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## Neural Modulation of Orthodontic Tooth Movement

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### 1. Introduction

Millions of people worldwide have orthodontic therapy for the treatment of dental malocclusions, craniofacial disorders, and simply to improve their appearance. However, orthodontic treatment has several major problems, including the long time braces must be worn, the pain involved during treatment, and the need to wear retainers to prevent relapse. Orthodontics could be improved. Understanding the mechanisms involved with orthodontic tooth movement represents a first step toward this goal. Improvements in the practice of orthodontics would have an immediate and significant impact on the millions of individuals undergoing orthodontic treatment worldwide.

Orthodontic tooth movement can be thought of as an interaction of mechanical force on biological tissue (Krishnan and Davidovitch, 2006; Wise and King, 2008). Much progress in orthodontics has involved finding better means to apply mechanical force to teeth. While advances have been made regarding the mechanics and materials used in orthodontics, there has been a relative plateau in the overall treatment outcomes. For example, a moderately difficult case still requires an average of 18-36 months for treatment, no different than 50 years ago. It is apparent that discoveries relating to biological manipulations may provide a path for significantly improving orthodontic practice.

It is thought that enhancing the speed of orthodontic tooth movement could be accomplished if bone remodeling occurred at an accelerated rate in the alveolar bone associated with the teeth being moved. While this has not been formally demonstrated in the clinic, animal studies strongly support this notion. For example, orthodontic tooth movement in a mouse model was accelerated by overexpressing Receptor Activator of Nuclear Factor Kappa B-Ligand (RANKL) (Kanzaki et al., 2006). RANKL promotes the formation and bone resorptive activity of osteoclasts, the specialized cells charged with bone resorption (Hofbauer and Heufelder, 2001). Conversely, inhibitors of osteoclast formation and activity including osteoprotegerin (OPG), integrin inhibitors, bisphosphonates and inhibitors of matrix metalloproteinases all slowed tooth movement (Holliday et al., 2003; Dolce et al., 2003; Kanzaki et al., 2004; Dunn et al., 2007). Although these studies showed that it is possible to manipulate the speed at which orthodontic tooth movement proceeds by altering osteoclast activity, the specific agents tested to date are probably inappropriate for orthodontic use in the clinic as there would be too much danger of off target effects. Such risks are unacceptable for orthodontic procedures. Although orthodontics as currently

practiced is imperfect, it is quite effective. Moreover, children are the most common patients in the orthodontic clinic; for biological manipulations to enhance orthodontics to be contemplated, they must be very safe.

Biological manipulation might be useful in orthodontics to prevent relapse. It is possible that enhancers of bone formation rates might be used to remodel alveolar bone to reduce incidence of relapse and minimize the use of retainers. In this case, it is possible that uncoupled stimulators of bone formation (ie regulation that stimulates bone formation without corresponding bone resorption) might prove ideal. As will be described below, modulators of sclerostin signaling, or other regulators of the Wnt-signaling pathway, are obvious candidates for this application (Paszty et al., 2010; Moester et al., 2010).

Pain is accepted as a necessary off target effect of orthodontics, and is typically treated using common non-prescription pain medications like acetaminophen. For theoretical reasons acetaminophen, which acts centrally, is considered better than ibuprophen or aspirin, which act on prostaglandins locally (Simmons and Brandt, 1992; Kehoe et al., 1996; Walker and Buring, 2001). After an initial period of discomfort (a few days) pain goes away until the next activation of the appliance. The initial activation is usually considered the most painful. In general, orthodontic pain has been considered manageable and acceptable to patients, or at least to the patient's parents, as a necessary component of orthodontic treatment. For this reason, despite its widespread use, relatively little effort has been expended to identify ways to reduce orthodontic pain. Interestingly, as more adults are undergoing orthodontic treatment, more attention has been paid to means for relieving orthodontic pain.

It is thought that pain can be reduced by modifying orthodontic procedures, particularly by using lighter forces to cause less damage and inflammation. Treatment of orthodontic pain is complicated by the fact that tooth movement may require inflammation, triggered by mechanical damage to tissues of the periodontal ligament (PDL) and associated alveolar bone, which is caused by the application of orthodontic force. Efforts to reduce the inflammation either by reducing force or by using local anti-inflammatory agents may compromise the process of tooth movement (Simmons and Brandt, 1992; Kehoe et al., 1996; Walker and Buring, 2001). In fact, there are very few studies that objectively address any of these questions in humans or even in animal models (Bergius et al., 2000; Giannopoulou et al., 2006; Eversole, 2006). For example, there currently are no animal models for studying levels of orthodontic force compared with levels of pain and the amount of tooth movement. Without proper studies, opinions on pain in orthodontics are now based largely on anecdotal evidence.

Orthodontic tooth movement is more complicated than simply applying force, causing mechanical damage and inflammation, followed by bone resorption as part of the response to inflammation and damage. Orthodontic tooth movement requires the presence of a functional PDL (Krishnan and Davidovitch, 2006; Wise and King, 2008). Ankylosed teeth do not move regardless of the amount of force applied to the tooth, or the amount of inflammation induced. The precise mechanisms by which the PDL transduces force to stimulate bone resorption to allow for movement of a tooth through bone are still mysterious. For example, it is known that RANKL is expressed at higher levels on the pressure side of a tooth, but the mechanism supporting the increased RANKL expression is not known.

Recent data demonstrate previously unsuspected links between the neural system and bone remodeling and offer potential strategies for improving orthodontic treatment. Taking advantage of these opportunities requires understanding in greater detail how the neural system is involved in the regulation of orthodontic tooth movement. 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*. Recent studies have indicated for example that the transient receptor potential (TRP) vanilloid 1 receptor (TRPV1), a key receptor in pain sensing, is also expressed in osteoclasts (Rossi et al., 2009; Rossi et al., 2011). TRPV1 is the receptor for capsaicin, the ingredient in red chili peppers that produces burning sensations (Caterina, 2007). Capsaicin and other TRPV1 agonists have been shown to stimulate osteoclast formation (Rossi et al., 2009). From this it is plausible that 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 a number of studies have indicated that it is

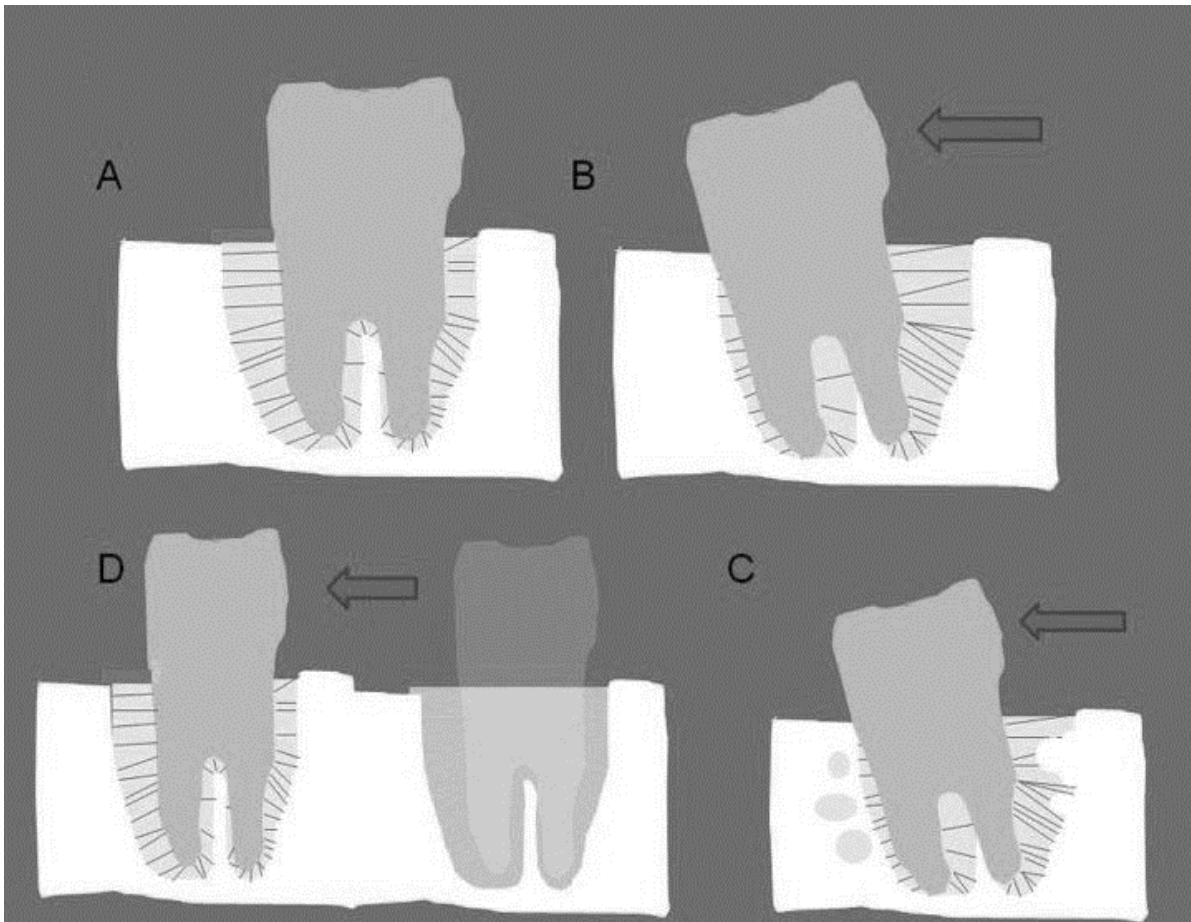


Fig. 1. Orthodontic tooth movement initiates with application of force (B) that compresses the PDL on the pressure side of the tooth, or stretches the periodontal ligament on the tension side. This leads to resorption on the pressure side and bone formation on the tension side (C) which accommodates the repositioning of the tooth (D). Goals of manipulation of tooth movement with bioactive agents include increasing the rate of tooth movement, reducing pain, and preventing relapse

effective in the reduction of pain measures for subjects suffering from arthritis, post-herpetic and diabetic neuropathies (Peikert et al., 1991; McCarthy and McCarty, 1992; Tandan et al., 1992; Watson et al., 1993; Caterina, 2007). 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.

In summary, opportunities exist for improving orthodontic treatment by enhancing orthodontic tooth movement, preventing relapse, and reducing pain associated with orthodontic procedures (Figure 1). Recent advances in understanding neuromodulation of bone remodeling present new means to affect all of these parameters, perhaps by using the same therapeutic molecule. To examine this in greater detail we will first briefly consider the essential elements of the regulation of bone remodeling, then examine connections between bone cells and neurons.

## 2. Bone remodeling

Bone remodeling can be thought of simply as a dialog between two cell types, osteoclasts and osteoblasts (Figure 2)(Martin et al., 2009). Osteoclasts are cells of the hematopoietic lineage that are specialized for bone resorption (Teitelbaum, 2007). Osteoblasts are mesenchymal and are specialized for bone formation (Askmyr et al., 2009). Although this is an oversimplification, for example T-cell are known to directly stimulate osteoclast formation and bone resorption (Weitzmann and Pacifici, 2005), and osteocytes are primary regulators of osteoblast bone formation (Winkler et al., 2003; Moester et al., 2010), it is clear

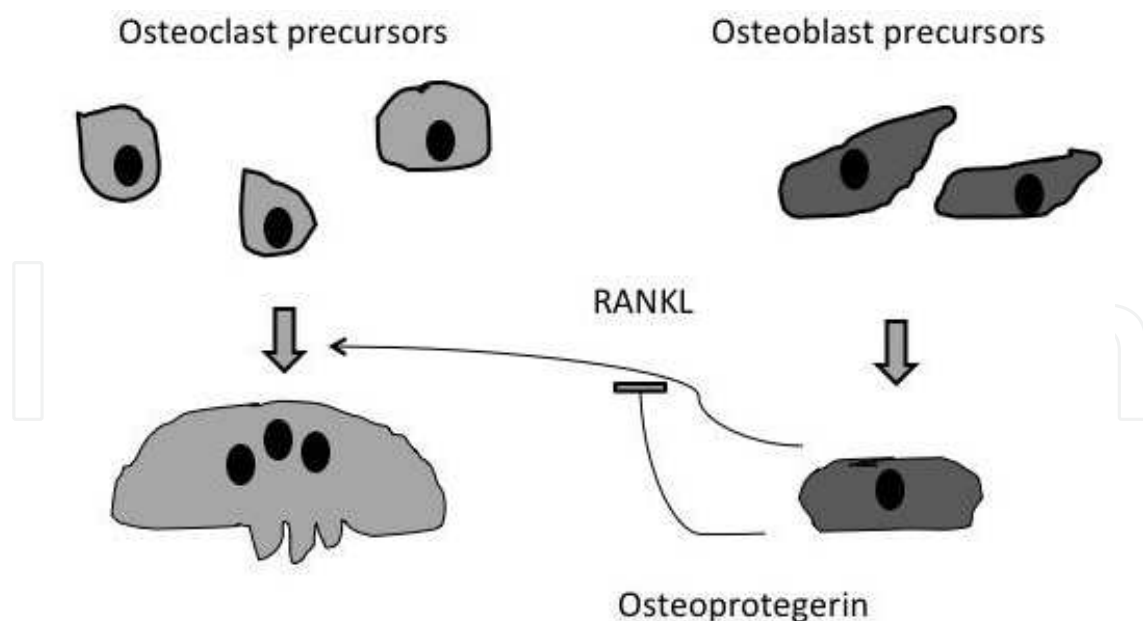


Fig. 2. RANKL produced by osteoblasts stimulates osteoclast formation and osteoclast bone resorption. Osteoprotengerin is also produced by osteoblasts and serves as a competitive inhibitor of RANKL. The humanized monoclonal antibody, denosumab, functions like osteoprotegerin.

that a major element of the regulation of bone remodeling is through expression by osteoblasts of RANKL. This stimulates its receptor, RANK, present on the surface of osteoclast precursors and osteoclasts, which induces osteoclast differentiation, survival and bone resorptive activity (Burgess et al., 1999; Kong et al., 1999). Osteoprotegerin, also produced by osteoblasts, serves as a competitive inhibitor of RANKL and by doing so reduces bone resorption (Hofbauer et al., 2004). Neural regulation of bone remodeling must occur within the constraints of this regulatory system.

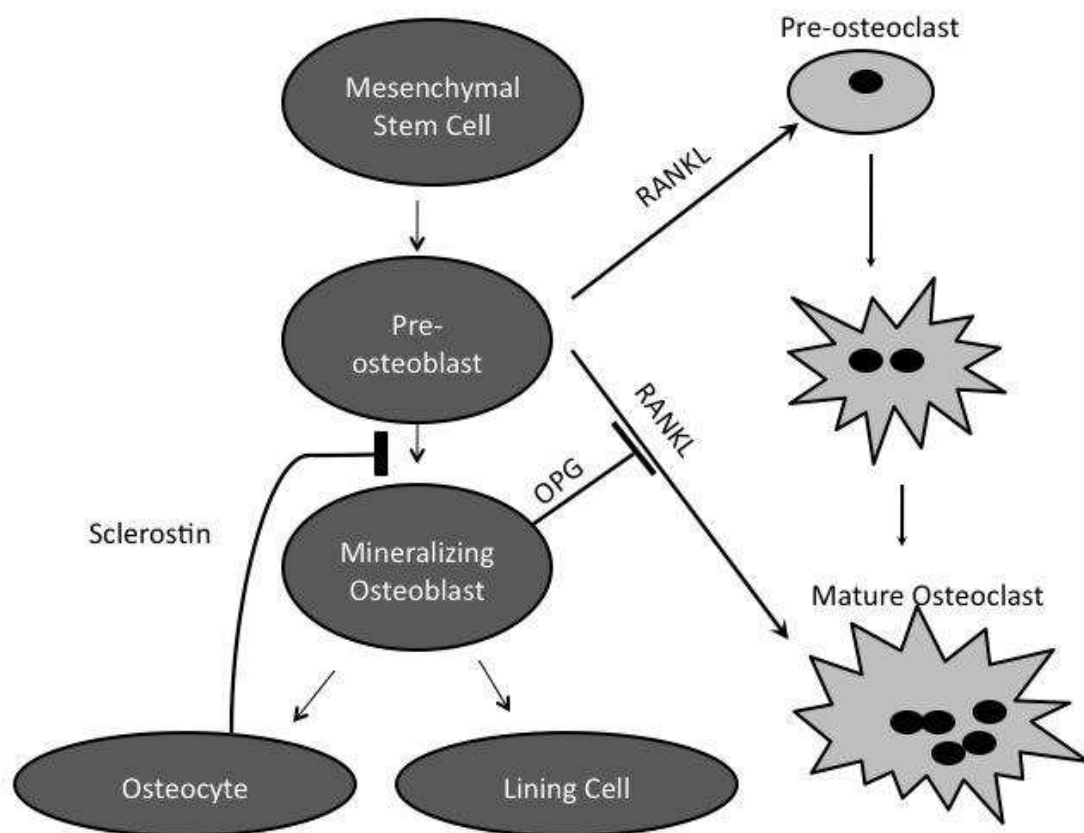


Fig. 3. Sclerostin is thought to inhibit differentiation of osteoblasts from a stage where they promote osteoclastic bone resorption to a stage where they form bone.

RANKL is a tumor necrosis factor (TNF)-related type II transmembrane protein expressed by osteoblasts, T-cells and a few other cell types (Xing et al., 2005). There was great excitement in the bone field in the late 1990s with the demonstration that RANKL was the long sought osteoclast differentiation factor (Lacey et al., 1998). Since the initial reports, this basic finding has been supported by a host of studies (Xing et al., 2005). RANKL binds its receptor RANK to stimulate osteoclast formation and activity. It also binds OPG, which resembles RANK but lacks a transmembrane domain, and serves as a soluble competitive inhibitor. Overwhelming evidence indicates the vital importance of this triad in bone remodeling and has led to the paradigm shown in Figure 2. With the discovery of RANKL came efforts to utilize inhibitors of RANKL in the development of pharmaceutical agents that inhibit osteoclast activity. Recently an anti-RANKL antibody-based pharmaceutical

(Denosumab) was generated by Amgen and approved as an anti-osteoporotic agent (Trade name Prolia) and for bone cancer (Xgeva) (Lewiecki, 2010; Castellano et al., 2011; Baron et al., 2011).

Sclerostin has recently been identified as a vital regulator of bone formation (Moester et al., 2010). Sclerostin is a controller of the Wnt-signaling pathway, which is crucial for modulating bone remodeling (Baron et al., 2006; Kubota et al., 2009). Sclerostin is thought to block the transition of osteoblasts from a step along their differentiation pathway where they produce RANKL, but do not form bone, to a point where they do not produce RANKL (or produce more osteoprotegerin) and do form bone (Figure 3)(Paszty et al., 2010). Thus higher levels of sclerostin will favor bone resorption and lower levels will favor bone formation. Taking advantage of this paradigm, efforts are underway to transition a humanized monoclonal antibody inhibitor of sclerostin to the clinic for the treatment of osteoporosis (Lewiecki, 2011). Sclerostin is one of several molecules that influence osteoblast activity by regulating the Wnt-signaling pathway (Baron et al., 2006).

### 3. Central control of bone remodeling

During the past decade evidence has accumulated that has shown that levels of bone remodeling and final bone structure is regulated in the central nervous system (Elefteriou, 2008; Wong et al., 2008; Karsenty and Oury, 2010). Three different mechanisms will be discussed in some detail, regulation through leptin signaling, neuropeptide Y and cannabinoid receptors. It is postulated that central regulation of bone remodeling represents a link with bone remodeling and energy metabolism (Karsenty and Oury, 2010). Leptin release by the hypothalamus for example has been shown to regulate both bone remodeling and insulin secretion (Baldock et al., 2002; Takeda, 2008; Kalra et al., 2009; Confavreux et al., 2009; Baldock et al., 2009; Qin et al., 2010; Zengin et al., 2010). Leptin is a 16 kD adipose-derived protein hormone, which plays a key role in regulating energy intake and expenditure. It has a major role in controlling appetite and metabolism.

Evidence suggests that leptin-regulated neural pathways control both bone formation and bone resorption. Mice lacking the gene encoding leptin (*ob/ob*) are obese and have higher bone mass than normal and higher rates of bone remodeling (Elefteriou et al., 2005). Intracerebroventricular infusion of leptin into the mice, under conditions where little or no leptin leaked into general circulation, led to normalization of both rates of bone remodeling and bone mass (Elefteriou et al., 2005). This strongly supported the idea that leptin regulates bone remodeling through a central relay, and this mode of regulation is vitally important in maintaining bone (Kalra et al., 2009; Karsenty and Oury, 2010).

The leptin receptor is expressed on three types of hypothalamic neurons, although its expression in the brain is not restricted to hypothalamic neurons (Karsenty and Ducey, 2006; Kalra et al., 2009). The three neurons in the hypothalamus are the arcuate nucleus, the ventromedial hypothalamic nucleus, and paraventricular nuclei. Lesioning of the arcuate nucleus using two independent strategies did not affect bone mass directly, or alter the ability of infusion of leptin to affect bone mass (Takeda and Karsenty, 2008). In contrast, lesioning ventromedial hypothalamic nuclei neurons in wild type animals resulted in a high bone mass/high bone turnover phenotype similar to that observe in the *ob/ob* mice. Infusion of leptin failed to normalize the bone phenotype in either lesioned wild type mice or the *ob/ob* mice (Guidobono et al., 2006). Taken together, these data suggested that the ventromedial hypothalamic nucleus neurons are required for leptin-dependent central regulation of bone remodeling.

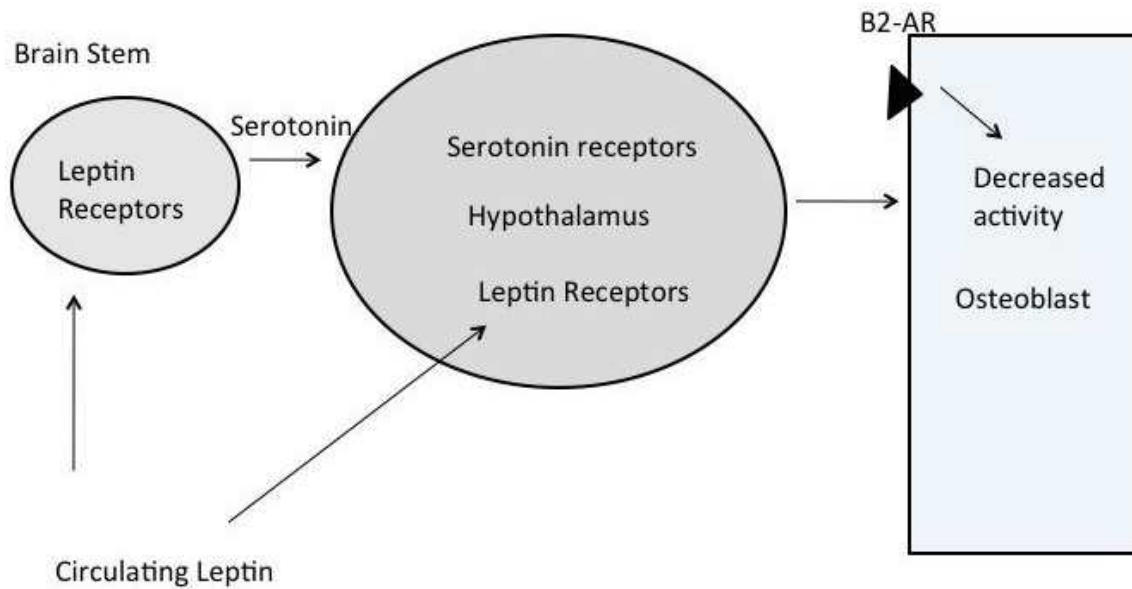


Fig. 4. Leptin stimulates receptors in the brain stem and hypothalamus leading to stimulation of  $\beta 2$  adrenergic receptors in osteoblasts which decrease the activity of osteoblasts

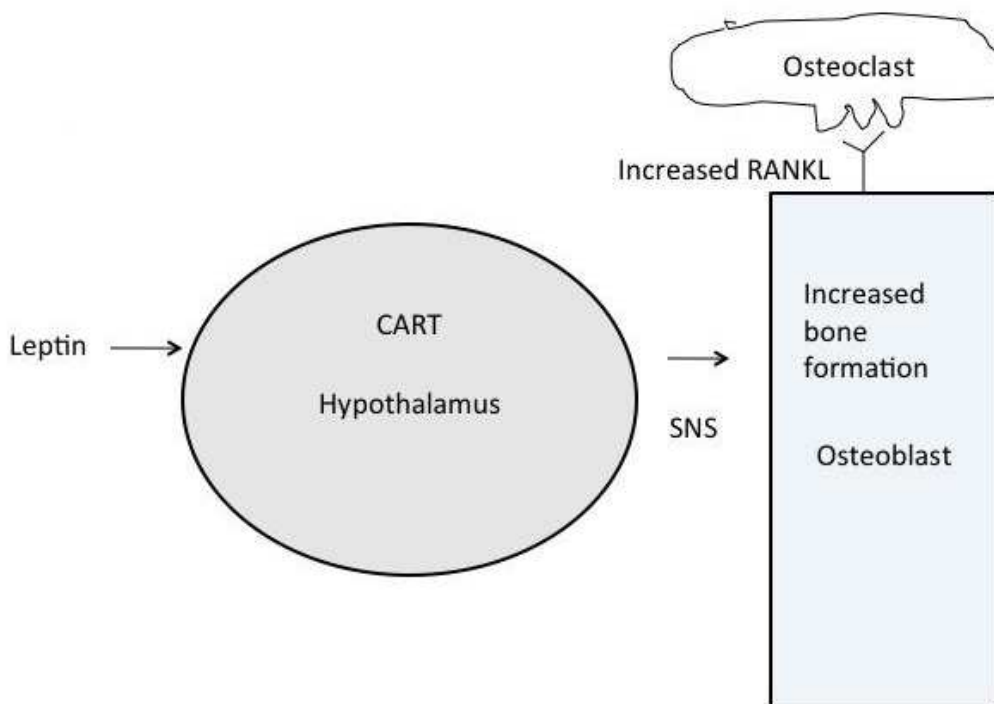


Fig. 5. Leptin stimulates cocaine- and amphetamine- regulated transcript expression which acting through the sympathetic nervous system to stimulate both increased bone formation by osteoblasts and increased resorption by osteoclasts



How then is this regulation mediated? One route is through dopamine  $\beta$ -hydroxylase, an enzyme required for the production of norepinephrine and epinephrine (Figure 4) (Yadav and Karsenty, 2009; Yadav et al., 2009). Mice lacking dopamine  $\beta$ -hydroxylase have a similar bone phenotype to the *ob/ob* mice, and leptin infusion of these mice failed to normalize bone parameters. Only one adrenergic receptor is expressed in osteoblasts,  $\beta$ 2 adrenergic receptor. Mice lacking one or both copies of the  $\beta$ 2 adrenergic receptor developed a high bone mass phenotype, and leptin infusion into mice lacking the  $\beta$ 2 adrenergic receptor decreased fat mass but did not normalize the bone parameters (Yadav and Karsenty, 2009; Yadav et al., 2009).

Another mechanism by which leptin mediates bone remodeling is via the cocaine- and amphetamine- regulated transcript (CART), a neuropeptide precursor protein (Figure 5) (Elefteriou et al., 2005). The level of CART expression in the hypothalamus and peripheral organs including the pancreas and adrenal glands is tied to levels of leptin. Simply, 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; CART represses RANKL expression of osteoblasts and thus reduces osteoclast formation and bone resorption (Elefteriou et al., 2005).

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 (Figure 6) (Sato et al., 2007). Although its receptor is not detected in bone cells, knockout of neuromedin U leads to a high bone mass phenotype. Treatment of leptin deficient mice with neuromedin U resulted in partial rescue of the high bone mass phenotype suggesting that neuromedin U is downstream of leptin in the bone remodeling regulatory pathway.

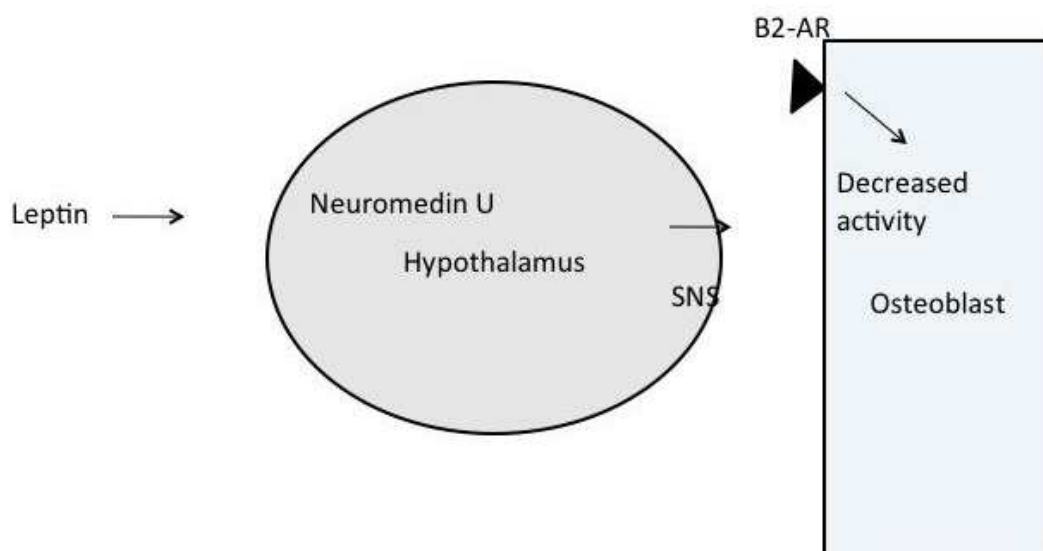


Fig. 6. Leptin also signals through the hypothalamus using a pathway involving neuromedin U and the sympathetic nervous system leading to stimulation of  $\beta$ 2 adrenergic receptor which decreases bone formation

Taken together this suggested that leptin regulates bone remodeling through several pathways. Although caution must be exercised in translating these results to humans, they

suggest a number of ramifications for humans with respect to orthodontic procedures. First, alterations in elements of this signaling pathway, for example 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  $\beta 2$  adrenergic receptor that increases signaling from the receptor may be associated with higher than normal bone mineral density, and increased rates of tooth movement.

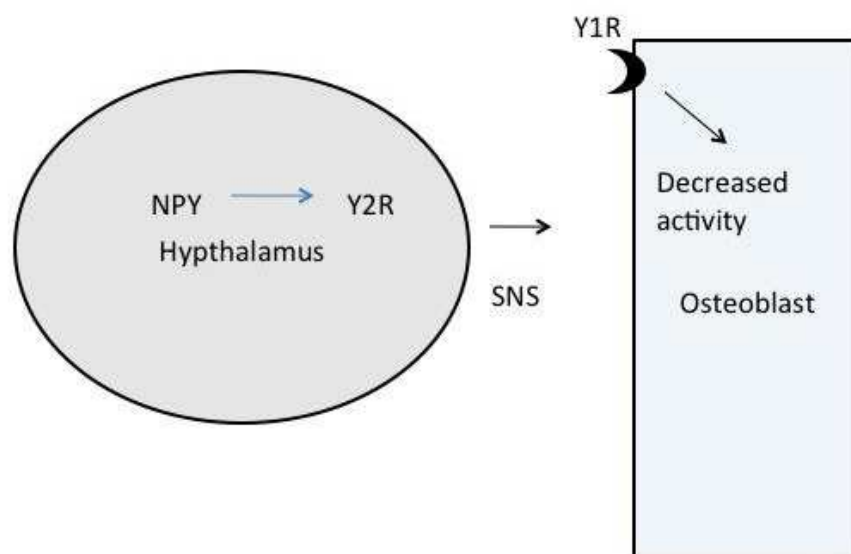


Fig. 7. Neuropeptide Y signals through Y2R receptors in the hypothalamus and Y1R receptors in osteoblasts to decrease osteoblast activity

Secondly, direct local stimulation of osteoblasts in the alveolar bone associated with specific teeth with  $\beta 2$  adrenergic receptor agonists might both enhance rates of tooth movement and increase the speed of bone formation at the tension side of the tooth, perhaps reducing the tendency to relapse. However, care would have to be taken in manipulating these pathways because of the associations of the adrenergic systems with cardiovascular diseases (Saini-Chohan and Hatch, 2009). In addition, a recent study indicated that SNPs in the  $\beta 2$  adrenergic receptor are associated with heterotypic ossification, which is associated with higher rates of fractures. Moreover, recent studies of bisphosphonate-associated oral osteonecrosis suggests that the condition is actually osteosclerosis, and may result from disorganization of normal bone remodeling rather than blocking of the process (Chiu et al., 2010; Treister et al., 2010). *While perturbation in normal bone remodeling on the surface may have favorable outcomes, great care must be taken due to the complexity of bone formation and remodeling which can lead to unexpected adverse consequences.*

Neuropeptide Y, a neurotransmitter that is widely expressed in both central and peripheral nervous systems, has been shown to regulate bone remodeling (Baldock et al., 2007; Baldock et al., 2009)(Figure 7). Knockout mice of either the neuropeptide Y1 or Y2 receptors yielded a high bone mass phenotype with enhanced osteoblast activity (Baldock et al., 2009). Neuropeptide Y receptors are, like the leptin receptor, expressed by cells of the hypothalamus. Knockout of Y2 in the hypothalamus is sufficient to induce a high bone density phenotype. However, knockout of Y1 in the hypothalamus did not alter bone homeostasis (Baldock et al., 2002; Baldock et al., 2007).

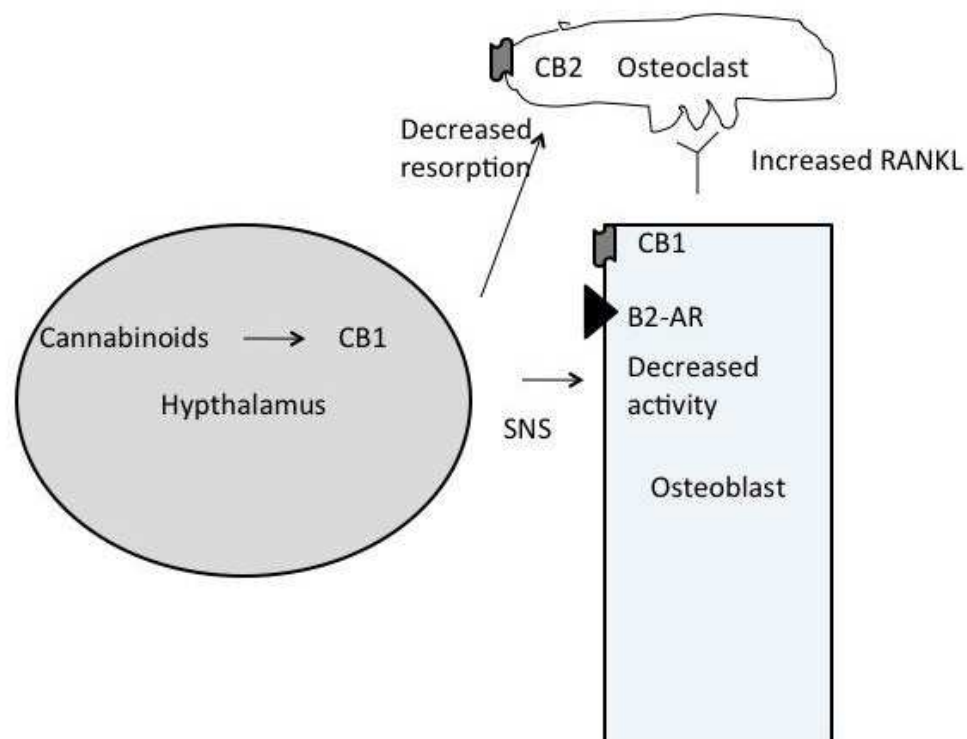


Fig. 8. Cannabinoid stimulate a central response that leads to decreased bone formation. The CB2 receptor of osteoclasts reduces osteoclast activity, but CB1 stimulation increases expression of RANKL which is pro-stimulatory

Recently, the Y1 receptor was knocked out specifically in osteoblasts using a Cre/Lox system (Baldock et al., 2007). It was shown that osteoblast specific knockout of Y1 was sufficient to increase bone mass and enhance bone remodeling. These data indicated that neuropeptide Y signaling could have a role in both central and local neural control of bone remodeling.

Neuropeptide Y signaling has been linked to food intake and like leptin, there are links between neuropeptide Y signaling and obesity (Munoz and Argente, 2002; Feletou and Levens, 2005). Neuropeptide Y receptors are found on pre- and post-synaptic neurons. Presumably activation of the receptors is tied to behavioral changes leading to alterations in food consumption. Whether it is possible to take advantage of neuropeptide Y signaling to influence bone remodeling associated with orthodontic applications is not clear, but most likely, means would have to be devised to deliver agonists locally.

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 (Davenport, 2005; Rossi et al., 2009) (Figure 8). Cannabinoid receptors are a class of G protein coupled membrane receptors. The cannabinoid receptors CB1 and CB2 play a key role in the maintenance of bone mass and are expressed on osteoblasts, osteoclasts and osteocytes. Deficiency in the hypothalamic receptor CB1 in mice has been shown to accelerate age-dependent osteoporosis. Agonists of CB2 reduce bone loss after ovariectomy in rodent models while increasing the thickness of the cortical bone. This makes CB2 a potential target for agents designed to modulate bone remodeling.

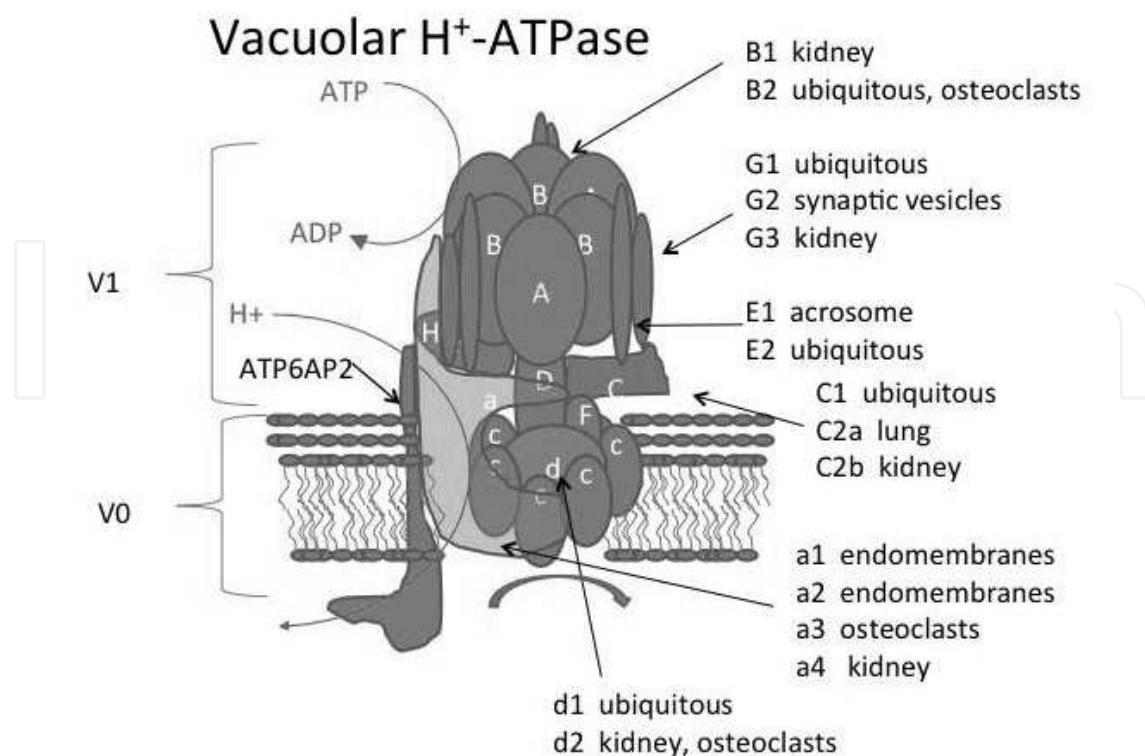


Fig. 9. V-ATPases are ubiquitously-expressed and are composed of many subunits. Some subunits are present in multiple isoforms. Osteoclasts, for example, contain the “housekeeping” isoforms of subunit a (a1, and a2) and the also express the a3 subunit which is required for bone resorption. ATP6AP2 (the prorennin receptor) links bone resorption to rennin/angiotensin signalling.

#### 4. Common molecular features shared by neurons and bone cells

##### 4.1 Specialized machinery for acidification

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 (CLC-7), which work in coordination in order to properly acidify compartments (Schaller et al., 2005; Hinton et al., 2009).

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 (Hinton et al., 2009). Certain specialized cell types express both the housekeeping subset of V-ATPases, and in addition, an additional subset that is involved in the specialized function of the cell type (Figure 9).

Osteoclasts, which are specialized to resorb bone, are a clear and well-characterized example of a cell type that uses V-ATPases for a specialized function (Blair et al., 1989; Holliday et al., 2005). Osteoclasts express normal housekeeping V-ATPases (Toyomura et al., 2003). In addition, they express a large subset that is destined for the plasma membrane of resorbing cells. 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 (Blair et al., 1989). These V-ATPases

then use ATP hydrolysis to pump protons against an electrochemical gradient to acidify an extracellular resorption compartment (Figure 10).

Different subsets of V-ATPases are distinguished by isoforms of particular subunits. Some subunits are present in only a single form and are present in all V-ATPases no matter what their function. Others have multiple isoforms that are derived from different genes. For example, there are four isoforms of the  $\alpha$  subunit ( $\alpha 1$ - $\alpha 4$ ). Subunits  $\alpha 1$  and  $\alpha 2$  are found in the housekeeping V-ATPases. The  $\alpha 3$ -subunit has been identified at high levels in osteoclasts, pancreatic beta cells, kidney epithelial cells and microglia (Li et al., 1999; Smith et al., 2001; Sun-Wada et al., 2006; Serrano et al., 2009). The  $\alpha 4$  subunit is restricted to epithelial cells of the kidney (Stover et al., 2002).

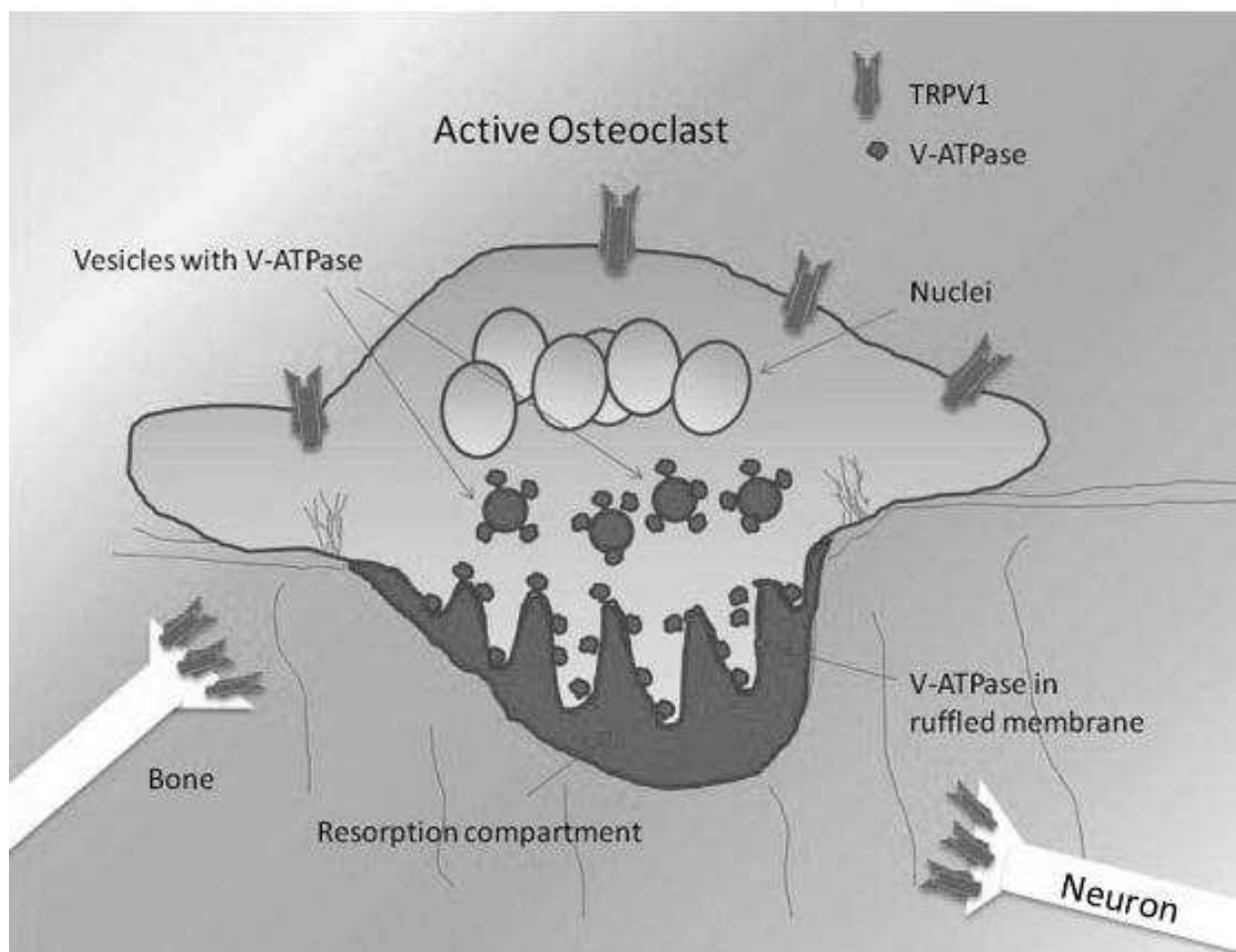


Fig. 10. Osteoclasts insert V-ATPases into the plasma membrane in a region known as the ruffled border. V-ATPases pump protons into the resorption compartment lowering the pH, which is crucial for bone resorption. TRPV1 is expressed on both osteoclasts, where agonists are proresorptive, and on neurons, where agonists reduce pain. This makes it possible that a single therapeutic agent can both increase the rate of tooth movement (which requires increased osteoclastic resorption) and reduce pain associated with orthodontic procedures.

Like osteoclasts, neurons also express subsets of V-ATPases that are utilized for specialized purposes (Moriyama et al., 1992). Neurons are thought to utilize V-ATPases to generate a driving force to power loading synaptic vesicles with neurotransmitters. In addition, there is

considerable evidence that a subunit is intimately involved in mediating the fusion of synaptic vesicles with the plasma membrane to allow dumping of neurotransmitters into the synaptic cleft (Hiesinger et al., 2005; Di et al., 2010).

Among the most exciting recent findings was the demonstration that a V-ATPase accessory protein, the pro-renin receptor (PRR, also known as ATP6AP2) forms a vital scaffold between V-ATPase and the Wnt-signaling pathway (Cruciat et al., 2010). Without PRR, mineralization was blocked in a mouse model. Whether PRR is also found in osteoclasts is not known, and whether the recent demonstration that PRR is found in the hypothalamus suggests that it may be another molecule by which central regulation of bone remodeling might occur remains to be explored (Takahashi et al., 2010). In this case, the primary known function of PRR is its involvement in renin-angiotensin signaling which is related to blood pressure and cardiac activity (Nguyen, 2011).

Along with sharing specialized functions of V-ATPases, both neurons and osteoclasts require the voltage-gated chloride channel CLC-7. This channel is thought to open to reduce voltage across membranes produced by the activity of electrogenic V-ATPases. Mutations in CLC-7 lead to both osteopetrosis and neurodegeneration (Kornak et al., 2001; Kasper et al., 2005)

#### **4.2 Sensing receptors shared by neurons and osteoclasts**

Both bone remodeling and sensory pain pathways share common inflammatory mediators, including TNF- $\alpha$ , prostaglandins, interleukins, and vasoactive neuropeptides (e.g., substance P), to name a few. Again, specifically targeting the intersection of these pathways may provide unique opportunities for development of innovative therapies related to bone disorders and specifically OTM. The transient receptor potential (TRP) channels is a class of receptors that are involved in sensory and pain processing. For example, The TRP vanilloid 1 receptor (**TRPV1**) is found primarily on neuronal c- and a- $\delta$  fiber nociceptors that are responsible for thermal/burning pain. TRPV1 is also a major transducer of inflammatory pain, especially under acidic conditions. Recent work demonstrated that TRPV1 is expressed in human **osteoclasts**, indicating that TRPV1 may promote bone resorption (Rossi et al., 2009; Rossi et al., 2011). Previous work with ultrapotent TRPV1 agonists such as resiniferatoxin (RTX) indicates that inflammatory pain can be eliminated (Neubert, et al. 2008). TRPV1 is activated in response to lowered pH, which is an important regulator of local bone resorption. TRPV1 is expressed on osteoclasts and agonists of TRPV1, capsaicin and resiniferatoxin (RTX), stimulate osteoclast differentiation at concentrations where neuronal pain sensors are not inactivated (Rossi et al., 2009; Rossi et al., 2011). Interestingly, agonists of TRPV1 induce overexpression of the cannabinoid receptor CB2 (Rossi et al., 2009; Rossi et al., 2011). The TRPV1 inhibitor capsazepine was also shown to inhibit both osteoclast and osteoblast differentiation (Idris et al., 2010). Together, this makes TRPV1 a potential integrator between the central nervous system and bone which may be involved in orchestrating both local bone remodeling changes in response to pH and possibly orthodontic force, and augmenting central modulation of bone remodeling. These data suggest that well documented agonists and antagonists of TRPV1 may prove to be ideal agents for manipulation of OTM in ways by which orthodontic practice may be improved. Increased understanding of OTM can also provide insight into mechanisms of bone biology.

Interestingly, agonists of TRPV1 induce overexpression of the cannabinoid receptor CB2 (Rossi et al., 2009; Rossi et al., 2011). Increased understanding of OTM can provide insight into mechanisms of bone biology. For example, this knowledge may have direct implications for the use of TRPV1 agonists in the treatment of pain and bone destruction associated with bone cancer [10] (Figure 10).

## 5. Summary

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. Proof-in-principle 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 avenues for understanding and manipulating orthodontic tooth movement and perhaps simultaneously reducing the discomfort associated with the procedures.

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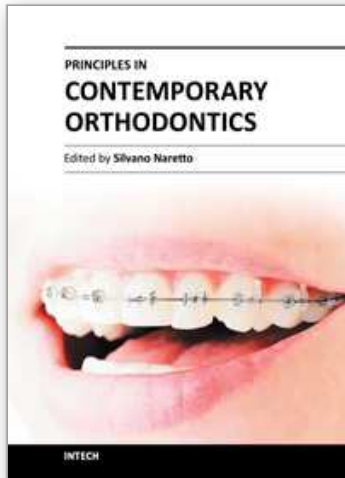
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Orthodontics is a fast developing science as well as the field of medicine in general. The attempt of this book is to propose new possibilities and new ways of thinking about Orthodontics beside the ones presented in established and outstanding publications available elsewhere. Some of the presented chapters transmit basic information, other clinical experiences and further offer even a window to the future. In the hands of the reader this book could provide an useful tool for the exploration of the application of information, knowledge and belief to some orthodontic topics and questions.

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