The Open Dentistry Journal
DOI: 10.2174/0118742106281444240219050149, 2024, 18, e18742106281444
ISSN: 1874-2106
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REVIEW ARTICLE **OPEN ACCESS**

Exploring the Painless Nature and Potential Mechanisms of Asymptomatic Irreversible Pulpitis: A Narrative Review

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Abstract:

Background: Considering the extensive innervation of the pulp tissue, asymptomatic irreversible pulpitis (AIP) or "silent pulpitis" represents a confounding clinical condition. Previous studies have attributed the painless nature of AIP to the inhibition of pulpal nociceptors by local endogenous analgesics. However, there is a lack of recent information concerning its painless nature, and paradoxically, patients with dental pain are diagnosed with AIP daily worldwide. In addition, no recent review has explored the potential AIP-related mechanisms.

Objective: This narrative review aims to explore and update the potential mechanisms involved in the painless nature of AIP to improve our current understanding of the asymptomatic character of this clinical condition.

Methods: An electronic search was performed in the PubMed and Scopus databases, using as search terms "asymptomatic irreversible pulpitis," "dental pulp," "endogenous opioids," "endogenous cannabinoids," "somatostatin," "GABA," "bombesin," "cortistatin," "galanin," and "specialized pro-resolving lipid mediators."

Results: Endogenous opioids, G protein-activated inwardly rectifying K^+ channels, endogenous cannabinoids, γ-aminobutyric acid, and neuropeptides (*i.e.* somatostatin, cortistatin, galanin, and bombesin) could be involved in AIP-related analgesia. Additionally, specialized pro-resolving lipid mediators, such as lipoxins, resolvins, maresins, and protectins, as well as oxytocin, phoenixin, opiorphin, and adipokines, could also be involved in this clinical condition.

Conclusion: This narrative review provides updated information on the potentially involved mechanisms in AIP. Nevertheless, the precise mechanisms responsible for the lack of symptoms in AIP remain to be elucidated, and further research is warranted.

Keywords: Asymptomatic irreversible pulpitis, Analgesia, Endogenous opioids, Endogenous cannabinoids, Neuropeptides, Phoenixin.

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Cite as: Cabrera-Abad D, Jara-Vergara V, Álvarez-Vásquez J. Exploring the Painless Nature and Potential Mechanisms of Asymptomatic Irreversible Pulpitis: A Narrative Review . Open Dent J, 2024; 18: e18742106281444.
http://dx.doi.org/10.2174/0118742106281444240219050149

Received: September 09, 2023
Revised: December 29, 2023
Accepted: January 25, 2024
Published: February 23, 2024

1. INTRODUCTION

The dental pulp is a highly vascularized, innervated connective tissue that provides vitality and sensitivity to teeth [1, 2]. This tissue experiences inflammatory reactions in response to dental caries, restorative procedures, dental trauma, and periodontal disease [3] — the first being the main threat to dental pulp [4]. However, pulpitis is the most common inflammatory disease in humans and other mammals [5] that can be reversible or irreversible. Irreversible pulpitis can be symptomatic or asymptomatic [6].

Considering the extensive nerve plexus of the pulp tissue, asymptomatic irreversible pulpitis (AIP) or "silent pulpitis" is a confounding clinical condition [7]. Patients do not experience pain (6) despite inherent inflammatory processes in the affected tooth. Several studies have identified local analgesic agents in the dental pulp, including endogenous opioids [8-10], cannabinoids [11, 12], gamma-aminobutyric acid (GABA) [13, 14], and somatostatin [10, 15]. These agents could inhibit pulpal nociceptors and may be responsible for the asymptomatic nature of AIP [7].

Despite these studies investigating the dental pulp, there is a lack of updated literature reviews that explore the factors involved in the asymptomatic nature of AIP, and the most recent foundational study on the painless nature of AIP dates back two decades [16]. Moreover, patients with dental diseases are diagnosed with AIP on a daily basis worldwide. Therefore, this narrative review aimed to compile updated information on potential factors involved in the mechanisms of analgesia underlying AIP to improve our current understanding of its painless nature and to provide insights for future studies elucidating the precise mechanisms underlying the lack of symptoms in AIP.

2. MATERIAL AND METHODS

We searched the available literature in the PubMed and Scopus databases to identify relevant articles published up to January 25, 2022, describing the expression of ligands and/or receptors or other factors that potentially regulate the asymptomatic nature of AIP. The following search terms were used: "asymptomatic irreversible pulpitis," "dental pulp," "endogenous opioids," "endogenous cannabinoids," "somatostatin," "GABA," "bombesin," "cortistatin," "galanin," and "specialized pro-resolving lipid mediators." Only articles published in English were included in the present study. The search was limited to clinical trials, *in vitro* studies, literature reviews, systematic reviews, and textbook chapters. Interim reports, abstracts only, letters, brief communications, studies that did not focus on the asymptomatic nature of AIP, and duplicated works were excluded. Subsequently, the titles and abstracts of relevant articles were reviewed, and a manual search of the references of each selected article was performed to complement the electronic search. Further, endodontic journals were examined to identify relevant articles "in press" or in "early view" status.

3. POTENTIAL FACTORS INVOLVED IN ANALGESIA DURING AIP

Factors that could potentially be involved in the mechanisms of analgesia underlying AIP include endogenous opioids, G protein-activated inwardly rectifying K^+ channels (GIRK), endogenous cannabinoids, γ-aminobutyric acid (GABA), neuropeptides (somatostatin, cortistatin, galanin, and bombesin), and specialized pro-resolving lipid mediators (*i.e.* lipoxins, resolvins, and maresins). We also included a section on miscellaneous factors that could potentially be involved in AIP, such as bacteria and their antinociceptive effects, oxytocin, phoenixin, opiorphin, and adipokines. All but bacteria are endogenous biomolecules potentially involved in the painless nature of AIP. The ligands/receptors of these biomolecules have already been identified in the dental pulp tissue and/or the trigeminal ganglion (TG). However, in some cases, information is not yet available (Table **1**).

3.1. Endogenous Opioids

The opioid system functions as an endogenous mechanism of antinociception through three pathways: inhibition of nociceptors at the supraspinal level, inhibition of nociceptors at the level of the dorsal horn of the spinal cord, and activation of the descending inhibitory pathways [15]. This system is distributed in both the central nervous system (CNS) and peripheral nervous system (PNS) [17-20]. It is comprised of endogenous opioid peptides (EOP) (*i.e.*, enkephalins, dynorphins, β-endorphins, and nociceptin/orphanin FQ) [17] released by T- and B-lymphocytes, monocytes, macrophages, and granulocytes [21-24]; and opioid receptors (OR) that are located in the nerve endings of the primary afferent fibers [25, 26]. Met-enkephalins, dynorphins, and β-endorphins have been found in the dental pulp [10, 27, 28]; however, the presence of nociceptin/orphanin has not yet been demonstrated.

The receptors found in the afferent sensory nerves are μ (MOR), δ (DOR), and κ (KOR) [17, 23, 29-32], along with the nociceptin/orphanin receptor (NOR), also known as the orphan opioid receptor-like receptor (ORL) [17, 33]. ORs, especially DOR, are involved in neuroprotection against hypoxia or ischemia [34-37]. They also inhibit voltage-gated Ca^{2+} channels [38], reduce the release of neurotransmitters [17], and allow neuronal hyperpolarization that is mediated by K^+ channels [39]. The presence of MOR [9] and DOR [40] in the dental pulp has been confirmed; however, the KOR expression has not yet been demonstrated.

Under normal conditions, the ORs are inaccessible due to the perineural barrier [41-43]; however, this is altered in initial inflammatory conditions that allow for the passage of ligands to their receptors [30]. In late inflammatory stages, the number of ORs increases, along with their axonal transport to the periphery [9, 24] and sprouting of new nerve endings [44, 45] that would explain the opioid analgesic activity in inflamed dental pulps [9]. In these states, β-endorphins become unstable due to their rapid metabolism; therefore, the resulting analgesia could be induced by their fragments after their biotransformation [46]. In contrast, a previous study showed that antinociception failed to increase despite the increased leukocyte recruitment, which could be attributed to the low amount of ORs in the early inflammatory stage [47]. The duration of inflammation could be a decisive factor in terms of the analgesic capacity of the endogenous opioid system, such that in both types of irreversible pulpitis (symptomatic and asymptomatic), an inflammatory process is established;

however, pain is absent in the latter scenario. In endogenous analgesia, the number of leukocytes, ORs, duration of inflammation, and binding efficiency of ORs with G-protein in neurons interact in a simultaneous manner [45, 48, 49].

Central and peripheral ORs interact in the initial inflammatory stages [47, 50-52]; however, in the late stages, only peripheral ORs function [23, 53, 54], demonstrating high participation of peripheral opioid mechanisms as inflammation advances and becomes more severe [48, 51, 55, 56]. Moreover, during chronic inflammation, at the central level, changes in the ORs are not observed, but the levels of EOP increase [32]. Therefore, further studies are required to determine the differences in central responses that occur at different times and in different types of dental injuries [57].

Bradykinin stimulation [58], orthodontic movements [59], and cavity preparation [60] increase the EOP levels in the dental pulp [15, 55, 61]. Moreover, other substances exert an antinociceptive effect as a secondary function by stimulating the release of EOPs in a similar manner to the effects exerted by substance P (SP) whose N-terminal fragment acts as a ligand for MOR [62, 63], calcitonin gene-related peptide (CGRP) that suppresses IL-2 production [64], and IL-4 that promotes change in the phenotype of macrophages from M1 to M2 and stimulates M2 to produce EOP in injured nerves [65]. Additionally, interleukin 1β (IL-1β), corticotropin-releasing factor (CRF) [66], norepinephrine, and CXCL2/3 stimulate the release of EOP by leukocytes [21, 50, 67-72], and thus, exert a peripheral analgesic effect [50, 69-71, 73]. Moreover, some opioid agonists exert anti-inflammatory effects, probably involving ORs on immune cells [74].

In contrast, M2 macrophages can help in resolving inflammatory pain by transferring their mitochondria to the neurons of the dorsal root ganglion (DRG) and stimulating the switch from neuronal glycolytic metabolism to more oxidative metabolism, which in turn regulates the neuronal activity and allows for the resolution of inflammatory pain away from the inflammation site [75]. An increase in the M2 levels has been observed in the TG as pulpitis progresses, showing anti-inflammatory effects [76]. Moreover, this analgesic effect could be attributed to the secretion of IL-10 because of its anti-inflammatory action [77-81] and a reduction in the expression of voltage-gated sodium channels and a number of currents sensitive to tetrodotoxin [82]. However, the resolution of inflammation is insufficient to resolve the pain [80].

3.2. GIRK

GIRK are G protein-activated effector ion channels [83] that participate in opioid-mediated antinociception in the CNS and PNS *via* hyperpolarization of the neuronal membrane, which in turn inhibits the propagation of action potentials [84-90]. At the spinal cord level, these receptors contribute to the analgesic effects of MOR and DOR but not those of KOR [88]. Furthermore, GIRK channels are crucial for galanin action, as GalR1 and GalR3 open the K^+ channels. For neuropeptide Y, which presynaptically depresses the miniature excitatory synaptic currents through the Y2 receptor, somatostatin activates the GIRK channels of SST4 receptors [91-95].

The GIRK 1 and 2 receptors are expressed in the TG neurons, thus contributing to peripheral opioid analgesia in the craniofacial region [96]. Therefore, these channels could be present in the dental pulp; however, to date, no study has confirmed this hypothesis.

3.3. Endogenous Cannabinoids

The endogenous opioid and cannabinoid systems are involved in antinociception through different pathways [97-104]. Moreover, they activate the G-protein-coupled receptors (GPCR) and can interact either directly (receptor heteromerization) or indirectly (cross-signaling) [97, 98, 105]. Moreover, cannabinoid receptors (CBRs) activate GIRK, which in turn reduces the release of neurotransmitters in the opioid system [106]. The endocannabinoid system has receptors (CB1R and CB2R), endogenous ligands (anandamide and 2-arachidonylglycerol), and enzymes that degrade and synthesize the latter, performing functions at the central and peripheral levels [107, 108]. This system is expressed in both the ascending and descending pain pathways, producing antinociception at the supraspinal, spinal, and peripheral levels [102, 109-112]. Additionally, lipopolysaccharides (LPS) increase the levels of anandamide and inhibit the enzyme fatty acid amide hydrolase (FAAH) in the lymphocytes [113], and increase the levels of 2-arachidonylglycerol (2-AG) in the macrophages and platelets [114].

CB1R and CB2R are mainly expressed in the nervous and immune systems, respectively [115-119], and the cells of these systems secrete endocannabinoids [23, 120, 121]. CB1Rs have been identified in various areas related to pain in the CNS, where they regulate signals from neurons originating from the nociceptive regions of the spinal cord, producing antinociception [110-112, 118]. CB1R of the ventrolateral periaqueductal gray matter (vlPAG) aids in modulating the nociceptive signals from the TG nerve, specifically in capsaicin-induced pulpal pain [122]. The exact mechanism of this modulation is unclear; however, CB1R in the PAG interacts with other systems to modulate the nociceptive signals [123, 124], such as orexin 1 receptors (OX1Rs). When activated, these receptors induce the release of 2-AG, which inhibits the release of GABA through the pre-synaptic CB1R—a phenomenon known as disinhibition [123]. Tonic inhibition of GABAergic transmission activates the vlPAG; thus, activating the descending pain inhibition pathway [125]. This demonstrates the antinociceptive effects of orexin-A on the vlPAG and its relationship with the endocannabinoid system [123].

The CBR signaling pathway acts through the inhibition of cyclic-AMP formation and modulation of Ca^{2+} and K^+ channels [126]. Different ligands differentially activate these signaling pathways through CB1R and CB2R—

which is termed the "biased signaling" [127]. Further studies at the pulp level are suggested as this signaling may preferentially provide higher analgesia. Additionally, the molecular mechanisms underlying the antinociceptive and antihyperalgesic effects of CBRs remain unclear [115]. Endocannabinoids, such as anandamide, 2-AG, and the other less-studied subtypes, including N-arachidonoyl-dopamine (NADA), noladin ether, and virodhamine, interact with receptors other than CB1R and CB2R [105, 128, 129].

In contrast, transient receptor potential vanilloid subtype 1 channels (TRPV1) are activated by anandamide and NADA and are co-expressed with CB1R and CB2R in some tissues, including the dental pulp [128, 130]. This co-expression or "cross-talk" between CBR and TRPV1 may be relevant in pulpal analgesia. It has long been known that only CBRs attenuate and TRPV1 increases nociception. However, studies have shown that TRPV1 activation potentiates the supraspinal pain inhibitory pathways, and desensitization of TRPV1 produces analgesia [131, 132]. Pre- and post-synaptic activation of TRPV1 or pre-synaptic activation of CB1R stimulates the output excitatory neurons through glutamate release or disinhibition of GABA tonic control, respectively, at the vlPAG level. This leads to glutamate release in the rostral ventromedial medulla (RVM) and activation of the "off" neurons in this area, with a subsequent antinociception [133, 134]. However, further studies are required to analyze the factors that activate these pathways.

TRP channels also induce peripheral antihyperalgesia and antinociception [135, 136]. However, their mechanism of action is complex, as they generate incoming ionic currents more associated with nociception. Partial activation of these channels may not necessarily generate neuronal excitation [137-139]. The incoming currents could fail to reach threshold levels to excite the nociceptors, or the slow depolarization of the membrane potential may inactivate these channels [140].

CB1R and CB2R expression in the dental pulp of humans and rats has been previously demonstrated [10, 11, 130, 141-143]. CB2R is expressed in the human pulp cells [130, 142] and myofascial fibroblasts [144], whereas CB1R is preferentially expressed in odontoblasts, odontoblast-like cells, and pulpal nerve fibers [11, 145]. Although the expression of CBRs has not been shown in dental pulp fibroblasts, it has been reported that fibroblasts have the necessary enzymes to produce endocannabinoids and act in an autocrine or paracrine way when interacting with leukocytes [144, 146, 147]. A previous study showed that there were no statistically significant differences in the expression of CB1R between painful and non-painful dental pulps [11].

In contrast, CB1R may be activated by stretching in the absence of a ligand [119], wherein hydrostatic pressure may directly activate OR and CBR, releasing endorphins and endocannabinoids, as has been reported at the PAG level [148]. In the dental pulp, an increase in pressure during an inflammatory process may activate these receptors, although this remains to be explored. However, the role of CB2Rs and their agonists has been investigated in pulpal antinociception [149] and in animal models of acute, chronic, and neuropathic pain [150].

CB2R agonists can inhibit inflammatory pain through their anti-inflammatory effects [151, 152]. Moreover, the expression of cytokines and CBR have a reciprocal regulatory relationship. Thus, the activation of these receptors in macrophages inhibits the production of proinflammatory cytokines [153], thus allowing the change from immune responses mediated by Th1 (proinflammatory) to Th2 (anti-inflammatory) through the CB2R [154]. Moreover, IL-4 increases the CB1R expression in leukocytes [155], and IFN-γ and IL-12 reduce the FAAH activity [113]. Taken together, the increase in CBR expression by cytokines could be a mechanism of autoregulation of inflammation [156].

3.4. GABA

GABA neurotransmitter plays a primary inhibitory role in the CNS and PNS [157-161]. When released at the neuronal synapses, it activates different classes of receptors or returns to the nerve terminals *via* a Na^+-dependent transporter [158-160]. Ionotropic receptors ($GABA_A$ and $GABA_C$) participate in rapid synaptic transmission and modulate neuronal activity by gating the chloride ions [13, 159], hyperpolarizing the neuronal membranes, and inhibiting the propagation of action potentials, leading to short-term, fast-acting inhibitory currents [157, 160]. In contrast, the slow-acting metabotropic receptors ($GABA_B$) belong to the GPCR superfamily and exert inhibitory actions through the inhibition of voltage-gated Ca^{2+} channels and GIRK activation [162-167]. These receptors have been found in the dental pulp tissue [13] and TG [163]. Furthermore, GABAergic neurons are activated at the trigeminal nuclear complex during tooth pulp stimulation [161].

However, inflammation, necrosis, or areas of pulpal hypoxia can increase the GABA levels above the nominal levels at rest, which may explain the absence of symptoms in these pulps [12, 13]. Neuroinflammation can be modulated by GABAergic signaling [157], as $GABA_B$ receptors are involved in pain management and analgesia; thus, GABA and $GABA_B$ receptors present in the human pulp may also be involved [164]. The clinical importance of peripheral $GABA_B$ receptors may be related to the peripheral analgesic effects of $GABA_B$ agonists that modulate or attenuated nociceptive behavior in the animal models of pain [165]. In a previous study [166], isovaline, baclofen, and GABA attenuated allodynia induced by prostaglandin E2 injection. Another study revealed that baclofen suppressed pain in small-diameter TG neurons in rats [162].

In contrast, GABAergic interneurons mediate the endogenous release of 5-hydroxytryptamine (5-HT). The 5-HT3 receptors are involved in antinociceptive effects [167] that are attenuated by the opioid antagonist naloxone, suggesting that these neurons may be associated with endogenous opioids [168].

3.5. Neuropeptides: Somatostatin, Cortistatin, Galanin, and Bombesin

Neuropeptides play a major role in the perception of pain [169], but some can mediate analgesic mechanisms [170]. In this section, we describe the potential analgesic roles of somatostatin, cortistatin, galanin, and bombesin in AIP.

3.5.1. Somatostatin (SST)

SST is a peptide hormone [171-173] that is widely distributed in the CNS and peripheral tissues [171, 174] and is produced by neurons and neuroendocrine, inflammatory, and immune cells in response to ions, nutrients, neuropeptides, neurotransmitters, hormones, growth factors, cytokines [173], and noxious heat or chemical stimuli [175]. There are two SST isoforms, SST-14 and SST-28, that differ in the number of amino acids [175-177] and five GPCR-type receptors (SSTR 1–5) [178].

SST performs antinociceptive functions [179-182] by affecting neurotransmission through its receptors, decreasing the conductance of voltage-gated Ca^{2+} channels [172, 183], and activating K^{+} channels [184-186]. SST decreases neurogenic inflammation [175] due to its inhibitory action [175, 187, 188] by decreasing the release of IFN-γ, reactive oxygen species, CGRP [175], SP [189], and immunoglobulins from B-cells [190]. Moreover, SST can regulate the pulpal blood flow [191] as the peptidergic nerves containing SST are distributed near the blood vessels [10, 192-194].

3.5.2. Cortistatin (CORT)

CORT, a cyclic neuropeptide, is predominantly expressed in the cerebral cortex [195-197], spinal cord neurons, GABAergic inhibitory interneurons [198-200], immune cells (lymphocytes, monocytes, macrophages, and dendritic cells) [201, 202], and to a lesser extent in endothelial cells, endocrine cells, peripheral nociceptive neurons, and smooth muscle cells [203] in response to noxious stimuli, cytokines, and tissue injury [197, 203].

CORT binds with a high affinity to different receptors, mainly SSTR 1–5 [192, 204], ghrelin receptor (GHSR1) [196, 197], and an unidentified selective CORT receptor [198]. It shares several functions with SST [205], such as suppression of nerve function and inhibition of cell proliferation [196, 206]; however, it has other functions, such as sleep induction, reduction of locomotor activity, and deactivation of inflammatory/autoimmune responses [196, 203, 206, 207]. Regarding adaptive immunity, CORT acts on CD4 T-lymphocytes, participates in the inhibition of differentiation and activation of Th1 and Th17 lymphocytes, and induces differentiation and activation of Th2 and Treg lymphocytes. As for innate immunity, CORT acts on macrophages/monocytes and participates in the inhibition of proinflammatory mediators, such as CGRP [205], TNF, IL-6, IL-12, IL-1, NO, GM-CSF, and CK, and increases the levels of IL-10 [208, 209]; thus, exerting anti-inflammatory effects. In contrast, its deficiency can exacerbate inflammatory pain responses [197, 210].

Finally, CORT is capable of deactivating microglia and astrocytes in an inflammatory environment [197, 211]. Activated glial cells play a critical role in the development and maintenance of nociceptive responses, especially at the spinal cord level [211]. Thus, CORT regulates inflammation-induced pain through deactivation, particularly by preventing the development of chronic pain. It also relieves hyperalgesia and allodynia and acts as a neuroprotector and neuroregenerator [205]. Furthermore, CORT mRNA and protein are detected in mature and newly developing odontoblasts. Thus, SSTR1 and CORT may have important functions in the regulation of pulpal inflammation and communication between odontoblasts and the nervous system [212] and may be involved in antinociceptive processes at the pulpal level. However, further studies are needed to confirm these hypotheses in the dental pulp.

3.5.3. Galanin (GAL)

GAL, a neuropeptide widely distributed in the CNS and PNS [213-216], is present in non-neuronal cells, such as keratinocytes, sweat glands, macrophages, and blood vessels [217]. It is expressed by immune cells during inflammation in an attempt to restore homeostasis [218] and exerts its physiological effects through three types of GPCRs [216, 219], namely GalR1, GalR2, and GalR3 [216, 220-224]. Previous studies have suggested that GAL and its receptors may be involved in the transmission and modulation of nociceptive information in the nervous system [225-230].

GAL has an antinociceptive effect [228, 231-235] *via* activation of GalR1 [226, 236-238] and GalR3, which causes neuronal hyperpolarization in response to increased K^{+} conductance [239], and also favors the release of enkephalins and endorphins in the primary afferent neurons that innervate the dental pulp [240]. The immunoreactivity of GalR1 has been observed in the axoplasm of unmyelinated nerve fibers (type C and Aδ) of the dental pulp [241, 243]. However, it can induce pronociceptive effects [224, 243] through the action of GalR2 [226, 236-238, 244-246] and activation of phospholipase C–protein kinase C pathway [247]. Nevertheless, the GAL action differs according to its concentration, where the activation of GalR2 changes from a Gq pathway (low GAL concentration) to a Gi/o-dependent pathway (high GAL concentration); therefore, it changes from a pro- to an antinociceptive-type signaling pathway [248]. However, the latter has not yet been observed in the dental pulp tissue.

3.5.4. Bombesin (BN)

The endogenous peptide, BN [249], and its homologues, neuromedin B (NMB) and gastrin-releasing peptide (GRP) are important neuromodulators in the brain [250, 251]. They function through three subtypes of G protein-coupled hepta-helical receptors, namely BB1, BB2, and BB3. NMB and GRP show high affinity and serve as endogenous ligands for BB1 and BB2 receptors, respectively [250], whereas BN activates both receptors

[251], and BB3 is an orphan receptor with low affinity for all these peptides.

BN increases the presynaptic release of GABA by facilitating the entry of extracellular Ca^{2+} [250], depolarizes GABAergic interneurons at the presynaptic level through the inhibition of KIRs and K^+ conductance, and increases the input resistance of interneurons. This suggests that BN reduces the conductance of the neuronal membrane [250]. Its antinociceptive action may be related to the release of GABAergic interneurons.

A previous study [13] demonstrated the significantly higher presence of specific GABA-like and BN/GRP-like immunoreactivity in the pulps of asymptomatic carious teeth than in normal teeth. Both peptides have been implicated in antinociception [13] and have been reported in TG neurons [252]. Their immunoreactivity has been observed within the pulpal nerves and pulp fibroblasts [13].

3.6. Specialized Pro-resolving Lipid Mediators (SPMs): Lipoxins, Resolvins, Maresins, and Protectins

The SPMs actively resolve inflammation to avoid the development of a chronic condition [253]. These endogenous lipid mediators act as immune response modifiers and selectively modulate and reduce the host response. They resolve inflammation [254] by clearing debris and infectious agents, reducing pain, and restoring the function of damaged tissues [255].

In contrast, several studies support the potent role of SPMs in reducing the different types of pain, including inflammatory and neuropathic pain [256-263], through GPCRs and different downstream mechanisms, such as the regulation of inflammatory mediators, TRP channels, and central sensitization [264].

Studies with animal models indicate that SPMs can reduce inflammatory, postoperative, and neuropathic pain *via* immune, glial, and neuronal modulation [265]. Additionally, SPMs are produced in small amounts *in vivo* (nano- or picograms), and thus, the doses used in experimental studies are of equal magnitude [262, 266, 267]. Despite the low doses, the analgesic and anti-inflammatory potency of SPMs is evident. Those doses are not comparable with the milligrams or grams used with analgesic agents, such as nonsteroidal anti-inflammatory drugs or opioids [268, 269].

Furthermore, SPMs could potentially participate in the asymptomatic nature of AIP *via* the resolution of inflammation and their anti-inflammatory effects. Nevertheless, such issues need to be clarified by well-established pulpal pain models. However, technical barriers pertaining to the instability, complex and delicate physicochemical nature, and metabolic inactivation of SPMs must be overcome [253].

3.7. Miscellaneous Mechanisms

3.7.1. Bacteria and their Antinociceptive Effects

Inflammation-induced pain is an adaptive response designed to protect the body from further injuries [270]. However, disease scenarios vary because some pathogens can block, reduce, or modulate pain during the disease cycle [271]. For instance, *Porphyromonas gingivalis* [270] is associated with destructive periodontal disease [270, 272], dental caries [273], endodontic infections, and odontogenic abscesses [274]. It exerts antinociceptive effects [270], where its LPS increases the levels of the potent anti-inflammatory cytokine IL-10 [270] and stimulates the peptide derived from human telomerase (GV1001) that has an anti-inflammatory effect without affecting the cell viability in the human dental pulp, as it allows for downregulating the expression of TNF-α and IL-6 [272]. However, the antinociceptive role of this bacterium has not yet been studied in AIP; thus, more studies are required.

Metagenomic studies have revealed that the human microbiome can generate many bioactive molecules, including histamine, epinephrine, and GABA [275-277]. Therefore, the possible antinociceptive actions of bacteria, such as *Lactobacillus* species [278, 279] (*Lactobacillus acidophilus* NCFM), induce the expression of the cannabinoid and μ-opioid receptor in the intestinal epithelial cells [280]. Whereas, *Bifidobacterium* species, such as *B. dentium*, also produce GABA [281-283], making neurons less likely to reach the threshold depolarization level [283].

In contrast, *M. ulcerans* can secrete mycobacterial polyketide mycolactone to induce analgesia by activating angiotensin II type 2 receptors (AT2R) and inducing hyperpolarization through activation of K^+ channels in nociceptors [271, 284]. Additionally, in acute staphylococcal infections [285], CGRP, GAL, and somatostatin can suppress TNF-α release from *S. aureus*-stimulated or heat-killed lipoteichoic acid macrophages. This indicates that the presence of these bacterial agents may induce the production of other substances that reduce inflammation and have analgesic action.

Finally, in the dental pulp, LPS from bacteria modulates the nociceptive activity through TLR4-mediated sensitization of TRPV1 to nociceptors [286]. Moreover, LPS could be detrimental if pathogenic factors suppress nociception because they can evade host detection and allow for the silent spread of infection.

3.7.2. Oxytocin (OXT)

OXT, a hormone and neuropeptide, induces antinociception [287-290] and participates in the endogenous opioid system [288]. At the TG level, the expression of OXT receptors (OXTR) in the nociceptive neurons (small A–δ fibers) has been confirmed [289, 290], and their expression increases during chronic inflammation [291]. Both OXT and vasopressin (V1A) and their associated receptors, namely OXTR and V1AR, respectively, induce analgesia in the sensory neurons [292-295], possibly because the peripheral antinociceptive action of vasopressin is due to an increase in the function of the GABAA receptor, inhibition of the acid-

sensitive ion channels [293, 296], and OXT by the direct desensitization of TRPV1 [297]. Therefore, the analgesic action may also be present in the dental pulp due to its expression in the TG. However, this requires further investigation.

3.7.3. Phoenixin

The neuropeptide, phoenixin, is expressed in the TG sensory neurons that may not be associated with antinociception in thermal pain models. However, phoenixin is associated with antinociception in the visceral pain models [298]. Phoenixin suppresses LPS-induced inflammation in the dental pulp cells, and its anti-inflammatory effects have been demonstrated by confirming the expression of its receptor, GPR173, in the human pulp cells [299]. Further studies should address its anti-inflammatory and potential analgesic properties.

3.7.4. Opiorphin

Enkephalins have a stronger analgesic effect than morphine, but this effect does not last because of the degrading enzymes, such as neutral endopeptidase and aminopeptidase-N [300]. Opiorphin is a peptide that acts as an inhibitor of these enzymes, thus prolonging the effects of enkephalins [300-302].

It is present in the blood, urine, semen, milk, tears, and saliva, although its highest concentrations have been observed in tears and saliva [303]. The more intense the pain due to inflammation is, the more the salivary opiorphin exists; however, its expression remains to be evaluated in the pulp tissue.

3.7.5. Adipokines

Adipokines play multiple physiological and pathological functions in the dental pulp, and some of them exert anti-inflammatory activity, such as adiponectin and ghrelin [304]; therefore, both adipokines could reduce pain in AIP due to their inherent anti-inflammatory activity. Although several adipokines have recently been identified [305], only a few of them have been studied in the pulp tissue [304]. Thus, their potential involvement in pulp inflammation and pain warrants further investigation.

Table **1** summarizes all the aforementioned factors that are potentially involved in AIP, their ligands/receptors identified in the dental pulp tissue and/or TG, and their potential analgesic-related mechanisms.

Table 1. Potential factors involved in AIP.

Potential Mechanism	Ligands Identified in the Dental Pulp or TG	Receptors Identified in the Dental Pulp or TG	Role Confirmed in AIP-related Analgesia	Potential Mechanisms Involved in the Painless Nature of AIP
Endogenous opioids	Dental pulp [8, 10, 15, 27, 28, 58-60].	Dental pulp [9, 40].	No	- Negative regulation of neurogenic inflammation [8]. - ORs up-regulation in late inflammatory stages, along with their axonal transport to the periphery [9, 24, 32, 57]. - Peripheral analgesia by the up-regulated expression of ligands and/or receptors [30-32]. - Anti-inflammatory effects [74]. - Pain modulation within the inflamed tissue by opioid peptides released from the immune cells [21-24, 47, 48, 51, 52, 67-72, 80]. - High involvement of the peripheral opioid mechanisms as inflammation advances [48, 51, 55, 56].
GIRK	N/A	TG [96].	No	Peripheral opioid-mediated analgesia [85, 87-89, 96].
Endogenous cannabinoids	N/A	Dental pulp [10, 11, 130, 141-145, 149].	No	- Anti-inflammatory and analgesic effects [136, 145]. - GIRK activation reduces the release of neurotransmitters [106]. - Increased analgesia through biased signaling [127]. - CB1 inhibits the neurotransmitter release on nerve terminals and CB2 modulates cytokine release on immune cells [130]. - Inhibition of inflammatory pain by anti-inflammatory effects [151-154]. - Cross-talk between CBR and TRPV1 may provide pulpal analgesia [130, 132].
GABA	Dental pulp [11].	Dental pulp [12, 164]. TG [163].	No	- GABA-mediated inhibitory neurotransmission [11, 12, 158, 159]. - 5-HT mediated GABAergic inhibition [167, 168]. - Hyperalgesia reduction by GABA peripheral analgesic effects [165]. - Blood flow regulation through inhibition of noradrenaline release in dental pulp [160].
Neuropeptides				
Somatostatin	Dental pulp [10].	Dental pulp [212].	No	- Anti-inflammatory neuropeptide that down-modulates a number of immune functions [175, 193]. - Decreases the neurogenic inflammation [175, 193]. - Inhibits CGRP release from the trigeminal neurons [205]. - Exerts antinociceptive functions [179-182, 187, 188]. - Decreases the conductance of voltage-gated Ca^{2+} channels [172, 183] and activates K^{+} channels [184-186].

(Table 1) contd.....

Potential Mechanism	Ligands Identified in the Dental Pulp or TG	Receptors Identified in the Dental Pulp or TG	Role Confirmed in AIP-related Analgesia	Potential Mechanisms Involved in the Painless Nature of AIP
Cortistatin	Dental pulp [212].	N/A	No	- Potent anti-inflammatory effect [195, 204, 211] by regulating immune tolerance 2009]. - Deactivation of inflammatory responses [196, 203, 206, 207]. - Decreases the presence/activation of Th1 and Th17 cells in the periphery [211]. - Inhibits pro-inflammatory mediators (TNF, IL-6, IL-12, IL-1, NO, and GM-CSF) and increases the levels of IL-10 [208, 209].
				- Relieves hyperalgesia and allodynia and acts as a neuroprotector and neuroregenerator [205]. - Analgesic effect in inflammatory [197] and neuropathic pain [210]. - Inhibits the CGRP release from the trigeminal neurons [205]. - Depresses the neuronal electrical activity [206].- Relieves hyperalgesia and allodynia and acts as a neuroprotector and neuroregenerator [205]. - Analgesic effect in inflammatory [197] and neuropathic pain [210]. - Inhibits the CGRP release from the trigeminal neurons [205]. - Depresses the neuronal electrical activity [206].
Galanin	Dental pulp [212]. TG [245].	Dental pulp [241]. TG [241, 245].	No	- Antinociceptive effect [225-235, 240]. - Opioid systems are involved in the galanin-induced antinociception [240].
Bombesin	Dental pulp [13]. TG [252].	N/A	No	- Antinociceptive effect [13]. - Depolarizes GABAergic interneurons at the presynaptic level and reduces the conductance of the neuronal membrane [250].
Specialized pro-resolving lipid mediators (SPMs)				
Lipoxins	N/A	N/A	No	- Potent pro-resolving and anti-inflammatory effects and analgesic action [264, 265].
Resolvins	N/A	N/A	No	- Potent pro-resolving and anti-inflammatory effects and analgesic action [264, 265]. - Analgesic effect in inflammatory pain [259, 260, 262, 269]. - Potent inhibition of TRP channels [261].
Maresins	N/A	N/A	No	- Potent pro-resolving and anti-inflammatory effects and analgesic action [264, 265].
Protectins	N/A	N/A	No	- Potent pro-resolving and anti-inflammatory effects and analgesic action [264, 265].
Miscellaneous mechanisms				
Antinociceptive bacteria	-	-	No	-*Porphyromonas gingivalis* LPS exerts antinociceptive effects *via* an increase in IL-10 levels [270]. -*Bifidobacterium* species, such as *B. dentium*, produce GABA [281-283].
Oxytocin	TG [290].	TG [290-292].	No	- Induces membrane hyperpolarization in pain-sensitive dorsal root ganglia neurons [287]. - Antinociceptive effect [287-290]. - Inhibits the activity of acid-sensing ion channels [293]. - Suppresses nociception of inflammatory pain via TRPV1-desensitization [297].
Phoenixin	TG [298].	Dental pulp [299].	No	- Suppresses the lipopolysaccharide-induced inflammation in dental pulp cells, suppressing the release of pro-inflammatory cytokines and inflammatory mediators [299].
Opiorphin	N/A	N/A	No	- Protects enkephalins from degradation and activates restricted opioid pathways specifically involved in pain control [300-303].
Adipokines	Dental pulp [304].	Dental pulp [304].	No	Some exert anti-inflammatory effects by inducing the secretion of anti-inflammatory interleukins or inhibiting the production of proinflammatory cytokines [304].

N/A: not available information.

CONCLUSION

This review presents up-to-date information on the painless nature of AIP. Factors that could potentially be involved in the mechanisms of analgesia underlying AIP include endogenous opioids, GIRK channels, endogenous cannabinoids, GABA, neuropeptides (somatostatin, cortistatin, galanin, and bombesin), and SPMs (lipoxins, resolvins, and maresins). We have also identified some miscellaneous factors that could play a role in AIP, such as bacteria with their antinociceptive effects, oxytocin, phoenixin, opiorphin, and adipokines, considering their potential analgesic-related mechanisms.

Nevertheless, the precise mechanisms responsible for the lack of symptoms in AIP remain to be elucidated, and further research is warranted despite the recent advances in science and technology. The available literature mainly investigated symptomatic irreversible pulpitis (SIP), where a recent study determined the levels of inflammation, oxidative stress, and extracellular matrix degradation biomarkers in SIP [305, 306]. Thus, it is compelling to

perform a similar biochemical mapping for AIP that helps elucidate the expression pattern of endogenous analgesic biomolecules. Furthermore, vascular, neural, cellular, and biochemical changes can occur without pain (8).

Moreover, it is important to highlight the chronic nature of AIP. In this regard, systemic chronic inflammation constitutes a health-damaging phenotype that is triggered by damage-associated molecular patterns, is persistent (non-resolving), has low-grade magnitude, leads to collateral damage, is age-related, and is silent (has no canonical standard biomarkers) [307]. The influence of these factors should be investigated to collect data concerning the analgesic features and pathophysiology of AIP in the context of the local microenvironment of the pulp tissue.

Furthermore, multiplatform data-integration models have been used to identify the differentially expressed genes to analyze the molecular mechanisms underlying pulpitis [308, 309]. Thus, they could improve our current understanding of the nature of AIP. Genetic and epigenetic characterization of pulpal inflammation can also help decipher the balance between proinflammatory and anti-inflammatory gene expression in AIP [310] and how it influences analgesia. This is especially relevant as several genes known to modulate pain and inflammation show a higher level of differential expression in patients with asymptomatic and mild pain compared to those with moderate to severe pain [311].

Regarding the limitations of this review, it must be highlighted that most studies were performed on animals, and AIP could not be differentiated from SIP. Furthermore, our search was confined to two electronic databases, potentially limiting the inclusion of relevant literature in our review. Despite these limitations, our study possesses notable strengths. We have meticulously compiled a substantial amount of data, contributing to an updated narrative review that delves into the potential mechanisms behind the asymptomatic nature of AIP. Notably, the latest report on the fundamentals of the painless nature of AIP describes a clinical study that was performed two decades ago [16]. Additionally, our findings could offer valuable insights for designing new studies aimed at identifying the precise molecular mechanisms responsible for the absence of symptoms in AIP.

Although the present review enlists some candidate ligands and/or receptors that potentially regulate the asymptomatic nature of AIP, no direct evidence supports these statements (Table **1**). Indeed, the literature regarding this topic is scarce. However, paradoxically, patients with dental diseases are diagnosed with AIP daily worldwide. Therefore, understanding the analgesia and biology behind AIP is necessary and could help improve the clinical diagnosis of pulp pathology, especially since recent investigations have shown a good correlation between the clinical symptoms of pulpitis and histological findings [312]. On the other hand, anecdotal reports among dentists confirm that in some AIP cases that may have had trauma or deep caries, the inflamed pulp tissue is open to the oral cavity. This would mean no or little increase in pulpal tissue pressure is induced, which is thought to be involved in the “asymptomatic” AIP condition. However, this assumption is very simplistic in explaining the potential biological fundamentals behind AIP.

Finally, other dental and medical pathologies share asymptomatic characteristics similar to those of AIP. These include symptomless pericoronitis [313, 314], chronic periodontitis [315], asymptomatic apical periodontitis [316-318], congenital painlessness disorders [319-321], painless neuropathies [322], *NGF* mutations [323], Buruli ulcer [324], and painless chronic pancreatitis [325-327]. Hence, analyzing the cellular, biochemical, and/or clinical findings from these conditions could help enhance our understanding of the possible mechanisms underlying the asymptomatic nature of AIP.

LIST OF ABBREVIATIONS

BN	=	Bombesin
CBRs	=	Cannabinoid Receptors
CORT	=	Cortistatin
EOP	=	Endogenous Opioid Peptides
FAAH	=	Fatty Acid Amide Hydrolase
GABA	=	Gamma-aminobutyric Acid
GAL	=	Galanin
GIRK	=	G Protein-activated Inwardly Rectifying K+ Channels
NADA	=	N-arachidonoyl-dopamine
NOR	=	Nociceptin/orphanin Receptor
OXT	=	Oxytocin
OX1Rs	=	Orexin 1 Receptors
SPMs	=	Specialized Pro-resolving Lipid Mediators
SST	=	Somatostatin
TRPV1	=	Transient Receptor Potential Vanilloid Subtype 1 Channel
vlPAG	=	Ventrolateral Periaqueductal Gray Matter
2-AG	=	2-arachidonylglycerol

AUTHORS’ CONTRIBUTIONS

D.P.C., V.C.J. and J.L.A. contributed to literature search, writing-original draft preparation, writing–review, and editing. J.L.A. contributed to conceptualization, methodology, critical revision of the article, supervision and project administration. All authors have read and agreed to the published version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This article is based on Daniela Paola Cabrera-Abad and Verónica Cristina Jara-Vergara undergraduate thesis.

The APC was supported by the Vice Chancellor's Office for Research of the University of Cuenca (VIUC).

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