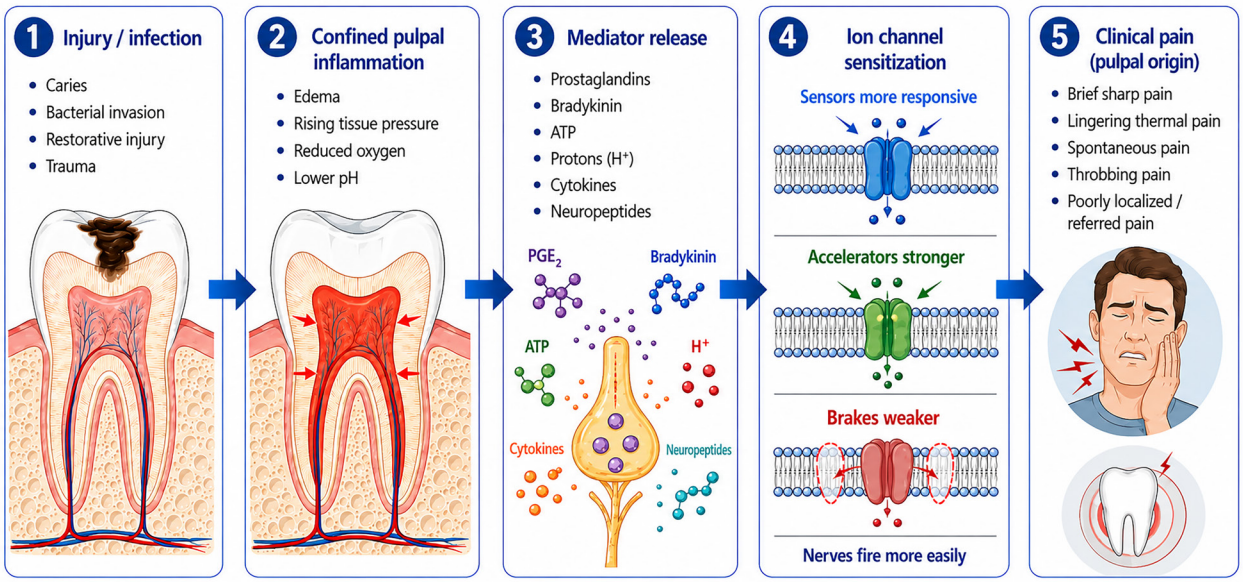


Fig. 1. From pulpal inflammation to sensitization of pulpal nociceptors. Caries, bacterial invasion, restorative injury, or trauma initiate inflammation within the rigid walls of dentin. Vascular leakage and edema increase tissue pressure, whereas impaired perfusion may reduce oxygenation and lower local pH. Prostaglandins, bradykinin, ATP, protons, cytokines, and neuropeptides then accumulate around pulpal nerve endings. These changes make sensory ion channels more responsive, strengthen excitatory sodium and calcium currents, and weaken the stabilizing influence of potassium channels. Pulpal nerves consequently fire more easily, helping explain the progression from brief, stimulus-evoked pain to lingering thermal pain, spontaneous or throbbing pain, and poorly localized or referred pain. Pain on biting or percussion is mediated mainly by sensitized mechanosensitive afferents in the periodontal ligament and apical tissues and is therefore not depicted in this figure.

penetration, tissue necrosis, and loss of sensory fibers (Erdogan et al., 2024). This apparent contradiction is clinically important: a painful pulp may still be mounting an effective defense, whereas reduced pain does not necessarily mean that inflammation or tissue destruction has improved (Walsh et al., 2026). Ion channel activity therefore links pain perception with blood flow changes, immune defense, and tissue injury within the same confined pulp space (Fehrenbacher et al., 2009; Zhan et al., 2021; Chung et al., 2026).

2.5 Ion channel plasticity during pulpal inflammation

Ion channels expressed by pulpal nociceptors do not constitute a fixed molecular system. Inflammation produces ion channel plasticity through rapid functional modulation and slower changes in channel abundance, trafficking, and distribution. Within seconds to minutes, protons and ATP can directly activate stimulus-gated channels, whereas bradykinin, prostaglandins, nerve growth factor, and cytokines modify existing channels through intracellular signaling. These processes can alter activation thresholds, opening probability, inactivation, or ionic current without changing channel number (Zhang et al., 2005; Camprubí-Robles et al., 2010).

Over longer periods, inflammation can modify gene transcription, protein synthesis, axonal transport, and membrane trafficking. These processes alter the abundance and location of channels available to regulate nociceptor firing. Studies of painful human dental pulp have demonstrated increased NaV1.7 and NaV1.8 immunoreactivity, and inflamed pulpal axons show increased TRPA1 expression (Renton et al., 2005; Luo et al., 2008; Kim et al., 2012). Conversely, Kv1.4 immunoreactivity is reduced in painful human pulp, potentially weakening potassium-dependent repolarization and the

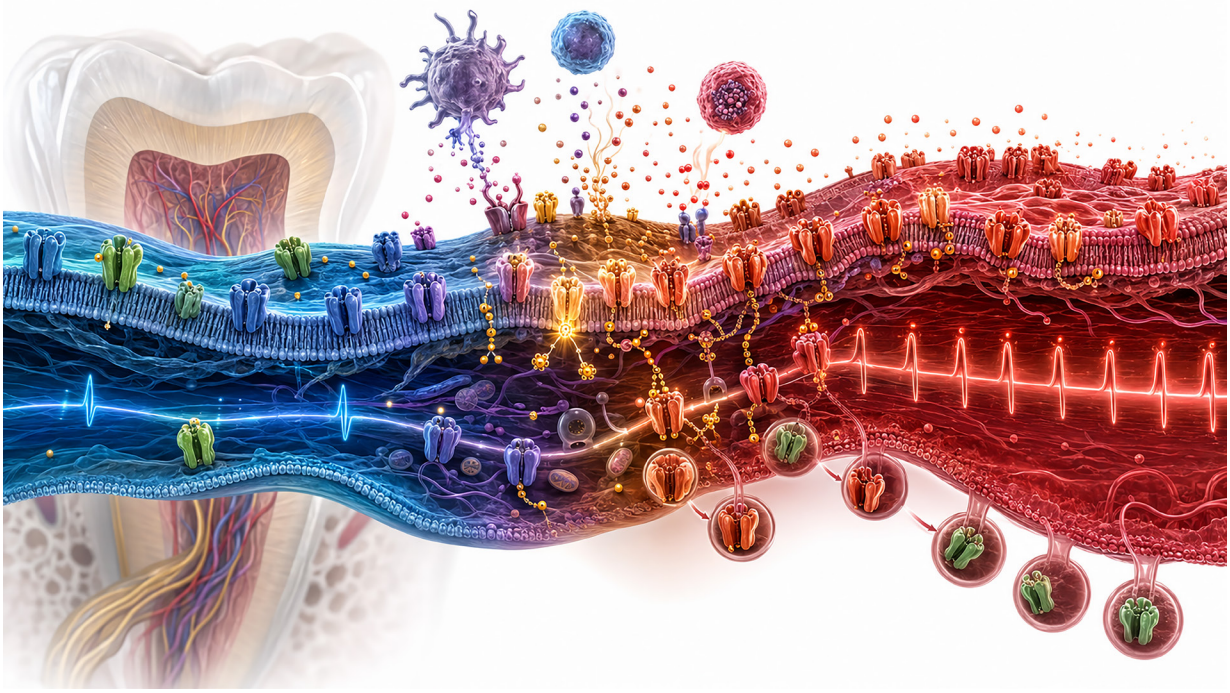


Fig. 2. Inflammation-induced ion channel plasticity in a pulpal nociceptor. The continuous transition from a relatively balanced, noninflamed state on the left to an inflamed, hyperexcitable state on the right illustrates rapid and longer-term regulation of ion channels. Inflammatory cells and mediators activate signaling pathways that modify existing channels, potentially lowering their activation thresholds, increasing opening probability, altering inactivation, or amplifying ionic currents. Sustained inflammation can also alter channel synthesis, axonal transport, membrane insertion, redistribution, and internalization. The resulting increase in excitatory channel activity, together with reduced inhibitory restraint, changes sparse stimulus-evoked firing into repetitive or spontaneous action-potential discharge. Channel shapes and colors are schematic and do not identify individual channel subtypes or represent quantitative changes in channel abundance.

restraint of repetitive firing (Wells et al., 2007). Inflammation may therefore strengthen excitatory sensors and accelerators while weakening inhibitory brakes. This phenomenon produces a transition from sparse stimulus-evoked firing to repetitive or spontaneous discharge (Figure 2).

Increased immunoreactivity should not be interpreted as a direct count of functional channels in the neuronal membrane. It may reflect greater protein abundance within individual axons, recruitment of additional channel-positive fibers, channel redistribution, or inflammation-associated nerve remodeling. Electrophysiologic confirmation is required to determine whether these anatomical changes produce greater or smaller ionic currents. Ion channel plasticity is therefore dynamic, channel-specific, and dependent on the location, severity, and duration of pulpal inflammation. This plasticity provides a mechanistic link between tissue inflammation, nociceptor hyperexcitability, and the transition from protective stimulus-evoked pain to lingering or spontaneous pain.

3. Ion Channels That Shape Endodontic Pain

An ion channel is a protein embedded in the nerve cell membrane that forms a narrow, selective pore. When the channel opens, electrically charged particles such as sodium, calcium, potassium, or chloride ions move across the membrane and change the electrical state of the nerve cell (Hille et

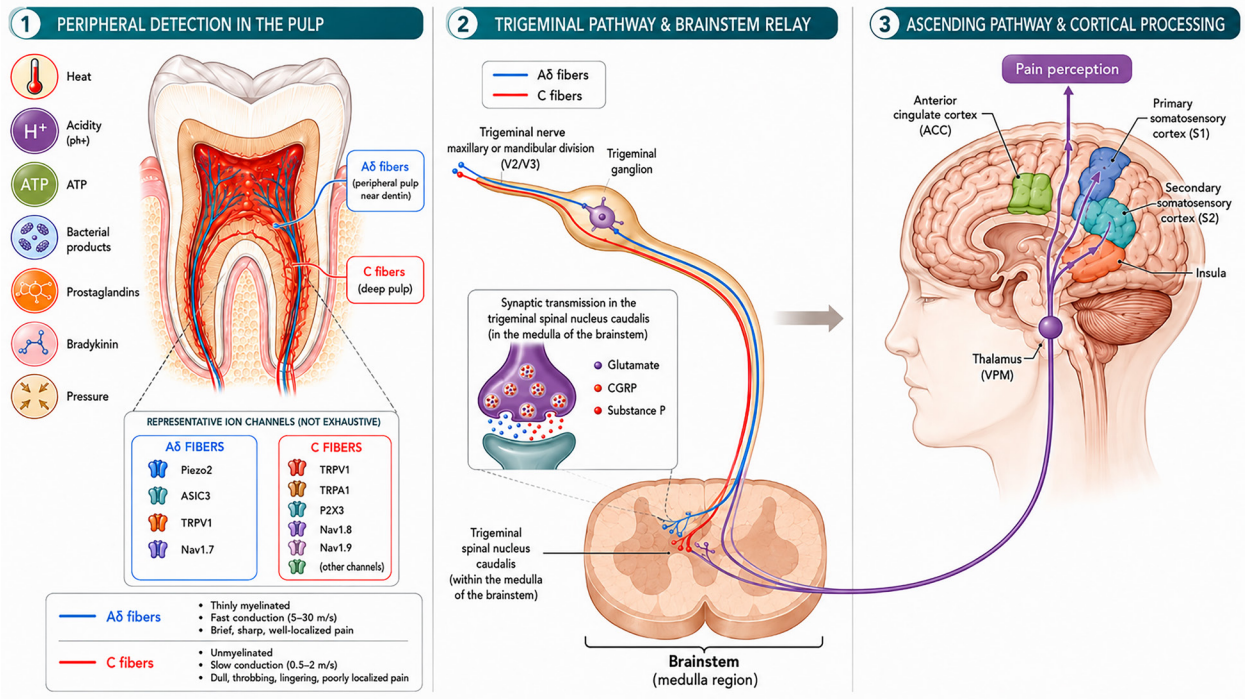


Fig. 3. Transmission of ion channel–dependent pain signals from the dental pulp to the cerebral cortex. Heat, acidity, extracellular adenosine triphosphate (ATP), bacterial products, prostaglandins, bradykinin, and increased tissue pressure activate or sensitize ion channels on pulpal Aδ and C fibers. Representative channels associated predominantly with Aδ fibers include Piezo2, acid-sensing ion channel 3 (ASIC3), transient receptor potential vanilloid 1 (TRPV1), and the voltage-gated sodium channel NaV1.7. Representative channels associated predominantly with C fibers include TRPV1, transient receptor potential ankyrin 1 (TRPA1), P2X3 receptors, NaV1.8, NaV1.9, and HCN channels. These assignments are not exclusive because several channels are expressed in both fiber populations. Thinly myelinated Aδ fibers conduct relatively rapid signals commonly associated with brief, sharp, and better-localized pain, whereas unmyelinated C fibers conduct more slowly and are more strongly associated with dull, throbbing, lingering, spontaneous, and poorly localized pain. Action potentials travel through the trigeminal nerve to neuronal cell bodies in the trigeminal ganglion and then to the trigeminal spinal nucleus caudalis in the medulla. Glutamate, calcitonin gene-related peptide (CGRP), and substance P contribute to synaptic transmission within the brainstem. Ascending signals then pass through the ventral posteromedial nucleus of the thalamus to cortical regions involved in sensory discrimination and the emotional experience of pain, including the primary and secondary somatosensory cortices, insula, and anterior cingulate cortex.

al., 1999). Some ion channels open in response to heat, acidity, chemicals, or mechanical pressure (i.e. stimulus-gated channels), whereas others respond to changes in membrane voltage (i.e. voltage-gated channels) (McCleskey & Gold, 1999).

Within this framework, ion channels determine which local changes are detected, whether an action potential begins, how often the nerve fires, and how quickly it returns to rest (McCleskey & Gold, 1999; Henry & Hargreaves, 2007). The following sections examine the evidence for individual sensor, accelerator, and brake channels.

Evidence ranges from studies of painful human pulp to experimental dental-afferent models and extrapolation from broader pain research. Localization establishes that a channel is present, not that it was active or caused the patient's pain (El Karim et al., 2011; Rouwette et al., 2015). Figure 3 summarizes peripheral activation and central transmission.

3.1 Transient receptor potential vanilloid 1

Transient receptor potential vanilloid 1 (TRPV1) is the most extensively studied sensory ion channel in inflammatory dental pain. It is a cation channel that opens in response to capsaicin, sufficiently high temperatures, and acidic conditions, allowing positively charged ions to enter the nerve ending and initiate depolarization (Caterina et al., 1997; Tominaga et al., 1998). Inflammation also makes TRPV1 easier to activate because bradykinin, nerve growth factor, prostaglandins, and intracellular protein kinases can lower its activation threshold or increase the number of channels present at the nerve-cell surface (Cesare & McNaughton, 1996; Premkumar & Ahern, 2000; Zhang et al., 2005). A temperature change that once produced a brief warning may consequently generate a larger and longer response. The main mechanisms by which TRPV1 is activated and sensitized are summarized in Figure 4.

Direct dental experiments confirm that TRPV1

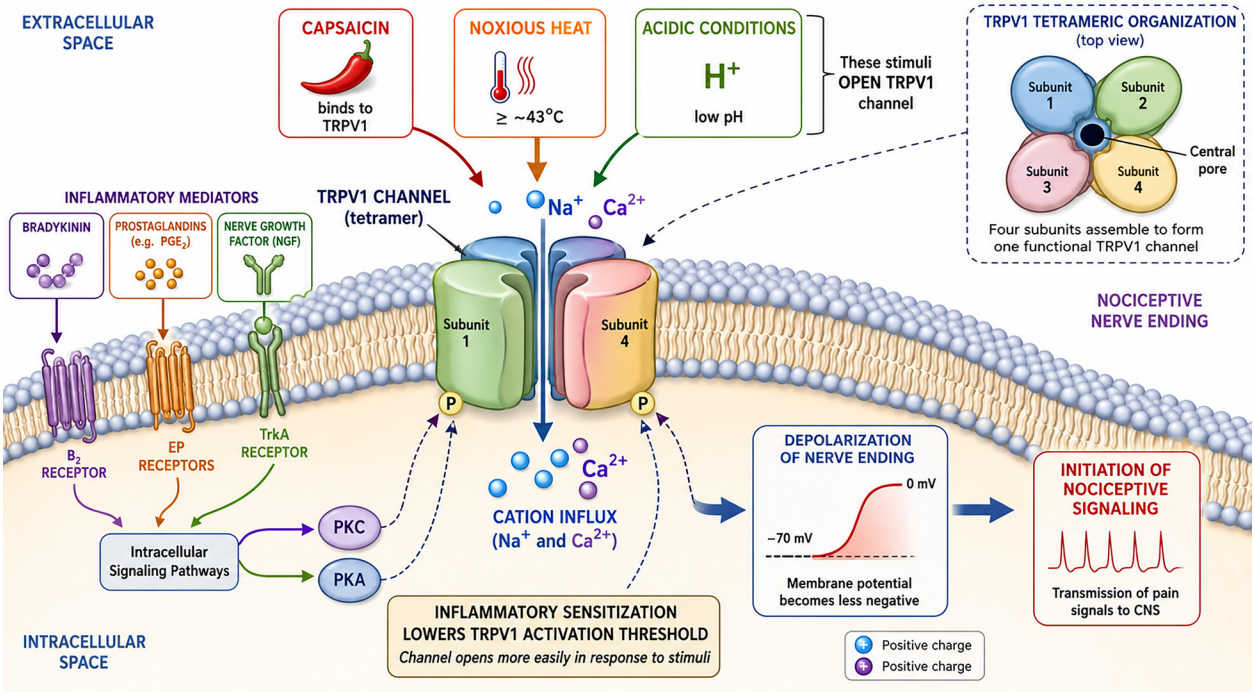


Fig. 4. Activation and sensitization of transient receptor potential vanilloid 1 (TRPV1) in a pulpal nociceptive nerve ending. Transient receptor potential vanilloid 1 (TRPV1) is a tetrameric nonselective cation channel composed of four subunits surrounding a central pore. Capsaicin, noxious heat, and acidic conditions can open the channel, allowing positively charged ions, particularly sodium (Na^+) and calcium (Ca^{2+}), to enter the nerve ending and initiate depolarization. Inflammatory mediators such as bradykinin, prostaglandins, and nerve growth factor act through their receptors and intracellular kinases, including protein kinase A (PKA) and protein kinase C (PKC), to lower the activation threshold of TRPV1. As a result, the channel opens more readily in response to noxious stimuli, thereby increasing nociceptor excitability and promoting pain signaling.

is functional in tooth-related nerves. These channels were identified in rat dental primary afferent neurons that respond to capsaicin (Chaudhary et al., 2001). Electrophysiological studies have demonstrated heat-responsive transient receptor potential currents in dental afferents (Park et al., 2006). Human pulp also releases CGRP after capsaicin stimulation (Fehrenbacher et al., 2009). This finding demonstrates that TRPV1 activation can trigger neuropeptide secretion as well as electrical activity. Neuropeptide release can influence pulpal vessels, immune-cell recruitment, and local inflammation (Erdogan et al., 2024).

TRPV1 is associated predominantly with small peptidergic C fibers but also occurs in some myelinated tooth-projecting afferents (Gibbs et al., 2011). TRPV1-positive fibers are found in painful and nonpainful human pulps, whereas experimental pulpitis increases TRPV1 expression in tooth-related trigeminal neurons (Renton et al., 2003; Chung et al., 2011; Cha et al., 2020). These findings implicate TRPV1 in inflammatory heat sensitivity, lingering thermal pain, chemical excitation, and neurogenic inflammation, but neither its presence nor its activity alone identifies symptomatic pulpitis or explains spontaneous pain (Fehrenbacher et al., 2009; Chung et al., 2011).

3.2 Transient receptor potential ankyrin 1 and other TRP channels

Transient receptor potential ankyrin 1 (TRPA1) detects chemical and oxidative tissue stress. It responds to reactive aldehydes, electrophilic compounds, irritants, and products generated during tissue injury (Bandell et al., 2004; Macpherson et al., 2007). These stimuli are relevant to pulpitis because bacterial injury, ischemia, immune activity, and lipid oxidation can create reactive compounds around still-vital nerve terminals (Zhan et al., 2021; Erdogan et al., 2024). Bradykinin can also sensitize TRPA1 through intracellular signaling (Wang et al., 2008).

The TRPA1 channel is often identified in the same small nociceptive neurons as TRPV1, allowing one nerve to respond to several inflammatory changes (Kim et al., 2011). Its role in clinical cold testing is less certain. Removing or blocking TRPA1 and transient receptor potential melastatin 8 (TRPM8) did not abolish dental-pulp responses to cold in an experimental model (Michot et al., 2018). Pulp cell studies also show that TRPA1 and TRPV4 can stimulate ATP release. Nevertheless, this finding demonstrates cell signaling only and does not provide direct evidence of conscious pain (Egbuniwe et al., 2014).

Transient receptor potential vanilloid 2 (TRPV2) is common in medium- and larger-diameter pulpal afferents and may contribute to myelinated sensory signaling, although a defined endodontic pain phenotype has not been established (Gibbs et al., 2011). Transient receptor potential vanilloid 4, TRPM3, transient receptor potential canonical (TRPC)5, and anoctamin 1 have plausible mechanical, osmotic, thermal, or amplifying roles. However, much of the dental evidence concerns expression or odontoblast biology (Lee et al., 2019; Chung et al., 2026). They should therefore be presented as emerging contributors (Chantadul et al., 2025).

3.3 Acid and ATP sensors

Acid-sensing ion channels (ASICs) open when the extracellular environment becomes acidic. Acid-sensing ion channel 3 (ASIC3) has been identified in rat trigeminal ganglion neurons, including populations expressing CGRP or parvalbumin (Ichikawa & Sugimoto, 2002). Acid-sensing ion channel proteins have also been detected in human odontoblasts, although this finding does not establish their contribution to pulpal nerve firing or conscious pain (Sole-Magdalena et al., 2011). The fall in pulpal blood pH during symptomatic pulpitis gives this mechanism direct clinical plausibility (Hosseinzadehfard et al., 2026). Protons can also

sensitize TRPV1 and alter other ionic currents. Hence, acid-related pain probably reflects low pH acting together with ischemia, ATP, inflammatory mediators, and tissue pressure (Fischer et al., 2010; Linley et al., 2010).

Purinergic receptors detect extracellular nucleosides and nucleotides. P1 receptors respond to adenosine, whereas P2 receptors comprise ATP-gated P2X ion channels and G protein-coupled P2Y receptors (Ralevic & Burnstock, 1998; North, 2002; Abbracchio et al., 2006; Eltzschig et al., 2012). P2X receptors are most relevant to sensory excitation because their opening produces cation influx and depolarization (North, 2002).

Adenosine triphosphate released from damaged cells, mechanically stressed tissues, immune cells, odontoblasts, and fibroblasts can activate P2X receptor channels. P2X3 receptors have been demonstrated in human dental pulp and in tooth-projecting trigeminal neurons (Alavi et al., 2001; Jiang & Gu, 2002). External dentin stimulation can induce ATP release within human teeth, and odontoblasts possess functional purinergic signaling systems that may transmit this signal toward adjacent nerve endings (Liu et al., 2015; Shiozaki et al., 2017).

Activation of purinergic receptors contributes to tooth-pulp-evoked nocifensive behavior and brainstem neuronal activity in rats (Adachi et al., 2010). P2X3 and heteromeric P2X2/3 receptors are therefore plausible contributors to persistent inflammatory input when continuing tissue injury sustains extracellular ATP release (Adachi et al., 2010; Lee et al., 2019). The proposed sequence linking ATP release during pulpal inflammation to P2X3-mediated nerve depolarization is illustrated in Figure 5. P2X7 should be distinguished from neuronal P2X3 because P2X7 is expressed prominently in immune and supporting cells and can promote the release of inflammatory cytokines (Fischer et al., 2010).

3.4 Piezo channels, periodontal mechanoreception, and pain on percussion

Piezo1 and Piezo2 are mechanically gated, nonselective cation channels that convert membrane

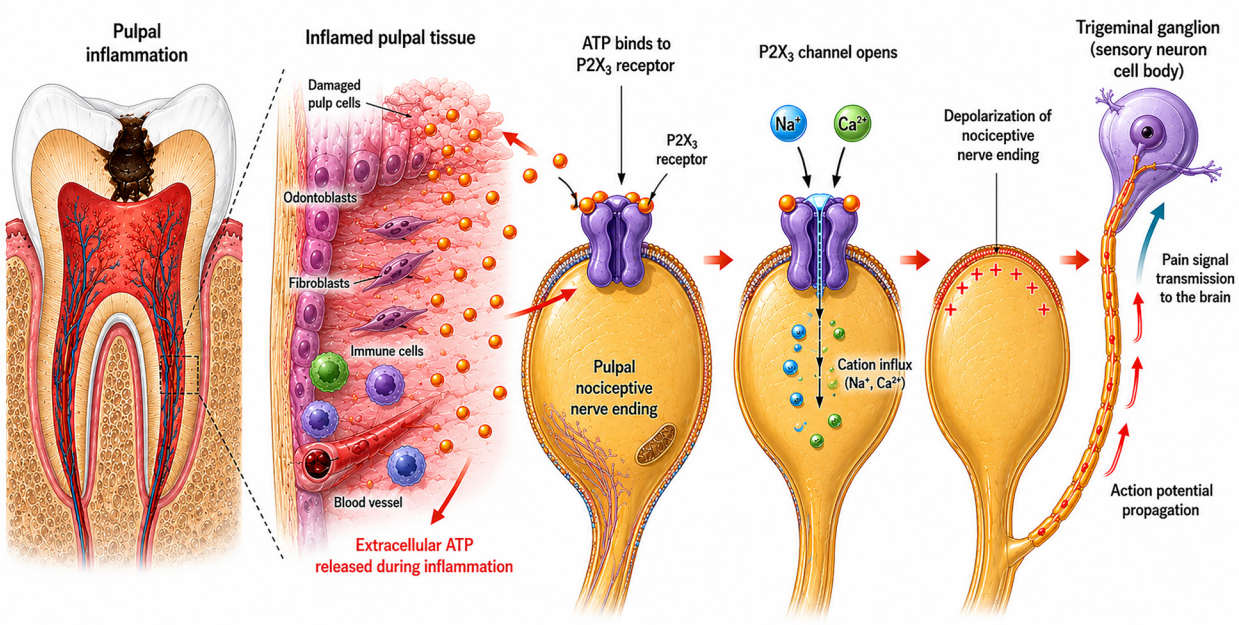


Fig. 5. Purinergic signaling through P2X3 receptors during pulpal inflammation. Tissue injury and inflammation within the dental pulp promote extracellular adenosine triphosphate (ATP) release from damaged pulpal cells, odontoblasts, fibroblasts, immune cells, and vascular cells. ATP diffuses through the inflamed tissue and binds to P2X3 receptors on nearby pulpal nociceptive nerve endings. P2X3 is an ATP-gated nonselective cation channel. Receptor activation permits sodium and calcium influx, depolarizes the nerve ending, and may initiate action potentials that propagate along the primary afferent fiber through the trigeminal ganglion toward brainstem nociceptive nuclei. Continued ATP release may therefore sustain sensory input during pulpal inflammation.

deformation into an inward ionic current (Coste et al., 2010). Opening of the channel allows positively charged ions, including sodium and calcium, to enter the cell and change its membrane potential. Piezo2 is the more plausible neuronal mechanotransducer because it is expressed in subsets of somatosensory neurons and produces rapidly adapting currents in response to mechanical deformation (Coste et al., 2010; Ranade et al., 2014). Piezo2 has been identified in mechanosensitive dental primary afferent neurons and is localized in pulpal axons, the sensory root, and the trigeminal ganglion (Won et al., 2017; Han et al., 2022). It is therefore a plausible detector of tissue deformation, vascular pulsation, and changing intrapulpal pressure. Activating mechanosensitive TRP and Piezo channels in odontoblasts can also generate impulses in nearby trigeminal neurons in coculture (Sato et al., 2018). Identification of Piezo2 expression in the dental pulp does not prove that it causes human pulpitis pain, and selective inhibition has not established its necessity in patients (Han et al., 2022). Intrapulpal Piezo signaling should also be separated from pain on biting or percussion, which mainly reflects sensitized periodontal ligament and apical afferents after disease has extended beyond the pulp.

The periodontal ligament contains highly sensitive mechanoreceptors that encode tooth displacement, force magnitude, and force direction and provide feedback for the control of biting and mastication (Trulsson, 2006). In healthy tissues, these receptors principally convey information about tooth loading and do not ordinarily produce pain. Pain on percussion occurs after inflammation has extended into the apical periodontal ligament and surrounding tissues, where displacement of the tooth deforms sensitized neural endings within an inflammatory environment. The mechanoreceptors that normally encode innocuous tooth movement must therefore be distinguished from nociceptors and mechanically sensitized afferents that generate pain during apical inflammation.

Broader sensory neuron research provides a possible mechanism through which Piezo2 could participate in percussion sensitivity. Inflammatory signaling was shown to increase Piezo2-mediated mechanically activated currents. This finding suggests that the channel's response to a given degree of deformation may be enhanced under inflammatory conditions (Dubin et al., 2012). Exchange protein directly activated by cAMP1 sensitized Piezo2 currents, lowered their mechanical activation threshold, and contributed to mechanical allodynia in experimental models (Eijkelkamp et al., 2013). Piezo2 knockdown attenuated this allodynia, providing functional evidence that sensitization of a low-threshold mechanotransducer can cause normally innocuous mechanical stimulation to become painful (Eijkelkamp et al., 2013). These experiments were performed in dorsal root ganglion neurons and non-dental pain models, however, and cannot establish an identical mechanism in periodontal afferents.

Sato et al. (2018) provide the most relevant direct dental evidence for functional Piezo-dependent mechanotransduction. However, they examined the dentin–pulp complex and not the periodontal ligament. Mechanical stimulation activated mechanosensitive TRP and Piezo channels in odontoblasts and generated action potentials in cocultured isolectin B4-negative, medium-sized trigeminal ganglion neurons. The study therefore demonstrates that mechanical deformation of a dental cell can be converted into signaling sufficient to excite an adjacent sensory neuron. However, the study does not provide direct evidence that Piezo channels are expressed in periodontal mechanoreceptor endings or that they mediate pain elicited by clinical percussion. Direct localization of Piezo2 in periodontal neural endings, electrophysiological recording from identified periodontal afferents, and selective inhibition or deletion during percussion-like stimulation are required in future studies before Piezo2 can be

considered responsible for pain on percussion.

3.5 Voltage-gated sodium channels

Voltage-gated channels respond to membrane-potential changes and regulate action-potential initiation, propagation, repolarization, repetitive firing, and transmitter release. In nociceptors, NaV channels generate and propagate action potentials, Kv channels repolarize the membrane and restrain discharge, CaV channels mediate calcium-dependent signaling and transmitter release, and HCN channels return hyperpolarized neurons toward threshold (Yu & Catterall, 2004).

The mammalian voltage-gated sodium channel family comprises nine classical subtypes, NaV1.1–NaV1.9, together with the related sodium channel protein Nax (Yu & Catterall, 2003). NaV1.7, NaV1.8, and NaV1.9 are particularly important in peripheral nociceptors that perform different tasks (Waxman & Zamponi, 2014; Goodwin & McMahon, 2021). Their distinct contributions to nociceptor excitation and action potential transmission are summarized in Figure 6.

NaV1.7 responds strongly to small, slowly developing depolarizations and helps determine whether a weak inflammatory signal reaches firing threshold

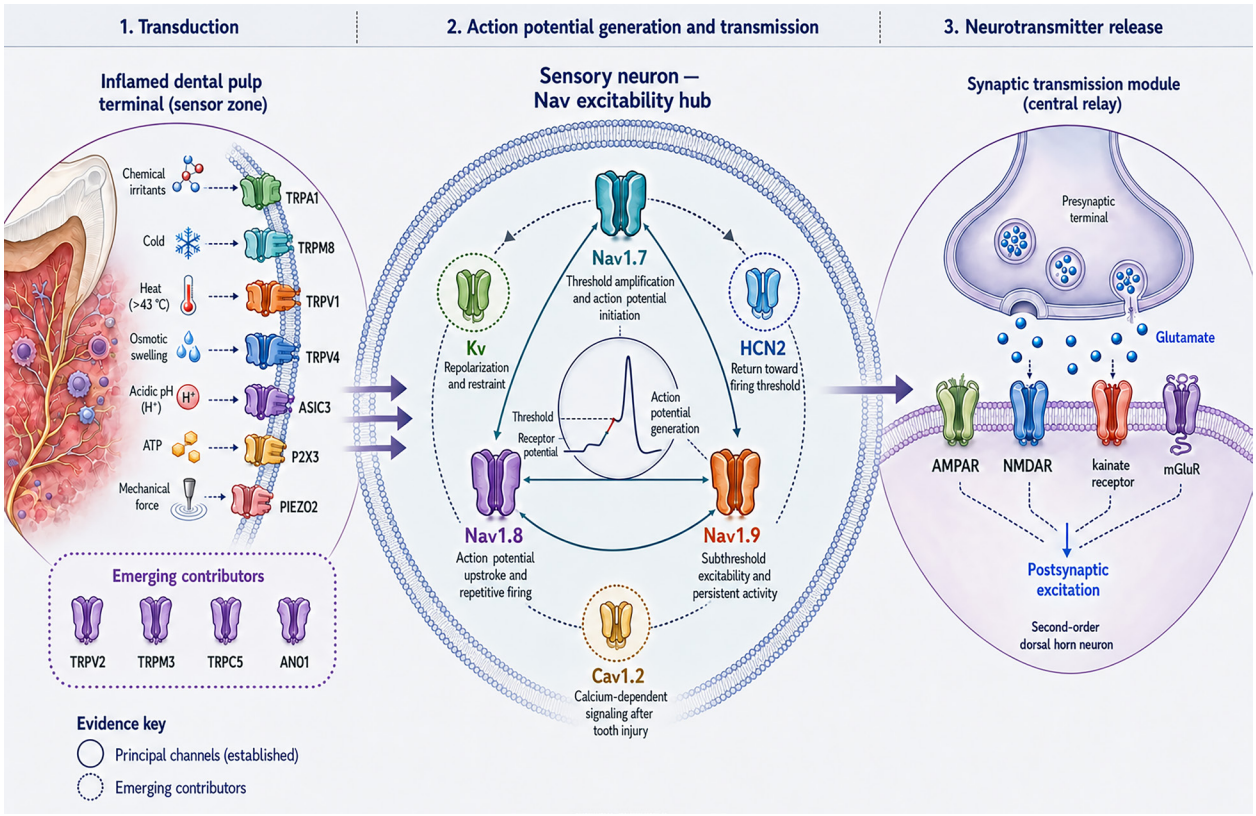


Fig. 6. Ion channels involved in the transduction, action-potential generation, and central transmission of endodontic pain. Noxious chemical, thermal, osmotic, acidic, purinergic, and mechanical stimuli activate specialized ion channels at sensory terminals within inflamed dental pulp. TRPA1, TRPM8, TRPV1, TRPV4, ASIC3, P2X3, and Piezo2 generate local receptor potentials. TRPV2, TRPM3, TRPC5, and anoctamin 1 are presented as emerging contributors because direct evidence linking them to endodontic pain is limited. When the receptor potential reaches threshold, NaV1.7 amplifies depolarization and facilitates action potential initiation. NaV1.8 contributes to the action potential upstroke and repetitive firing, whereas NaV1.9 increases subthreshold excitability and persistent activity. Voltage-gated potassium channels promote repolarization and restrain repetitive discharge. HCN2 facilitates return toward firing threshold, and CaV1.2 participates in calcium-dependent signaling after tooth injury. Transmission of the action potential to the central terminal induces glutamate release. Glutamate activates AMPA, NMDA, kainate, and metabotropic glutamate receptors on second-order dorsal horn neurons, producing postsynaptic excitation. Abbreviations: ANO1, anoctamin 1; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASIC3, acid-sensing ion channel 3; CaV, voltage-gated calcium channel; HCN2, hyperpolarization-activated cyclic nucleotide-gated channel 2; Kv, voltage-gated potassium channel; mGluR, metabotropic glutamate receptor; NaV, voltage-gated sodium channel; NMDAR, N-methyl-D-aspartate receptor; P2X3, P2X purinoceptor 3; TRP, transient receptor potential.

(Waxman & Zamponi, 2014). Painful human pulps show increased NaV1.7 immunoreactivity, including accumulation around intact and structurally altered nodal regions (Luo et al., 2008; Beneng et al., 2010). Selective trigeminal NaV1.7 inhibition reduces pulpitis-related neuronal activity in an experimental rat pulpitis model (Kwon et al., 2021).

NaV1.8 becomes especially important after a nociceptor has already depolarized. It carries much of the rising phase of the action potential in small sensory neurons and permits repeated firing under inflammatory conditions (Renton et al., 2005; Waxman & Zamponi, 2014). Increased NaV1.8 immunoreactivity has been demonstrated in painful human pulp, giving this channel direct clinical-tissue evidence (Renton et al., 2005). NaV1.8 is particularly relevant to persistent C-fiber activity, although it is not exclusive to one fiber class (Renton et al., 2005; Chung et al., 2026).

NaV1.9 produces a small persistent current near the resting membrane potential. It can keep the membrane slightly depolarized and make weak inflammatory inputs more likely to trigger firing (Waxman & Zamponi, 2014). NaV1.9 has been localized in human dental pulp and trigeminal sensory structures (Wells et al., 2007a). However, direct evidence connecting it with a defined human pulpitis pain phenotype is limited. Neural protein measurements from extirpated pulps also show that painful disease changes the neural compartment, although tissue-level quantification cannot identify which change is causative (Warren et al., 2008).

These NaV changes may contribute to anesthetic difficulty, but tissue acidity, rapid firing, tetrodotoxin-resistant currents, altered nodal organization, and central amplification also influence the clinical "hot tooth" (Henry & Hargreaves, 2007; Yu & Abbott, 2018).

3.6 Potassium channels: the electrical brakes

Potassium channels return the nerve membrane toward its resting state and limit repetitive discharge (Fischer et al., 2010; Waxman & Zamponi, 2014). Painful human pulp shows reduced expression of the voltage-gated potassium channel Kv1.4 (Wells et al., 2007b). This finding suggests that pulpal hyperexcitability may arise partly from loss of an inhibitory current. The Kv1.1 and Kv1.2 channels can also act as mechanical and electrical brakes in sensory neurons, although direct endodontic evidence is limited (Waxman & Zamponi, 2014).

Kv7 channels, two-pore-domain potassium channels, and calcium-activated potassium channels also stabilize resting potential or shorten the action potential (Linley et al., 2010; Waxman & Zamponi, 2014). Direct human endodontic evidence for these channels is sparse (Lee et al., 2019). Clinically, pain can increase because excitatory channels become stronger, because potassium braking becomes weaker, or because both changes occur together (Fischer et al., 2010; Waxman & Zamponi, 2014).

3.7 Voltage-gated calcium channels and HCN-gated channels

Voltage-gated calcium channels open after depolarization and permit calcium entry at nerve terminals. This calcium entry promotes release of glutamate, CGRP, substance P, and other transmitters (Waxman & Zamponi, 2014). Tooth injury alters the localization of the L-type calcium channel CaV1.2 in pulpal nerve fibers, Schwann cells, odontoblasts, and fibroblasts (Westenbroek et al., 2004). The contribution of individual calcium channel subtypes to human pulpitis pain has not been tested through selective clinical intervention (Lee et al., 2019).

Hyperpolarization-activated cyclic nucleotide-gated channels can move a recently active nerve back toward firing threshold after the membrane becomes more negative. Experimental inflammation increases HCN current and excitability in C-fiber nociceptors but not Aδ nociceptors; deletion of HCN2 from nociceptive neurons reduces inflammatory pain behavior (Emery et al., 2011; Weng et al., 2012).

The HCN2 channel is therefore a plausible contributor to persistent C-fiber firing. However, its role as a major cause of human pulpal pain has not been demonstrated (Weng et al., 2012; Ciotu et al., 2019).

3.8 What this evidence means clinically

Stimulus-gated and voltage-gated channels operate sequentially (Figure 7). TRPV1, ASIC3, P2X3, or Piezo2 generates a graded receptor potential at the peripheral terminal; if threshold is reached, NaV1.7 facilitates initiation, NaV1.8 carries much of the action-potential inward current, and NaV1.9 regulates subthreshold excitability. The impulse then propagates along an Aδ or C fiber, and Ca^{2+} influx through permeable transducer channels contributes to intracellular signaling and sensitization. Table 1 summarizes the clinical implications and evidence for individual channels.

No symptom maps uniquely to one channel. Lingering thermal pain may begin with sensitized TRP channels but also depends on NaV amplification, calcium-dependent transmitter release, potassium restraint, and continuing inflammation. Spontaneous pain similarly reflects convergent excitatory currents and neuroimmune feedback, whereas percussion pain recruits periodontal and apical afferents. Accordingly, Table 1 grades evidence by direct relevance to human endodontic pain; expression and localization are interpreted separately from functional channel activity.

4. Integrating Ion Channels with Aδ- and C-Fiber Pain Phenotypes

Dividing pulpal pain into Aδ- and C-fiber phenotypes provides a useful physiological framework, but it should not imply a one-to-one relationship among a symptom, a fiber class, and an ion channel. This section considers how the channels summarized in Table 1 function collectively and how inflammation changes the relative contributions of myelinated and

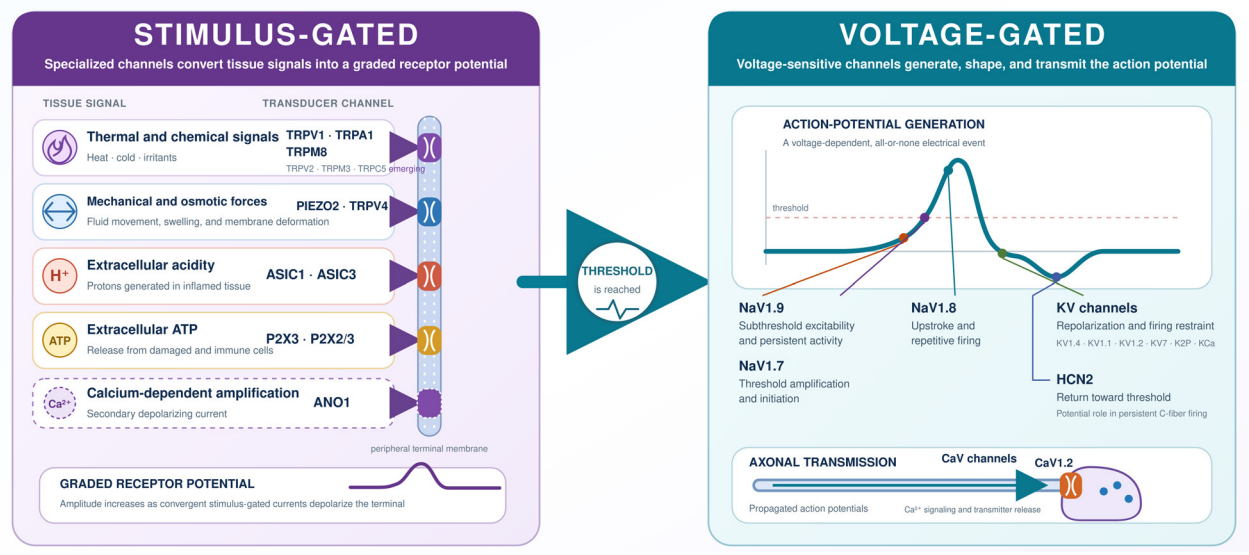


Fig. 7. Functional organization of stimulus-gated and voltage-gated channels in endodontic nociception. Stimulus-gated channels at the peripheral sensory terminal convert thermal, chemical, mechanical, osmotic, acidic, and purinergic signals into graded receptor potentials. Opening of these channels produces an inward current (receptor potential) carried primarily by Na^+ and, depending on channel selectivity, Ca^{2+}. The resulting membrane depolarization functionally couples stimulus detection to voltage-gated channel activation. If the graded receptor potential reaches threshold, voltage-gated NaV channels convert the local response into a propagated action potential. Ca^{2+} entering through Ca^{2+}-permeable stimulus-gated channels may also contribute to intracellular signaling and peripheral sensitization. Abbreviations: ANO1, anoctamin 1; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; CaV, voltage-gated calcium channel; HCN2, hyperpolarization-activated cyclic nucleotide-gated channel 2; KV, voltage-gated potassium channel; NaV, voltage-gated sodium channel; P2X, purinergic P2X receptor; PIEZO2, Piezo-type mechanosensitive ion channel component 2; TRP, transient receptor potential.

Table 1. Major ion channels implicated in endodontic pain

Ion channel or family	Principal stimulus or electrical role	Predominant afferent association	Direct dental or endodontic evidence	Clinical interpretation	Confidence*
Transient receptor potential vanilloid 1 (TRPV1)	Detects noxious heat and protons; becomes sensitized by inflammatory mediators and can trigger calcitonin gene-related peptide release.	C-fiber predominant, with partial expression in myelinated Aδ afferents.	Capsaicin- and heat-responsive dental afferents; immunoreactivity in human pulp; calcitonin gene-related peptide release from human pulp; trigeminal upregulation after experimental pulpitis (Chaudhary et al., 2001; Renton et al., 2003; Fehrenbacher et al., 2009; Chung et al., 2011).	Strong candidate for inflammatory heat sensitivity, lingering thermal pain, chemical excitation, and neurogenic inflammation; does not explain spontaneous pain alone.	Moderate-high
Transient receptor potential ankyrin 1 (TRPA1)	Detects reactive oxygen species, electrophilic products, and chemical tissue injury; can be sensitized by bradykinin.	Mainly small C-fiber nociceptors; frequent overlap with TRPV1.	Pulpal and odontoblast expression and adenosine triphosphate release have been demonstrated; dental cold responses persist after TRPA1 or TRPM8 inhibition (Wang et al., 2008; Egbuniwe et al., 2014; Michot et al., 2018).	May contribute to oxidative and chemical pain in pulpitis, but its role in human pulpal pain and clinical cold testing is not established.	Low-moderate
Transient receptor potential vanilloid 2 (TRPV2)	Possible high-threshold thermal and mechanical signaling.	More strongly associated with myelinated, neurofilament-positive dental afferents; Aδ-associated pattern.	Anatomical tracing shows substantial TRPV2 expression in pulpal afferents, including many neurofilament-positive neurons (Gibbs et al., 2011).	Possible contributor to rapid myelinated dental signaling, but no defined endodontic pain phenotype or targeted intervention has been established.	Low-moderate
Other transient receptor potential channels and anoctamin 1 (TRPV4, TRPM3, TRPC5, ANO1)	Potential mechanical, osmotic, noxious-heat, cold, or depolarization-amplifying functions.	Mixed or uncertain.	Evidence is derived mainly from expression studies, odontoblast experiments, or noninflammatory dental sensation rather than channel-targeted pulpitis studies (Egbuniwe et al., 2014; Lee et al., 2019; Chung et al., 2026).	Emerging mechanisms that should not yet be matched to specific pulpitis symptoms.	Low
Acid-sensing ion channels 1 and 3 (ASIC1 and ASIC3)	Open during extracellular acidification and generate depolarizing currents.	Small nociceptive afferents; C-fiber association is plausible but not exclusive.	ASIC3 is present in trigeminal neurons, and acid-sensing proteins occur in human odontoblasts. Pulpal pH falls during symptomatic pulpitis, but no selective human analgesic study has been performed (Ichikawa & Sugimoto, 2002; Sole-Magdalena et al., 2011; Hosseinzadehfard et al., 2024, 2026).	May contribute to pain in acidic, ischemic, or severely inflamed pulp, usually in cooperation with TRPV1, adenosine triphosphate, and inflammatory mediators.	Low-moderate
Adenosine triphosphate-gated P2X3 and P2X2/3 receptors (P2X3 and P2X2/3)	Convert extracellular adenosine triphosphate released by damaged or stressed cells into depolarizing current.	Small nociceptive afferents, including C fibers and some Aδ fibers.	P2X receptors occur in human pulp and tooth-projecting trigeminal neurons; human dentin stimulation releases adenosine triphosphate; experimental purinergic blockade reduces tooth-pulp-evoked nocifensive and brainstem responses (Alavi et al., 2001; Jiang & Gu, 2002; Adachi et al., 2010; Liu et al., 2015; Shiozaki et al., 2017).	Plausible source of continuing inflammatory input when tissue injury repeatedly releases adenosine triphosphate. P2X7 acts more indirectly through immune and supporting cells.	Moderate
Piezo-type mechanosensitive ion channel component 2 (Piezo2)	Opens during membrane deformation and detects mechanical force.	δ-associated pattern in small myelinated dental afferents.	Functional Piezo2 expression has been demonstrated in mechanosensitive dental primary afferents and localized in pulpal axons, sensory roots, and trigeminal ganglia (Won et al., 2017; Han et al., 2022).	May detect intrapulpal deformation, vascular pulsation, or pressure. It should not be used as a direct explanation for biting or percussion pain arising from apical tissues.	Moderate

Table 1. (continued) Major ion channels implicated in endodontic pain

Ion channel or family	Principal stimulus or electrical role	Predominant afferent association	Direct dental or endodontic evidence	Clinical interpretation	Confidence*
Voltage-gated sodium channel NaV1.7 (NaV1.7)	Amplifies small, slowly developing depolarizations and helps the nerve reach firing threshold.	Aδ and C fibers.	Expression is increased in painful human pulp, with accumulation near intact and remodeled nodal regions; selective trigeminal inhibition reduces pulpitis-related neuronal activity (Luo et al., 2008, 2010; Beneng et al., 2010; Kwon et al., 2021).	Strong evidence for lowered firing threshold and enhanced pulpal excitability; may contribute to evoked and spontaneous pain and anesthetic difficulty.	High
Voltage-gated sodium channel NaV1.8 (NaV1.8)	Supports the action-potential upstroke and repeated firing in depolarized or inflamed nociceptors.	C-fiber predominant, but not exclusive.	NaV1.8 immunoreactivity is increased in painful human dental pulp (Renton et al., 2005).	Likely supports persistent or repetitive C-fiber activity and may contribute to anesthetic difficulty in inflamed pulp.	Moderate-high
Voltage-gated sodium channel NaV1.9 (NaV1.9)	Produces a persistent subthreshold sodium current that keeps the neuron closer to firing threshold.	C-fiber predominant.	NaV1.9 expression has been reported in human dental pulp and trigeminal ganglion, but functional pulpitis evidence is limited (Wells et al., 2007a)..	May help sustain spontaneous firing and responsiveness to inflammatory mediators; clinical importance remains uncertain.	Low-moderate
Voltage-gated potassium channel Kv1.4 (Kv1.4)	Provides a repolarizing current that restrains repeated firing.	Mixed pulpal axons; precise Aδ/C distribution is uncertain.	Kv1.4 expression is reduced in painful human pulp (Wells et al., 2007b).	Direct example of a weakened electrical brake in pulpal pain. Reduced expression is associative and has not yet been reversed therapeutically.	Moderate-high
Voltage-gated calcium channels (CaV channels)	Permit calcium entry after depolarization and trigger neurotransmitter and neuropeptide release.	Aδ and C fibers.	Tooth injury alters calcium-channel localization, and calcium-dependent neuropeptide release has been demonstrated in human pulp; direct channel-targeted pain studies are lacking (Westenbroek et al., 2004; Fehrenbacher et al., 2009).	Amplify communication at peripheral and central terminals rather than serving as the primary sensor of pulpal injury.	Low-moderate
Hyperpolarization-activated cyclic nucleotide-gated channels (HCN channels)	Generate a pacemaker-like inward current after hyperpolarization and can move an active nerve back toward firing threshold.	C-fiber relevance is strongest; dental distribution is mixed.	Inflammation increases HCN current in C-fiber nociceptors, and HCN2 deletion reduces inflammatory pain in non-dental models. A major causal role in human pulpitis has not been demonstrated (Emery et al., 2011; Weng et al., 2012; Ciotu et al., 2019)..	Plausible contributor to persistent or spontaneous C-fiber firing; currently an extrapolated mechanism in human endodontic pain.	Low-moderate
Piezo-type mechanosensitive ion channel component 2 (Piezo2)	Opens during membrane deformation and detects mechanical force.	δ-associated pattern in small myelinated dental afferents.	Functional Piezo2 expression has been demonstrated in mechanosensitive dental primary afferents and localized in pulpal axons, sensory roots, and trigeminal ganglia (Won et al., 2017; Han et al., 2022).	May detect intrapulpal deformation, vascular pulsation, or pressure. It should not be used as a direct explanation for biting or percussion pain arising from apical tissues.	Moderate

*Note. Confidence reflects how directly the available evidence relates to human endodontic pain, not the overall biological importance of the channel. Aδ- and C-fiber assignments are predominant patterns rather than exclusive distributions. Pain on biting or percussion is mediated mainly by sensitized mechanosensitive and nociceptive afferents in the periodontal ligament and apical tissues, not by pulpal afferents.

Abbreviations. Aδ, A-delta; ANO1, anoctamin 1; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; CaV, voltage-gated calcium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; K2P, two-pore-domain potassium channel; Kv, voltage-gated potassium channel; NaV, voltage-gated sodium channel; P2X, ATP-gated P2X purinoceptor; TRP, transient receptor potential.

unmyelinated afferents. The terms Aδ-predominant and C-fiber-predominant describe prevailing patterns of activity, not mutually exclusive neuronal populations.

4.1 Aδ-predominant stimulus-evoked pain

Aδ fibers are thinly myelinated afferents with faster conduction velocities than unmyelinated C fibers. Their terminals are concentrated near the pulp–dentin interface, where hydrodynamic fluid movement and deformation of the dentin–pulp complex can produce rapid depolarization. Human electrophysiological studies demonstrated close temporal agreement between cold-evoked intradental Aδ activity and the perceived intensity of sharp, shooting dental pain (Ahlquist & Franzén, 1994). This relationship provides comparatively direct evidence for Aδ involvement in rapidly initiated, stimulus-dependent pain.

Several ion channel classes cooperate in rapid, stimulus-evoked signaling (Figure 7). Mechanosensitive or thermosensitive channels generate the receptor potential, NaV1.7 amplifies this depolarization near threshold, other sodium channels generate and propagate the action potential, potassium channels regulate repolarization, and calcium channels participate in transmitter release. Piezo2 and TRPV2 are plausible contributors to myelinated dental signaling, although neither defines a human endodontic pain phenotype. In one retrograde-labeling study, approximately 71% of tooth-pulp-projecting trigeminal neurons expressed the myelinated-axon marker NF200, and TRPV2 was common in medium- and large-diameter pulpal neurons (Gibbs et al., 2011). These findings demonstrate that pulpal nociception includes a substantial myelinated component.

4.2 C-fiber-predominant inflammatory pain

Pulpal C fibers are unmyelinated, slowly conducting, and polymodal. These fibers are polymodal nociceptors because individual afferents can respond to multiple noxious thermal, mechanical, and chemical stimuli through the combined activity of several stimulus-gated ion channels. Their activation is associated predominantly with delayed, dull, aching, throbbing, burning, lingering, spontaneous, or poorly localized pain. Single-fiber recordings from cat dental pulp showed that C fibers responded to heat, cold, pulpal pressure, potassium chloride, and bradykinin. Many developed continuing discharge after heat or pressure stimulation (Jyväsjärvi & Kniffki, 1992). This finding provides a physiological basis for persistent pain after removal of the initiating stimulus.

No single channel generates the C-fiber-predominant phenotype. TRPV1, TRPA1, ASICs, and P2X3 convert inflammatory heat, reactive products, acidity, and extracellular ATP into depolarizing currents. NaV1.7, NaV1.8, and NaV1.9 amplify and sustain firing; reduced potassium conductance weakens electrical restraint; and HCN currents may return a recently hyperpolarized membrane toward threshold (Figure 7). Persistent C-fiber activity therefore reflects the combined effects of continuing tissue injury, inflammatory sensitization, excitatory channel activity, and loss of inhibitory conductance.

4.3 Overlapping recruitment during pulpal inflammation

Progression from rapid evoked pain to lingering or spontaneous pain should not be perceived as a discrete switch from Aδ to C fibers. Inflammation lowers activation thresholds, alters channel regulation, and recruits overlapping myelinated and unmyelinated afferents. TRPV1, for example, is often associated with peptidergic C fibers, but TRPV1-positive tooth-projecting neurons can also express markers of myelination (Gibbs et al., 2011). NaV1.7 occurs in both populations and can amplify either stimulus-evoked or continuing inflammatory input.

Early or spatially limited pulpal injury may therefore produce predominantly stimulus-dependent Aδ activity, whereas increasing acidity, tissue pressure, immune signaling, and cellular injury progressively recruit polymodal C fibers. Both populations may remain active in advanced pulpitis. Central convergence and sensitization further weaken any direct correspondence between peripheral fiber activity and the patient's verbal description of pain. Clinical pain qualities may suggest the dominant physiological pattern. However, they cannot identify a particular fiber class or molecular channel with diagnostic certainty.

5. Ion Channels in Specific Endodontic Pain States

Endodontic diagnoses combine pulpal vitality, inflammation, apical involvement, and symptoms but do not define discrete molecular states. Applying channel mechanisms can clarify clinical pain patterns, provided that evidentiary differences are retained: painful pulpitis and symptomatic apical periodontitis have direct human expression data, whereas pulp necrosis, acute apical abscess, and postoperative pain rely more on anatomical inference and experimental models.

5.1 Reversible pulpitis

Reversible pulpitis is commonly associated with pain elicited by cold, osmotic change, or dentinal fluid movement that subsides after removal of the stimulus. This pattern is compatible with activation of pulpal Aδ fibers, which conduct rapidly and produce relatively sharp, localized pain. TRPM8, TRPV4, Piezo2, and other mechanosensitive or thermosensitive channels may generate the initial receptor potential, after which NaV channels initiate and transmit the afferent impulse.

This interpretation should be applied cautiously. A clinical diagnosis of reversible pulpitis does not define the histological extent of inflammation or identify the activated fiber population. C fibers and multiple transducer channels may already participate even when pain is brief and stimulus dependent. No human study has demonstrated a channel profile unique to reversible pulpitis. The most defensible interpretation is therefore that the clinical phenotype reflects limited or spatially restricted sensitization in a still vital pulp, with insufficient evidence to assign it to one ion channel or afferent class

5.2 Symptomatic irreversible pulpitis

Symptomatic irreversible pulpitis is characterized by exaggerated thermal responses, lingering pain that continues after removal of the stimulus, spontaneous pain, impaired localization, and episodic throbbing. These features indicate recruitment of a broader nociceptive network. Thermal, acidic, purinergic, mechanical, and inflammatory inputs converge at pulpal terminals, and continued depolarization permits activity in both Aδ and C fibers.

Human tissue provides the strongest channel-specific evidence: painful pulp shows increased NaV1.7, NaV1.8, and NaV1.9 immunoreactivity but reduced Kv1.4 immunoreactivity (Renton et al., 2005; Wells et al., 2007a, 2007b; Luo et al., 2008; Beneng et al., 2010). This pattern is consistent with enhanced action-potential initiation and repetitive firing with reduced repolarizing restraint.

Purinergic and TRP signaling may increase the depolarizing input reaching these voltage-gated channels. P2X3 is widely distributed in human pulpal fibers, and 79.4% of the examined P2X3-positive fibers co-expressed TRPV1 (Kim & Kim, 2007). This anatomical overlap permits ATP, protons, heat, and inflammatory mediators to act on convergent nociceptive populations. It must be stressed, however, that colocalization alone does not establish their contribution to a specific clinical symptom.

Experimental studies add functional evidence. Rat pulpitis increases TRPV1 and c-Fos expression; NaV1.7 inhibition reduces trigeminal neuronal activity; and the P2X3/P2X2/3 antagonist A-317491

reduces nociceptive behavior and trigeminal inflammatory signaling (Cha et al., 2020; Kwon et al., 2021; Chen et al., 2024). These models establish biological plausibility but do not reproduce the microbial diversity or temporal progression of human pulpitis.

The clinical phenotype of symptomatic irreversible pulpitis is therefore best explained by cooperating channel systems. Transducer channel sensitization increases the initiating current, sodium channels convert that current into repetitive firing, and reduced potassium conductance weakens electrical restraint. No single molecular alteration explains lingering, spontaneous, and referred pain in every patient.

5.3 Pulpal necrosis

Completely necrotic pulp tissue contains no functional afferent terminals and cannot generate neuronal action potentials. Pain associated with a diagnosis of pulp necrosis must originate from residual vital radicular tissue, extension of inflammation into the periodontal and periapical tissues, or persistent excitation within trigeminal pathways.

Clinical diagnosis of necrosis is based primarily on sensibility testing, which assesses neural responsiveness and does not directly measure pulpal perfusion or histological viability (Afkhami et al., 2024). Apparently nonresponsive teeth may retain islands of vital or inflamed radicular tissue. Consequently, neither the site of pain generation nor the relevant channel population can be determined from a negative sensibility response alone.

Once infection and inflammatory mediators reach the apical tissues, the nociceptive substrate shifts from intrapulpal terminals to periodontal and periapical afferents. Protons, extracellular ATP, inflammatory lipids, cytokines, proteases, and tissue pressure could engage ASIC, P2X, TRP, G-protein-coupled receptor, and voltage-gated channel pathways in these tissues. Direct comparisons of channel activity in completely necrotic and partially vital human teeth have not been reported. These mechanisms should therefore be identified as plausible consequences of apical inflammation, not established molecular features of pulp necrosis.

5.4 Symptomatic apical periodontitis

Tenderness to percussion is the defining sensory feature of symptomatic apical periodontitis. It indicates mechanical allodynia in the periodontal ligament and periapical tissues. The predominant sensory substrate has shifted from pulpal afferents to sensitized periodontal, osseous, and lesion-associated nociceptive fibers.

Recent human evidence substantially strengthens the ion channel basis of this condition. Obadah and colleagues examined 20 periapical biopsy specimens collected during endodontic microsurgery. Symptomatic lesions had approximately sixfold greater sensory innervation density than asymptomatic lesions and showed increased expression of the nociceptor-associated channels NaV1.8 and NaV1.9. Most identified nerve fibers demonstrated strong NaV1.8 immunoreactivity (Obadah et al., 2026). These findings provide direct evidence of neural remodeling and enrichment of sodium channel-expressing nociceptive fibers in symptomatic human apical disease. Nevertheless, the cross-sectional design cannot determine whether increased innervation initiates pain or develops in response to persistent inflammation.

Piezo2 is a potential contributor to mechanically evoked dental pain because it is expressed in tooth-projecting trigeminal neurons and pulpal afferents (Han et al., 2022). However, direct localization of Piezo2 in periodontal nociceptive endings and selective functional testing during percussion-like stimulation have not been reported. The channel should therefore be presented as a candidate mechanotransducer, not as the established molecular cause of percussion sensitivity. Other stimulus-gated ion channels such as ASIC, P2X, TRPV1, TRPA1, and TRPV4 may also respond to the

acidic, purinergic, inflammatory, and mechanically distorted environment of an apical lesion. However, their specific contributions to symptomatic human apical periodontitis require direct testing.

Reduced mechanical pain thresholds in adjacent and contralateral teeth indicate that sensitization may extend beyond the affected tooth (Kayaoglu et al., 2020; Alelyani et al., 2020). This finding is compatible with, but does not by itself confirm, central sensitization from sustained peripheral input. The responsible ion channels have not been identified in humans.

5.5 Acute apical abscess

An acute apical abscess adds purulent inflammation, tissue distension, acidosis, immune cell accumulation, and high concentrations of extracellular damage signals to the mechanisms present in apical periodontitis. These conditions are compatible with ASIC activation by protons, P2X activation by ATP, TRPV1 and TRPA1 sensitization by inflammatory products, and mechanosensitive-channel activation by tissue pressure. NaV1.8 and NaV1.9 may permit continued firing in sensitized periapical nociceptors.

Direct human studies comparing ion channel expression in acute apical abscesses have not been identified. Severe spontaneous pain and tenderness should therefore be interpreted as the integrated result of inflammatory transduction, mechanical distortion, peripheral sensitization, and continuing trigeminal input. Current evidence does not permit assignment of acute abscess pain to a particular ion channel subtype.

5.6 Postoperative endodontic pain

Mechanical instrumentation, extrusion of debris or irrigants, residual microbial products, obturation-related irritation, and altered occlusal loading can provoke postoperative inflammation in periodontal and periapical tissues. The resulting release of ATP, protons, prostaglandins, cytokines, and proteases can reactivate the transduction and excitability pathways already involved in symptomatic apical periodontitis.

Direct molecular studies of ion channel expression in human postoperative endodontic pain have not been identified. Accordingly, postoperative pain should not be described as a separate channel-defined disorder. It is more accurately interpreted as renewed or continuing activation of pulpal, periodontal, and apical nociceptive mechanisms, modified by the severity of preoperative inflammation and any preexisting peripheral or central sensitization. Persistent or increasing pain also requires consideration of residual infection, occlusal overload, procedural complications, nerve injury, referred pain, and nonodontogenic disease.

6. Therapeutic Implications

Ion channels provide therapeutic targets at several stages of pulpal nociception: stimulus transduction at peripheral terminals, action-potential initiation and propagation in Aδ and C fibers, and neurotransmitter release from their central terminals (Figure 8). The clinical maturity of interventions directed at these stages varies substantially. Nonselective NaV inhibition by local anesthetics is well established in endodontic care, whereas subtype-selective NaV inhibitors and drugs targeting TRP, P2X, ASIC, Piezo, Kv, CaV, or HCN channels are supported mainly by experimental evidence. These interventions should be considered adjuncts because ion channel modulation cannot eliminate microbial infection, necrotic tissue, or intrapulpal inflammation.

6.1 Established NaV blockade with local anesthetics

Local anesthetics bind the intracellular pore of open or inactivated voltage-gated sodium channels, producing use-dependent blockade of action-potential initiation and conduction in pulpal Aδ and

C fibers (Wang & Strichartz, 2012).

Anesthesia may be difficult to achieve in teeth with symptomatic irreversible pulpitis (Figure 9). Tissue acidosis reduces the proportion of local anesthetic molecules available to cross neuronal membranes, and inflammatory mediators increase nociceptor excitability. Changes in sodium-channel expression may also contribute. Painful human dental pulp contains increased NaV1.7 and NaV1.8 immunoreactivity, and NaV1.9 produces persistent subthreshold currents that may promote firing despite partial sodium-channel blockade (Renton et al., 2005; Wells et al., 2007).

Supplemental infiltration, intraligamentary, intraosseous, or intrapulpal injection can increase anesthetic exposure after an inadequate inferior alveolar nerve block, but none provides NaV-subtype selectivity.

6.2 Selective inhibition of nociceptor NaV channels

NaV1.7 is an attractive target because it amplifies receptor potentials and helps determine whether a pulpal nociceptor reaches firing threshold. In rat and mouse pulpitis models, NaV1.7 expression and trigeminal ganglion activity increased following pulpal application of allyl isothiocyanate. Administration of the selective NaV1.7 inhibitor ProTx-II reduced neuronal hyperactivity and markers associated with neuronal activation (Kwon et al., 2021; Lee et al., 2024). These findings provide direct preclinical evidence for NaV1.7 inhibition in pulpitis. However, ProTx-II has not been evaluated as an endodontic analgesic in humans.

NaV1.8 is particularly relevant to the action potential upstroke and repetitive firing of nociceptive neurons. Increased NaV1.8 immunoreactivity in

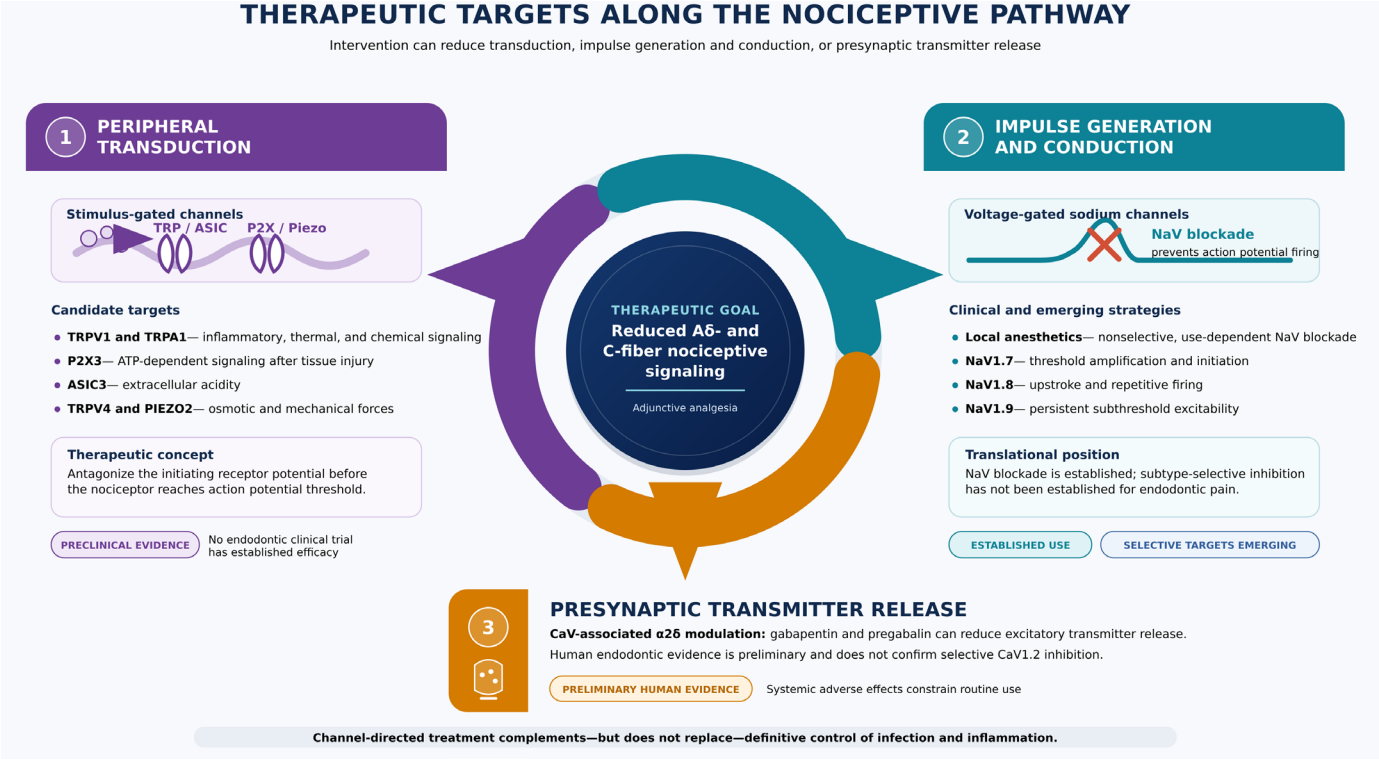


Fig. 8. Channel-directed therapeutic intervention points in endodontic nociception. Ion channel activity may be modified at three stages of Aδ- and C-fiber signaling: stimulus transduction at peripheral sensory terminals, NaV-dependent action-potential initiation and propagation, and CaV-dependent neurotransmitter release at central terminals. Local anesthetics provide established, nonselective NaV blockade. Gabapentinoids provide preliminary human evidence for CaV-associated modulation, whereas subtype-selective NaV inhibitors and antagonists of TRP, P2X, ASIC, Piezo, and HCN channels are supported predominantly by preclinical evidence. The evidence labels indicate the current clinical maturity of each therapeutic strategy. Channel-directed analgesia is intended to reduce nociceptive signaling and does not replace definitive control of pulpal or periapical infection and inflammation.

painful human pulp strengthens its translational relevance (Renton et al., 2005). The selective NaV1.8 inhibitor suzetrigine was approved by the U.S. Food and Drug Administration in 2025 for moderate-to-severe acute pain in adults. Its clinical trials involved pain after abdominoplasty and bunionectomy, not pulpal or postoperative endodontic pain (Jones et al., 2023; U.S. Food and Drug Administration, 2025). To date, there is no identified endodontic clinical trial of suzetrigine. Diagnosis-specific trials are therefore needed before its effectiveness in symptomatic pulpitis or post-treatment endodontic pain can be inferred.

NaV1.9 may be relevant to ongoing C-fiber activity because it generates a persistent current near resting membrane potential. However, clinically suitable selective NaV1.9 inhibitors have not been established. Its contribution may also be difficult to isolate because NaV1.7, NaV1.8, HCN2, and several stimulus-gated channels converge on the same excitability state.

6.3 Targeting stimulus-gated channels

Stimulus-gated channels offer an opportunity to reduce the receptor potential before action potential generation. P2X3 is among the most directly investigated targets. Adenosine triphosphate released from damaged pulp, immune cells, and other local cells activates P2X3-containing purinergic receptors on pulpal afferents. In a rat model of lipopolysaccharide-induced pulpitis, the P2X3 antagonist A-317491 reduced pain-related behavior, trigeminal neuronal activation, and associated inflammatory signaling (Chen et al., 2024). No human endodontic trial has yet established the efficacy of P2X3 antagonism.

TRPV1 and TRPA1 antagonists could reduce heat-, chemical-, and inflammation-evoked depolarization of pulpal C fibers and subsets of Aδ fibers. Evidence from dental cell experiments and non-endodontic dental pain models indicates biological plausibility. However, direct clinical evidence in pulpitis is absent. Inhibition of a single TRP channel may also

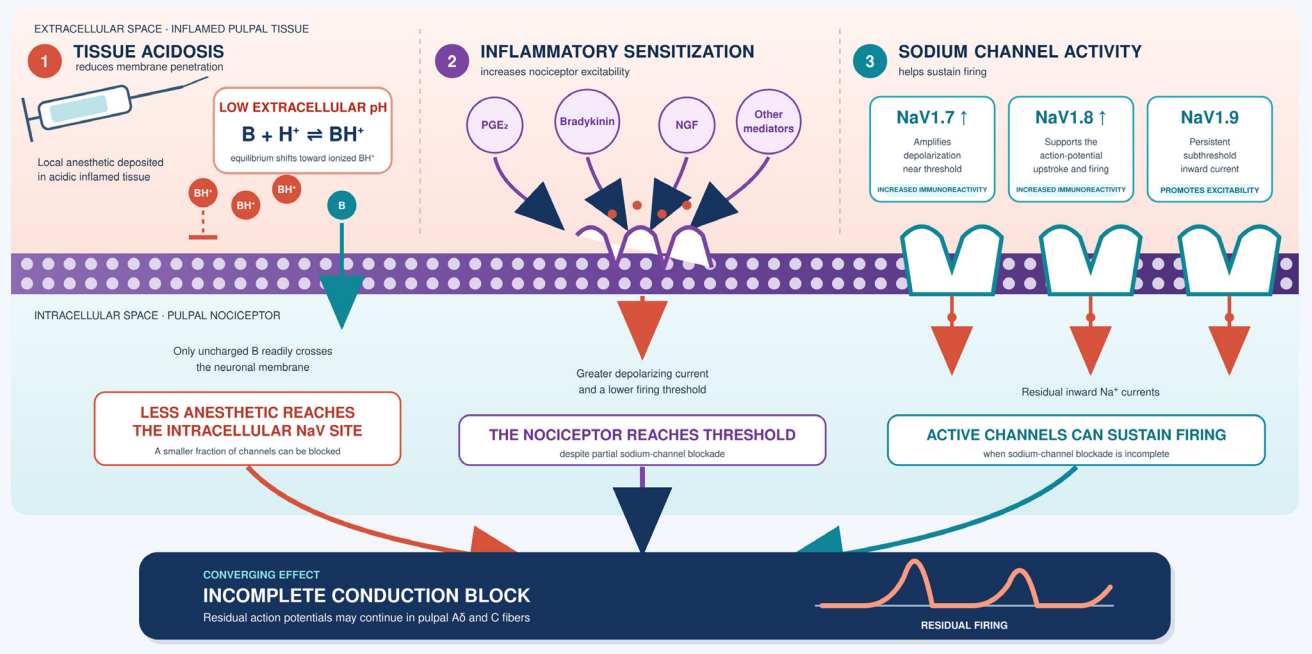


Fig. 9. Mechanisms contributing to incomplete local anesthesia in symptomatic irreversible pulpitis. Low extracellular pH shifts the local anesthetic equilibrium toward the ionized form (BH^+), reducing the proportion of uncharged base (B) available to cross the neuronal membrane and reach the intracellular NaV binding site. Inflammatory mediators, including prostaglandin E_2, bradykinin, and nerve growth factor, increase depolarizing currents and lower the nociceptor firing threshold. Increased NaV1.7 and NaV1.8 immunoreactivity in painful human pulp may enhance threshold amplification and action-potential firing, whereas the persistent subthreshold NaV1.9 current promotes excitability. These mechanisms can converge to produce incomplete sodium-channel blockade, permitting residual action potentials in pulpal Aδ and C fibers. Abbreviations: BH^+, protonated local anesthetic; B, uncharged local anesthetic base; NaV, voltage-gated sodium channel; NGF, nerve growth factor; PGE_2, prostaglandin E_2.

be insufficient because thermal, acidic, osmotic, mechanical, and inflammatory signals activate overlapping populations of TRP, ASIC, P2X, and Piezo channels. ASIC3, TRPV4, and Piezo2 are therefore credible mechanistic targets, although therapeutic studies directly relevant to human endodontic pain are scanty.

6.4 CaV-associated and HCN modulation

Gabapentin and pregabalin bind the α2δ auxiliary subunit associated with voltage-gated calcium channels, reducing channel trafficking and excitatory transmitter release. In a randomized clinical trial involving 90 patients undergoing root canal treatment, pretreatment with 300 mg gabapentin or 75 mg pregabalin produced lower postoperative pain scores than placebo (Verma et al., 2022). This study provides preliminary human evidence for calcium channel-associated modulation. Gabapentinoids do not selectively block the CaV1.2 pore, however. Hence, the findings cannot be interpreted as clinical confirmation that CaV1.2 is the principal calcium-channel target in endodontic pain. The modest sample size and potential systemic adverse effects also limit routine application.

HCN2 may facilitate recurrent firing by returning nociceptive neurons toward threshold following hyperpolarization. Ivabradine, a clinically available but nonselective HCN inhibitor, did not reduce spontaneous pain, heat-pain threshold, punctate hyperalgesia, or flare responses in a human capsaicin model, although it reduced dynamic mechanical allodynia (Tanaka et al., 2022). This was an experimental cutaneous-pain study and not an endodontic trial. Cardiac HCN4 inhibition and the absence of HCN2-selective clinical agents further restrict current translation.

6.5 Translational priorities

No subtype-selective ion channel drug currently has direct clinical evidence sufficient to replace conventional local anesthesia or definitive root canal treatment. The strongest near-term opportunities are improving NaV blockade in inflamed pulpal afferents and evaluating selective NaV1.8 inhibition in diagnosis-specific dental trials. P2X3 and TRP antagonists may be suited to localized administration because their targets operate near the inflamed pulp terminal, potentially limiting systemic exposure.

Trials should use predefined pain phenotypes and report anesthetic success, evoked pain, lingering thermal pain, spontaneous pain, and postoperative pain separately. Combining human expression studies with functional recordings and controlled trials is essential to determine whether molecular selectivity produces clinically meaningful analgesia.

7. Evidence Limitations and Future Research

7.1 Evidence limitations

Evidence linking ion channels to Aδ- and C-fiber signaling in endodontic pain is heterogeneous and predominantly preclinical. Rodent pulpitis induced by allyl isothiocyanate, lipopolysaccharide, or mechanical injury permits channel manipulation and trigeminal recording, but it does not reproduce the microbial diversity, tissue pressure, disease duration, or treatment history of human disease. Species differences in tooth anatomy, channel expression, and nociceptor composition further limit translation. The acute, standardized injuries also omit variation in disease stage and prior analgesic or endodontic treatment. Behavioral measures such as grooming or withdrawal cannot reproduce patients' sensory descriptions.

Human evidence is mainly immunohistochemical. Altered NaV1.7, NaV1.8, or Kv1.4 staining associates channels with disease but does not establish membrane activity, fiber type, or causality. Studies are often small, use healthy third molars as controls, and include clinically heterogeneous cases. Pain intensity and duration are commonly

recorded without standardized measures of evoked, lingering, spontaneous, or mechanical pain, reducing phenotypic resolution and comparability among studies. Diagnostic categories also correlate imperfectly with histologic inflammation, creating potential misclassification when channel abundance is compared between reversible and irreversible pulpitis (Dastpak et al., 2023).

Attribution to Aδ or C fibers is another major limitation. Fiber identity is frequently inferred from axon diameter, myelination, conduction velocity, or established channel associations. Few dental studies directly combine selective fiber recording with channel manipulation. Channel expression also overlaps between afferent populations and changes during inflammation. Evidence from pulpal models therefore cannot be applied automatically to symptomatic apical periodontitis, acute apical abscess, or postoperative pain, where periodontal and osseous afferents contribute.

A transparent evidence hierarchy is needed. Greatest weight should be given to channel-targeted clinical interventions, followed by functional experiments in human pulpal or periapical tissue and human expression studies linked to defined pain phenotypes. Animal experiments involving selective pharmacologic or genetic manipulation provide mechanistic evidence but require human validation. Anatomical localization alone and extrapolation from nonodontogenic pain should generate hypotheses, not clinical claims.

7.2 Future research priorities

Future studies should obtain human tissue from carefully phenotyped patients, recording diagnosis, disease duration, medication exposure, age, systemic health, and separate measures of sharp evoked pain, lingering thermal pain, spontaneous pain, percussion sensitivity, and anesthetic failure. Spatial transcriptomics and multiplex imaging could map channels within neuronal, immune, vascular, odontoblastic, and stromal niches. Single-cell or single-nucleus sequencing requires retrograde labeling or validated neuronal markers because human pulp atlases emphasize nonneuronal cells and current dental-afferent sequencing is largely murine (Opasawatchai et al., 2022; Lee et al., 2023).

Molecular observations require functional confirmation through electrophysiology, calcium imaging, selective antagonists, gene silencing, or rescue experiments. Longitudinal sampling before and after pulpotomy, pulpectomy, drainage, or root canal treatment could determine which channel changes resolve after source control and which predict persistent pain. Clinical trials should initially evaluate targets with convergent human and animal evidence, particularly NaV1.7, NaV1.8, P2X3, and selected TRP channels. Outcomes should include anesthetic success and Aδ- and C-fiber–associated pain phenotypes, not a single composite pain score. Local delivery deserves specific evaluation to determine whether channel modulation can achieve analgesia without impairing protective sensation, cardiac or central nervous system function, pulpal defense, or tissue repair.

8. Conclusion

Endodontic pain arises from the coordinated activity of stimulus-gated and voltage-gated ion channels in pulpal and periapical afferents. TRP, ASIC, P2X, and Piezo channels convert thermal, chemical, acidic, and mechanical tissue signals into graded receptor potentials. NaV1.7, NaV1.8, and NaV1.9 then determine action-potential initiation and repetitive firing, with Kv, CaV, and HCN channels regulating repolarization, excitability, and synaptic transmission.

These mechanisms contribute to characteristic but overlapping Aδ- and C-fiber pain phenotypes. Aδ fibers are associated predominantly with rapid, sharp, and stimulus-evoked pain, whereas polymodal C fibers contribute more strongly to lingering, spontaneous, throbbing, and poorly

localized pain. These assignments are functional tendencies, not exclusive divisions, because inflammation changes channel expression and recruits overlapping afferent populations.

Current clinical channel modulation is based mainly on nonselective NaV blockade by local anesthetics. Selective NaV1.7, NaV1.8, P2X3, TRP, and other channel-directed interventions offer translational potential, but direct human endodontic evidence is limited. Progress will require standardized pain phenotyping, functional studies of human pulpal and periapical tissue, and controlled trials linking channel modulation to specific Aδ- and C-fiber–associated outcomes. Such evidence could enable more precise analgesia without displacing definitive control of pulpal or apical infection and inflammation.

Acknowledgments

This work received no external funding.

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