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Transient Receptor Potential (TRP) Channels in Dental Pain: Molecular Mechanisms, Sensitization, and Therapeutic Prospects

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Abstract*—Transient receptor potential (TRP) channels are polymodal, non-selective cation channels that translate thermal, mechanical, and chemical cues into intracellular signals, and they have emerged as key molecular transducers of dental pain arising predominantly from dentin hypersensitivity and pulpitis. This review aims to synthesize experimental, molecular, and clinical evidence on TRP channel classification, structure, and distribution across dental primary afferent neurons, odontoblasts, periodontal ligament cells, and temporomandibular joint tissues, and to evaluate mechanisms of activation, sensitization, and therapeutic opportunities. Evidence from immunohistochemistry, mRNA-based profiling, single-cell RT-PCR, calcium imaging, patch-clamp electrophysiology, behavioral assays, and in vivo neurophysiology indicates that TRPV1, TRPA1, TRPM8, and TRPV4 (with additional roles proposed for TRPM3) mediate modality-specific responses to heat (>43°C), cooling (<25°C), noxious cold (<17°C), chemical irritants, and mechanical deformation, primarily via Ca2+ influx and enhanced excitability. Odontoblasts function as sensory–secretory intermediaries: TRP activation elevates intracellular Ca2+ and triggers ATP release via pannexin-1 hemichannels and glutamate release involving CaV1.2-dependent coupling, thereby engaging purinergic P2X and metabotropic glutamate receptors on adjacent afferents to amplify nociceptive transmission. Inflammation further potentiates pain by cytokine- and prostaglandin-driven TRP sensitization and trafficking, while bacterial products can directly activate TRPA1; neuropeptide release supports neurogenic inflammation and central sensitization within trigeminal pathways. Genetic polymorphisms in TRP genes may contribute to inter-individual pain phenotypes and inform precision analgesia. Therapeutic prospects include TRPV1 desensitization (capsaicin), TRPV1 antagonism (e.g., capsazepine) with nanogel-based localized delivery, TRPA1/TRPM8 antagonists, and natural modulators such as eugenol and cannabinoids, although ubiquitous TRP expression and thermoregulatory adverse effects complicate translation. Addressing mechanotransduction uncertainties, expanding human-relevant models (including organ-on-chip), and integrating multi-omics are key to advancing targeted dental pain management.*

***Keywords*—** *Transient receptor potential channels, Dental nociception, Odontoblast signaling, TRPV1, TRPA1, TRPM8, Inflammatory sensitization, Purinergic signaling, Nanodelivery systems, Personalized analgesics.*

I. Introduction

1.1 Overview of TRP Channels in Sensory Physiology

Transient Receptor Potential (TRP) channels comprise a large and diverse ion channel superfamily identified as critical components of sensory physiology. These channels serve as biological sensors for a wide range of physical and chemical stimuli, including temperature changes, mechanical forces, osmolality alterations, and chemical ligands. Mammals express 28 distinct TRP channel proteins categorized into seven major subfamilies based on amino acid sequence homology: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPN (no-mechano-potential), TRPP (polycystin), and TRPV (vanilloid) [1].

Functionally, TRP channels operate as polymodal sensory receptors, meaning they respond to multiple types of stimuli. They play essential roles in various physiological processes, including thermosensation (the detection of hot and cold), mechanosensation (the detection of mechanical forces), chemosensation (detection of chemical stimuli), nociception (pain perception), and modulation of cellular homeostasis. For example, TRPV1, a member of the vanilloid subfamily, is well-known as a receptor for capsaicin, heat, and low pH, and is intimately involved in pain transduction cascades. Similarly, TRPA1 channels detect a variety of noxious chemical and mechanical stimuli and are expressed in sensory neurons capable of nociception [2].

Beyond their sensory functions, TRP channels participate in transducing environmental cues into intracellular signals by allowing the influx of cations, predominantly calcium (Ca^{2+}), sodium (Na^{+}), and magnesium (Mg^{2+}), which are crucial for action potential generation and neuronal excitability. The unique crystal structures of TRP channels, combined with their surface localization on cells, underlie their rapid responsiveness and dynamic modulation, making them attractive drug targets for various diseases, particularly those involving pain and inflammation [3].

1.2 Significance of Dental Pain and TRP Channels Role

Dental pain represents a significant clinical and public health issue that substantially impairs quality of life, productivity, and imposes considerable economic burdens globally. It arises from various etiologies, notably dentin hypersensitivity and pulpitis-associated pain, which are common complaints in dental practice. Dentin hypersensitivity manifests as a sharp pain triggered by exposure to thermal, chemical, or mechanical stimuli due to loss or disruption of protective enamel or cementum, while pulpitis-associated pain

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emanates from inflammation within the dental pulp, often secondary to carious lesions or trauma [4].

At the molecular level, dental pain signals originate primarily from activation of specialized ion channels and receptors in dental primary afferent neurons (DPAs) and odontoblasts, which transduce peripheral environmental stimuli into electrical signals perceived as pain. Notably, TRP channels have emerged as principal molecular transducers in this process due to their polymodal sensitivity and localization within dental tissues. They contribute to the detection of noxious thermal stimuli, mechanical perturbations through fluid shifts within dentinal tubules, chemical irritants, and inflammatory mediators [5]. Such roles highlight the importance of TRP channels not only in acute nociception but also in pain sensitization processes that may prolong or amplify dental pain states.

Moreover, dental nerves, particularly trigeminal nociceptors, innervate these tissues intensely and play a critical role in transmitting peripheral noxious stimuli centrally. They also interact with non-neuronal cells via neurotransmitters and neuropeptides that regulate the inflammatory environment, further influencing pain perception and tissue homeostasis [6]. Understanding TRP channels' function in these contexts provides insights into the pathophysiology of dental pain and opens avenues for targeted therapeutic interventions.

1.3 Aim and Scope of Review

This review aims to synthesize existing experimental, molecular, and clinical data concerning the involvement of TRP channels in dental pain from a comprehensive perspective. The focus is on the molecular classification of TRP channels, their distribution in dental tissues, mechanisms of activation by various stimuli, and their roles in physiological and pathological dental pain. By incorporating recent findings and expanding the reference base with additional studies, this manuscript intends to provide a robust and detailed analysis that informs both the scientific community and clinical practitioners.

A key feature of this review is the inclusion of a graphical abstract designed to visually summarize the key cellular players, TRP channel subtypes, signaling mechanisms, and potential therapeutic targets in dental pain. This visualization aims to clarify the complex interplay between odontoblasts, dental primary afferent neurons, and inflammatory mediators in the context of TRP channel-mediated nociception. Furthermore, the review encompasses advances in pharmacological modulation of TRP channels, including emerging nanotechnological delivery systems, and evaluates ongoing challenges and prospects for clinical translation [7], [8]. The overall objectives encompass not only a detailed academic synthesis but also identification of critical research gaps and future directions.

II. Molecular Structure and Classification of TRP Channels

2.1 Subfamilies and Structural Features

Transient receptor potential channels are non-selective cation channels that assemble predominantly as tetramers, forming a central ion-conducting pore. They share a conserved transmembrane architecture characterized by six membrane-spanning helices (S1–S6), with a pore-forming loop between S5 and S6, similar to voltage-gated ion channels but display distinct gating and regulation mechanisms [1].

Based on sequence homology and functional characteristics, mammalian TRP channels are classified into seven subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPN (no-mechano-potential or NOMPC, though TRPN is absent in mammals), TRPP (polycystin), and TRPV (vanilloid) [1]. Each subfamily exhibits unique features regarding ion selectivity, gating stimuli, and regulatory interactions.

Structurally, TRP channels possess specific domains contributing to their gating properties. For example, ankyrin repeats in TRPA1 influence channel activation by electrophilic compounds, while TRPV channels contain ankyrin repeats that facilitate temperature sensitivity and ligand binding. The direct binding between specific channel domains such as the Pre-S1 and TRP-like domains mediates gating and functional regulation by phosphatidylinositol-4,5-bisphosphate (PIP_2), a lipid modulator. Such intramolecular interactions have been elucidated in TRPP channels and extend to other TRP families like TRPM8 and TRPV1, indicating a shared mechanism regulating channel opening and desensitization [9].

Ion selectivity varies among TRP channels but generally favors divalent cations like Ca^{2+} and Mg^{2+}, as well as monovalent cations Na^+ and K^+. This permeability allows them to function as key transducers converting diverse extracellular stimuli into intracellular calcium signals, thereby influencing neuronal excitability and downstream signaling cascades essential to the sensory experience, including pain [10].

2.2 Expression Patterns in Oral and Dental Tissues

TRP channels are widely expressed across numerous oral tissues critical for sensory function and homeostasis. In dental contexts, major expression sites include odontoblasts—the specialized cells lining the dental pulp responsible for dentinogenesis; dental primary afferent neurons (DPAs) residing predominantly in the trigeminal ganglion innervating dental pulp and dentin; periodontal ligament cells; and chondrocytes of the temporomandibular joint (TMJ) **[2]**.

Specifically, subtypes such as TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRPM3, and TRPM8 have been detected in DPAs and associated oral structures, suggesting their involvement in detecting thermal, mechanical, and chemical stimuli relevant to dental pain. Immunohistochemical, mRNA expression, and functional studies confirm their presence in trigeminal neurons, where they contribute to sensory transduction of noxious and innocuous stimuli **[**11**]**.

Within odontoblasts, evidence points to the expression of channels including TRPA1 and TRPV4, which modulate calcium influx and ATP release, integrating these cells into nociceptive circuits via paracrine signaling. Periodontal ligament cells, contributing to the structural integrity of teeth,

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also exhibit TRP channels that regulate mechanosensation and may participate in remodeling and pain signaling [12].

Furthermore, the TMJ chondrocytes express TRPs that mediate mechanical and inflammatory stimuli transduction, revealing TRP channels' roles beyond classical sensory neurons and odontoblasts, encompassing broader oral tissue physiology and pain mechanisms [2].

2.3 Functional Genomics and Polymorphisms

Genomic analyses have revealed polymorphisms in genes encoding TRP channels that influence individual variability in sensory sensitivity, including pain and taste perception. Notably, variations in the TRPV1 gene affect nociception thresholds and salt taste sensitivity, highlighting the polymodal functions of TRP channels across sensory modalities and the potential for personalized therapeutic strategies in pain management [13].

Further research suggests that genetic variability in TRP channels may underlie susceptibilities to chronic pain conditions, including dental pain and neuropathies, through alterations in channel function, expression, or regulation. These polymorphisms may inform precision medicine approaches that tailor treatment based on genetic profiles, although clinical implementation still requires extensive validation [14].

Understanding functional genomics of TRP channels also aids in elucidating mechanisms of pain hypersensitivity and resilience, providing a foundation for developing targeted modulators that accommodate patient-specific channelopathies [4].

III. Expression and Localization of TRP Channels in Dental-Related Cells

3.1 Dental Primary Afferent Neurons (DPAs)

Dental primary afferent neurons are the initial neural elements responsible for sensing stimuli within the dental pulp and transmitting pain signals centrally. Studies employing retrograde tracing combined with single-cell reverse transcription polymerase chain reaction (RT-PCR) and immunohistochemistry have revealed distinct subsets of DPAs expressing thermo-sensitive TRP channels, including TRPV1 (heat-sensitive), TRPM8 (cold-sensitive), and TRPA1 (noxious cold and chemical-sensitive) [11].

Functional assays using calcium imaging indicate that specific DPAs respond to stimuli corresponding to known activation thresholds of these channels—capsaicin activates TRPV1-positive neurons at temperatures exceeding 43°C, menthol stimulates TRPM8-expressing neurons at cooling below 25°C, and TRPA1 responds to noxious cold below 17°C and to chemical agonists such as allyl isothiocyanate. Interestingly, individual neurons may express multiple TRPs, suggesting polymodal sensory capacities crucial to the complex nature of dental pain signals.

The localization of TRP channels on DPAs is complemented by expression of TTX-resistant sodium channels (NaV1.8), indicative of nociceptive neuron specialization. These neurons participate in integrating mechanical, thermal, and chemical signals from dental tissues, signaling pain upon pathological activation or sensitization [3].

3.2 Odontoblasts: Sensory and Secretory Roles

Odontoblasts, traditionally known for synthesizing dentin, have now been recognized as sensory cells contributing to pain transduction in dental tissues. Molecular profiling demonstrates that odontoblast-like cells express TRPA1, TRPV1, TRPV4, and TRPM8 channels. The activation of these channels stimulates an increase in intracellular calcium, leading to the release of ATP, which acts as a paracrine messenger to adjacent dental nerve fibers [12].

ATP release from odontoblasts via pannexin-1 hemichannels, mediated by TRP channel activation, facilitates intercellular communication and the initiation of nociceptive signaling. This mechanism supports the view that odontoblasts function as mechanosensitive and chemosensitive cells detecting fluid movement and noxious stimuli within dentinal tubules, contributing directly to pain initiation [16].

Additionally, glutamate release by odontoblasts, regulated by the activation of calcium channels such as CaV1.2 and TRP channels, establishes further excitatory communication with pulp sensory neurons. This dual signaling involving ATP and glutamate suggests a complex transduction pathway in which odontoblasts serve as critical intermediaries between environmental stimuli and neuronal activation [17].

3.3 Periodontal Ligament Cells and Temporomandibular Joint (TMJ)

Beyond the pulp, TRP channels expressed in periodontal ligament cells contribute to mechanosensation essential for maintaining tooth stability and alveolar bone remodeling. These channels detect mechanical stretch and osmotic changes, thereby regulating cellular responses that maintain periodontal tissue homeostasis [2].

In the temporomandibular joint, TRP channels present in chondrocytes contribute to mechanotransduction and inflammatory signaling. TRP-mediated detection of mechanical stress and inflammatory mediators in the TMJ is implicated in the pathophysiology of TMJ disorders, which often include chronic facial pain and dysfunction. The modulatory roles of TRPs in TMJ cartilage and joint tissues underscore their broader involvement in oral tissue physiology and pain beyond the dental pulp [5].

Recent reviews emphasize the interplay between TRP channels and neuroimmune factors in these tissues, further highlighting their role in sustaining neuroinflammation and peripheral sensitization relevant to temporomandibular disorders and associated pain syndromes [18].

IV. Molecular and Cellular Mechanisms of TRP Channel-Mediated Dental Pain

4.1 Thermal and Mechanical Stimuli Transduction

TRP channels are polymodal detectors of thermal and mechanical stimuli, pivotal to the transduction of dental pain. The well-characterized activation thresholds correspond to physiological and pathological conditions: TRPV1 is activated

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by potentially harmful heat exceeding 43°C, TRPM8 senses innocuous cold below 25°C, and TRPA1 responds to potentially noxious cold below 17°C as well as chemical irritants [11].

These channels transduce stimuli into electrical signals by allowing cation influx, predominantly calcium, leading to neuronal depolarization. The classic hydrodynamic theory of dentin hypersensitivity posits that fluid movement within dentinal tubules, triggered by thermal or mechanical stimuli, activates mechanosensitive nociceptors resulting in pain. Recent evidence supports a complementary role for TRP channels, particularly TRPV4 and TRPM3, as candidate mechanotransducers that detect such fluid flow or tissue deformation. Their involvement refines the understanding of dental pain transduction by integrating molecular mechanisms into traditional theories [19].

Odontoblasts participate actively in this process by responding to mechanical and thermal stimuli through TRP channels, releasing signaling molecules such as ATP to activate adjacent dental afferents. This crosstalk between odontoblasts and neurons forms a cellular basis for the initiation and modulation of pain in response to environmental stimuli [4].

4.2 Inflammatory Sensitization of TRP Channels

Inflammation of the dental pulp, as seen in pulpitis, involves a robust immune response that drives chronic pain through the sensitization of TRP channels. Inflammatory mediators, including cytokines and prostaglandins, induce post-translational modifications in TRP channels and promote their increased trafficking to nociceptive nerve terminals, thereby enhancing their sensitivity to thermal, chemical, and mechanical stimuli [4].

Furthermore, bacterial products, such as those derived from carious lesions, can directly engage TRPA1 channels on DPAs, amplifying nociceptive signaling independently of inflammatory mediators. This direct activation contributes to acute pain episodes characteristic of dental infections [5].

Neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), released in response to TRP channel activation, contribute to local vasodilation, plasma extravasation, and recruitment of immune cells, sustaining a pro-inflammatory and pro-nociceptive environment. This neuroimmune crosstalk enhances peripheral and central sensitization processes, precipitating persistent dental pain states [15].

4.3 Purinergic and Glutamatergic Signaling in Dental Pain

ATP acts as a pivotal signaling molecule in the modulation of dental pain. Mechanical stimulation of odontoblasts activates their TRP channels, triggering the release of ATP through pannexin-1 channels. The extracellular ATP then binds to purinergic P2X receptors expressed on nearby dental primary afferents, resulting in neuronal depolarization and pain transduction [16].

The odontoblasts also mediate glutamate release, facilitated by activation of CaV1.2 calcium channels and TRP channels, contributing to excitatory neurotransmission to sensory neurons. This glutamatergic signaling occurs via metabotropic glutamate receptors (mGluRs) on afferent neurons, further amplifying nociceptive transmission [17].

This dual purinergic and glutamatergic communication forms a robust pathway for odontoblast-neuron crosstalk, linking mechanical and chemical stimuli to the generation of pain signals in dental tissues. It highlights the functional complexity of TRP channel-mediated nociception and identifies multiple molecular nodes as potential therapeutic targets [20].

V. Electrophysiological Evidence and Functional Studies

5.1 Calcium Imaging and Patch Clamp Studies

Calcium imaging in isolated DPAs and odontoblast-like cells has been invaluable in demonstrating the functional expression of TRP channels. Application of specific agonists—capsaicin for TRPV1, menthol for TRPM8, and icilin for TRPA1—elicits marked increases in intracellular calcium concentrations indicative of channel activation. Patch clamp electrophysiology further confirms the corresponding inward cationic currents in neurons responding to these stimuli, characterizing channel properties such as ion selectivity and gating kinetics [11].

Co-expression of TRP subtypes in individual neurons allows these cells to respond to multiple stimuli modalities, explaining the polymodal nature of dental sensory neurons and the variable pain experiences in patients. This overlap also suggests functional redundancy and potential complex interactions among channel subtypes in pain transduction pathways [3].

5.2 In Vivo Neurophysiological Studies

In vivo studies employing broad-spectrum TRP channel blockers like lanthanum chloride ($LaCl_3$) demonstrate a direct reduction in nociceptive neuronal firing in response to noxious cold stimulation of the dental pulp in rodent models. Electrophysiological recordings from the primary somatosensory cortex reveal that $LaCl_3$ suppresses high-frequency firing of nociceptive neurons and inhibits spontaneous neuronal activities, effects that are reversible upon washout, confirming specificity [21].

Behavioral studies corroborate these findings, showing diminished pain responses to noxious stimuli upon pharmacological TRP channel blockade. These data provide functional evidence linking TRP channels mechanistically to dental pain generation and offer proof-of-concept support for TRP channel-targeted therapeutics [22].

5.3 Role in Central Sensitization and Neuroplasticity

TRP channel activation promotes neurotransmitter release at central synapses within the trigeminal nucleus caudalis (TNC), where second-order neurons process orofacial nociceptive inputs. These central interactions facilitate neuroplastic changes such as wind-up and long-term potentiation (LTP), mechanisms underpinning central sensitization that contribute to chronic pain states, including

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those associated with temporomandibular disorders (TMDs) [18].

Animal models of migraine and TMD emphasize the role of TRPA1 and other TRP channels in mediating hyperalgesia and allodynia through upregulation of nociceptive neuropeptides and sensitization of central neurons. Pharmacological modulation of these channels attenuates central sensitization phenomena, suggesting a therapeutic avenue for managing persistent dental and orofacial pain [23].

VI. Pharmacological Modulation of TRP Channels in Dental Pain

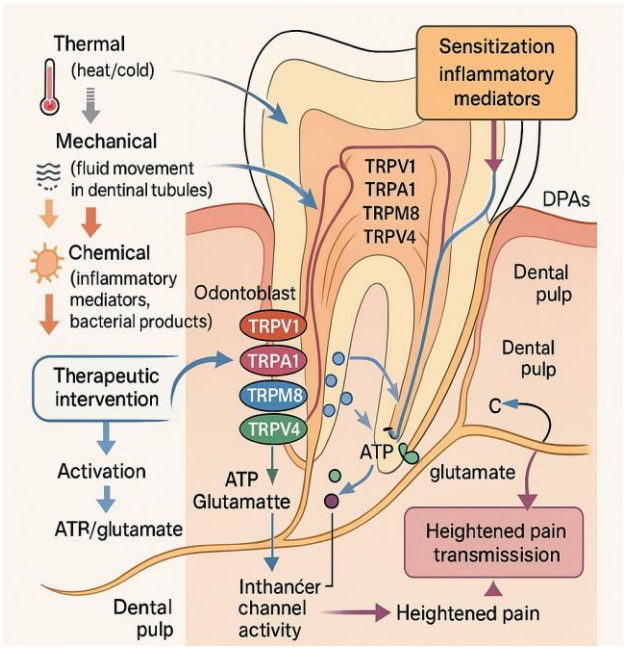

Figure 1: Graphical abstract of TRP Channel-Mediated Dental Pain Pathway: Cellular and Molecular Mechanisms in Tooth Sensitivity [4], [12], [16], [11]

6.1 TRPV1 Agonists and Antagonists

Capsaicin, a natural agonist of TRPV1, has been utilized therapeutically to induce desensitization of nociceptive fibers, thereby reducing neuropathic pain. High-dose capsaicin patches are in clinical use for neuropathic conditions and show promise in dental pain scenarios, particularly in pulpitis-induced neuropathic changes [7].

Advances in drug delivery include the development of nanogel systems encapsulating TRPV1 antagonists such as capsazepine, facilitating localized and sustained release within dental tissues. These systems demonstrate effective channel modulation with minimal cytotoxicity in odontoblast-like cells, reducing potential systemic side effects and improving clinical feasibility [8].

The clinical advancement of TRPV1 antagonists faces challenges such as adverse thermoregulatory side effects, necessitating precise targeting in the oral cavity. Nonetheless, capsaicin and capsazepine-based therapies represent promising adjuncts or alternatives to conventional analgesics in managing dental pain [24].

6.2 TRPA1 and TRPM8 Targeting Drugs

TRPA1 antagonists are emerging as potent modulators of inflammatory and neuropathic pain pathways. Preclinical studies reveal their ability to reduce neurogenic inflammation and hyperalgesia in models related to migraine and temporomandibular disorders. TRPM8 channel modulators are also under investigation, aiming to alleviate cold hypersensitivity associated with dental pain states [22].

While several small-molecule antagonists have entered early-phase clinical trials, translation to approved therapies remains challenged by issues of efficacy and adverse effects. Nonetheless, the therapeutic potential of targeting TRPA1 and TRPM8 channels in dental pain conditions remains high given their crucial sensory roles and accessibility [25].

6.3 Plant-Derived Compounds and Cannabinoids

Natural compounds such as capsaicin and eugenol exhibit modulatory effects on TRP and purinergic channels relevant to dental pain. Capsaicin activates and subsequently desensitizes TRPV1 receptors, reducing nociceptor excitability, a mechanism leveraged therapeutically [23]. Eugenol, extensively used in dentistry, inhibits ATP-induced P2X receptor currents and voltage-gated ion channels in trigeminal neurons, contributing to its analgesic efficacy [26].

Cannabinoid ligands interact with multiple TRP channel subtypes (TRPV1, TRPA1, TRPM8), modulating their activity and providing analgesic and anti-inflammatory effects. Endocannabinoids such as anandamide and synthetic cannabinoids modulate TRP channel function, bridging the gap between cannabinoid receptor signaling and TRP-mediated pain pathways, highlighting a complex analgesic interplay [27].

These natural products and endocannabinoid interactions support the development of integrative strategies combining traditional and modern pharmacotherapies for dental pain.

VII. Clinical Applications and Therapeutic Strategies

7.1 Current Practices in Dental Pain Management

Traditional management of dental pain primarily involves pharmacological agents like non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, often complemented by restorative procedures such as caries removal. However, these approaches are sometimes insufficient, have notable side effects, or lack specificity for the underlying molecular pain mechanisms [28].

TRP channel-targeted treatments offer alternative or adjunct therapies. For example, warming local anesthetics prior to injection reduces pain perception, potentially through the modulation of TRPV1 nociceptor activity, illustrating the clinical relevance of understanding TRP function in pain control [29].

Emerging pharmacological agents focusing on TRP channels provide opportunities for more effective and targeted dental pain relief, emphasizing the ongoing evolution of dental pain management beyond symptom control towards molecular precision.

7.2 Emerging Drug Delivery Systems

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Nanotechnology-based delivery such as gelatin nanogels encapsulating TRPV1 antagonists enable localized, sustained release directly within dental tissues, minimizing systemic exposure and associated adverse effects. Such systems have demonstrated promising stability, efficacy, and low cytotoxicity in preclinical odontoblast models, supporting their potential in dental analgesia [8].

Similarly, advances in biomaterials and regenerative medicine incorporate TRP channel modulation to support tissue repair and reduce pain during pulp regeneration. These integrative approaches merge pain control with functional restoration, signaling a paradigm shift in clinical dental therapies [24].

7.3 Potential for Personalized Medicine

Genetic variability in TRP channel genes influences individual pain thresholds and therapeutic responses, underscoring the need for personalized approaches. Incorporating genomic data into clinical practice could optimize analgesic regimens, enhance efficacy, and minimize adverse effects in dental patients. Biomarker development and patient stratification based on TRP channel polymorphisms remain areas for future clinical research [13].

Precision medicine approaches leveraging knowledge of TRP channel physiology may lead to individualized pain management protocols, especially for chronic or refractory dental pain cases [14].

VIII. Research Gaps and Future Directions

9.1 Gaps in Understanding TRP Channel Physiology in Dental Pain

Despite significant advances, critical gaps persist in the comprehensive understanding of TRP channels in dental pain. The exact roles and mechanisms of mechanotransduction, especially concerning channels like TRPV4 and TRPM3, remain incompletely defined, with conflicting evidence regarding their contributions [11].

A majority of functional data originate from animal models, necessitating translation into human dental tissues to confirm physiological relevance. The roles of less studied TRP subfamilies such as TRPC, TRPML, and TRPP in oral tissues are poorly characterized, representing an opportunity for discovery with potential clinical implications [30].

9.2 Challenges in Clinical Translation

Clinical trials targeting TRP channels face hurdles related to side effects such as impaired thermoregulation and inadequate efficacy, limiting progression to approved dental therapeutics. The ubiquitous nature of TRP channels demands precise tissue targeting and selective subtype modulation to avoid systemic adverse effects [24].

Developing effective delivery modalities overcoming biological barriers and off-target effects remains a major challenge, necessitating continued interdisciplinary research integrating pharmacology, materials science, and molecular biology [7].

9.3 Emerging Technologies and Methodologies

Innovations in human-based preclinical models, including organ-on-chip systems mimicking dental microenvironments, promise enhanced translatability of TRP channel studies. Advanced imaging and electrophysiological techniques enhance the resolution and functional assessment of TRP channels in situ [2].

Integration of multi-omics approaches, combining genomics, proteomics, and metabolomics, will facilitate personalized medicine and biomarker identification, optimizing therapeutic targeting of TRP channels in dental pain [1], [30].

IX. Conclusion

10.1 Summary of TRP Channels' Roles in Dental Pain

Transient receptor potential channels play indispensable roles in transducing thermal, mechanical, and inflammatory stimuli into neuronal signals within dental tissues. Their expression in odontoblasts, dental primary afferent neurons, periodontal ligaments, and associated oral structures underpins dental nociception. The coordinated activation and sensitization of these channels orchestrate complex pain experiences characteristic of dental pathologies.

10.2 Potential of TRP-Targeted Therapeutics

Therapeutic targeting of TRP channels holds considerable promise to advance dental pain management, offering specificity and improved efficacy with potentially fewer side effects compared to conventional analgesics. Novel delivery systems and understanding genetic variability are critical for success.

10.3 Final Remarks and Outlook

Continued multidisciplinary research integrating molecular, cellular, neurophysiological, and clinical perspectives is essential to surmount existing challenges and develop effective, targeted interventions. The graphical abstract provides a concise educational tool to facilitate understanding of TRP channel-mediated dental pain mechanisms.

Future clinical trials and integrative treatment approaches informed by this growing body of knowledge are anticipated to transform dental pain therapy significantly [4], [8], [7].

List of Abbreviations

Abbreviatio	Full Form
TRP	Transient Receptor Potential
TRPV1	Transient Receptor Potential Vanilloid
TRPA1	Transient Receptor Potential Ankyrin 1
TRPM8	Transient Receptor Potential Melastatin
TRPV4	Transient Receptor Potential Vanilloid 4
DPAs	Dental Primary Afferent Neurons
TMJ	Temporomandibular Joint
ATP	Adenosine Triphosphate
CGRP	Calcitonin Gene-Related Peptide
PIP_2	Phosphatidylinositol 4,5-Bisphosphate
Ca^{2+}	Calcium Ion
Na^{+}	Sodium Ion
Mg^{2+}	Magnesium Ion
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
P2X	Purinergic Receptor

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	(Ligand-Gated Ion Channel)
mGluRs	Metabotropic Glutamate Receptors
RT-PCR	Reverse Transcription Polymerase Chain Reaction
$LaCl_3$	Lanthanum Chloride
TTX	Tetrodotoxin
NaV1.8	Voltage-Gated Sodium Channel Type 1.8
CaV1.2	Voltage-Gated Calcium Channel Type 1.2

REFERENCES

1. Zhang M, Ma Y, Ye X, Zhang N, Pan L, Wang B (2023) TRP (transient receptor potential) ion channel family: structures, biological functions and therapeutic interventions for diseases. Springer Nature. https://doi.org/10.1038/s41392-023-01464-x
2. Chalazias A, Plemmenos G, Evangeliou E, Piperi C (2021) Pivotal role of Transient Receptor Potential Channels in oral physiology. Curr Med Chem. https://doi.org/10.2174/0929867328666210806113132
3. Hossain MZ, Bakri M, Yahya F, Ando H, Unno S, Kitagawa J (2019) The Role of Transient Receptor Potential (TRP) Channels in the Transduction of Dental Pain. Int J Mol Sci 20(3):526. https://doi.org/10.3390/ijms20030526
4. Bamps D, Vriens J, De Hoon J, Voets T (2020) TRP Channel Cooperation for Nociception: Therapeutic Opportunities. Annu Rev Pharmacol Toxicol. https://doi.org/10.1146/annurev-pharmtox-010919-023238
5. Lee K, Lee BM, Park CK, Kim YH, Chung G (2019) Ion channels involved in tooth pain. Int J Mol Sci 20(9):2266. https://doi.org/10.3390/ijms20092266
6. Luo, Y., Suttle, A., Zhang, Q., Wang, P., & Chen, Y. (2021). *Transient receptor potential ion channels in orofacial pain*. Molecular Neurobiology, 58(6), 2836–2850. https://doi.org/10.1007/s12035-020-02262-9
7. Chantadul V, Rotpenpian N, Arayapisit T, Wanasuntronwong A (2025) Transient receptor potential channels in dental inflammation and pain perception: A comprehensive review. Heliyon 11(2):e41730. https://doi.org/10.1016/j.heliyon.2025.e41730
8. Bernal Cepeda LJ, Jiménez RA, Velandia Romero ML, Acosta Guzmán P, Castellanos JE (2024) Modulation of TRPV1 on odontoblast-like cells using capsazepine loaded nanogels. Pharmaceutics 16(3):355. https://doi.org/10.3390/pharmaceutics16030355
9. Paulsen CE, Armache JP, Gao Y, Cheng Y, Julius D (2015) Structure of the TRPA1 ion channel suggests regulatory mechanisms. Nature 520(7548):511–517. https://doi.org/10.1038/nature14367
10. Owsianik G, Talavera K, Voets T, Nilius B (2006) Permeation and selectivity of transient receptor potential channels. Annu Rev Physiol 68:685–717. https://doi.org/10.1146/annurev.physiol.68.040204.101406
11. Caterina MJ, Julius D (2015) The pivotal role of transient receptor potential channels in oral physiology and dental pain. Curr Oral Health Rep 2(3):100–109. https://doi.org/10.1007/s40496-015-0047-2
12. Egbuniwe O, Grover S, Duggal AK, Mavroudis A, Yazdi M, Renton T, Di Silvio L, Grant AD (2014) TRPA1 and TRPV4 activation in human odontoblast-like cells stimulates ATP release. J Dent Res 93(9):911–917. https://doi.org/10.1177/0022034514544507
13. Dias J, Prescott SL, Woodside CM (2015) Interactions between chemesthesis and taste: Role of TRPA1 and TRPV1 channels. Front Physiol 6:249. https://doi.org/10.3389/fphys.2015.00249
14. Zhang X, Maksimovic S, Shapiro AM, Wood JN (2012) Transient Receptor Potential Channel Polymorphisms Are Associated with Somatosensory Function in Neuropathic Pain Patients. PLoS Genet 8(1):e1002997. https://doi.org/10.1371/journal.pgen.1002997
15. Bautista, D. M., Siemens, J., Glazer, J. M., Tsuruda, P. R., Basbaum, A. I., Stucky, C. L., Jordt,S.E.,&Julius,D.(2007).The menthol receptor TRPM8 is the principal detector of environmental cold. Nature, 448(7150), 204–208. https://doi.org/10.1038/nature05910
16. Shibukawa Y, Tsumura T, Arima M, Shimizu M, Sato T, Suzuki T (2015) Intercellular odontoblast communication via ATP mediated by pannexin 1 following transient receptor potential channel activation. J Physiol 593(18):4161–4175. https://doi.org/10.1113/JP270292
17. Utami JP, Shibukawa Y (2020) Linkages of CaV1.2, glutamate, and odontoblasts in the mechanism of tooth pain. Dentino J Ked Gi 5(1):110–115. https://doi.org/10.22146/dentino.8123
18. Yi Y, Zhou X, Xiong X, Wang J (2021) Neuroimmune interactions in painful temporomandibular disorders: Mechanisms and treatment implications. J Leukoc Biol 110(3):553–563. https://doi.org/10.1002/JLB.3MR0621-731RR
19. Chung G, Oh SB (2013) TRP channels in dental pain. Open Pain J 6(Suppl 1:M5):31–36. https://doi.org/10.2174/1876386301306010031
20. Shibukawa Y, Sato M, Kimura M, Sobhan U, Shimada M, Tazaki M (2015) Odontoblasts as sensory receptors: Transient receptor potential channels, pannexin 1, and ionotropic ATP and glutamate receptors mediate intercellular odontoblast–neuron signal transduction. Pflugers Arch 467(4):843–863. https://doi.org/10.1007/s00424-014-1551-x
21. Ichikawa H, Sugimoto T (2015) La^{3+} Alters the Response Properties of Neurons in the Mouse Primary Somatosensory Cortex during Noxious Cold Stimulation of Dental Pulp. J Neurophysiol 114(5):2769–2777. https://doi.org/10.1152/jn.00217.2015
22. He Y, Wang Y, Kong X (2018) Inhibition of TRPA1 and TRPV1 attenuates spontaneous and bite-evoked pain behaviors following masseter inflammation in mice. Neuropharmacology 135:539–547. https://doi.org/10.1016/j.neuropharm.2018.04.012
23. Fakih R, Zanella A, Pietra C, Mariani P, Gazerani P (2019) Antagonism of TRPA1 channels attenuates hyperalgesia and central sensitization in rodent models of migraine and temporomandibular joint pain. Int J Mol Sci 20(4):815. https://doi.org/10.3390/ijms20040815
24. Szallasi A, Cortright DN, Blum CA, Eid SR (2007) The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof of concept. Nat Rev Drug Discov 6(5):357–372. https://doi.org/10.1038/nrd2217
25. Weyer AD, Neely GG (2016) Nociceptive TRP channels: Sensory detectors and transducers in multiple pain pathologies. Pharmacol Rev 68(3):631–687. https://doi.org/10.1124/pr.115.011056
26. Li HY, Lee BK, Kim JS, Jung SJ, Oh SB (2008) Eugenol inhibits ATP-induced $P2X_3$ receptor currents in trigeminal ganglion neurons. Korean J Physiol Pharmacol 12(6):315–321. https://doi.org/10.4196/kjpp.2008.12.6.315
27. De Petrocellis L, Ligresti A, Moriello AS, Aviello G, Stott CM, Izzo AA (2012) Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type 1 and melastatin type 8. J Pharmacol Exp Ther 343(1):7–19. https://doi.org/10.1124/jpet.112.196037
28. Walsh LJ, Gentile MG (2011) Drug therapy in dental practice: Nonopioid and opioid analgesics. J Calif Dent Assoc 39(1):37–44. PMID: 21355459
29. Aravena PC, Barrientos C, Troncoso C, Coronado C, Sotelo Hitschfeld P (2018) Effect of warming anesthetic on pain perception during dental injection: a split mouth randomized clinical trial. Local Reg Anesth 11:9–13. https://doi.org/10.2147/LRA.S147288
30. Nilius B, Szallasi A (2014) Transient Receptor Potential channels as drug targets: From the science of basic research to the art of medicine. Pharmacol Rev 66(3):676–814. https://doi.org/10.1124/pr.113.008268

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