Neurological mechanisms involved in orthodontic tooth movement: A contemporary review

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Abstract

Tooth movement by orthodontic force application includes remodeling changes in dental and surrounding investing tissues, dental pulp, periodontal ligament, alveolar bone, and gingiva. These tissues, when exposed to varying degrees of magnitude, frequency, and duration of applied force, undergo various macroscopic and microscopic changes. Orthodontic tooth movement differs markedly from physiological dental drift or tooth eruption that is characterized by the abrupt creation of compression and tension regions in the periodontal ligament. Orthodontic tooth movement can occur rapidly or slowly, depending on the physical characteristics of the applied force, and the subsequent biological response of the periodontal ligament. These force-induced strains alter the periodontal ligament’s vascularity and blood flow, resulting in local synthesis and release of various key molecules, such as neurotransmitters, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites. These molecules can evoke many cellular responses by various cell types in and around teeth, providing a favorable microenvironment for tissue deposition or resorption. Studies in the early 20th century mainly analyzed the histological changes in paradental tissues after tooth movement. Those studies showed extensive cellular activities in the mechanically stressed periodontal ligament involving fibroblasts, endothelial cells, osteoblasts, osteocytes, and endosteal cells. Current literature has much data on molecular responses to orthodontic force. Therefore, the focus of this review is on the in-depth analysis of neurological mechanisms involved in the causation of orthodontic tooth movement.

Keywords: Inflammation, innervation, neurological, neural modulation, orthodontic tooth movement, pain

Introduction

Tooth movement by orthodontic force application involves remodeling changes in dental and paradental tissues, including dental pulp, periodontal ligament, alveolar bone, and gingiva. These tissues, when exposed to varying degrees of magnitude, frequency, and duration of mechanical loading, express extensive macroscopic and microscopic changes. Orthodontic tooth movement differs markedly from physiological dental drift or tooth eruption. The former is uniquely characterized by the abrupt creation of compression and tension regions in the periodontal ligament. Physiological tooth movement is a slow process that occurs mainly in the buccal direction into cancellous bone or because of growth into cortical bone. Orthodontic tooth movement can occur rapidly or slowly, depending on the physical characteristics of the applied force, and the biological response of the periodontal ligament. These force-induced strains alter the periodontal ligament’s vascularity and blood flow, resulting in local synthesis and release of various key molecules, such as neurotransmitters, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites. These molecules can evoke many cellular responses by various cell types in and around teeth, providing a favorable microenvironment for tissue deposition or resorption. Studies in the early 20th century attempted mainly to analyze the histological changes in paradental tissues after tooth movement. Those studies showed extensive cellular activities in the mechanically stressed periodontal ligament involving fibroblasts, endothelial cells, osteoblasts, osteocytes, and endosteal cells. Current literature has much data on molecular responses to orthodontic force.
Optimal Orthodontic Force

The classic definition of optimal force by Schwarz\(^6\) in 1932 was “the force leading to a change in tissue pressure that approximated the capillary vessels’ blood pressure, thus preventing their occlusion in the compressed periodontal ligament” (20-25 g/cm\(^2\) of root surface).

According to Schwarz, forces below optimum produce no reaction, whereas forces above that level lead to tissue necrosis, thus preventing frontal resorption of the alveolar bone. The optimal orthodontic force acts as a mechanical stimulus that evokes a cellular response that aims to restore equilibrium by remodeling periodontal supporting tissues. So, the mechanical input that leads to the maximum rate of tooth movement with minimal irreversible damage to the root, PDL, and alveolar bone is considered to be optimal.

Theories of Orthodontic Tooth Movement

Two main mechanisms for tooth movement have been proposed: the application of pressure and tension to the PDL and bending of the alveolar bone.

The pressure tension theory

Classic histologic research about tooth movement by Sandstedt (1904),\(^5\) Oppenheim (1911),\(^6\) and Schwarz (1932)\(^6\) led them to hypothesize that a tooth moves in the periodontal space by generating a “pressure side” and a “tension side.” On the pressure side, the PDL displays disorganization and diminution of fiber production. Here, cell replication decreases seemingly due to vascular constriction. On the tension side, stimulation produced by stretching of PDL fiber bundles results in an increase in cell replication. This enhanced proliferative activity leads eventually to an increase in fiber production. On the side away from the direction of tooth movement, the PDL space is enlarged, and blood vessels dilate. Expanded vessels that are only partially filled can be seen on the tension side of the PDL.

The bone-bending theory

Farrar\(^9\) was the first to suggest, in 1888, that alveolar bone bending plays a pivotal role in orthodontic tooth movement. When an orthodontic appliance is activated, forces delivered to the tooth are transmitted to all tissues near force application. These forces bend bone, tooth, and the solid structures of the PDL. Bone was found to be more elastic than the other tissues and to bend far more readily in response to force application. The active biologic processes that follow bone bending involve bone turnover and renewal of cellular and inorganic fractions. This reorganization proceeds not only at the lamina dura of the alveolus, but also on the surface of every trabeculum within the corpus of bone.

Bioelectric signals in orthodontic tooth movement

In 1962, Bassett and Becker\(^10\) proposed that, in response to applied mechanical forces, there is the generation of electric potentials in the stressed tissues. These potentials might charge macromolecules that interact with specific sites in cell membranes or mobilize ions across cell membranes. The concave side of orthodontically treated bone is electronegative and favors osteoblastic activity, whereas the areas of positivity or electrically neutral convex surfaces showed elevated osteoclastic activity.

The bending of the bone causes two classes of stress-generated electrical effects: Enhanced cellular activities in the PDL and alveolar bone and rapid tooth movement. These findings suggest that bioelectric responses (piezoelectricity and streaming potentials) propagated by bone bending incident to orthodontic force application might function as cellular first messengers. Piezoelectricity is a phenomenon observed in many crystalline materials, in which a deformation of a crystal structure produces a flow of electric current as electrons are displaced from one part of the lattice to another. Apart from inorganic crystals, it was found that organic crystals could also exhibit piezoelectricity. When mechanical forces are applied, cells, as well as the extracellular matrix (ECM) of the PDL and alveolar bone, respond concomitantly, resulting in tissue remodeling. In response to these physicochemical events and interactions, cytokines, growth factors, CSFs, and vasoactive neurotransmitters are released, initiating and sustaining the remodeling activity, which facilitates tooth movement.

Signaling Molecules and Metabolites in Orthodontic Tooth Movement

Arachidonic acid metabolites

Arachidonic (eicosatetraenoic) acid, the main component of phospholipids of the cell membrane, is released due to the action of phospholipase enzymes.

Prostaglandins in tooth movement

Prostaglandins are important mediators of mechanical stress. Clinical and animal studies have identified the role of prostaglandins E1 (PGE1 and PGE2) in stimulating bone resorption.

There is a direct action of prostaglandins on osteoclasts in increasing their numbers and their capacity to form a ruffled border and effect bone resorption.\(^11\) The binding of these signal molecules to cell membrane receptors leads to enzymatic conversion of cytoplasmic adenosine triphosphate (ATP) and guanosine triphosphate into adenosine monophosphate (cyclic AMP [cAMP], and guanosine monophosphate (cyclic GMP [cGMP], respectively. These latter molecules are known as intracellular second messengers.

The intracellular second-messenger systems

Sutherland and Rall\(^12\) established the second-messenger basis for hormone actions in 1958. The first messenger (a hormone or another stimulating agent) binds to a specific receptor on the
cell membrane and produces an intracellular chemical second messenger.

The cAMP pathway

Internal signaling systems translate many external stimuli to a narrow range of internal signals or second messengers. cAMP and cGMP are second messengers involved in bone remodeling.[13] In response to any hormonal and mechanical stimulus, bone cells produce cAMP in vivo and in vitro. Alterations in cAMP levels are responsible for the synthesis of polyamines, nucleic acids, and proteins and secretion of other cellular products.

Through phosphorylation of specific substrate proteins by its dependent protein kinases, action of cAMP is mediated. But, on the contrary, cGMP is considered to be an intracellular regulator of both endocrine and non-endocrine mechanisms.

Vitamin D and diacylglycerol

A 1, 25, dihydroxycholecalciferol (1, 25, DHCC) has a potent role in calcium homeostasis and acts as a first messenger.[14,15] It is a potent stimulator of bone resorption by inducing differentiation of osteoclasts from their precursors. A decrease in the serum calcium level stimulates secretion of parathyroid hormone, which in turn increases excretion of PO$_4$,$^{−}$, reabsorption of Ca from the kidneys, and hydroxylation of 25, hydroxycholecalciferol to 1, 25, DHCC.

Cytoskeleton-ECM interactions

Applied mechanical forces are transduced from the strained ECM to the cytoskeleton through cell surface proteins. Adhesion of the ECM to these receptors can induce the reorganization of the cytoskeleton, secretion of stored cytokines, ribosomal activation, and gene transcription.[16]

Role of the ECM

The ECM is primarily a collection of fibrous proteins embedded in a hydrated polysaccharide gel. This important tissue component mainly contains macromolecules such as collagen and glycosaminoglycans, secreted at a local level by cells such as fibroblasts, osteoblasts, and chondroblasts.[17] The roles of the ECM are to provide a physical framework for the cells that are responsible for its production and to function as a medium regulating cellular identity, position, proliferation, and fate.

Molecules associated with the mechanotransduction

Histochemical and immunohistochemical studies have demonstrated that, during the early phases of orthodontic tooth movement, PDL fluids are shifted, and cells and ECM are strained. In areas where tension or compression evolves under the influence of the orthodontic appliance, vasoactive neurotransmitters are released from distorted nerve terminals.

In the PDL, most terminals are near blood-vessel walls. So, the released neurotransmitters interact first with capillary endothelial cells. In response, the endothelial cells express receptors that bind circulating leukocytes, promoting their migration by diapedesis out of the capillaries.

These migratory cells secrete many signal molecules, including cytokines and growth factors, some of which might be categorized as inflammatory mediators that stimulate PDL and alveolar bone lining cells to remodel their ECM. This force-induced remodeling facilitates movement of teeth to areas in which bone had been resorbed.[14] All paradental cells, with the exception of migratory leukocytes, must be attached to the ECM that surrounds them. This attachment is essential for cell survival.

Innervation and Inflammation Incident to Orthodontic Tooth Movement

Innervation of dental tissues

Dental tissues receive sensory, sympathetic and parasympathetic innervation, but the majority of the nerve fibers belong to the trigeminal sensory neurons. In addition to nerves having their perikarya in the trigeminal ganglion, the PDL receives axons from the mesencephalic trigeminal nucleus. Periodontal nerve endings consist of mechanoreceptors, mostly Ruffini-like and nociceptors.[18] Both endings can change their structures in response to external stimuli, such as orthodontic force.

The mechanoreceptors are low-threshold, respond to stretch, and are concentrated between the fulcrum and the apex of the tooth and respond to even minor stretching of the PDL.

Nociceptors are high-threshold, activated by heavy forces, tissue injury, and inflammatory mediators and belong either to the unmyelinated C fibers or small myelinated Aδ fibers. They occur less frequently than the mechanoreceptors in the PDL but predominate in the pulp. Under physiological conditions, periodontal and pulpal nociceptors are silent in terms of electrophysiology, but not inactive. They contain various neuropeptides including calcitonin gene-related peptide (CGRP) and substance P (SP), which are synthesized in the perikaryon and transported to both central and peripheral processes. These neuropeptides are routinely stored in peripheral and central nerve terminals, and are released when these terminals are strained.

Peripheral the neuropeptides are released in the tissues where they take part in tissue homeostasis. Centrally CGRP and SP, in addition to other neuropeptides, act as neurotransmitters.[19] Nociceptor endings in the PDL and pulp demonstrate plasticity in response to different stimuli. Pulpitis, traumatic occlusion, and orthodontic tooth movement induce sprouting of CGRP- and SP- containing nerve fibers, and increase in neuro-peptide intensity.

Thus, orthodontic tooth movement affects the number, functional properties, and distribution of both mechanosensitive and nociceptive periodontal nerve fibers.

Neural responses to mechanical forces[20]

Orthodontic tooth movement alters the neutral state of both mechanoreceptors and nociceptive PDL nerve fibers, affecting
the release of biologically active proteins, leading to local neurogenic inflammation and the release of neuropeptides such as CGRP and SP.

Since most PDL neurons are wrapped around blood vessels, including capillaries, endothelial cells are probably the first to interact with neuropeptides, which in turn bind circulating leukocytes, facilitating their migration from the capillaries. Chemokines activate integrins on the leukocyte cell surface to promote firm adhesion. The migration of leukocytes by the chemoattractant gradient and their arrival in the PDL signify the onset of an acute inflammation, which is essential for tooth movement into newer locations. Signaling molecules released by these migrating leukocytes (cytokines, growth factors, and CSFs) interact with various dental and paradental cells and stimulate them to initiate and sustain the tissue remodeling.

Monocytes, lymphocytes, and mast cells express receptors for neuropeptides, which transduce signals intracellularly and evoke cellular responses, such as cytokine release, production of other neuropeptides, changes in the expression of mediators, or direct release of inflammatory mediators. In addition, CGRP and SP also serve as vasodilators, increasing vascular permeability, flow, and plasma extravasations.

Often, this plasma contains molecules derived from the diet, medications, remedies, drugs, hormones, and inflammatory mediators that originated in remote diseased organs, which might influence the course of mechanotherapy, by virtue of their interaction with cells.

The various neural responses to mechanical forces are explained in Flow Chart 1. These responses include altered cytokine synthesis and release, production of other peptides that may amplify response or cause the release of additional neuropeptides, changed expression of adhesion receptors, or direct release of mediators. Neuropeptides can also directly influence connective tissue cells, either by inducing their proliferation, or by changing the expression of surface molecules. Expression of classic cytokines and their corresponding receptors by endocrine and nervous tissue cells occurs.

In addition to this peripheral action, the affected neurons release neurotransmitters centrally, in the trigeminal nucleus, causing pain shortly after appliance activations in persons undergoing orthodontic treatment. The short delay in the onset of pain is due to the initial resistance of the tissue fluids. The gradual movement of these fluids from areas of compression to zones of tension facilitates the development of ECM strain and the entire process of mechanotransduction.

**Pain and tooth movement**

Tooth movement-associated tissue remodeling, an inflammatory process, might induce painful sensations, particularly after activation of the orthodontic appliance.

After 24 h of force application, C-fos (immunoreactive neurons known to be involved in the transmission of nociceptive information) expression is noted ipsilaterally in the trigeminal subnucleus caudalis and bilaterally in the lateral parabranchial nucleus. These fos-like immunoreactive neurons are distributed in other brain regions such as the neocortex, dorsal raphe, and thalamic nucleus.

Nociceptive information by tooth movement is transmitted and modulated in several regions of the brain. These stimuli activate endogenous pain control systems, including descending monoaminergic pathways. Thus, there appears to be an indirect nociceptive mechanism operating during tooth movement that evokes a delayed and continuous nociceptive response, which is expected to limit masticatory function during active tooth movement.

A recent report by Hattori et al. in 2004, showed the effects of administration of MK-801 (a non-competitive antagonist of N-methyl-D-aspartate receptors), intra-peritonially before tooth movement in rats. The results suggest a blockade of N-methyl-D-aspartate receptors along with the neuronal suppression of trigeminal sensory nuclear complex. These effects were found to increase the neuronal activity in the descending antinociceptive system, including nuclear raphe magnus, dorsal raphe nucleus, and Edinger–Westphal nucleus. These results

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**Flow chart 1:** Neural response to mechanical forces and subsequent tooth movement
indicate a pharmacological way to decrease pain perception during orthodontic tooth movement.

**Cytokines in Orthodontic Tooth Movement**

Cytokines are extracellular signaling proteins that act on nearby target cells in low concentrations in an autocrine or paracrine fashion in cell-to-cell communications.

Cytokines that were found to affect bone metabolism, and thereby orthodontic tooth movement, include interleukin 1 (IL 1), IL-2, IL-3, IL-6, IL-8, tumor necrosis factor alpha (TNF), gamma interferon (IFN), and osteoclast differentiation factor. The most potent among these is IL-1, which directly stimulates osteoclast function through IL-1 Type 1 receptor, expressed by osteoclasts.[23]

Secretion of IL-1 cytokines is triggered by various stimuli, including neurotransmitters, bacterial products, other cytokines, and mechanical forces. Their actions include attracting leukocytes and stimulating fibroblasts, endothelial cells, osteoclasts, and osteoblasts to promote bone resorption and inhibit bone formation. Osteoblasts are target cells for IL-1, which in turn conveys messages to osteoclasts to resorb bone.

TNF, another pro-inflammatory cytokine elicits acute or chronic inflammation and stimulate bone resorption. TNF directly stimulates the differentiation of osteoclast progenitors to osteoclasts in the presence of macrophage-CSF. IFN is better known as a potent inducer of major histocompatibility complex antigens in macrophages, which is an early marker of immune activation during inflammation. It also evokes the synthesis of other cytokines, such as IL-1 and TNF. IFN can cause bone resorption by apoptosis of effector T-cells.

Receptor activator of nuclear factor kappa B-Ligand (RANKL)/RANK/osteoprotegerin (OPG) system have a role in inducing bone remodeling. The TNF-related ligand RANKL and its two receptors, RANK, and OPG, are involved in this remodeling process. RANKL is, in fact, a regulator of osteoclast formation and activation that in turn leads to the production of osteoresorptive effect by many hormones and cytokines. It is expressed on osteoclast cell lineage and exerts its effect by binding the RANK receptor present on osteoclast lineage cells. This process leads to rapid conversion of hematopoietic osteoclast precursors to mature osteoclasts.[24]

OPG that is also a receptor produced by osteoblastic cells that compete with RANK for RANKL binding. Its effects on bone cells are inhibition of terminal stages of osteoclast differentiation, suppression of activation of matrix osteoclasts and induction of apoptosis. Thus, the controlled bone remodeling is directly related to a balance between RANK-RANKL binding and OPG production. OPG exists in both membrane - bound and soluble forms, and that its expression is up-regulated by CD40 stimulation.

CD40 is a cell surface receptor that belongs to the TNF receptor family. It is seen in a variety of cells, such as B-lymphocytes, monocytes, dendrite cells, IL-6- and IL-8-secreting cells, such as endothelial cells, basophils, epithelial cells, and fibroblasts.

**Neural Modulation of Orthodontic Tooth Movement**

RANKL promotes the formation and bone resorptive activity of osteoclasts that are the specialized cells charged with bone resorption.

Conversely, inhibitors of osteoclast formation and activities including OPG slow tooth movement.

There may be unsuspected links between the neural system and bone remodeling and offer potential strategies for improving orthodontic treatment. Neurons and the bone cells involved in the remodelling required for orthodontic tooth movement share numerous molecular components and it may be possible to identify agents that can at the same time increase the speed of orthodontic tooth movement while reducing pain. For example that the transient receptor potential vanilloid 1 receptor (TRPV1), a key receptor in pain sensing, is also is expressed in osteoclasts. TRPV1 is the receptor for capsaicin, the ingredient in red chili peppers that produces burning sensations.[25,26]

Capsaicin and other TRPV1 agonists have been shown to stimulate osteoclast formation. A single agent, an appropriate agonist of TRPV1, may be able to both relieve orthodontic pain and significantly reduce the time required for orthodontic procedures.

Capsaicin is already a FDA-approved treatment for clinical pain and it is indicated that it is effective in the reduction of pain measures for subjects suffering from arthritis, post-herpetic and diabetic neuropathies.

As such, an adapted approach might be feasible in the clinic using capsaicin, or other agonists of TRPV1, to easily and safely facilitate the goal of improving orthodontic outcomes.

Sclerostin is crucial for modulating bone remodeling. It is thought to block the transition of osteoblasts from a step along their differentiation pathway where they produce RANKL, but do not form bone or to a point where they do not produce RANKL (or produce more OPG) and do form bone. Thus, higher levels of sclerostin will favor bone resorption and lower levels will favor bone formation.

**Central Control of Bone Remodeling**

Three different mechanisms: Regulation through leptin signaling, neuropeptide Y and cannabionoid receptors. It is postulated that central regulation of bone remodeling represents a link with bone remodeling and energy metabolism.

Leptin release by the hypothalamus for example has been shown to regulate both bone remodeling and insulin secretion. It regulates bone remodeling through a central relay, and this mode of regulation is vitally important in maintaining bone. The ventromedical hypothalamic nucleus neurons are required for leptin-dependent central regulation of bone remodeling.[27]

This regulation is mediated through first route that is through dopamine β-hydroxylase, an enzyme required for the production of norepinepherine and epinephrine. Only one adrenergic receptor is expressed in osteoblasts, β2 adrenergic receptor.

Another mechanism by which leptin mediates bone remodeling is via the cocaine- and amphetamine- regulated
transcript (CART), a neuropeptide precursor protein. CART expression is stimulated by leptin, and osteoclastic resorption decreases in relation to the amount of CART expressed. This action of CART is mediated through osteoblasts. Neuromedin U is a neuropeptide expressed in hypothalamic neurons and in the small intestine has also been also been implicated as a component of the leptin regulatory pathway. Thus, it is suggested that leptin regulates bone remodeling through several pathways.

Single nucleotide polymorphisms (SNPs) in one or more the genes encoding elements of the pathway may have consequences for the general rate and efficacy of orthodontic procedures in an individual. For example, an SNP in β2 adrenergic receptor that increases signaling from the receptor may be associated with higher than normal bone mineral density, and increased rates of tooth movement.

Secondly, direct local stimulation of osteoblasts in the alveolar bone associated with specific teeth with β2 adrenergic receptor agonists might both enhance rates of tooth movement and increase the speed of bone formation on the tension side of the tooth, perhaps reducing the tendency to relapse.

Neuropeptide Y, a neurotransmitter that is widely expressed in both central and peripheral nervous systems, has been shown to regulate bone remodeling. Either the neuropeptide Y1 or Y2 receptors yield a high bone mass phenotype with enhanced osteoblast activity. Neuropeptide Y receptors are, like the leptin receptor, expressed by cells of the hypothalamus. It is possible to take advantage of neuropeptide Y signaling to influence bone remodeling associated with orthodontic applications.

A third route by which bone remodeling can be regulated centrally in through endocannabinoid signaling, which has been shown modulate bone remodeling through central and peripheral cannabinoid receptors.

**Specialized Machinery for Acidification**[^28]

Evidence has emerged that osteoclasts share a number of molecular features with neural cells. These include the specialized use of vacuolar H+ -ATPase (V-ATPase), chloride channel protein 7, which work in coordination in order to properly acidify compartments.

The V-ATPase is a multisubunit enzyme (11-13 subunits) that is expressed in all cells and is required for “housekeeping” acidification of vesicular compartments including lysosomes, late endosomes, compartments of uncoupling receptor and ligand, elements of the golgi and phagosomes.

Osteoclasts that are specialized to resorb bone are a clear and well-characterized example of a cell type that uses V-ATPases for a specialized function. Osteoclasts express normal housekeeping V-ATPases. When an osteoclast contacts, activation signals associated with the bone surface, the specialized subset of V-ATPases is transported to a subdomain of the plasma membrane called the ruffled plasma membrane or ruffled border.

These V-ATPases then use ATP hydrolysis to pump protons against an electrochemical gradient to acidify an extracellular resorption compartment.

**Sensing Receptors Shared by Neurons and Osteoclasts**[^28]

Both bone remodeling and sensory pain pathways share common inflammatory mediators, including TNF, prostaglandins, ILs, and vasoactive neuropeptides (e.g. SP).

Specifically targeting the intersection of these pathways may provide unique opportunities for development of innovative therapies related to bone disorders and specifically OTM.

**Piezocision-Assisted Orthodontic Treatment**

Piezocision-assisted orthodontic treatment is a newly innovated, minimally invasive surgical technique that was basically designed to reduce the duration of orthodontic tooth movement.

Microsurgical interproximal openings are made in the buccal portion of gingival so that piezoelectric knife can create the bone injury that in turn leads to transient demineralization and subsequent accelerated and rapid tooth movement. For the very first time when this procedure was described, cuts were made simultaneously in the maxilla and the mandible.

Recently, this technique has attained a more staged approach in which selected portions or segments of the arch being treated are demineralized at different times during orthodontic treatment to help achieve specific results. In a study done by Keser and Dibart[39] in 2013, the correction of a Class III malocclusion was done in a total treatment time of 8 months by this technique.

**Conclusion**

The relationship of nerves to tooth movement has been a matter of considerable research. Denervation of dental tissues by sectioning the inferior alveolar nerve has proven to be a suitable model system for analyzing effenter actions of sensory nerves. Such studies clearly demonstrate the regulatory role of the sensory nerve fibers in the control and development of inflammatory reactions during orthodontic tooth movement. Thus, the dental tissue reactions are a result of both direct and indirect activity of the neuropeptides released from periodontal nerve endings after application of orthodontic force.

Biological manipulation to improve orthodontic procedures is in its infancy, but it appears possible to both improve the speed and efficacy of tooth movement, and to reduce associated discomfort. Experiments have been performed in animal models, but translation to the clinic will require greater understanding of the processes involved.

Recent studies uncovering mechanisms by which bone remodeling is controlled by central mechanisms and demonstrating that osteoclasts and neurons share regulatory molecules, although they are used for different purposes, open new insights for understanding and manipulating orthodontic tooth movement and perhaps simultaneously reducing the discomfort associated with the procedures.
References


