



Review

The roles of the sympathetic nervous system in osteoporotic diseases: A review of experimental and clinical studies

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ABSTRACT

With the rapid aging of the world population, the issue of skeletal health is becoming more prominent and urgent. The bone remodeling mechanism has sparked great interest among bone research societies. At the same time, increasing clinical and experimental evidence has driven attention towards the pivotal role of the sympathetic nervous system (SNS) in bone remodeling. Bone remodeling is thought to be partially controlled by the hypothalamus, a process which is mediated by the adrenergic nerves and neurotransmitters. Currently, new knowledge about the role of the SNS in the development and pathophysiology of osteoporosis is being generated. The aim of this review is to summarize the evidence that proves the involvement of the SNS in bone metabolism and to outline some common osteoporotic diseases that occur under different circumstances. The adrenergic signaling pathway and its neurotransmitters are involved to various degrees of importance in the development of osteoporosis in postmenopause, as well as in spinal cord injury, depression, unloading and the complex regional pain syndrome. In addition, clinical and pharmacological studies have helped to increase the comprehension of the adrenergic signaling pathway. We try to individually examine the contributions of the SNS in osteoporotic diseases from a different perspective. It is our hope that a further understanding of the adrenergic signaling by the SNS will pave the way for conceptualizing optimal treatment regimens for osteoporosis in the near future.

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1. Introduction

Osteoporosis is defined as a skeletal disorder characterized by a low bone mass and structural deterioration of bone tissue. Its consequences are compromised bone strength and an increased risk of fracture. Bone is a highly intriguing, living tissue that undergoes remodeling throughout a person's whole life through the anabolic function of the osteoblasts and the catabolic function of the osteoclasts. The two processes are tightly coupled to maintain a dynamic balance, which results in a stable and strong bone mass in adults. When this balance is upset, causing a predominance of bone resorption over bone formation, bone loss can be triggered, resulting in an increased susceptibility to fractures (Akune et al., 2002). Skeletal health is mainly dominated by genetic mechanisms (Zelzer and Olsen, 2003). In contrast, bone remodeling is thought to be regulated by nutritional status (Nakamura, 2006), humoral factors (Clowes et al., 2005; Janssens et al., 2005), and biomechanical stress (Burr et al., 2002; Klein-Nulend et al., 2005). More recently, though, mounting evidence has revealed the pivotal role of the sympathetic nervous system (SNS) in the maintenance of bone health and devel-

opment of osteoporosis. Even in patients with anorexia nervosa, restrictive behaviors were found not to be the only reason for bone loss, instead the activation of the SNS through β_2 -adrenergic signaling in the osteoblasts was additionally blamed for exacerbating bone loss. Consequently, more research has been centered on neuroskeletal pathways (Kumar et al., 2010). Both sympathetic and sensory nerve fibers have been identified to exist in bone tissue; in this article, we focus on the role of the SNS, since less knowledge has so far been acquired on the function of the sensory nerves in bone. We have reviewed the recent updates to our understanding of the roles of the SNS in osteoporosis and related evidence of the association between the SNS and osteoporotic diseases obtained from experimental and clinical observations. We subsequently discuss the potential underlying mechanisms. A synopsis of the roles played by the SNS in a number of osteoporotic diseases is illustrated by a flow diagram (Fig. 1). The studies reviewed herein intend to offer new insights into the roles of the sympathetic nervous system in bone remodeling.

2. Sympathetic innervation and transmitters

The SNS forms one of the three parts of the autonomic nervous system, together with the enteric and parasympathetic systems. It serves to induce the fight-or-flight response; most importantly, it is

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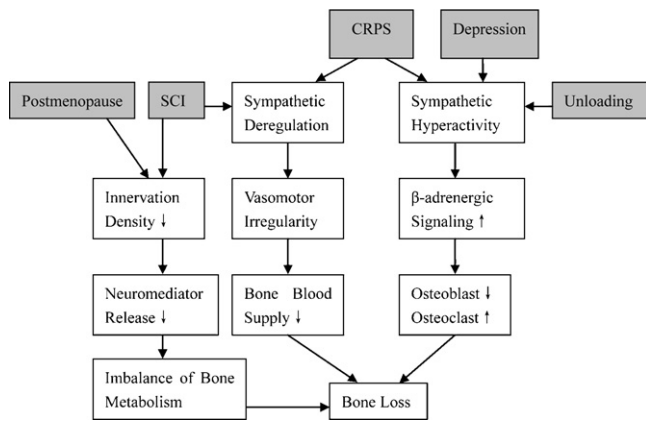


Fig. 1. Synopsis of the roles played by the SNS in a number of osteoporotic diseases.

activated at a basal level in order to maintain homeostasis in tissue and in the organs (Ray, 1955). Bone is not a uniformly solid material. In adults, the hard cortical bone in the outer layer accounts for 80% of the total bone mass, whereas the trabecular bone, filling the bone interior, makes up the remaining 20%. Without exception, bone metabolism is also modulated by the SNS. However, the regulation of bone turnover by the SNS hardly drew attention until both experimental and clinical evidence had demonstrated the neural innervation of bone (Mach et al., 2002; Serre et al., 1999). Immunohistochemical studies showed that sympathetic and sensory nerve fibers are present in the periosteum and bone, with greatest density around the growth plates and in the metaphysis of long bones, forming parallel networks that accompany blood vessels adjacent to the bone trabeculae. In cortical bone, nerve fibers run within the Haversian and Volkmann's canals. Dense neural networks are

in close contact with bone cells, strongly implying a physiological role in the innervation of bone tissue (Asmus et al., 2000; Burt-Pichat et al., 2005; Hill and Elde, 1991; Hohmann et al., 1986; Martin et al., 2007; Togari, 2002). Furthermore, β -adrenergic and neuropeptide receptors have been detected on osteoblastic and osteoclastic cells (Nagata et al., 2009; Togari, 2002). Most recently, an *in vitro* co-culture study of murine superior cervical ganglia and osteoclast-like cells demonstrated that there exists a direct neurite-osteoclastic cell communication via the adrenergic receptors (Suga et al., 2010). These results suggest a neuroendocrine regulation in the integrity maintenance and repair processes of bone.

Sympathetic denervation causes abnormal bone formation and resorption, which indicates a SNS mediation in bone remodeling. Excision of the superior cervical ganglion or chemical sympathectomy with guanethidine in rats increased bone resorption (Haug et al., 2003; Kim et al., 2009), which may be attributable to an increase in the surface and number of osteoclasts (Cherruau et al., 2003; Ladizesky et al., 2003). The chemical sympathectomy with guanethidine in adult rats not only led to a decreased bone mass, but also an altered bone architecture by regulating deposition rather than resorption (Pagani et al., 2008). Opposite results, namely that bone resorption was impaired by guanethidine treatment, were also reported (Cherruau et al., 1999).

Genetic murine models with autonomic dysfunctions induced by pharmacological intervention have made it possible to collect reliable evidence of the fact that neuronal pathways control bone mass. They have also facilitated the exploration of specific factors functioning within the SNS. Dopamine β -hydroxylase (D β H) deficient mice, incapable of producing norepinephrine, displayed a high bone mass phenotype (Li et al., 2001) (Table 1). In agreement with this result, mice and rats treated with the nonselective β -adrenergic blocker propranolol exhibited an increased bone mass (Minkowitz et al., 1991), whereas mice treated with the non-

Table 1
Effects of gene ablation on bone phenotype abnormalities.

Studies [first author (publication year)]	Specific gene knock-out	Physiological function of gene	Bone phenotype alteration	Notes
Ducy et al. (2000)	Ob/ob Db/db	Leptin secretion Leptin receptor	High bone mass (in vertebrae and long bones, increased number of trabeculae, cortical bone not affected)	High bone mass despite hypogonadism and hypercortisolism
Takeda et al. (2002)	Dopamine β -hydroxylase (Dbh)	An enzyme necessary for generating norepinephrine and epinephrine	High bone mass (in vertebrae and long bones, high trabecular bone volume with increased osteoblast number and BFR)	High bone mass despite hypogonadism and hypercortisolism
Pierroz et al. (2004, 2005)	β -1,2 Adrenergic Receptor (Adrb1,2)	Adrb1: heart muscle contraction	Low bone mass	1. Significantly lower BMD at total body 2. Marked inhibition of bone formation, suggesting that the higher bone formation in <i>Adr2R^{-/-}</i> require β 1 adrenergic signaling
Elefteriou et al. (2005)	β 2 Adrenergic Receptor (Adrb2)	Adrb2: smooth muscle relaxation, involvement in the control of bone remodeling	High bone mass (increased BV/TV, BFR, osteoblast number and decreased osteoclast proliferation)	1. More severe high bone mass than ob/ob or wt mice receiving β -blockers 2. No significant decrease in bone mass following OVX. 3. Leptin icv infusion failed to reduce the bone mass in <i>Adrb2^{-/-}</i>
Yan et al. (2007)	Adenylyl cyclase 5 (AC5)	Downstream mediator of β 2-AR signaling	Bone quality preserved in old mice	Greater bone peak torque, shear modulus, and shear stress than old mice
Bouxsein et al. (2009)	β -1,2,3 Adrenergic Receptor (Adrb1,2,3)	Adrb3: enhancement of lipolysis in adipose tissue	High bone mass	Increased cortical bone mass in male mice, but no protection from estrogen deficiency on trabecular bone microarchitecture

BV/TV: bone volume/tissue volume; BFR: bone formation rate; BMD: bone mineral density; OVX: ovariectomy, icv: intracerebroventricular; wt: wild type.

Table 2
Bone phenotype alteration studies by pharmacological approaches.

Studies [first author (publication year)]	Bone phenotype alteration	Notes
Propranolol: non-selective β -adrenergic antagonist Minkowitz et al. (1991)	High bone mass	1. Increased bone formation, improved antitortional force in nonsurgical rats 2. Increased callus and bone union in fracture model
Takeda et al. (2002)	High bone mass (in vertebrae and long bones)	1. Increased osteoblast number and BFR in wt mice 2. Preventive effect in OVX mice against bone loss
Levasseur et al. (2003)	High bone mass (BMD is rescued in the unloading rat model)	1. Preventive effect on BMD and trabecular bone microarchitecture in suspended or immobilized rats 2. Unloading-induced increase in osteoclastic activity was suppressed
Kondo et al. (2005)	High bone mass	1. Lower osteoclast surface, higher osteoblast activity and MAR 2. Better preventive effect against bone loss following OVX with a lower dose propranolol
Bonnet et al. (2006)	High bone mass	Increased osteoblast number and surface, partially rescued the bone loss following OVX in mice
Pierroz et al. (2006)	High bone mass	Moderately decreased BMD and trabecular area, increased trabecular number in OVX rats
Zhang et al. (2007)	High bone mass	Increased BFR in stressed mice with a low dose propranolol
Yirmiya et al. (2006)	High bone mass	Mechanical loading enhanced cortical bone formation in mice, but no further improvement with propranolol
de Souza et al. (2005)	No difference	No effect on unloading-induced bone loss in both cortical and trabecular bone, but increased tibial trabecular thickness in control mice
Marenzana et al. (2007)	No difference	
Isoproterenol: non-selective β -adrenergic agonist Takeda et al. (2002)	Low bone mass (in vertebrae and long bones)	Decreased BFR and osteoblast number without affecting body weight in ob/ob or wt mice
Kondo et al. (2005)	Low bone mass	Reduced bone mass in loaded mice, and unloading no longer further reduced bone mass
Pierroz et al. (2005)	Low bone mass	Reduced BMD gain at total body and spine, and modestly decreased femur lengthening.
Clenbuterol or salbutamol: β 2-AR selective agonists Bonnet et al. (2005)	Low bone mass	1. Lower BMC and biomechanical properties in rat 2. Clenbuterol reduced BMD and trabecular bone microarchitecture

OVX: ovariectomy; wt: wild type; BFR: bone formation rate; icv: intracerebroventricular; MAR: mineral apposition rate; BMD: bone mineral density; BMC: bone mineral content.

selective β -agonist isoproterenol or the β 2-AR selective agonists clenbuterol or salbutamol showed a low bone mass (Table 2).

To add a further perspective, β -blockers are widely prescribed for elderly patients with hypertension or coronary heart disease. This fact provides an opportunity to examine their effect from clinical perspectives. Many observations obtained from case-control analyses or cohort studies of patients showed that β -blockers are associated with a higher bone mineral density (BMD) or a reduced risk of fracture (de Vries et al., 2007; Gage et al., 2006; Meisinger et al., 2007; Schlienger et al., 2004; Schoofs et al., 2005; Sosa et al., 2010). However, not all epidemiological investigations are in agreement (Jensen et al., 1991; Rejnmark et al., 2004). It is noteworthy that Rejnmark et al. (2004) in a first study reported that β -blockers did not affect bone mass in perimenopausal women, and that even an increased fracture risk (OR, 3.3; 95%CI, 1.1–9.4) was observed after adjustment for potential confounders. Two years later, however, the authors drew an opposing conclusion that the risk of any fracture was reduced by 9% (OR, 0.91; 95%CI, 0.88–0.93) in users of β -blockers after adjustment for potential confounders, based on a larger, nationwide, population-based case-control study (Rejnmark et al., 2006).

3. SNS: a bridge between leptin-dependent central control and bone remodeling

After menopause, women with a lower body weight tend to lose bone mass more rapidly compared to heavier women. The protective effect of obesity against bone loss is ascribed to a higher percentage of body fat. This phenomenon aroused great interest in the potential protective effects of leptin on bone mass (Lovejoy, 2003). Leptin, a 16 kDa multifunctional adipocyte-derived hormone, is known to regulate reproduction and the energy metabolism through its cytokine receptor ObRb located in the ventromedial hypothalamic neurons. It has also emerged as an important factor in the modulation of bone mass (Ahima and Flier, 2000). Leptin is a powerful inhibitor of bone formation *in vivo*. High bone mass was found in leptin-deficient (ob/ob) mice. Intracere-

broventricular (ICV) infusion of leptin without detectable leakage into the general circulation caused bone loss in both wild-type and leptin-deficient mice by inhibiting the osteoblastic function. Of note, bone formation is inhibited at lower doses of leptin than those necessary to cause the loss of body weight (Karsenty, 2006). Furthermore, wild-type mice displayed a high bone mass phenotype after ventromedial hypothalamic neurons had been destroyed by gold thioglucose. The phenotype was nearly identical to that of the ob/ob mice. Subsequently, these impaired mice were found to have no response to the antiosteogenic effect of ICV leptin (Takeda et al., 2002). These findings strongly support a central, hypothalamic relay of bone mass regulation.

The link between a leptin-dependent central control and bone remodeling deserves exploration. Ob/ob mice have a low sympathetic tone; a genetic or pharmacological ablation of adrenergic signaling results in a leptin-resistant high bone mass. This supports the notion that the central effect of leptin on bone is mediated by the SNS (Takeda et al., 2002). Another unequivocal argument is that leptin fails to increase bone resorption in Dbh^{-/-} mice, adrb2-deficient mice or β -blocker pretreated mice, even when the leptin dose decreases fat pad (Eleftheriou et al., 2005). The results suggest that SNS integrity is indispensable for leptin antiosteogenic function. On the other hand, osteoblastic and osteoclastic cells are equipped with β 2 adrenergic receptors and neuropeptide receptors. The β 2 adrenergic receptor is so far the only adrenergic receptor known to be expressed in osteoblasts (Moore et al., 1993; Togari, 2002). These observations suggest that the antiosteogenic function of leptin is mediated by the SNS through the β 2 adrenergic receptor. Dense and intimate nerve endings have been found to be in contact with bone cells and bone marrow, suggesting a neural regulation of bone remodeling (Serre et al., 1999). Taken all together, the completed puzzle could potentially look as follows: leptin acts on a population of neurons located in the ventromedial hypothalamus which subsequently stimulates the noradrenergic sympathetic nerve fibers to release norepinephrine. The norepinephrine then specifically binds to β 2 adrenergic receptors expressed on the osteoblasts to inhibit osteoblast activity, and thus inhibits bone formation. At the same

time, the adrenergic nerves may activate the receptor activator of the NF- κ B ligand (RANKL) in osteoblasts and trigger RANKL-mediated osteoclastogenesis and bone resorption (Elefteriou et al., 2005).

4. Postmenopausal osteoporosis

Postmenopausal osteoporosis is a heterogeneous disorder characterized by a progressive loss of bone tissue after ovariectomy or loss of ovarian function and by an increase in risk of fracture. Considerable evidence has accumulated to suggest that changes in the estrogen and cytokine levels during menopause and in aging women have a dominant influence on the bone loss in postmenopausal osteoporosis (Kimble et al., 1996; Rossouw et al., 2002). In fact, the involvement of the SNS remained veiled until the revelation of the most recent findings: (1) β 2-adrenergic receptor-deficient mice exhibited a high bone mass phenotype, whereby bone resorption was inhibited even after ovariectomy, highlighting the indispensable role of sympathetic signaling in bone resorption caused by hypogonadism (Elefteriou et al., 2005). (2) A dramatic decrease of nerve profile density occurred in post-ovariectomized rats, proving the interconnection between the nervous system and bone loss after ovariectomy (Burt-Pichat et al., 2005). The release of neuromediators is influenced by a decrease in nerve fiber density which is essential for bone cell function and for bone remodeling (Bliziotis et al., 2001; Gu and Publicover, 2000; Itzstein et al., 2001).

A number of studies have been undertaken using adrenergic antagonists to investigate the influence of the SNS on bone in ovariectomized (OVX) murine models or in postmenopausal women. Pierroz et al. reported that a β -adrenergic blockade may partially rescue bone loss following OVX in adult mice by preventing a general BMD decrease, but not specifically in the spine or femur (Pierroz et al., 2006). Propranolol did not improve microarchitectural parameters in the lumbar vertebrae, but increased the femur cross-sectional and the medullary areas. However, the interpretation of these results should be approached with caution, for some studies indicated a dose-dependent effect of propranolol on bone tissue. Bonnet et al. examined the preventative effect of propranolol on the trabecular and cortical bones in OVX rats after various doses of propranolol had been injected subcutaneously over a period of 10 weeks (Bonnet et al., 2006). Bone architecture was preserved by 0.1 mg/kg/day propranolol, thanks to a higher trabecular number and thickness. Rats treated with 5 mg propranolol were partially protected from bone loss following ovariectomy, whereas rats treated with 20 mg propranolol did not show a significant difference in bone architecture compared to the OVX rats. They concluded that a low dose of propranolol prevented an increase in the number of osteoclasts in the OVX rats and improved their bone formation parameters. Another study with OVX rats also reported that propranolol treatment improved the decreased BMD and trabecular area, increased trabecular number (TbN), and lowered trabecular separation to some extent in OVX rats (Zhang et al., 2007).

Consistent with the animal data, clinical observations and trials on postmenopausal women produced similar findings. Pasco et al. analyzed the data of 1344 postmenopausal women, all of whom were β -blocker users, and found that β -blockers were positively correlated with a higher BMD at the total hip and ultradistal forearm after adjustment for age, anthropometry, and thiazide use (Pasco et al., 2004). The odds ratio for fractures associated with β -blocker use was 0.68 (95% CI, 0.49–0.96). Likewise, Bonnet et al. reviewed 158 postmenopausal women who were taking β -blockers. The odds ratio for any fracture in the β -blocker users was 0.58 (95% CI, 0.36–0.94), whereby β -blocker use was associated

with a higher BMD at the femoral neck and lumbar spine (Bonnet et al., 2007).

However, there are incidents of contradictory conclusions in both animal experiments and clinical observations. Bouxsein et al. showed that mice lacking β -adrenergic receptors had an increased bone mass. At the same time, though, they were not protected from the deleterious effects of estrogen deficiency on the trabecular bone microarchitecture (Bouxsein et al., 2009). A β -adrenergic blockade could only partially salvage the bone loss induced by OVX in adult mice (15 weeks old) (Pierroz et al., 2006), which is inconsistent with the reported full preventative effect against hypogonadism in young OVX mice (4 weeks old) (Takeda et al., 2002). The discrepancy may indicate that the effects of a β -adrenergic blockade of the bone remodeling balance were modulated by other humoral or endocrine factors influenced by the different developmental stages of the mice. As can be seen from Table 2, most studies supported a positive role of β -blockers on bone mass following OVX, unloading or stress. In contrast, the two studies by de Souza et al. (2005) and Marenzana et al. (2007) showed no significant improvement in cortical and trabecular bone. The divergence could be explained by the various murine models (unloading, stress, OVX, fracture, and intact), diverse administration approaches (oral, subcutaneous, and intraperitoneal) and time parameters (intermittent, continuous), different development stages (young, adult), and most importantly, varying dosages. At the same time, some prospective or observational studies failed to identify an association between β -blocker treatment and fracture risk in perimenopausal or older women (Levasseur et al., 2005; Reid et al., 2005; Rejnmark et al., 2004; Sosa et al., 2010). The results of the observational studies of β -blocker use are perplexing to some degree, not in the least due to a number of convergence factors, such as varying prescription indications, differing dosages and simultaneous consumption of concomitant medication. Clinically, the argument about the influence of β -blockers on bone mass seems to be endless (Table 3). Therefore, only definitive, randomized and controlled trials of β -blockers, with fracture as the clinical endpoint, will be able to get solid evidence supporting the hypothesis that a pharmacological blockade of the β -adrenergic system could contribute to postmenopausal bone health.

5. Osteoporosis after spinal cord injury

Spinal cord injury causes osteoclastic resorption and severe pan-skeletal bone loss (Morse et al., 2008), occurring rapidly and predominantly in the pelvis and the lower extremities. A marked deterioration was seen not only in BMD and bone mineral content (BMC), but also in the trabecular microarchitecture (Lazo et al., 2001; Maimoun et al., 2002; Zehnder et al., 2004). Traditionally, the pathogenesis of osteoporosis following spinal cord injury (SCI) is thought to be similar to that of disuse (unloading) (Kiratli et al., 2000; Uebelhart et al., 1995). Undoubtedly, unloading is a crucial factor in the development of osteoporosis after SCI, but bone loss occurring in the upper extremities in paraplegics indicates that different mechanisms are involved in SCI (Frey-Rindova et al., 2000; Sabo et al., 2001). In our laboratory, SCI and hindlimb cast immobilization (HCI) rats were utilized to study the differences in bone loss (Liu et al., 2008b). The HCI model is used universally to study unloading osteoporosis. We found that SCI-induced sublesional bone loss in young rats at an early stage was associated with an increase in the density of substance P-immunoreactivity nerve fiber innervation and a decrease in neurofilament 200-immunoreactivity. The dry weights and ash weights of the tibiae in SCI were remarkably reduced compared with those in HCI. The SCI rats had a lower areal BMD in the proximal tibiae compared with the HCI rats (–14%). The cortical thickness and cortical area of the tibial midshafts in SCI were lower than in HCI (–23%, –33% respectively).

Table 3
Bone phenotype alteration studies by β -blocker use in clinical trials.

Studies [first author (publication year)]	Study design	Case/control or cohort size	Number of β -blocker user	Age or mean age (year)	Bone phenotype alteration or fracture risk change	OR or HR for fractures with 95% CI
Jensen et al. (1991)	Observational (case-control)	200/200	13, men and women	≈ 80	No significant association	OR: 0.85 (0.35–2.12) for femoral neck fracture
Pasco et al. (2004)	Observational (case-control)	569/775	171, postmenopausal women	≥ 50	Higher BMD (total hip and ultradistal forearm)	OR: 0.68 (0.49–0.96) for any fracture, adjusted by age, weight, height, medication use
Rejnmark et al. (2004)	Observational (case-control)	2016	38, perimenopausal women	50 (48–52)	BMD is not affected. Associated with a threefold increased fracture risk	OR: 3.3 (1.1–9.4) adjusted by age, weight, BMD, medication use and life style
Schlienger et al. (2004)	Observational (case-control)	18,441/72,778 (women) 12,160/48,041 (men)	640 (women) 292 (men)	30–79	Associated with a reduced risk for any fracture	OR: 0.85 (0.77–0.93) (women) OR: 0.66 (0.58–0.75) (men) adjusted by age, smoking, BMI and medication use
Levasseur et al. (2005)	Prospective (cohort)	7598	283, postmenopausal women	80.5 ± 3.8	Higher BMD (femoral neck, ward triangle), but no difference after adjustments	OR: 1.2 (0.9–1.5) adjusted by medication use, physical activity, alcohol consumption
Reid et al. (2005)	Observational (cohort)	8412	1099, postmenopausal women	≈ 77	Higher BMD (total hip, os calcis), but no difference after adjustments	HR: 0.87 (0.75, 1.00) for any fracture, adjusted by age, weight, smoking, medication use
Schoofs et al. (2005)	Observational (cohort)	7892	not reported, men and women	>55	Long term use (>4 years) is associated with a reduced risk of fractures (upper arm, hip, pelvis)	HR: 0.67 (0.46–0.97) for non-vertebral fracture adjusted by age, sex, BMD, BMI, medication use
Gage et al. (2006)	Observational (cohort)	14564	≈ 2838 , men and women	≈ 80	Associated with a reduced risk of fractures (vertebral, wrist, hip)	OR: 0.84 (0.70–1.00) adjusted by age, sex, race, falls risk, medications use
Turker et al. (2006)	Prospective (case-control)	50/100	50, men and women	60–80	Higher BMD (total hip, spine) associated with an increase in BMD	Not reported
Rejnmark et al. (2006)	Observational (case-control)	124,655/373,962	35,838, men and women	43.44 ± 27.39	Associated with a reduced risk of fracture	OR: 0.91 (0.88–0.93) adjusted by medication use, prior fracture
de Vries et al. (2007)	Observational (case-control)	22,247/22,247 (UK) 6763/26,341 (Dutch)	2013 (UK) 4447 (Dutch) men and women	>18 (>65 years 80%)	Current use is associated with a decreased risk of hip/femur fracture	OR: 0.82 (0.74–0.91) (UK) OR: 0.87 (0.80–0.95) (Dutch) adjusted by medication use, weight
Bonnet et al. (2007)	Observational (cohort)	499	158, postmenopausal women	41–96 (65.2 ± 9.3)	Higher BMD with better trabecular microarchitecture (femoral neck, spine)	OR: 0.58 (0.36–0.94) adjusted by age, weight medication use, smoking
Meisinger et al. (2007)	Observational (cohort)	1793	219, men and women	55–74	Associated with a reduced risk of fractures	HR: 0.60 (0.37–0.96) adjusted by age, sex, BMI, medication and life style
Sosa et al. (2010)	Observational (case-control)	74/111	60, postmenopausal women with CHD	51	β -Blockers were positively associated with fragility fractures	OR: 1.58 (0.96–1.94) adjusted by medication, weight
Yang et al. (2010)	Observational (cohort)	2203 (women) /1285 (men)	411 (women) 262 (men)	>50	Higher BMD at the femoral neck and lumbar spine	OR: 0.71 (0.54–0.93) (W) 0.54 (0.34–0.86) (M) adjusted by age, BMD, and life style

BMD: bone mineral density; BMI: body mass index; current use: β -blocker use within 3 months prior to the assessment; medication use: those having potential influence on bone metabolism, like corticosteroids, statins, thiazides; CHD: coronary heart disease.

In the SCI tibiae, the mineralizing surface, mineral apposition rate, and surface based bone formation rate were significantly higher than in the HCl groups (12%, 47%, and 29% respectively). In the compression test, the ultimate load, the energy of the ultimate load, and Young's modulus of the proximal tibiae in the SCI rats were signif-

icantly lower than in the HCl rats (Liu et al., 2008a,b). These results demonstrate that neural factors are involved in the pathogenesis of osteoporosis after SCI, and that the bone loss caused by disuse is not identical to bone loss in SCI. Neural mechanisms have been catching more attention recently; these should not be neglected.

As mentioned above, sympathectomy or denervation could alter bone remodeling due to changes in bone formation and resorption. Innervation density has been observed to decrease remarkably after sciatic neurectomy (Burt-Pichat et al., 2005). In accordance, innervation density and neuropeptide production decrease in the sublesional bones, resulting in an imbalance between bone formation and resorption (Zehnder et al., 2004).

Bone denervation can result in an imbalance of local bone metabolism, and thus in bone loss. Denervation after SCI also could impair vasoregulation, which in turn affects the otherwise intact blood supply to sublesional bones. SCI induces a partial or complete disruption of the neural pathways from the central nervous system to the peripheral SNS, which gives rise to an abnormal sympathetic innervation as a result of an anatomical reorganization of pathways in the spinal cord (Krassioukov et al., 1999; Munakata et al., 1997; Schmid et al., 1998). Thereafter, the opening of the intravenous bone shunts induces an anomalous hemodynamic effect and a stasis of the venous and capillary blood flow (Chantraine et al., 1986; Minaire et al., 1984). Vascular modification is detrimental to bone metabolism; a decrease in the nutritive blood flow and reduction in the gas exchange is likely to increase bone resorption by promoting osteoclast formation due to the deterioration of the local microenvironment of the endosteal surface (Chantraine et al., 1979). A significant local vascularization in the metaphyseal–epiphyseal areas of long bones would be affected remarkably by a secondary intramedullary blood stasis caused by vasomotoric disorders. Consequently, the destruction of vasoregulation is another important factor in the development of osteoporosis after SCI.

Undoubtedly, the SNS is involved in various physiological functions and plays a decisive role in many aspects of maintaining homeostasis. A disruption of the neural pathways from the brain to the peripheral SNS after SCI results in multifaceted physiological modifications, which in turn interact with each other and contribute to osteoporosis. Therefore, to identify the role of each contributory factor in osteoporosis is highly complex and difficult.

6. Depression-induced osteoporosis

Depression is a common psychological disorder that affects about 5–10% of women and 1–2% of men (Meller et al., 1997; Robins et al., 1984), or more than 5% of the population (Blazer et al., 1994). Depression-induced osteoporosis is characterized by a significant decrease in the bone mass of the hip and the spine (Jacka et al., 2005). The possible associations between depression and osteoporosis have been examined widely. However, conflicting data exist as to whether or not depression is a risk factor for bone loss. Studies have shown that the BMD decreases in major depressive disorder (MDD), with a BMD reduced by 6–15% compared to the healthy controls (Altindag et al., 2007; Jacka et al., 2005; Kahl et al., 2006; Mussolino, 2005; Petronijevic et al., 2008). Meanwhile, a number of authors have found no such correlation (Kavuncu et al., 2002; Whooley et al., 2004; Yazici et al., 2005). A study measuring the BMD, plasma cortisol levels, as well as the osteocalcin and C-telopeptide levels of 35 premenopausal women diagnosed with MDD and of 30 healthy women concluded that MDD had no significant effect on BMD and bone turnover markers (Yazici et al., 2005). In contrast, a recent study that applied similar parameters examined 36 premenopausal women suffering from MDD. They arrived at opposite results, considering depression to be a risk factor for osteoporosis in premenopausal women (Altindag et al., 2007). A cross-sectional study examined 25 premenopausal women with MDD who received no medical treatment for depression. Compared to 15 healthy women, the mean BMD in the lumbar spine and proximal femur in the depressed women was significantly lower (12% and 11%, respectively) (Yazici et al., 2003). In a longitudinal assess-

ment of 18 depressed patients above 40 years of age that included at least 24 months of follow-up, MDD was found to correlate with increased bone loss, whereby it was found to be more obvious in men than in women (Schweiger et al., 2000). A recent meta-analysis comparing individuals diagnosed with depression with others free from depression found that the association between depression and BMD is stronger in women than in men, and stronger in premenopausal than in postmenopausal women (Yirmiya and Bab, 2009). The discrepancy in these results is possibly due to the use of different diagnostic tools and scales applied to estimate the severity, type and nature of depression.

Notably, several recent meta-analyses of prospective clinical studies conducted by comparing the risk of osteoporotic fractures and bone loss between individuals suffering from depression and others free from depression have demonstrated depression to be a risk factor for low BMD (Cizza et al., 2010; Wu et al., 2009; Yirmiya and Bab, 2009). A further prospective study examined the association of symptoms of depression and bone mass in 207 otherwise physically healthy adolescent girls aged from 11 to 17 (Dorn et al., 2008). The authors found that the girls with more depressive symptoms were more likely to have a lower total body BMC. Overall, these results might implicate the causal relationship between depression and an increased incidence of fractures.

Since depression, particularly the melancholic type, is associated with a pronounced and enduring central and peripheral hyper-noradrenergic state (Wong et al., 2000), the remarkable increases in norepinephrine (NE) levels, particularly within bone tissue, might contribute to an accrual of lower peak bone mass, bone loss, and osteoporosis risk. Thereby, depression appears to be a significant risk factor for low BMD, causing bone loss through activation of the SNS (Bab and Yirmiya, 2010).

Yirmiya et al. utilized a chronic mild stress (CMS) murine model, which experienced a drop to <50% in bone mass comparing with controls in the fourth week (Yirmiya et al., 2006). In order to confirm that the inhibition of bone formation is mediated by the activation of the SNS, a number of additional observational studies were carried out using stress models: (1) When the stressed mice were treated with imipramine, an antidepressant drug, attenuation of the skeletal structural deterioration was accompanied by an inhibition of the CMS-induced restraint of bone formation, whereas bone resorption remained unaffected. (2) There was no statistical difference in body weight and locomotor activity compared with the control group, which excluded the possible impact of body weight and motility in stress mode. (3) Serum testosterone levels were unaltered, showing that sex hormones were not involved in this model, thus excluding sex hormone induced bone loss. (4) The level of norepinephrine released from sympathetic nerve endings was markedly increased in the trabecular bone. (5) Treatment with β -blocker propranolol orally at a dosage with no effect on the behavioral parameters attenuated the deterioration in bone mass and structure. (6) A reduction in the number of osteoblasts was observed, which is consistent with the observation that sympathetic antagonists ameliorate bone loss by increasing the osteoblast number (Eleftheriou et al., 2005; Takeda et al., 2002).

Interestingly enough, body weight is known to be positively correlated with bone mass in adults, even moderate obesity offers a protective effect against osteoporosis. Women suffering from depression tended to weigh more than those free from depression (Henry et al., 2000; Onyike et al., 2003), however, the greater body mass failed to spare them from bone loss.

Undoubtedly, neuroendocrine mechanisms may also play a key role in depression-induced osteoporosis. Some studies showed that a depression-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis resulted in low BMD or BMC in adult humans. Theoretically, the increased activation of the hypothalamic-pituitary-adrenal axis could promote hypercortisolism, which in

turn could inhibit the recruitment and differentiation of osteoblasts and increase the number and activity of osteoclasts, thus accelerating bone turnover and bone loss (Carroll et al., 2007; Manelli and Giustina, 2000). Some studies measured the serum corticosterone in depressed patients (Azpiroz et al., 1999; Yirmiya et al., 2006). However, their inconsistent results make it unclear, whether the elevation of the serum corticosterone induced by depression is sufficient to trigger the negative bone remodeling process. Other hormonal changes, such as the hyposecretion of estrogen and testosterone, deficiency in growth hormone, and increase in the IL-1 and IL-6 concentration, also contribute to bone loss (Alessi et al., 2005; Bajayo et al., 2005; Cizza et al., 2001; Franchimont et al., 2005; Reynolds et al., 2005). Poor lifestyles such as smoking, drinking and unhealthy diets, as well as restricted physical activity resulting from depression and the consumption of specific psychotropic drugs are potential contributory factors (Kinjo et al., 2005; Misra et al., 2004). There is a growing body of research on these aspects (Misra et al., 2004; O'Keane and Meaney, 2005; Richards et al., 2007; Williams et al., 2008). Depression is a complex condition interweaving the central nervous system with endocrine disorders. The mechanisms of the development of osteoporosis in patients with depressive illnesses and the involved brain-to-bone pathways need to be unraveled by future research.

7. Unloading-induced osteoporosis

It has been known that mechanical loading can positively influence bone health. Cross-sectional studies of athletes reveal the anabolic effect of mechanical stress on bone (Elloumi et al., 2006; McClanahan et al., 2002). Consistent with the anabolic effects of mechanical stimuli, a prolonged absence of mechanical stimuli due to aging, bed rest, cast immobilization and weightlessness in spaceflight can result in bone loss (Basso and Heersche, 2006; Kondo et al., 2005; Rucci et al., 2007; Serhan, 2004). In long-duration spaceflight, the crew members experience substantial bone loss at a rate of approximately 1–1.5% per month. The bone loss is also found to be site-specific, with a greater loss in the appendicular bones of the lower extremities than in the spine, and type-specific, with a greater decline in trabecular bone volume than in the cortical bone volume (Lang et al., 2004). Bed rest studies have yielded similar results. The BMD of healthy males confined to bed rest for 17 weeks decreased by 0.9–1.3% per month in the tibiae, femora, and lumbar vertebrae. Some studies showed that the decrease in BMD after 12 weeks of bed rest even reached 4–10% (Bloomfield, 1997).

Although the mechanisms underlying disuse-induced osteoporosis have not yet been fully explained, the speculation that the central nervous system regulates bone mass via the SNS has prompted studies to investigate the role of the SNS in the bone mechano-adaptive response. Accumulating evidence from laboratory studies suggests that the β -adrenergic pathway of the SNS plays a key role in bone remodeling under mechanical loading (Baek and Bloomfield, 2009; Kondo et al., 2005).

Kondo et al. (2005) adopted tail-suspended rats as an unloading model to investigate the possible SNS contribution. They concluded that osteoblast suppression and osteoclast activation following unloading leads to bone loss via the SNS. Accordingly, they report the following: (1) Hindlimb unloading reduces bone volume. (2) Treatment by propranolol, a β -adrenergic blocker acting at receptor levels, mitigated the bone loss induced by unloading. This is in concert with the results by Levasseur et al. (2003). (3) Guanethidine was administered to selectively deplete norepinephrine in the postganglionic adrenergic nerves, which suppressed unloading-induced bone loss. (4) Isoproterenol, a β -adrenergic agonist, reduced bone mass in loading mice, but no further bone mass

reduction was observed by unloading. These results proved the concept that the SNS is involved in the unloading-induced bone loss signaling pathway, whereby the signaling could be suppressed by sympathetic blockers. In addition, bone mass preservation induced by propranolol was observed primarily in the trabecular bone. Similarly, the deactivation of the SNS by sciatic neurectomy had no effect on the load-induced cortical bone formation (de Souza et al., 2005). These findings indicate that the SNS may regulate the trabecular bone mass, but not the cortical bone mass. However, controversy remains, since a recent study concluded that both cortical and trabecular bone manifest an adaptive response under dynamic loading; this, however, only seems to occur in local loading bones (Sugiyama et al., 2010). One study shows that skeletal sensitivity varies in response to different levels and frequencies of mechanical signals (Judex et al., 2009). These data might implicate site-specific effects of mechanical loading.

Although the results of some studies do not support the idea that the SNS plays a major role in the mechanical loading response of bone, whereby some even negate the findings that a blockade of the β -adrenergic signaling has an influence on the mechano-adaptive response of bone (Marenzana et al., 2007), more and more studies are arguing in favor of the SNS contributing to bone regulation. Further studies are needed to reach an affirmative conclusion regarding the definite function of the SNS in unloading-induced bone loss. A clear illustration of the mechanisms involved will be beneficial for the diagnosis and therapy for long-term bedridden patients and for astronauts on long-duration space missions.

8. Complex regional pain syndrome induced osteoporosis

The reflex sympathetic dystrophy syndrome (RSDS) was first reported when post traumatic bone dystrophy was observed clinically. This disease is a painful and disabling limb disorder accompanied with swelling, autonomic dysfunction, increased bone resorption and patchy osteoporosis (Adami et al., 1997). However, with a deepening understanding of the pathophysiology of the disease, it was recognized that the dysfunction of the SNS was not the sole cause. Inflammation and hypoxia also play a part in the pathogenic mechanism. Consequently, the term complex regional pain syndrome (CRPS) was officially introduced (Stanton-Hicks et al., 1995). Nonetheless, SNS still plays a vital, if not a crucial role.

The relation between RSDS and osteoporosis remains debatable. Patchy bone loss is considered attributable to a regional sympathetic hyperactivity or sympathetic dysfunction (Goldstein et al., 2000; Kurvers, 1998; Laroche et al., 1997). However, the exact pathological mechanism is still poorly understood. Since osteoporosis related to CRPS is mainly localized in the affected limb with limited detriment, and since pain is usually the main complaint when CRPS patients see a doctor, the study of the bone loss mechanism in CRPS is being paid little attention. Most evidence has been provided by empirical studies. An increase in sympathetic outflow is supported by the observation that central sympathetic stimulation provokes pain, abnormal vasoconstriction and sympathetic skin reflexes in CRPS patients (Drummond and Finch, 2004). On the other hand, adrenergic receptor hypersensitivity is another possible explanation, which is endorsed by the observed increase in pain after intradermal injections of norepinephrine on the affected side of CRPS patients, and the absence of significant pain induced by the norepinephrine injections in the unaffected side and in the controls (Ali et al., 2000). Furthermore, a decrease in epidermal, sweat gland, and vascular innervation was noted in the CRPS affected side (Albrecht et al., 2006). The catecholamine serum level measured in the affected side of CRPS patients was decreased instead of ele-

vated, which is in support of a local hypersensitivity (Wasner et al., 1999).

Despite the controversy, adrenergic blocking agents are widely administered for the treatment of CRPS in order to attenuate the vasoconstriction induced by sympathetic hyperactivity, with satisfactory results achieved in some patients (Breuer et al., 2008). Therefore, we may postulate that unlike the direct regulation in osteoblasts and osteoclasts, the sympathetic dysfunction of bone loss in the case of CRPS is probably caused more indirectly. On the one side, sympathetic deregulation causes vasomotoric irregularities, an imbalance between vasoconstriction (which is influenced by norepinephrine) and vasodilation, which in turn influences the blood supply to the bone and bone metabolism. On the other side, sympathetic hyperactivity causes osteoclast hyperactivity probably via inflammatory cytokines (Boyce et al., 2006), which would be confirmed by the studies that bisphosphonates, which are antiosteoclastic agents, improve the BMC in patients with CRPS (Breuer et al., 2008; Kubalek et al., 2001; Tran de et al., 2010; Varenna et al., 2000). Curiously enough, bone loss was also found in the asymptomatic contralateral hand or foot in patients with unilateral CRPS. The reason for this was explained to be the change of sympathetic tone in CRPS and contralateral sympathetic innervation (Goldstein et al., 2000; Kurvers et al., 1994). This theory is supported on an anatomical basis: some preganglionic sympathetic nerve fibers were projected to the contralateral sympathetic ganglions, and contralateral body regions were innervated by some postganglionic sympathetic nerve fibers (Gerova and Gero, 1980).

Based on these results emanating from experimental and clinical studies, it is reasonable to assume that the SNS and other mediators are involved in a complex network of interactions, resulting in an increased bone resorption and patchy osteoporosis in CRPS. The mechanisms of CRPS have not yet been fully understood. To address this, studies from both clinical and etiological perspectives would be helpful.

9. Concluding remarks

There now exist numerous studies on the sympathetic neural signaling of the bone remodeling regulation and the influence of the β -adrenergic pathway on bone metabolism. The reasons why the SNS has attracted more and more attention are evident: First, the sympathetic neural pathway is so far the only identified link between the leptin-dependent central control and bone cells. Second, a β -adrenergic stimulation or inhibition resulting in bone mass change is feasible with current pharmacological means. Third, despite conflicting reports, more inspiring and promising results have been published, which encourage in-depth studies to get concrete evidence. Therefore, sympathetic neural signaling may open a novel and potential treatment avenue for the prevention or reversal of bone loss.

Much work is still required to clarify the sympathetic neural signaling in bone remodeling, but some concrete issues can already be addressed. Gene mutation that is involved in the SNS function and that leads to bone mass abnormalities, facilitates the unraveling of the functions of specific neuroendocrine factors. However, generalized knockout mouse studies are still stricken with many puzzling aspects. Consequently, conditional site-specific knockout mice, including β 2-AR, will be critical in addressing these questions.

In humans, the role of β 2-AR expressed in osteoblasts remains obscured, because it has mostly been studied in murine models. The scarcity of human bone tissue prevents further exploration, not in the least since the murine experiment cannot fully reflect the actual mechanism in the human body. On the other hand, there is no conclusive evidence supporting the speculation that a phar-

macological blockade of the β -adrenergic signaling ameliorates or prevents bone loss associated with spinal cord injury, postmenopause, depression, unloading and CRPS. Despite this, more and more clinical reports are yielding affirmative results on the association between β -blocker use and a reduced risk of fracture in people of advanced age (Table 3). Murine studies on the dose effect of β -blockers even suggest a better preventative effect of propranolol against OVX or depression when administered at a lower dose (Bonnet et al., 2006; Yirmiya et al., 2006). A further experiment found no significant harmful effects on heart hemodynamic parameters in rats receiving low doses of β -blocker (Bonnet et al., 2008). This potentially has a clinical impact, since β -blockers administered at a high dosage could cause a decrease in the heart rate, contractility, conduction velocity and metabolic changes within the body, and could even have a fatal effect. The ideal outcome would be the prevention of bone loss from deleterious factors at a low dose without affecting normal physiological activities. Hence, more prospective, randomized and controlled clinical trials and carefully designed animal experiments are necessary to get convincing results.

The investigation of the role of the SNS has shed light on the treatment or prevention of osteoporosis, but many other questions still linger and need to be answered. How the SNS interacts with other endocrine factors and mechanical loading to regulate bone remodeling is one such question. It furthermore needs to be investigated, if the SNS has the same or different effect on trabecular and cortical bone, and what the specific mechanism is for either of the two. Another aspect to be investigated is whether the SNS is the only link between the hypothalamus and bone cells. If not, it has to be ascertained what the concrete interaction between them is.

In summary, the light at the end of the tunnel in preventing or curing osteoporosis still is far off, not in the least due to the complexity of the role of SNS pathways in bone remodeling.

Conflicts of interest

The authors claim no conflicts of interest.

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