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Minireview

Autonomic neural signals in bone: Physiological implications for mandible and dental growth

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Abstract

Signals derived from the autonomic nervous system exert potent effects on osteoclast and osteoblast function. A ubiquitous sympathetic and sensory innervation of all periosteal surfaces exists and its disruption affects bone remodeling. Several neuropeptides, neurohormones and neurotransmitters and their receptors are detectable in bone. Bone mineral content decreased in sympathetically denervated mandibular bone. When a mechanical stress was superimposed on mandibular bone by cutting out the lower incisors, an increase in bone density ensued providing the sympathetic innervation was intact. A lower eruption rate of sympathetically denervated incisors at the impeded eruption side, and a higher eruption rate of denervated incisors at the unimpeded side were also observed. A normal sympathetic neural activity appears to be a pre-requisite for maintaining a minimal normal unimpeded incisor eruption and for keeping the unimpeded eruption to attain abnormally high velocities under conditions of stimulated incisor growth. These and other results suggest that the sympathetic nervous system plays an important role in mandibular bone metabolism.
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Keywords: Bone metabolism; Autonomic innervation; Sympathectomy; Superior cervical ganglion; Neurotransmitters; Neuropeptides; Tooth eruption

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Introduction

The skeleton is a specialized and dynamic organ that undergoes continuous regeneration. It consists of highly specialized cells, mineralized and non mineralized connective tissue matrix and spaces that include the bone marrow cavity, vascular canals, canaliculi, and lacunae. Removal of bone (resorption) is the task of osteoclasts while formation of new bone is the task of osteoblasts.

Development and differentiation of osteoblasts and osteoclasts are locally controlled by growth factors and cytokines produced in the bone marrow microenvironment as well as by adhesion molecules that mediate cell-cell and cell-matrix interactions. Signals derived from the endocrine and autonomic nervous systems also exert potent effects on osteoclast and osteoblast development and differentiation (Tan et al., 1999; Manolagas and Weinstein, 1999; Cardinali et al., 2003). Indeed, a ubiquitous autonomic innervation of all periosteal surfaces exists and its disruption may affect bone remodeling control and lead to various bone diseases (e.g., osteogenesis imperfecta). Patients with neurological disorders exhibit localized osteopenia and bone fragility (Gillespie, 1963), altered fracture healing (Freehafer and Mast, 1965) and excessive callus formation (Hardy and Dickson, 1963).

Neurotransmitter signaling in bone cells had been researched sporadically before Rahman et al. showed effects of VIP on bone cell activity in vitro (Rahman et al., 1992a,b). Since then, a number of studies have explored the subject more fully and to review some of them is the aim of the present article, which is focused on results obtained in the field of projection of the superior cervical ganglia (SCG) territory, the first sympathetic ganglion of the paravertebral chain, which includes the mandibular bone.

Bones are innervated by autonomic nerves

Bone and periosteum are innervated by both autonomic and sensory nerves (Miller and Kashara, 1963; Milgram and Robinson, 1965; Duncan and Shim, 1977; Reimann and Christensen, 1977; Hohmann et al., 1986; Bjurholm et al., 1988b). Autonomic nerve fibers are found in the periosteum, endosteum, and cortical bone and, in many cases, the free-running fibers are associated with blood vessels that entered the bone through Volkmann's canals (Parker et al., 1986; Fristad et al., 1994; Buma et al., 1995). One potential role for these fibers is blood flow regulation. For example, maxillary pulpar pressure is modified by the stimulation of different ganglia, the electrical stimulation of SCG producing local vasoconstriction while that of the pterygo-palatine ganglion causing vasodilatation (Boivin et al., 1979).

Developmental studies on the autonomic innervation of bone in rodents indicate that, starting from postnatal day 4, nerve fibers and terminals are observed (Sisask et al., 1996). Noradrenergic sympathetic nerves were discerned first at birth in the perichondrial tissue and within the bone on postnatal day 4. Autonomic cholinergic fibers exhibited a similar temporal and regional pattern. Diaphyseal parts were first innervated on postnatal day 4, while the fibers extended into the metaphysis and the epiphysis at postnatal days 8–10, concomitant with the first signs of mineralization (Sisask et al., 1996). Collectively, the results suggest that autonomic innervation of bone is related to the mineralization process.

A number of neuropeptides, neurohormones and neurotransmitters are detectable in bone, among them substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) (Hill and Elde, 1991; Fristad et al., 1994; Brown et al., 1997; Cornelissen et al., 1998; Jacobsen et al., 1998; Chole and Tinling, 1998). As in most parts of the body, fibers containing

NPY are most likely to arise from noradrenergic sympathetic neurons while VIP fibers are most probably cholinergic, of parasympathetic origin in cranial regions and of sympathetic origin in the trunk.

In dental pulp, SP fibers were mostly found in the central parts as well as in relation to the odontoblasts and disappeared after transection of the inferior alveolar nerve (Olgart et al., 1977). In contrast, superior cervical ganglionectomy (SCGx) did not affect SP immunoreactive nerve fibers. SP and CGRP immunoreactivity was also observed in membranes of the lumbar facet joint and in the synovium and adjacent bone in rats. In the synovium, SP fibers occur in the lining cell layer, with some of them branching towards the joint space. In the sublining layer of the synovium, both types of fibers were observed mainly near the blood vessels (Ahmed et al., 1993, 1994a,b; Iwasaki et al., 1995). SP/CGRP fibers are almost certainly derived from unmyelinated (C-fiber) sensory neurons, most likely to be nociceptors. In addition, sensory innervating fibers can be relevant for bone growth, as it is indicated in studies in which work load decreased by surgical denervation, tenotomy, immobilizing casts or weightlessness (Nordsletten et al., 1994; Madsen et al., 1998).

Several histochemical studies also revealed that both osteoblast and osteoclast express neuropeptidergic and noradrenergic receptors. For example, mRNAs expression of CGRP-R, NPY-R, VIP-1R and beta2-R, but not of SP-R, VIP-2R, PACAP-R, beta1-R and beta3-R was characterized in human periosteum-derived osteoblastic cells and osteosarcoma-derived cells (Bjurholm et al., 1988a,b; Lerner et al., 1994; Togari et al., 1997). Mouse calvarial osteoblasts expressed functional VIP-2R, as revealed by a VIP-stimulated osteoblastic alkaline phosphatase biosynthesis and bone noduli formation via a cyclic AMP-dependent phenomenon (Lundberg et al., 2001).

A feedback relation between bone formation and autonomic nerves was revealed by the demonstration that type 2 and 6 bone morphogenetic proteins induce mRNAs for several neuropeptide and neurotransmitter synthetic enzymes in vitro (Fann and Patterson, 1994). Collectively, the data suggest the possibility that anabolic processes in bone are under the control of the autonomic nervous system (Lundberg et al., 1999).

It is interesting that the amino acid glutamate, the principal excitatory neurotransmitter in the central nervous system, is also demonstrable in bone; glutamate fibers are most likely to be of sensory origin. Mason et al. first reported that bone and bone marrow cells express glutamate transporters (Mason et al., 1997). Subsequently, it was showed that osteoblasts and osteoclasts express glutamatergic receptors, mainly the ionotropic N-methyl-D-aspartate (NMDA) receptor 1 subunit, and that a monoclonal antibody against this subunit inhibited bone resorption in vitro (Chenu et al., 1998; Patton et al., 1998; Espinosa et al., 1999; Itzstein et al., 2001). The specific antagonist of NMDA, MK 801, rapidly decreased the percentage of actively resorbing osteoclasts but had not effect on osteoclast attachment to bone and did not induce osteoclast apoptosis (Itzstein et al., 2000). These results suggest that NMDA receptors may be involved in adhesion-induced formation of the sealing zone required for bone resorption. In electron microscopic studies of glutamatergic nerve fibers, nerve processes showing local dilatations in contact with bone marrow and bone cells were demonstrated (Serre et al., 1999). A local regulation of the glutamate transporter protein was also shown. Mechanical loading of rat ulna produced a down regulation of glutamate transporter in cortical bone, with up regulation of the protein in the periosteal surface. The data suggest that glutamate transporter is involved in coupling mechanical loading to skeletal modeling and that its regulation may be an early response of osteocytes to mechanical loading of bone (Mason et al., 1997).

A link between bone sensory and autonomic fibers was indicated by the efficacy of capsaicin, a neurotoxin that eliminates SP-containing sensory fibers, to blunt sympathectomy-induced bone

resorption (Lundberg et al., 1999). It is interesting that the administration of β-adrenoceptor agonists (e.g., clenbuterol, dobutamine) reduced net bone loss in denervated hind limbs (Zeman et al., 1997) and decreased the scoliosis seen after a partial transection of rat spinal cord (Zeman et al., 1991). Therefore, immunohistochemical and biochemical studies of nervous system components in bone reflect not only sensory and vascular regulatory functions by neurotransmitters, but also a potentially local neurohormonal control of bone cell activity.

Sympathetic denervation affects bone remodeling

In order to understand the significance of the autonomic innervation in bone metabolism, experiments employing both surgical (Sandhu et al., 1987; Schwartzman and McLellan, 1987; Sherman and Chole, 1995, 1996; Jacobsen et al., 1998; Ladizesky et al., 2000, 2001; Ohtori et al., 2001a,b; Ladizesky et al., 2003) or chemical (Singh et al., 1981, 1982; Herskovits and Singh, 1984; Hill et al., 1991; Cherruau et al., 1999, 2003) denervation were performed.

An easy-to-manipulate anatomical region to examine the acute and chronic effects of sympathetic denervation is the SCG territory (Cardinali and Romeo, 1991). Axons leaving the SCG provide sympathetic innervation to facial structures, the skull and the neck, including the hemimandibular bone. In the rat, SCG ganglionic neurons are grouped in three main associations: (i) a rostral group that projects via the internal carotid nerve (about 35% of SCG neurons), (ii) a caudal group that projects via the external carotid nerve (about 50% of SCG neurons), and (iii) a caudal group that sends descendent projections through the cervical sympathetic trunk (about 15% of SCG neurons) (Bowers and Zigmond, 1979). Topographical studies of functional subpopulations of neurons in the rat SCG indicated that individual neurons have very limited projection fields and almost absent contralateral innervation of bilateral targets (Bowers and Zigmond, 1979). A peculiarity of the innervation provided via external carotid nerve (like that to the mandibular bone) is that some of the innervating ganglionic perikarya are located in the middle and/or inferior sympathetic cervical ganglia and send their axons through the SCG and the external carotid nerves (Bowers and Zigmond, 1981; Romeo et al., 1986).

Several strategies have been employed to examine the neuroendocrine consequences of SCG manipulation. In some cases, a ‘‘deprivation experiment’’ was performed by examining the sequelae of SCGx some weeks after surgery. In other cases, the transient postsynaptic activation that occurred either after electrical stimulation of the cervical sympathetic trunk to the SCG (Melander et al., 1974) or during the early phase of anterograde (Wallerian) degeneration of the sympathetic nerve endings in SCGx animals was analyzed (‘‘degeneration reaction’’) (Cardinali et al., 1982). In the case of chronic studies, the surgical denervation has clearly more advantages than, for example a general chemical sympathectomy obtained by injecting the adrenergic neurotoxin 6-hydroxydopamine. Indeed, the general toxic effects of the drug can never be ruled out, and a number of autonomic systemic reflex sequels arise, making it difficult to interpret the results obtained.

Sandhu et al. were the first to examine the effect of a unilateral SCGx on bone remodeling at rat incisor and molar root sockets (Sandhu et al., 1987). Following sympathectomy, periosteal and endosteal apposition as well as the rate of mineralization decreased and an increase in the number of osteoclasts and in active and inactive bone resorption surfaces was seen. Since independent, sham-operated rats were used as controls, rather than the contralateral sham-operated side of the same

animal, any possible systemic effects of hemi-Gx could not be ruled out (Sandhu et al., 1987). Subsequent studies using a similar experimental approach confirmed the initial results (Sherman and Chole, 1995, 1996).

An increase in percentage of periosteal surface of the mandible occupied by osteoclasts during remodeling was reported in rats treated neonatally with guanethidine (Sherman and Chole, 2001). As noted above, a major criticism for studies employing drugs which interfere with sympathetic autonomic function is that any systemic effect on hormonal mechanisms controlling bone processes cannot be excluded.

In order to assess in an anatomically specific way the effect of local sympathectomy on bone physiology, we examined the effect of unilateral SCGx on growth and bone mineral content and bone mineral density of the ipsi and contralateral hemimandibles (Ladizesky et al., 2000). One month-old female Wistar rats were used. A unilateral SCGx and a contralateral sham-operation were performed 15 or 30 days prior to sacrifice. A significant increase in the weight of the hemi-mandibular bone ipsilateral to SCGx was found as compared to the contralateral, sham-operated side. Total bone mineral content of the hemi-mandibular bones decreased in the side ipsilateral to SCGx. Since no difference in densitometrically determined bone mineral areas between innervated and denervated hemi-mandibles was found, bone mineral density (i.e. bone mineral content/bone mineral area ratio) was also significantly lower in the hemi-mandible ipsilateral to SCGx. This effect of local denervation was presumably dependent on the chronic deprivation of adrenergic neurotransmitter input at a local level, since there is evidence that bone tissue is responsive to stimulation with adrenoceptor agonists (Garbarino and Greene, 1984; Moore et al., 1993). In view of the age of the animals (1 month old) the modifications in bone mass caused by denervation could be due to changes in preexisting tissue as well as to modification of developmental growth.

Sympathetic denervation modifies tooth growth

Because of their similarities to teeth of limited eruption like human teeth, the erupting incisors of the rats are commonly used as models of tooth eruption (Burn-Murdoch, 1995). If a lower incisor is kept short to stop it being bitten it erupts at about twice the rate of unshortened incisors. This paradigm of unimpeded (shortened incisor) and impeded (unshortened incisor) eruption, introduced by Bryer more than 40 years ago (Bryer, 1957), has allowed the analysis of systemic and local auto/paracrine factors modifying tooth eruption (Giglio et al., 1987; Burn-Murdoch, 1992). It also can be used as an experimental model of mechanical stress for the mandibular bone.

The autonomic nervous system is one of the factors modifying tooth eruption. Teeth are innervated by unmyelinated sympathetic axons originating in the ipsilateral SCG, and by unmyelinated and small myelinated sensory axons, most of them terminal branches of larger parent axons in the trigeminal nerve. The sympathetic nerve endings contain norepinephrine while sensory dental axons contain SP-like immunoreactivity. Other neuropeptides are also present in dental nerves, like VIP and NPY (Byers, 1984; Fristad et al., 1994; Ngassapa, 1996). Adrenergic nerves end at the odontoblast/predentine border, in the predentine adjacent to the odontoblast processes, and as free endings in the middle part of the predentine (Inoue et al., 1992). In situations of degenerative autonomic neuropathy an overall marked reduction in pulpar innervation with an absence of large nerve bundles and the subodontoblastic plexus have been reported in humans (Rodd et al., 1998).

About 75 years ago, Leist first reported a stimulatory effect of sympathetic denervation on rodent incisor eruption rate (Leist, 1927). Significant acceleration of eruption rate by sympathetic denervation was also observed in other studies (King, 1937; Bryer, 1957), but not in all (Taylor and Butcher, 1951; Miller, 1957). At best, early reports indicated a transient effect of SCGx on rodent incisor eruption rate. More recently, acceleration of movement of rabbit and cat incisors shortly after SCGx or adrenergic drug injection were observed (Moxham, 1981; Aars and Linden, 1982; Aars, 1982a,b; Ohyama and Yamaguchi, 1999).

In view of the above described effects of SCGx on mandibular bone, we examined the effect of a unilateral SCGx on the eruption rate of ipsilateral and contralateral rat incisors in two experimental situations: (i) without any further manipulation; (ii) after the ipsi—or contralateral lower rat incisor had been cut out of occlusion (Ladizesky et al., 2001). Animals were studied for up to 30 days after surgery. Impeded and unimpeded eruption rates of the lower incisors were determined every 2 days (Main and Adams, 1965; Aladdin and Burn-Murdoch, 1985). Two experiments were performed. In a first experiment, the eruption rate of ipsilaterally denervated incisors was similar to that of contralaterally innervated incisors, when assessed for up to 28 days after surgery. In a second experiment, under conditions of unilateral unimpeded eruption of incisors performed ipsilaterally or contralaterally to a unilateral SCGx, a significantly lower eruption rate of denervated incisors at the impeded eruption side, and a significantly higher eruption rate of denervated incisors at the unimpeded side were observed (Fig. 1).

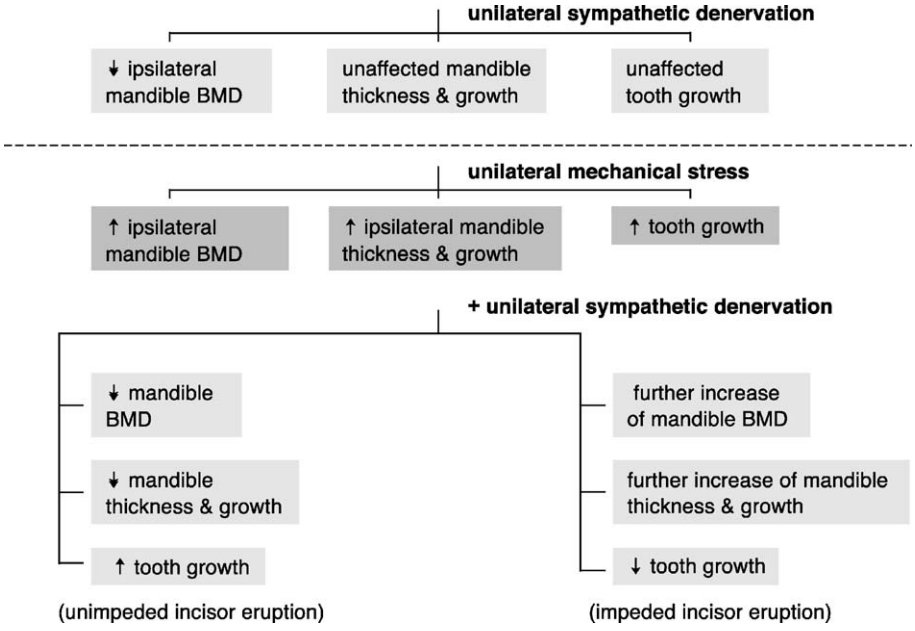

Fig. 1. Diagram summarizing the effect of unilateral sympathetic denervation on rat mandibular bone. The effect of a unilateral SCGx on bone mineral density (BMD), morphometric assessment of mandible thickness and growth, and eruption rate of ipsilateral and contralateral incisors were analyzed in two experimental situations: (i) without any further manipulation; (ii) after a unilateral mechanical stress given by cutting the ipsi—or contralateral lower incisor out of occlusion. For further explanation, see text.

The lack of effect of SCGx on eruption rate in animals under a normal impeded incisor eruption on both sides agreed with previous observations (Taylor and Butcher, 1951; Miller, 1957). Indeed, our results indicated that incisor eruption is not modified by a local sympathetic denervation unless the contralateral lower rat incisor was cut out of occlusion. When this was done, sympathetically denervated incisors exhibited higher eruption rates at the unimpeded eruption side and lower eruption rates at the impeded side (Fig. 1).

Why only under situation of a mechanical stress by unimpeded eruption an effect of sympathetic denervation emerges deserves to be further explored. Risnes et al. (Risnes et al., 1995) reported that under conditions of unilateral unimpeded eruption, the rate of eruption of the uncut (impeded) contralateral incisor attains about 140% of the baseline rate. Moreover, neither the unimpeded nor the impeded incisors returned to control values immediately after the period of unimpeded eruption ended, but showed transient changes in their lengths and eruption rates (Burn-Murdoch, 1999). Therefore, an accelerated eruption, presumably affecting morphogenesis and histogenesis of the rat lower incisors, is a pre-requisite for the effect of sympathetic denervation to occur. The involvement of sensory fibers (e.g., SP-containing fibers) in this phenomenon deserves to be considered. In middle ear bone a link between peripheral sensory and autonomic fibers was indicated by the efficacy of capsaicin, a neurotoxin that eliminates SP-containing sensory fibers, to blunt sympathectomy-induced bone resorption (Sherman and Chole, 1995). It should be noted that the effect of sympathetic denervation remained essentially the same since the beginning of the experiment under conditions of ipsi—or contralateral unimpeded eruption (Ladizesky et al., 2001). This happened regardless of the different phases of postsynaptic activity that ensue after cutting the sympathetic nerves noted above. Our results indicate that, regardless of transient postsynaptic hyperactivity caused by supraliminal transmitter release from degenerating varicosities, the effect of SCGx was always the same, i.e. a lower eruption rate at the impeded eruption side and a higher eruption rate at the unimpeded side.

Therefore, a normal presynaptic neural activity, and not merely an augmented transmitter release, seems to be a pre-requisite for maintaining a minimal normal unimpeded incisor eruption and for keeping the unimpeded eruption to attain abnormally high velocities under conditions of stimulated incisor growth. This dual role of the autonomic nervous system on organ's activity is found in several other tissues, like endocrine and immune tissues. For example, a normal sympathetic output maintains basal cell proliferation in lymph nodes and curtails overstimulation following an antigen challenge (Esquifino and Cardinali, 1994; Cardinali and Esquifino, 1998; Cardinali et al., 2000).

It is interesting that extensive exocytosis of granular vesicles occurs in noradrenergic nerve endings located as free nerve endings near the areas of collagen formation in the predentin (Arwill et al., 1973; Johnsen, 1985; Inoue et al., 1992). This finding suggests an active regulatory role of sympathetic nerves on predentin collagen. In addition, SCGx augmented ^{3}H-fucose incorporation into murine predentinal matrix, indicating a regulatory role for the sympathetic nervous system in the control of glycoprotein synthesis by odontoblasts (Chiego et al., 1983). Since the rate of turnover of collagen in periodontal ligament is closely associated with the process of tooth eruption (Bertseen et al., 1974; Taverne, 1993), the possibility that sympathetic nerves could modulate the presence and maturation of collagen and its possible function in the process of tooth eruption should be considered.

Tooth eruption requires alveolar bone resorption and the presence of the dental follicle, a loose connective tissue sac that surrounds each tooth. Such bone resorption involves the follicle in that mononuclear cells enter it to form osteoclasts which resorb bone. Eruption genes, like colony-stimulating factor-1, c-fos, and monocyte chemotactic protein-1, are expressed maximally in the dental

follicle at the time of the critical initial cellular event of tooth eruption (Wise et al., 1998, 1999). These phenomena may be under the control of sympathetic nerves since SCGx increased the number of osteoclasts and bone resorption surfaces in rat incisor and molar root sockets (Sandhu et al., 1987).

Sympathetic denervation affects bone depending on superimposed mechanical stress

The disparate effect of SCGx on bone weight and bone mineral content and density above discussed indicated the occurrence of dissimilar effects of sympathetic nerve endings on matrix and mineral content of mandibular bone. To examine this last possibility we undertook a study designed to assess changes in volumetric bone density (vBMD) and in mandible's morphometric assessment in SCGx rats (Giglio and Lama, 2001). The study looked to analyze the effect of a unilateral SCGx on total, cortical and trabecular vBMD and mandible's morphometry, under two experimental situations: (i) without any further manipulation; (ii) after the mechanical stress caused by cutting ipsi—or contralateral lower rat incisors cut out of occlusion (Ladizesky et al., 2003).

Two experiments were performed. In a first experiment the effect of a unilateral SCGx and a contralateral sham-operation was assessed. In a second experiment half of the animals received a left SCGx and half a right SCGx, together with their respective contralateral sham-operations. Every 2 days the lower right incisors were shortened with a diamond disk to make them unimpeded (unimpeded eruption rate), the left incisors remaining impeded (impeded eruption rate) (Fig. 1).

It has been proposed that jaws consist of a number of skeletal units, each unit being considered a relatively independent functional component (Moss, 1968, 1969; Moore, 1973). Each component includes both skeletal as well as non-skeletal tissues. To assess the effect of the different experimental manipulations on mandible's skeletal units, a periapical radiograph of each hemimandible was obtained by using a Roentgen source located at 90° on the centre of the film (Giglio and Lama, 2001). vBMD was examined by peripheral computed tomography (pQCT) to analyze total, cortical and trabecular bone (Jiang et al., 1998). Two separate regions of interest were manually selected as follows: for cortical vBMD, on the bone cortical region at the lower ramus; for trabecular vBMD, in the medullar zone beneath. Such sub-regions are mainly influenced by neuromuscular functional demands and are of clinical interest (Kiliaridis et al., 1996).

Only a few mandibular morphometric parameters decreased significantly after sympathetic denervation in rats subjected to a unilateral SCGx and a contralateral sham-operation. vBMD decreased significantly after sympathetic denervation. Further analysis indicated higher morphometric indexes in denervated mandibles than in the innervated ones under impeded incisor eruption conditions, and lower morphometric indexes in denervated mandibles than in the innervated ones under unimpeded incisor eruption conditions. Unimpeded eruption augmented total volumetric bone density providing the innervation was intact and caused opposite effects on cortical volumetric bone density in the presence of innervation (increase) or absence of innervation (decrease). Trabecular volumetric bone density decreased significantly after sympathetic denervation. These results indicated that for most morphometric measurements in sympathetically denervated mandibles, growth was greater under impeded incisor eruption conditions, and smaller under unimpeded incisor eruption conditions than in innervated mandibles. At least for cortical bone, 70% of observed variation had been attributed to changes in porosity that in this case, would correspond to the microstructural changes secondary to an altered mechanical stimulus (unimpeded incisive eruption in a sympathetically denervated bone). Therefore,

combination of unimpeded eruption and ganglionectomy revealed best the osteopenia arising from cutting mandible's sympathetic nerves. The changes were also reflected in the adjacent trabecular zone (Ladizesky et al., 2003).

An ideal natural experiment to test the applicability and validity of the above discussed concepts on sympathetic innervation on bone surrounding the teeth in humans could be the examination of patients with Claude Bernard-Horner's syndrome, where there is a long lasting, often unilateral, sympathetic denervation of the head.

Concluding remarks

Bone strength and therefore its resistance to fracture are strongly correlated with the mass and orientation of the load-bearing extracellular matrix. The matrix is in turn the result of the orchestrated activity of osteoblasts and osteoclasts that form and model/remodel the tissue. Changes in bone mass and architecture are linked directly to the regulated activity of those cells, and therefore to the endocrine, paracrine and autocrine influences on them.

One possible mechanism for such a delicate control is the ubiquitous sympathetic innervation of all periosteal surfaces, acting through effects similar to those herein discussed. Disruption of neural control of modeling can lead to bone disease like osteogenesis imperfecta. Potential mechanisms for the effects of sympathectomy may include disinhibition of resorption, secondary to the elimination of periosteal sympathetics, as well as indirect vascular effects.

The proposed effect of autonomic nerves in bone is not without experimental background in other tissues. For example, the autonomic nervous system affects the amplitude of proliferative responses like that occurring during the immune reaction or after a reduction of the erythrocyte mass (Esquifino and Cardinali, 1994; Cardinali and Esquifino, 1998; Cardinali et al., 2000). In turn, the activity of sensory fibers in the vicinity of proliferating bone cells may help to serve to build up in the brain a viscerotopic map not dissimilar from that of dermatomes as far as the cutaneous structure.

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