

REVIEW

Current advances in orthodontic pain

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Orthodontic pain is an inflammatory pain that is initiated by orthodontic force-induced vascular occlusion followed by a cascade of inflammatory responses, including vascular changes, the recruitment of inflammatory and immune cells, and the release of neurogenic and pro-inflammatory mediators. Ultimately, endogenous analgesic mechanisms check the inflammatory response and the sensation of pain subsides. The orthodontic pain signal, once received by periodontal sensory endings, reaches the sensory cortex for pain perception through three-order neurons: the trigeminal neuron at the trigeminal ganglia, the trigeminal nucleus caudalis at the medulla oblongata and the ventroposterior nucleus at the thalamus. Many brain areas participate in the emotion, cognition and memory of orthodontic pain, including the insular cortex, amygdala, hippocampus, locus coeruleus and hypothalamus. A built-in analgesic neural pathway—periaqueductal grey and dorsal raphe—has an important role in alleviating orthodontic pain. Currently, several treatment modalities have been applied for the relief of orthodontic pain, including pharmacological, mechanical and behavioural approaches and low-level laser therapy. The effectiveness of nonsteroidal anti-inflammatory drugs for pain relief has been validated, but its effects on tooth movement are controversial. However, more studies are needed to verify the effectiveness of other modalities. Furthermore, gene therapy is a novel, viable and promising modality for alleviating orthodontic pain in the future.

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INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or is described in terms of such damage. With no exception, orthodontic pain is perceived as discomfort, dull pain and hypersensitivity in affected teeth.^{1–2} In most circumstances, pain motivates individuals to withdraw from damaging situations. However, because human beings are well acquainted with the fact that orthodontic pain is a normal adverse effect of tooth movement, orthodontic pain is well accepted by most orthodontic patients. Orthodontic pain is commonly referred to as tooth discomfort induced by orthodontic tooth movement, whereas a broader definition of orthodontic pain refers to any painful sensation, for example, mucosal ulcer, tongue discomfort and gingival lesion, caused by orthodontic appliances.^{3–4} The former and narrower definition of orthodontic pain is used in this review, unless indicated otherwise. In this review, we aimed to provide a current understanding of orthodontic pain, such as its characteristics, mechanisms, neural circuits and clinical management.

CHARACTERISTICS OF ORTHODONTIC PAIN

Orthodontic pain, defined as orofacial pain induced by orthodontic tooth movement, is commonly encountered in daily orthodontic practice.^{5–6} Orthodontic pain, with a prevalence of 72%–100%,^{1–2,5} is perceived as soreness, pressure and tension in the affected teeth.

Orthodontic force, once exerted on teeth, initially activates sensory receptors in periodontal tissues and results in a cascade of nociceptive pain processing and transduction in both the peripheral and central nervous systems that is ultimately perceived by orthodontic patients. Orthodontic pain can be perceived during almost all treatment procedures: separator placement, initial wire engagement, banding, wearing elastics, rapid maxillary expansion and debonding.^{7–11} It has been well documented that orthodontic pain begins 12 h after applying orthodontic force, peaks after 1 day, gradually diminishes 3–7 days thereafter and returns to baseline levels after 1 month.^{12–14} Although orthodontic pain subsides in most patients 1 week following orthodontic treatments, >40% of adolescent patients reported orthodontic pain after 1 week, indicating the potential long duration of orthodontic pain.¹⁵ Moreover, orthodontic pain is more than a painful sensation for patients, it decreases patients' health-related quality of life¹⁶ and interferes with patients' masticatory performance and speech. Animal studies have indicated that orthodontic pain results in emotional stress¹⁷ and transient learning and memory deficits.¹⁸

MECHANISMS OF ORTHODONTIC PAIN

Once orthodontic forces are applied on teeth, marked responses occur at parodontal tissues, including periodontal tissues and the dental pulp.^{19–21} A cascade of self-limiting inflammatory reactions, including

cellular, vascular, neural and immunological reactions, act in an orchestrated way to ultimately result in orthodontic pain and tooth movement. In effect, orthodontic pain and orthodontic tooth movement are two interrelated and dependent biological events with local inflammation being their common mechanism. The products of local inflammation (for example, prostaglandin and bradykinin) act on sensory endings to incite painful sensations.^{22–24} Therefore, the mechanisms underlying orthodontic pain lie in periodontal inflammatory responses induced by orthodontic forces. The periodontal inflammation response includes three components: vascular, cellular and chemical events. The three components interact with each other and form a network. For clarity, these three components will be discussed separately in this review, but, to recapitulate, they are intrinsically intercorrelated. The mechanisms of orthodontic pain are illustrated in Figure 1.

Vascular events

Optimal orthodontic force, coined by Schwarz in 1932, was defined as the force ($20\text{--}25\text{ g}\cdot\text{cm}^{-2}$) leading to a change in tissue pressure that approximated the capillary blood pressure in the compressed periodontal tissues.²⁵ Thus, when optimal forces are applied on teeth, the vascular vessels at the compressed sites are squeezed and local ischaemia ensues.²⁶ The local ischaemia incites an increased anaerobic

respiration in periodontal cells (for example, fibroblasts) and a subsequent acidosis. The resulting local acidic signals are transduced to painful signals by a cardinal molecule: acid-sensing ion channel 3 (ASIC3). ASIC3, an ion channel receptor described for H^+ , has been well documented to be expressed on periodontal sensory endings.²⁷ Once a periodontal acidic microenvironment occurs following the application of orthodontic forces, abundant local H^+ binds to ASIC3 on periodontal sensory endings and elicits painful sensations.²⁸ Moreover, a dual role of ASIC3 in orthodontic pain may exist. It has been reported that ASIC3 is expressed in mechanoreceptors (Ruffini body) within periodontal tissues, imparting its role in mechanosensation for orthodontic forces.²⁷ However, given that orthodontic force is mild in nature, the contribution of orthodontic force mechanosensation to pain has been neglected. This mechanism could explain the phenomenon that orthodontic patients feel no pain or just mild pain within the early hours following orthodontic force application,^{12–14} given that orthodontic force-induced local inflammation occurs $\sim 12\text{ h}$ later.

The painful sensation mediated by ASIC3, once transmitted to trigeminal neurons at the trigeminal ganglia, stimulate trigeminal neurons to release several neurogenic mediators both centrally (trigeminal nucleus) and peripherally (periodontal tissues), including but not limited to calcitonin gene-related peptide (CGRP) and

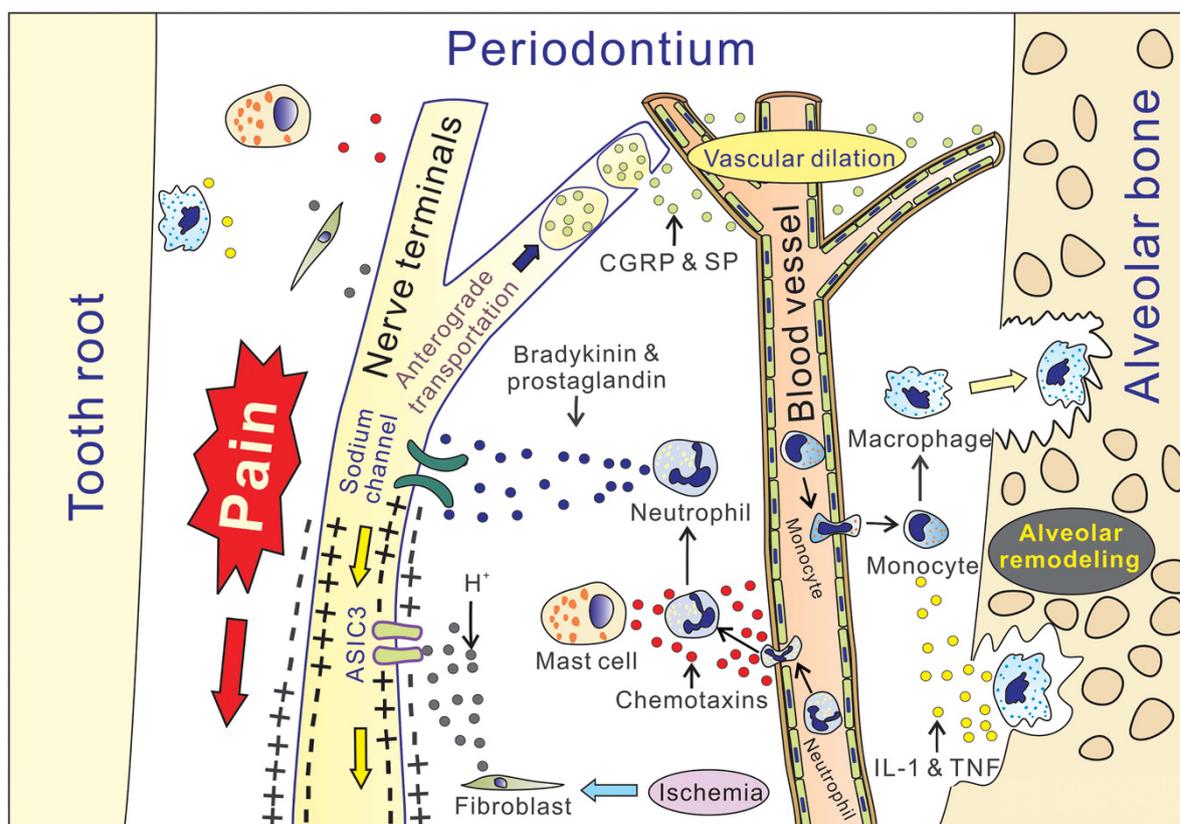


Figure 1 The mechanisms underlying orthodontic pain. The dental root (left) moves in the direction of force towards the alveolar bone (right) with the periodontium between them. Upon vascular compression and local ischaemia, periodontal cells, mainly fibroblasts, undergo anaerobic respiration and cause local acidosis. The proton ion (H^+) binds to ASIC3 receptors on sensory endings to generate pain. As local ischaemia progresses, mast cells and fibroblasts release various chemotaxins to recruit leucocytes, for example, neutrophils and monocytes. These leucocytes release abundant inflammatory mediators (for example, bradykinin and prostaglandin) and cytokines (for example, IL-1 and TNF). Bradykinin and prostaglandin bind to sensory endings to generate painful sensations. The released cytokines amplify local inflammation and stimulate monocyte-derived macrophages to participate in alveolar bone remodelling. Moreover, via anterograde transportation, sensory endings release various neurogenic mediators (for example, CGRP and SP) to dilate local blood vessels and enhance local inflammation, amplifying local painful sensation and alveolar remodelling. CGRP, calcitonin gene-related peptide; IL, interleukin; SP, substance P; TNF, tumour necrosis factor.

substance P (SP).^{19–20,29–30} These released neurogenic mediators cause local vascular dilation and augment local inflammation,³¹ which in turn promote trigeminal sensory endings to release CGRP, thereby amplifying orthodontic pain in a positive-feedback loop.³⁰ It is noteworthy that these neurogenic mediators have been reported to stimulate the production of prostaglandins,³² which could enhance orthodontic pain because prostaglandins could generate painful sensations upon binding to sensory endings.³³

Moreover, this ischaemic and acidic microenvironment ignites periodontal endothelial cells and fibroblasts to release nitric oxide (NO). This signalling molecule increases periodontal vascular permeability.^{34–35} Once periodontal vascular permeability increases, abundant leucocytes, including neutrophils, monocytes and lymphocytes, are recruited to periodontal tissues.^{36–40} Upon activation at periodontal tissues, these cells release various chemokines, cytokines and inflammatory mediators that further amplify local inflammation and cause a painful sensation.^{33,41}

Cellular events

Once local inflammation occurs, vascular permeability increases and numerous leucocytes, including neutrophils, mast cells, macrophages, T cells and monocytes, are recruited and infiltrate periodontal tissues.^{36–40} In response to local inflammation, periodontal mast cells and macrophages release various mediators that facilitate leucocyte recruitment to periodontal tissues.⁴² Among these mediators, histamine and tumour necrosis factor- α (TNF- α) released from mast cells stimulate adhesion protein upregulation in vascular endothelial cells.⁴³ In turn, these upregulated adhesion proteins on endothelial cells facilitate leucocyte adhesion and transmigration through vascular vessels. Moreover, following extravasation from the blood, leucocytes migrate towards periodontal sites. This process is mediated by chemotaxins. In particular, neutrophil chemotaxis to periodontal tissues is primarily dependent on mast cell-derived CXCL2.^{44–45} By contrast, different types of leucocytes use different molecules for chemotaxis, for example, recruitment of monocytes is governed by monocyte chemoattractant protein 1, which is upregulated in response to orthodontic forces.³⁶ Recent research has indicated that two types of macrophages are differentiated from monocytes in inflammatory conditions: M1 and M2 macrophages.⁴⁶ The M1 macrophage promotes phagocytosis and cell damage, whereas the M2 macrophage facilitates cell proliferation and healing,^{47–48} suggesting that a balance between M1 and M2 determines tissue damage and healing. A recent study revealed that M1 macrophages promote alveolar bone resorption following the application of orthodontic force,³⁷ suggesting that M1 macrophages are important pro-inflammatory cells in orthodontic pain. However, the role of M2 macrophages or M1/M2 macrophage balance in orthodontic pain merits further investigation.

Chemical events

As mentioned above, various leucocytes and inflammatory cells are recruited and activated in periodontal tissues. These cells release abundant inflammatory mediators, chemokines and cytokines within periodontal tissues, including but not limited to IL-1, IL-6, prostaglandin, TNF- α , interferon-gamma (IFN- γ), macrophage-colony-stimulating factors (M-CSF) and vascular endothelial growth factor (VEGF).^{33,41,49–51} These mediators act in concert to incite and amplify local inflammation in the early stages of orthodontic pain. IL-1, IL-6, TNF- α , IFN- γ and M-CSF are active in stimulating osteoblasts and osteoclasts that participate in periodontal bone remodelling and subsequent tooth movement,^{52–55} which in turn augments local inflammation. Moreover, M-CSF stimulates the conversion of

monocytes to macrophages and the recruitment and differentiation of osteoclasts,⁵¹ which enhance local inflammation and subsequent painful sensation. In particular, the locally released prostaglandin generates a painful sensation by binding to periodontal sensory endings.²²

As orthodontic pain progresses, the body's built-in analgesic mechanisms are activated to alleviate pain and to prevent damage to periodontal tissues, which is the basic difference from periodontitis. These analgesic mechanisms are complex and still poorly understood. However, what is clear is that endogenous opioid or opioid-like molecules and neural pathways may participate in these analgesic processes,⁵⁶ which will be explained in detail in the next section of this review. At this stage, the painful sensation subsides and the aforementioned VEGF promotes local neovascularization and bone remodelling. At the next appointment, when orthodontic forces are re-applied, this cycle re-occurs.

NEURAL CIRCUITS AND REGULATION OF ORTHODONTIC PAIN

Orthodontic pain transmission pathways

The neural circuits for the transmission of orthodontic pain are illustrated in Figure 2. Orthodontic tooth movement, once applied on teeth, is received by periodontal sensory endings as nociceptive stimuli. The nociceptive stimuli are transmitted ultimately to somatosensory cortex via three-order neurons. The first-order neurons are trigeminal neurons that are located at the trigeminal ganglia. Trigeminal neurons, being pseudounipolar neurons, possess both peripheral and central processes. Their peripheral processes run peripherally to facial skin, periodontal tissue and oral mucosa, and form sensory endings that receive nociceptive, mechanical and thermal sensations. Moreover, their central processes project centrally to synapse with the second-order neurons, the trigeminal nucleus caudalis, which are located in the medullar oblongata. Trigeminal nucleus caudalis is a nucleus that extends almost the whole medulla cephalocaudally. Then, after entering the medulla, the axons in the central processes of the trigeminal neurons travel caudally to synapse with the trigeminal nucleus. In turn, the trigeminal nucleus send fibres to form the trigeminothalamic tract that decussates to the contralateral side and ascends to make synapses with the ventroposterior nucleus of the thalamus. Subsequently, the thalamus sends fibres to many areas of the brain, including the hippocampus, amygdala, insular cortex and somatosensory cortex, and these brain areas project fibres to converge and integrate orthodontic pain information at the sensory cortex. Finally, orthodontic patients perceive orthodontic pain and generate their emotions (for example, anxiety and unpleasant feelings) and memory towards orthodontic pain. The trigeminal nucleus at the medulla oblongata sends fibres to activate the facial nucleus and the activated facial nucleus in turn innervate facial muscles via the facial nerve to produce facial grimacing and eye closure.⁵⁷ This mechanism is generated as a revolution for animal sociality because its aim is to nonverbally express pain and to alert companions.^{58–59} This mechanism could explain facial grimacing and eye closure that occurs in some orthodontic patients when undergoing power chain mounting or wire engaging procedures. Moreover, this mechanism provides justification for assessing pain levels through facial expressions in animal models of orthodontic pain.⁶⁰

Among the three-order neurons that regulate orthodontic pain, the trigeminal neurons at the trigeminal ganglia are by far the most studied. Following orthodontic pain, numerous molecules are upregulated in the trigeminal ganglia, for example, P2X3 and CGRP.^{61–64} These molecules change the biological characteristics of trigeminal neurons, for example, increased excitability.⁶⁵ With increased

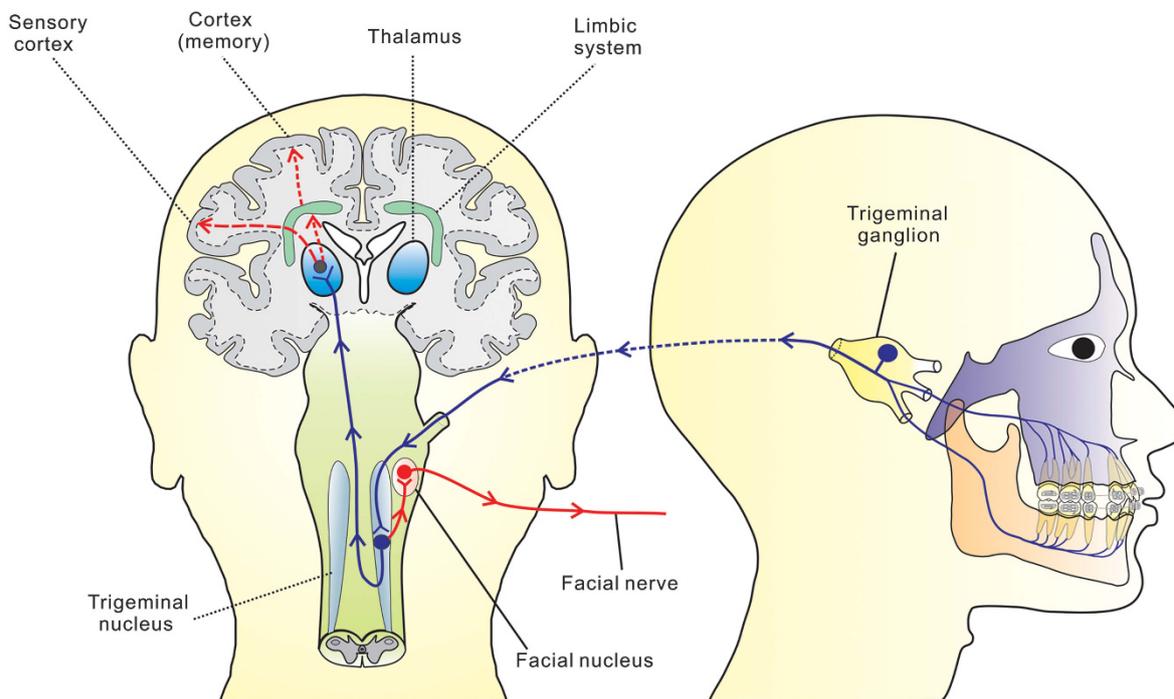


Figure 2 Pain transmission pathways for orthodontic pain.

excitability, trigeminal neurons are more readily stimulated, resulting in thermal and mechanical hyperalgesia.^{66–67} This mechanism could explain the phenomenon that a gentle bite causes pain in orthodontic patients suffering from orthodontic pain. The mechanisms underlying sensitization of trigeminal neurons could be better explained by the interactions between trigeminal neurons and satellite glial cells. In the trigeminal ganglia, satellite glial cells (90%) outnumber neurons (10%). Abundant satellite glial cells wrap one neuron to form a functional unit with gap junctions and paracrine communications.^{68–70} Our studies (not yet published) and those published elsewhere have consistently revealed that CGRP is upregulated in trigeminal neurons following tooth movement.⁶⁴ The resulting upregulated CGRP is released from trigeminal neurons and sensitises their surrounding satellite glial cells.^{71–72} Upon sensitization, the satellite glial cells release NO, and released NO in turn enhances CGRP synthesis in trigeminal neurons,⁷³ rendering this process a positive-feedback loop. The upregulated CGRP, on the one hand, increases the excitability of trigeminal neurons and, on the other hand, is anterograde-transported to periodontal tissues, resulting in amplification of orthodontic pain.³⁰ Orthodontic pain is regulated through the interactions between trigeminal neurons and satellite glial cells at the level of the trigeminal ganglia. However, more research of second- or third-order neurons is encouraged to unravel the exact regulatory mechanisms for orthodontic pain.

Emotion and cognition of orthodontic pain

As presented in Figure 3, the insular cortex, located within the lateral sulcus, harbours reciprocal connections with the thalamus, limbic system and cerebral cortices, and has an important role in pain perception, emotion and cognition.⁷⁴ Subjective pain experiences are generated by the integration of afferent pain signals with the available personal cognitive state,⁷⁵ which could explain that individual perceptions of orthodontic pain differ greatly in clinical

practice.^{76–77} A seminal study revealed that the insular cortex may be importantly involved in the integration of pain information with previous cognitive information,⁷⁵ probably through reciprocal connections between the insular cortex and the cerebral cortex. The role of the insular cortex in the integration of orthodontic pain is further supported by our previous functional magnetic resonance imaging (MRI) study, wherein the insular cortex was revealed to be activated among orthodontic patients following separator placement.⁷⁸ When patients were in positive cognitive states (for example, distracted from pain and taking a placebo), through interactions between the insular cortex and cerebral cortex, the activity of the insular cortex could be reduced and pain relieved,^{79–80} which explains the analgesic mechanisms of attention distraction and placebo effect on pain. Similarly, in our clinical practice, we could apply attention distraction and placebo to relieve orthodontic pain, which was partially supported by our previous study in which cognitive behavioural treatment (CBT) was found to alleviate orthodontic pain,⁸¹ and by a study reported elsewhere in which high physical activity (distraction from pain) relieved orthodontic pain.⁸²

A large body of evidence indicates that orthodontic pain can generate negative emotions (for example, anxiety) among orthodontic patients.^{83–86} Moreover, negative emotions would in turn exacerbate orthodontic pain among orthodontic patients.^{87–88} Thus, orthodontic pain and negative emotions are intertwined, and this connection could be explained by the role of limbic system. As is well documented, the limbic system, located at the medial rim of the brain, consists of several structures (for example, the hippocampus and amygdala) with complex and looped connections that participate in emotion and memory.⁸⁹ As mentioned above, the ventroposterior nucleus of the thalamus relays orthodontic pain signals to the cortex. In turn, the orthodontic pain signal at the thalamus is sent to the amygdala; this process was confirmed by a study in which orthodontic tooth movement activated the amygdala.⁹⁰ Then, the amygdala processes

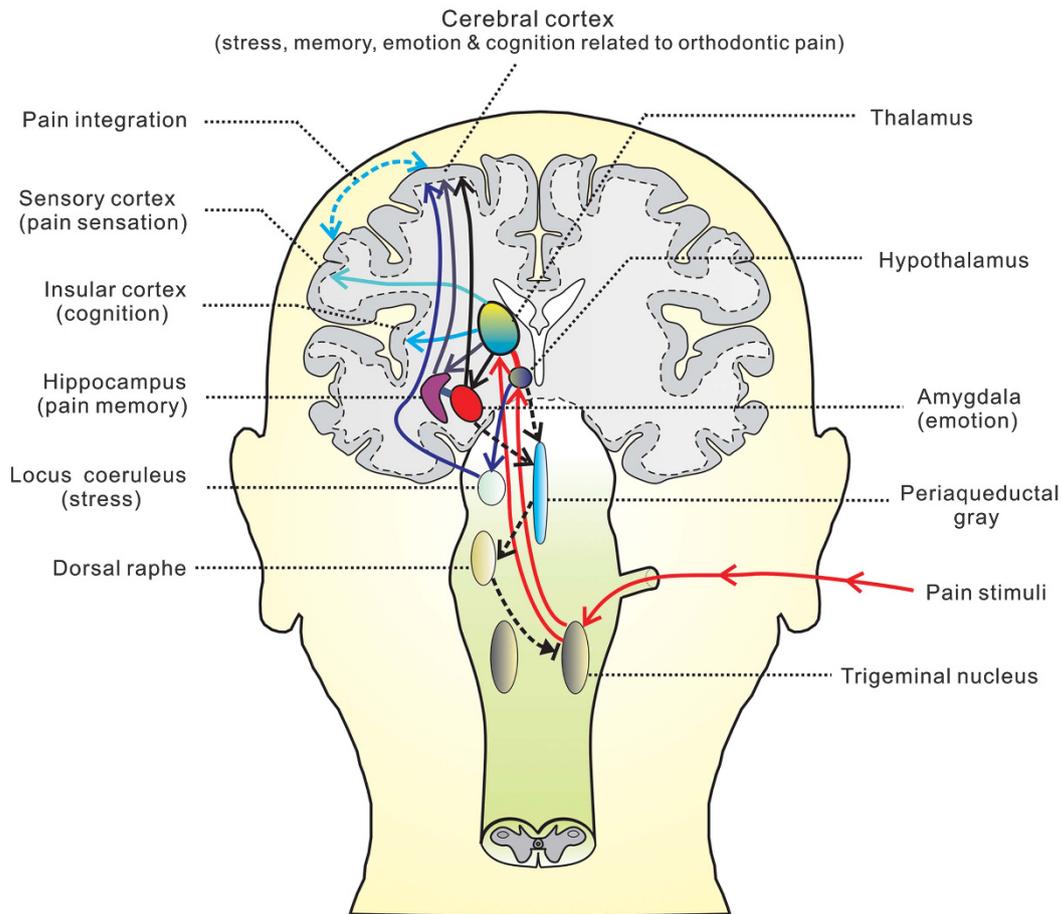


Figure 3 Neural circuits of orthodontic pain.

the pain signals and sends its processed information to the cortex where pain is perceived and anxiety is generated. In turn, the information about anxiety is transmitted from the cortex to the amygdala and then to a regulatory descending system (periaqueductal grey-dorsal raphe) that ultimately influences the trigeminal nucleus and subsequent pain sensations.⁹¹

A seminal study found that previous pain experience could influence the perception of orthodontic pain.¹⁵ Moreover, it has been revealed that the sensitivity of the trigeminal nerve is higher in patients who had previous orthodontic pain.⁹² These results indicate that memory of orthodontic pain alters pain perception among orthodontic patients. The effect of pain memory on pain perception could be explained by the role of hippocampus.^{93–96} Once orthodontic pain is perceived at the level of the cortex, the cortex searches for pain memory and, if it exists, pain memory information is sent to limbic system for processing. The processed pain memory information is returned to the cortex where present pain information and pain memory information are integrated, thereby altering current pain perception. An animal study found that orthodontic pain could impair memory and learning through inducing hippocampal neuron apoptosis.^{18,97} This finding was reinforced by another study in which chronic pain was revealed to interfere with memory formation in the hippocampus.⁹⁸ This effect of pain on the hippocampus may be a built-in strategy to alleviate chronic pain, but the effect on orthodontic pain in humans need to be validated in future studies.

Several animal studies have revealed that orthodontic pain could cause stress,^{17,99} which could be explained by the role of the locus coeruleus given that orthodontic pain activates the locus coeruleus.¹⁰⁰ The locus coeruleus, the major noradrenergic nucleus of the brain, projects fibres to extensive areas throughout the neuraxis and has an essential role in the regulation of arousal and autonomic activity.¹⁰¹ Once orthodontic pain signals arrive at the trigeminal nucleus, the information about orthodontic pain is transmitted through the trigeminohypothalamic tract to the hypothalamus,¹⁰² which relays this information to the locus coeruleus. Once activated, the locus coeruleus activates the sympathetic system and causes stress.¹⁰¹ Moreover, the activated locus coeruleus results in the enhancement of alertness and arousal,¹⁰³ which could partially explain the phenomenon that some orthodontic patients wake up in the deep night due to high levels of orthodontic pain.

Analgesic neural circuits for orthodontic pain

Orthodontic pain, as mentioned above, peaks on the 1st day and gradually wanes through the 5th day following orthodontic tooth movement.^{12–14} The high pain levels at the initial stages of each episode of orthodontic treatment are aimed to alert humans about the nociceptive stimuli. However, the pain levels decrease gradually afterwards, indicating that an intrinsic built-in analgesic mechanism dominates the late stages of each episode of orthodontic treatment. Humans possess many intrinsic analgesic mechanisms that could be activated in response to pain. Endogenous opioid, in particular, is the

most extensively studied mechanism.¹⁰⁴ In response to orthodontic pain, endogenous opioid and opioid receptors are upregulated in the trigeminal nucleus,^{56,105} which act in concert to exert an intrinsic analgesic effect on orthodontic pain. However, in this review, we will focus on a neural circuit that exerts pain modulation: the periaqueductal grey—dorsal raphe—trigeminal nucleus.⁹¹ The periaqueductal grey, the grey matter located around the cerebral aqueduct in the tegmentum of the midbrain, is a major component of the descending pain inhibitory system.¹⁰⁶ The periaqueductal grey contains endogenous opioid-releasing neurons that may contribute to its analgesic function.¹⁰⁷ The dorsal raphe, located at the midline of the brainstem, is a part of the raphe nucleus and has an important role in pain modulation.¹⁰⁸ As presented in Figure 3, the trigeminothalamic tract that carries the fibres from the trigeminal nucleus to the thalamus has connections with the periaqueductal grey and dorsal raphe. Once orthodontic pain occurs, the periaqueductal grey and dorsal raphe is activated.¹⁰⁰ The activated periaqueductal grey receives fibres from the amygdala and brain cortex, which tailor the activity of the periaqueductal grey so that it sends analgesic signals only at late stages of each episode of orthodontic treatment.⁹¹ Once the periaqueductal grey is permitted by the amygdala and the cortex to send signals, it activates the dorsal raphe, and the activated dorsal raphe in turn regulates the activity of the trigeminal nucleus,^{109–110} thereby relieving orthodontic pain.⁹¹ Furthermore, it has been reported that the periaqueductal grey could be activated by listening to music,¹¹¹ which could explain the phenomenon that listening to music alleviates orthodontic pain.¹¹² However, the exact mechanisms by which listening to music activates the periaqueductal grey are poorly understood. The mechanisms are probably associated with the limbic system and the locus coeruleus, but the exact neural mechanisms merit further functional MRI studies.

MANAGEMENT OF ORTHODONTIC PAIN

Orthodontic pain is inevitably an adverse effect of orthodontic treatment. To date, numerous modalities have been invented to alleviate orthodontic pain in clinical practice, including pharmacological approaches,^{113–115} mechanical approaches,^{116–117} laser irradiation therapy^{68–69} and behavioural approaches.^{14,81} Furthermore, a novel modality for pain relief—gene therapy—is gaining popularity and may be promising in future pain relief among orthodontic patients.

Pharmacological approach

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for the relief of orthodontic pain for decades. Their effectiveness in orthodontic pain relief has been validated, but their by-product—reducing the rate of tooth movement—is still being debated,^{118–120} making NSAIDs not routinely applied for pain control in orthodontic practice.¹²¹

As mentioned above, prostaglandin is a pro-inflammatory mediator that causes painful sensations by binding to sensory endings and promotes tooth movement by stimulating bone remodelling.^{122–123} It has been well documented that the synthesis of prostaglandin is mediated by COX enzymes and that NSAIDs inhibit the activity of COX enzymes.¹²⁴ Therefore, NSAIDs could relieve orthodontic pain by inhibiting the release of prostaglandin. Because prostaglandin promotes local inflammation and bone remodelling, decreased levels of prostaglandin following NSAID intake could inhibit osteoclasts and reduce the rate of tooth movement.¹¹⁸ Moreover, a second mechanism by which NSAIDs impede orthodontic tooth movement has been proposed in which NSAIDs interfere with collagenase activity and procollagen synthesis, which results in impeded periodontal remodelling.¹²⁵ Various types of NSAIDs are now available for

orthodontic patients, for example, acetaminophen, ibuprofen and celecoxib. Their individual superiority in pain control and efficacy in avoiding impeding tooth movement vary among different studies.^{122,126–128} However, regardless of each NSAID's superiority, it has been verified that almost all NSAIDs are effective in alleviating orthodontic pain, but their effects on the rate of tooth movement need to be validated in further studies.

Mechanical approach

Mechanical approaches have been proposed to relieve orthodontic pain, including vibration, chewing gums, biting wafers and acupuncture.^{129–133} Vibration is applied to patients' teeth through a vibrating device that is placed in their mouths. Patients are instructed to chew gum and bite wafers to alleviate orthodontic pain. Moreover, acupuncture is performed through inserting systemic needles at Hegu (LI4), which is located at the dorsum of the hand between the first and second metacarpal bones.^{130,134} The proposed mechanism for vibration, chewing gum and biting wafers lies in the fact that mechanical stimuli activate mechanoreceptors that transmit tactile signals while suppressing the transmission of painful signals.¹³⁵ This process could explain the phenomenon that rubbing the skin of a painful site can relieve pain. In addition, as mentioned above, orthodontic forces squeeze periodontal vascular vessels and cause local ischaemia and subsequent local inflammation. Vibrations restore normal circulation and thus reduce pain.¹²⁹ However, controversy exists for the effectiveness of vibration in relieving orthodontic pain.^{116–117,129,136} Due to scarce evidence, the effectiveness of chewing gum and biting wafers needs to be verified. Although acupuncture has been revealed to be effective for orthodontic pain relief,^{130,134} the mechanisms by which acupuncture relieves orthodontic pain remain largely unknown.¹³⁷ Therefore, the effectiveness of the mechanical approach in relieving orthodontic pain necessitates further validation.

Low-level laser therapy

Low-level laser therapy has been extensively applied for pain relief in both medical and dental practice.^{138–139} Its applications has also been extended for the relief of orthodontic pain.¹⁴⁰ Low-level laser therapy is accomplished through applying laser irradiation to the whole dental arch. A large body of evidence has confirmed the effectiveness of low-level laser therapy in alleviating orthodontic pain.^{141–143} However, its effectiveness has been refuted in several other studies.^{144–145} Moreover, several systematic reviews and meta-analyses have produced controversial results.^{146–148} These inconsistencies may be attributed to different irradiation durations and dosages. Thus, irradiation protocols need clarification, and their effectiveness necessitates further verification.

Behavioural approach

Behavioural approaches that are applied to relieve orthodontic pain include CBT,⁸¹ physical activity⁸² and music therapy.¹¹² These behavioural modalities share a common feature: reassurance and attention distraction. It has been well documented that orthodontic patients feel anxiety and stress following orthodontic pain, and an immediate follow-up could significantly reduce their orthodontic pain levels,^{83–85} justifying that reassuring orthodontic patients may be a viable approach for controlling orthodontic pain. CBT, a form of psychotherapy, uses several treatment sessions to correct patients' negative attitudes and decrease their anxiety. As mentioned above, elevated anxiety increases patients' pain sensations through limbic-system-mediated neural pathways. CBT, through reducing patients' anxiety, has been revealed to be effective in relieving orthodontic pain

in clinical practice.^{14,81} Furthermore, music therapy and physical activity, through distracting patients' attention via the insular cortex-mediated neural pathways, have been revealed to alleviate orthodontic pain in clinical practice.^{82,112} However, due to scarce evidence, the efficacy of behavioural therapy in orthodontic pain relief should be further confirmed.

Gene therapy

Gene therapy is defined as a method that delivers genes or DNA sequences to target cells that can transiently or stably express those genes or DNA sequences to alter the biological functions of those cells. Pain relief could be achieved through delivering endogenous opioid genes into neurons.¹⁴⁹ Gene therapy for the alleviation of cancer pain has been applied in a clinical trial of humans, and acceptable outcomes were achieved.¹⁵⁰ Different types of viral vectors have been developed for transducing genes of interest into target cells, including adenovirus,¹⁵¹ lentivirus,¹⁵² herpes simplex virus¹⁵³ and adeno-associated virus.¹⁵⁴ In particular, herpes simplex virus, by virtue of its neurotropism, is advantageous in gene therapy for neural disorders, including pain.¹⁵⁵ It has been reported that gene therapy could be effective in alleviating trigeminal pain in rats through delivering an opioid gene into the trigeminal ganglia via herpes simplex virus.¹⁴⁹ Similarly, herpes simplex virus can be used to deliver endogenous opioid genes or RNA interference sequences against pro-inflammatory genes (for example, CGRP) into the trigeminal ganglia to relieve orthodontic pain. At present, the application of gene therapy in clinical practice is limited by its biosafety concerns.¹⁵⁶ Nevertheless, its potential biosafety concerns may be addressed in the near future, and it may become a viable and mainstream treatment strategy for orthodontic pain relief.

CONCLUSION

Orthodontic pain, an inflammatory pain, shares many similar features with common inflammation, but it has specific hallmarks. The exact molecular mechanisms of the pathogenesis of orthodontic pain are still poorly understood. Although the sensory pathways have been well documented, its collateral pathways, including those related to emotion, memory and cognition, are largely unknown. Thus, further functional MRI studies are urgently needed for delving into their exact neural pathways. Although NSAIDs have been validated to be effective in relieving orthodontic pain, its effects on tooth movement have yet to be verified. The effectiveness of other modalities, that is, mechanical approaches, low-level laser therapy and behavioural approaches, needs further confirmation. Furthermore, gene therapy, a novel and viable modality, is promising in the treatment of orthodontic pain in the future.

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