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Review

Neuronal control of bone and muscle

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ABSTRACT

The functional interplay between bone and muscle that enables locomotion is a fundamental aspect of daily life. However, other interactions between bone and muscle continue to attract attention as our understanding of the breath and importance of this inter-relationship continues to expand. Of particular interest is the regulatory connection between bone and muscle, which adds a new insight to the coordination of the bone/muscle unit. We have appreciated the importance of neuronal signaling to the control of bone turnover and muscle contraction, but recent data indicate that neuronal inputs control a far wider range of bone and muscle physiology than previously appreciated. This review outlines the role of the sympathetic nervous system and neuronal/neuropeptide inputs upon the regulation of bone and muscle tissue, and the potential for co-regulatory actions, particularly involving the sympathetic nervous system.

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Contents

Neuronal control of bone remodeling

Bone is remodeled, repaired and replaced throughout life by means of basic multicellular units, consisting of osteoclasts and osteoblasts acting in a coordinated fashion to resorb existing bone and form new bone in its place. Remodeling allows bone tissue to adapt its structure and mass to mechanical demands to ensure maximal strength with minimal bone mass [1]. The prevailing paradigm of skeletal homeostasis is that bone remodeling is controlled in a predominantly endocrine manner, while simultaneously responding to local mechanical stimuli driven by load and in response to skeletal muscle mass, strength and contraction. However, the recent discovery of bone regulation by the central nervous system represents an emergent area of study that is identifying novel regulatory axes between the nervous system and

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bone. A direct role of the nervous system in bone cells is strongly supported by immunocytochemistry studies which revealed the presence of innervation and receptors for neuropeptides in bone cells [2]. Moreover, retrograde trans-synaptic tracing has identified neuronal tracts from the femoral bone marrow linked direct to the central nervous system [3]. Taken together, these findings suggest the existence of neuronal signaling between the brain and the cells of the bone. Studies in mouse mutant models have provided the most powerful evidence for direct central control of bone mass, which will form the basis of the review.

Leptin deficiency and bone

Leptin, an adipokine, is primarily secreted into the circulation by white adipocytes at levels of positively correlated with percentage body fat, which facilitates its role as an adipostat [4]. The initial identification of a direct neuronal output from the hypothalamus to the bone came about from study of leptin. Leptin signaling deficiency in the mutant (*ob*/*ob*) mice or inactivation of the leptin receptor Ob-Rb (*db*/*db*) produces complex, multi-system phenotypes, consistent with the loss of leptin signaling paralleling a starvation signal. As a result, the most characteristic change in *ob*/*ob* or *db*/*db* mice is extremely obesity, however, these mice also display skeletal alterations. Cancellous bone volume is increased in *ob*/*ob*, associated with increased bone turnover favoring bone formation [5]. At the same time, another group reported leptin as a potent stimulator of bone growth in *ob*/*ob* mice; leptin treatment in 4-week-old *ob*/*ob* mice increased cortical mineral content of the femora [6]. The leptin treatment also increased femur length, total body bone area, bone mineral content and density compared to vehicle-treated controls. Thus, it appears that leptin has opposing effects on cancellous and cortical bone in *ob*/*ob* mice. Further analysis supported the envelope specific effects in leptin-deficient mice. Consistent with both initial studies, cancellous bone volume was greater in *ob*/*ob*, associated with elevated turnover [7], while total body bone mineral content, cortical area and mineralizing surface of the femur were reduced compared to normal mice [6,8–11]. Leptin treatment increased whole body BMC and endosteal bone formation in the *ob*/*ob* mice but not in wild type mice [12]. These data indicate that the largest effect of leptin deficiency on the skeleton is a reduction in cortical bone formation. Moreover, the mechanism of this action has revealed a new regulatory axis to the bone, the sympathetic nervous system.

Sympathetic nervous system regulation of bone mass

The existence of hypothalamic-mediated effects on the bone through endocrine hormone release from the pituitary has long been appreciated. In recent years, the discovery of a central locus for the regulation of bone mass has been one of the most exciting developments in the area of bone metabolism, and has revealed regulatory associations between the bone that were previously unknown. Although, leptin deficiency is characterized by numerous endocrine changes, a humoral pathway was ruled out by parabiosis experiments in *ob*/*ob* mice [13]. This indicated that leptin signaling in the brain (supplied by brain-only supplementation, icv) was responsible for the skeletal changes, without the necessity of a humoral signal. The ventro-medial hypothalamus (VMH) was identified as the source of the leptin signaling and origin of the anti-osteogenic signal to cancellous bone. Thus sympathetic activity was likely the important downstream of central leptin. Subsequent studies support the involvement of sympathetic nervous system (SNS) in central leptin signaling on bone regulation. Osteoblasts and osteoclasts were found to express functional β2-adrenergic receptors (β2AR) [13]. Consistent with a role for SNS signaling in the bone, mice deficient in β2AR showed increased cancellous bone volume [14] while deletion of a downstream mediator of β2AR signaling, adenylyl cyclase 5, protects against age-related bone loss [15]. When β2AR were blocked with non-selective antagonist propranolol, cancellous bone mass was increased in wild type mice and disruption of dopamine β-hydroxylase, an enzyme generating adrenaline and noradrenaline, exhibited greater cancellous bone mass in mice. Importantly, reducing adrenergic signaling protected the bone from the cancellous bone loss following icv leptin; through loss of dopamine β-hydroxylase in wild type mice and propranolol treatment in *ob*/*ob* [13]. β2AR remained unchanged after icv leptin infusion [13]. This novel role of β adrenergic signaling in the bone completed the central leptin signaling pathway to the bone.

Neuropeptide Y system and bone

The role of leptin in the hypothalamus was followed by the identification of a number of central pathways to the bone. One neuronal system of particular importance to the bone is the neuropeptide Y (NPY) system. The NPY system consists of 3 ligands; NPY, peptide YY (PYY), and pancreatic polypeptide (PP) mediating its effects via G protein-coupled receptors, of which five have been identified to date: Y1, Y2, Y4, Y5 and y6 [16,17]. NPY, a 36-amino acid peptide, is widely expressed in the central and peripheral nervous systems, and is present in both sympathetic and parasympathetic nerve fibers, often co-released with noradrenaline during nerve stimulation; it also circulates in the blood. Very early studies demonstrated that NPY treatment in osteoblastic cell lines inhibited the cAMP response to parathyroid hormone and norepinephrine [18,19], suggesting the presence of functional Y receptors on bone cells and a possible regulatory role for NPY in the bone.

Similar to leptin, NPY-mediated effects in the bone was confirmed in mutant mouse models. Two Y receptors, Y1 and Y2, have been connected with bone homeostasis. These receptors are abundant in the hypothalamus as well as in peripheral nerves [20–22]. The first Y receptor model evaluated for skeletal activity was $Y2^{-/-}$, due to the known co-expression of Y2 and leptin receptors on neurons within the arcuate nucleus [23,24]. Initial analysis of germline $Y2^{-/-}$ mice were similar to those following conditional deletion of Y2 receptors in the hypothalamus, demonstrating a role for central Y2 receptors in this pathway and the first specific gene deletion in the hypothalamus to alter bone homeostasis. They revealed a greater cortical and cancellous bone volume associated with a greater bone formation rate [8,25]. Bone resorption parameters were unchanged except for a modest increase in osteoclast number. Importantly, the skeletal changes observed in germline $Y2^{-/-}$ mice and hypothalamic $Y2^{-/-}$ mice occurred in the absence of any measurable changes in bone active endocrine factors. Thus these findings suggest that the bone anabolic effects after Y2 receptor deletion are mediated by a neuronal mechanism and not by endocrine effectors of bone turnover.

Similar to the phenotype resulting from Y2 receptor deletion, germline Y1 receptor deficiency resulted in a generalized anabolic phenotype with greater cortical bone and cancellous accrual, although with an additional increase in bone resorption [26]. However, unlike the anabolic effects in hypothalamus-specific Y2 deletion [49], loss of hypothalamic Y1 receptors had no effect on bone homeostasis indicating a non-central mechanism for Y1 action in the bone. The existence of a direct Y1-mediated effect on bone anabolism was further suggested following identification of Y1 expression in osteoblastic cells in vivo [26]. NPY treatment of calvarial osteoblast cultures markedly decreased cell numbers, an effect absent in cultures from Y1 receptor knockout mice, indicating functional osteoblastic Y1 receptors. The direct regulation of osteoblasts by NPY was confirmed in osteoblast-specific Y1 receptor knockout mice, which displayed an increase in bone formation similar to germline Y1 null mice [27]. Loss of Y1 receptor has also been demonstrated to regulate mesenchymal stem cell activity and mineralization of osteoblastic cultures in vitro [28]. In addition, NPY is produced by osteoblasts and elevation of NPY production in osteoblast-specific NPY transgenic mice shown an opposing phenotype

to Y1 receptor deletion, with greater bone volume and bone formation [29]. The integration of NPY within the osteoblast lineage was confirmed by a study demonstrating the NPY and Y1 receptor are expressed in differentiation-dependent manner, and respond to loading, a fundamental aspect of bone physiology [30]. Adding a new dimension to neuronal/bone interactions, a recent study, which produced an osteoblast-specific deletion of p38a–Mapk14 demonstrated alterations in bone homeostasis, but also increased energy expenditure and reduced adiposity, which were associated with reduced NPY production by osteoblasts, and blocked by i.p. NPY administration. However taken together these models confirmed an NPY-mediated pathway from the arcuate nucleus of the hypothalamus to the osteoblast, as well as an active NPY loop within the osteoblast lineage.

NPY-leptin interaction

Hypothalamic-mediated control of bone homeostasis was identified in leptin deficient as well as in NPY receptor deficient mice. Interestingly, both NPY and leptin have a close association within the hypothalamus, suggesting the possibility of common signaling pathway. NPY is a critical downstream mediator of leptin-deficient starvation signaling in the hypothalamus. Moreover, a significant proportion of NPY-ergic neurons co-express the leptin receptor in the arcuate nucleus [31], and NPY expression is upregulated following the reduction in leptin due to starvation [32–34] and in leptin-deficient *ob*/*ob* mice [35]. Leptin receptors are also present in other nuclei in the hypothalamus, including the ventromedial hypothalamus, from which the leptin-mediated pathway to the bone was shown to originate [13]. Thus whether they were separate or coordinate pathways was not known.

Several reports suggested that leptin and NPY-mediated pathways to the bone were similar. This was supported by findings in $Y2^{-/-}$;*ob*/*ob* double mutant mice with no additive effect on cancellous bone volume or formation [8]. Additionally, male $Y2^{-/-}Y4^{-/-}$ double knockout mice revealed a synergistic increase in cancellous bone volume compared with $Y2^{-/-}$ mice [36]. This gender-specific effect was coincident with a marked reduction in plasma leptin in male, but not in female $Y2^{-/-}$ $Y4^{-/-}$ mice [36], suggesting an additive antiosteogenic effect of the Y2 and leptin on the bone. Moreover, when NPY was continuously administered into wild type mice, mimicking the increase in *ob*/*ob*, the treatment reduced cancellous bone volume suggesting that NPY and leptin might use different pathways to control bone mass [5]. The nature of the relationship was examined in $NPY^{-/-}$;*ob*/*ob* double mutant mice [37]. $NPY^{-/-}$ null mice display an anabolic phenotype similar to $Y2^{-/-}$ and $Y1^{-/-}$ mice, with greater cancellous and cortical mass and bone formation [38]. NPY levels are markedly elevated in *ob*/*ob* mice, as a direct effect of reduced activation of the leptin receptor in NPY-ergic neurons [39]. Loss of NPY in *ob*/*ob* mice had very specific effects upon bone metabolism, with a correction of the cortical deficit through a correction of bone formation; however there was not change in cancellous bone. This model indicated that the NPY-mediated pathway from the arcuate is responsible for the cortical deficiency in ob/ob mice, while the SNS pathway from the VMH is responsible for the cancellous increase in ob/ob.

Cannabinoid system

Endocannabinoids signal via two cannabinoid receptors, CB1 and CB2, and these receptors, similar to NPY receptors, couple to inhibitory G proteins [40]. Endocannabinoids are generated as needed whereas other neurotransmitters are released from vesicles [41]. CB1 is expressed predominantly by the cells in the central nervous system (CNS) [42], whereas CB2 is expressed primarily in peripheral tissues [43]. While it has been reported that osteoclasts and osteoblasts abundantly express cannabinoid receptors [71], they have also been shown to play a role in the control of bone homeostasis by a centrally mediated mechanism. Mice with inactivation of the central CB1 receptor have increased bone mineral density and additionally they are protected against ovariectomy-induced bone loss [44]. Moreover, it has been shown in in vitro studies that the pharmacological cannabinoid receptor antagonists such as, AM251 (CB1), SR144528 (CB2) and AM630 (CB2) inhibit osteoclastogenesis and bone resorption while the compounds AM251 and SR144528 inhibit osteoclastic bone resorption in vivo, thus protecting against ovariectomy induced bone loss [44]. Furthermore, mice lacking CB1 receptor were resistant to the inhibitory action of AM251 on osteoclast formation indicating cannabinoid antagonism inhibits osteoclasts which is partly mediated by the CB1 receptor [44].

CB2-knockout mice have a distinctly accelerated age-related cancellous bone loss and cortical expansion without changes in cortical thickness [45]. In spite of the bone loss, $CB2^{-/-}$ mice exhibit high bone turnover, increased mineral appositional rate and bone formation rate [45]. Furthermore, both osteoblasts and osteoclasts express functional CB2 receptors, and CB2 signaling contributes to the maintenance of bone mass by directly stimulating stromal cells/osteoblasts and by inhibiting monocytes/osteoclasts [45]. Taken together, these data suggest that the cannabinoid receptor signaling is required for maintenance of bone mass.

Melanocortins

Melanocortins are a complex family comprising five G-protein coupled melanocortin receptors (MCRs), identified as receptors MC1–5, and a number of endogenous ligands [46,47]. Among the five receptors of this system, melanocortin 4 receptor (MC4R) is expressed in hypothalamic neurons and has a role in regulation of bone homeostasis. It has been reported that patients deficient in MC4R exhibit high bone mineral density resulting from a decrease in bone resorption [48]. Importantly, the greater BMD is still evident following correction of the obesity that is characteristic of MC4R deficiency [48]. Mechanistic studies in mice have enabled dissection of this pathway to the bone, and interestingly, have implicated another hypothalamic neuropeptide, cocaine- and amphetamine-regulated transcript (CART). Hypothalamic CART expression is increased in $MC4R^{-/-}$ mice, which display a high bone mass phenotype due to decreased osteoclast number and function [14,49], as evident in human studies. Additionally, MC4R mutant mice lacking one or two copies of CART exhibited a significantly lower bone mass [14,49], demonstrating increased CART signaling, is critical to the low-bone-resorption/high-bone mass phenotype observed in MC4R-deficient mice. CART has also been implicated in the resorption phenotype evident in *ob*/*ob* mice [14]. Thus CART signaling may be an axis of convergence for melanocortin and leptin signaling, both of which have powerful effects upon energy metabolism and body composition as well as bone homeostasis.

Neuromedin U

NMU is a neuropeptide expressed in the hypothalamus and small intestine. It is a known target of sympathetic activation [50]. NMU null mice have increased bone mass and bone formation, via a central hypothalamic pathway [51]. NMU2 receptor is expressed in the paraventricular nucleus (PVN), and central infusion of NMU rescued the high bone mass of $NMU^{-/-}$ mice. NMU and its receptors are not detectable in the bone and in vitro NMU treatment did not alter osteoblast activity. Interestingly, NMU treatment decreased the high cancellous bone mass of *ob*/*ob* mice, indicating a role for NMU downstream of leptin to regulate bone formation. Consistent with this, $NMU^{-/-}$ mice were resistant to the skeletal effects leptin and β2AR agonists. NMU signaling thus provides another aspect of the transmission of the leptin signaling to the bone.

Neuronal control of muscle development and contraction

Neuronal inputs are fundamental to muscle physiology, regulating many aspects of development and function. Skeletal muscle contraction

remains the principle mechanism for muscle–bone interaction, and muscle contraction is primarily governed by the central and somatic nervous systems (CNS and SoNS, respectively), which provide the voluntary signals required to induce muscle contraction. Briefly, in skeletal muscle contraction, an action potential from the CNS stimulates individual motor neurons which activate a proportion of muscle fibers. A single motor neuron stimulates only a proportion of muscle fibers within a muscle. The somatic motor neurons which innervate muscles are activated via an α motor neuron, which provides the signals necessary to control skeletal muscle contraction. Mechanistically, the activation of the motor unit complex (which consists of multiple motor neurons and muscle fibers) stimulates the sarcoplasmic reticulum to release calcium and initiate contraction. Activation of an action potential and the subsequent calcium influx causes acetylcholine (neurotransmitter) release, which activates the neuromuscular junction (NMJ) of the stimulated skeletal muscle fibers and both produces and releases noradrenaline, a potent β2AR agonist. This activation causes a shift in the fiber's sodium/potassium gradient, promoting an action potential which triggers a cascade of events described by the sliding filament theory to generate muscle contraction. The force generated from contracting skeletal muscle then induces compression and micro-strain in bone tissue, which are some of the most potent inputs to structural and metabolic activity in the skeleton. Thus bone tissue is reliant upon neuronal actions in the muscle for its growth and development.

The interplay between the bone and muscle occurs throughout life, beginning embryonically with patterning of the somites, through to the effect physical forces play on bone strength and development during every-day life. The latter has been refined in the mechanostat theory, which remains a widely accepted concept of muscle–bone interaction. Briefly, the skeletal muscle provides loading forces during contraction which are essential for bone development, maintenance and modeling/remodeling [52]. This muscle–bone interaction involves a complex system of genetic, metabolic, endocrine, paracrine and neuronal signals which together support the muscle as a principal source of anabolic stimulus in the bone.

Sympathetic nervous system and skeletal muscle

The β-adrenergic receptors have been shown to regulate cardiovascular, respiratory, metabolic and reproductive function. Three isoforms have been identified (β1, 2 and 3) which are part of the G-protein coupled receptor superfamily. As is the case in the bone, the β2AR is the most abundant isoform in the skeletal muscle and functions via a number of pathways including the Akt and/or protein kinase A (PKA) signaling pathways [53]. Much of the information regarding the effects of β-AR signaling in the skeletal muscle has come from studies investigating the potential therapeutic benefits of synthetic βAR agonists, such as *Clenbuterol*, *albuterol*/*salbutamol* and *formoterol*, which are typically used in the treatment of asthma, in inducing muscle hypertrophy [54] and more recently reducing skeletal muscle wasting/atrophy [55].

Muscle atrophy is a hallmark of many diseases including inherited neurological disorders, chronic diseases (such as cancer, heart disease and stroke) as well as following denervation (post spinal cord injury). β2AR agonists have been shown to reduce muscle degeneration and improve function in many of these situations [55,56], supporting a strong signaling response/role for this pathway in the skeletal muscle. For example, in Duchenne muscular dystrophy (DMD), a progressive X-linked skeletal muscle disease, β2-AR agonist administration (*Clenbuterol or formoterol*) has been shown to increase skeletal muscle mass, morphology and function in the *mdx* mouse model of DMD [57]. In addition, clinical trials using *salbutamol* have also resulted in improvements in muscle mass and function in human DMD patients [58]. Similarly, β2AR signaling plays an important role in stimulating skeletal muscle growth [56], development [59] and the regulation of regeneration [60,61] in healthy populations.

The study of leptin deficiency has firmly established the hypothalamus and SNS as a critical factor in the control of bone remodeling and skeletal muscle function. As outlined above, leptin regulates cancellous bone formation via β2AR signaling in osteoblasts and osteoclasts. Similarly, β2AR signaling plays an important role in stimulating skeletal muscle growth in both damage/disease and healthy populations. Thus β2AR provides a possible link between this common signaling pathway regulating the production and maintenance of both the muscle and bone. While we and others have outlined that the CNS drives voluntary muscle contraction and is the primarily mechanical exchange between the bone and muscle, SNS signaling and the release of noradrenaline/epinephrine is the primary β2AR activator in the skeletal muscle and a key signaling pathway in maintaining muscle mass. To date research has focused on the genetic, metabolic and endocrine/paracrine interactions between the muscle and bone with the key goal of determining how the muscle and bone 'communicate', neuronal interplay may be a novel mechanism by which these two tissues are co-regulated.

Co-ordinate regulation of the bone and muscle by neuronal pathways

Research supports a direct role of the sympathetic nervous system and β2AR signaling in the bone. In contrast, these signals act only indirectly in the muscle however; the β2AR signaling pathway may still play a common role in regulating muscle–bone interactions. While further research is required to determine the interactions between this pathway in both the skeletal muscle and bone; there are several lines of evidence that point to coordinate regulation of both the bone and muscle by the neuronal system. As mentioned above, leptin signaling is a powerful regulator of bone formation, through modulation of sympathetic signaling in the cancellous bone. The leptin deficient, *ob*/*ob* mice display increased cancellous bone due to reduced SNS signaling, however, they also have markedly reduced muscle mass [62], despite their profoundly increased bodyweight. The gastrocnemius, extensor digitorum longus and soleus muscle mass as well as fiber size are significantly lower in *ob*/*ob* mice [63]. This reduced muscle mass and increased cancellous bone coincident with the reduced sympathetic tone of *ob*/*ob*, is consistent with greater muscle mass and bone loss associated with β2 agonist therapy [55,64]. The exact signaling mechanism involved however, may be complex. The bone and muscle express leptin receptors, however they occur most prominently in the hypothalamus of the brain [65]. In addition, β2AR are also expressed upon both the osteoblasts and skeletal muscle [42,63]. Thus muscle mass may be regulated by adrenergic pathways secondary to leptin signaling in the hypothalamus, indicating that central leptin-responsive pathways may coordinate regulation of both the bone and muscle (Fig. 1). Alternatively/in addition, direct signaling may also be involved. Reports of the effect of peripheral leptin treatment on the muscle have proven inconsistent, with improvements [63], or no change [62]. However, a recent study examined both peripheral (s.c.) or central (icv) leptin administration [62]. Bartell and colleagues examined the response of the bone and muscle to s.c. and icv leptin administration [62]. Interestingly, both s.c. and icv leptin resulted in marked body weight and fat mass losses, while gastrocnemius weight was significantly elevated by both. The loss of weight and fat is indicative of increased sympathetic tone secondary to central leptin signaling, and suggest that the skeletal muscle may also be regulated by central neuronal outputs form hypothalamic leptin-sensitive neurons. In addition, these responses were accompanied by elevated IGF-1 levels, again consistent with a response to central leptin signaling, and also likely to promote muscle anabolism. Critically, the SNS is known to play a pivotal role in controlling the storage and partitioning of energy substrates in many tissues, including the skeletal muscle, regulating glucose and glycogen economies. Thus, as the bone emerges as a regulator of energy homeostasis, it may join the muscle as a target for central regulatory control of the whole body energy economy. In addition, SNS regulates protein metabolism in muscle, and like osteoblasts, myoblasts respond in an anabolic manner

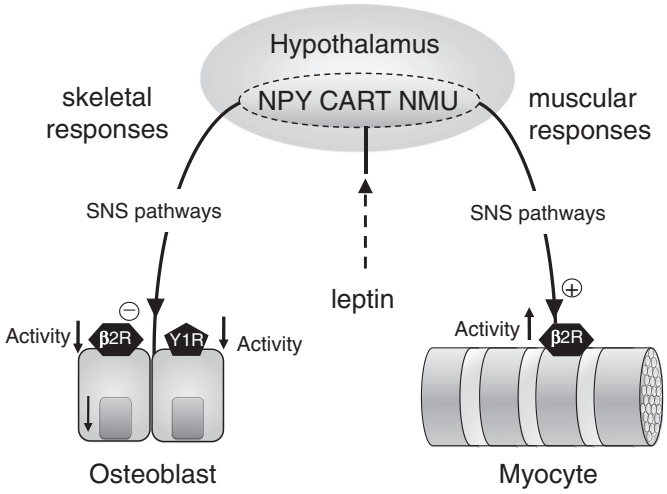

Fig. 1. Sympathetic co-regulation of the bone and skeletal muscle. The hypothalamus acts as a coordination center for a myriad of inputs, including endocrine factors, such as leptin. These are integrated to regulate sympathetic outflow, such as noradrenaline and NPY, which act directly upon osteoblast and myocytes to modulate cell function. ⬇ Reduction/inhibition; ⬆ Increase/activation. ⊖ Negative; ⊕ positive response.

to β2AR modulation [66]. In this manner, the bone and muscle, being such significant contributors to energy utilization, are targets for central energy regulatory axes, functioning both via autonomic and endocrine pathways.

Conclusion

The bone and muscle are closely linked in a functional manner, designed to act in tandem to provide locomotion. As such, their development is tied together by the requirements for a successful musculoskeletal system. The co-ordination of this multi-organ system is complex, and our understanding of the role of neuronal factors is far from complete. Recent understanding of the importance of neuronal signaling in the bone has suggested the potential for similar pathways to muscle. Indeed, the SNS appears to be a critical mediator of osteoblast and myocyte biology. Given the close association of sacropenia and fracture [67], the continued expansion of our knowledge of these interactions between bone and muscle regulation may provide novel opportunities for therapy.

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