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Review

Central regulation of bone mass

Iris P.L. Wong[a], Ayse Zengin[a], Herbert Herzog[b], Paul A. Baldock[a,*]

[a] Bone and Mineral Research Program, Garvan Institute of Medical Research, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia
[b] Neuroscience Research Program, Garvan Institute of Medical Research, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia

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ABSTRACT

The traditional view of skeletal homeostasis as a primarily endocrine activity has been expanded in recent years following the identification of direct neural pathways controlling bone homeostasis via central relays. Powerful control over both anabolic and catabolic activities have been isolated to neurons of the hypothalamus, enabling large changes in bone mass to be achieved by minute changes in the levels of these central neural signals. Initiated by studies of leptin and expanding rapidly, the breadth and complexity of this regulatory axis to bone is sure to increase. Critically though, the translation of these findings into therapeutic interventions is likely to present a greater challenge. However, the contribution to our understanding that these initial studies are making indicates an exciting potential to help to alleviate the growing challenge presented by musculoskeletal disease.

Contents

1. Control of bone remodelling

The skeleton is a dynamic set of tissues, constantly remodelling itself by the coordinated removal and replacement of minute quanta of bone by dedicated cell types, the osteoclast and osteoblast, respectively. A delicate balance between these processes is essential for maintaining both the mechanical and mineral homeostatic functions of the skeleton. Imbalance can lead to weakening which, unfortunately, is all too common, with fragility fractures due to osteoporosis extremely prevalent in the aging population, and associated with marked morbidity and mortality [1].

Historically, the prevailing view has been that bone remodelling is controlled in a predominantly endocrine manner, whilst simultaneously responding to local mechanical stimuli. Recently however, there is increasing evidence that the central nervous system contributes direct regulatory influence upon bone homeostasis via efferent neural connections. Immunocytochemistry studies initially revealed the presence of innervation and receptors for neuropeptides in bone cells, which strongly support a direct role of the nervous system in these cells ([2] – for review). More recently, retrograde trans-synaptic tracing has identified neural tracts from the

* Corresponding author. Tel.: +61 2 9295 8244; fax: +61 2 9295 8241.
E-mail addresses: i.wong@garvan.org.au (I.P.L. Wong), a.zengin@garvan.org.au (A. Zengin), h.herzog@garvan.org.au (H. Herzog), p.baldock@garvan.org.au (P.A. Baldock).
URL: http://www.garvan.org.au (P.A. Baldock).

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femoral bone marrow linked direct to the central nervous system [3]. Together, these observations indicate the existence of a neuronal pathway between the brain and the bone. However, it was murine mutant models that provided the most powerful evidence for direct central control of bone mass and the importance of these murine studies to the increase in our knowledge is without question. The relevance of these models to human health, however, is yet to be fully realized, as such, where possible, human studies will be included to highlight the potential of this emerging and exciting field.

2. Dichotomous skeletal effect of leptin in mice

Interestingly, the initial identification of a direct neural output from the hypothalamus to bone came about from study of a circulating factor, leptin. Leptin, a 16 kDa protein, is a hormone secreted primarily by white adipose tissue, circulating in proportion to adipose stores and acting as an adipostat [4]. In 2000, several studies describing the skeletal effects of leptin using mutant mouse models were published. Histomorphometric analyses showed that mice lacking leptin (*ob*/*ob*) or its receptor (*db*/*db*) had higher cancellous bone volume associated with increased bone turnover [5]. This occurred despite concurrent hypogonadism and hypercortisolism, which favour bone resorption, establishing leptin's powerful anti-osteogenic effect on cancellous bone. Conversely, later that year, another group reported leptin as a potent stimulator of bone growth in *ob*/*ob* mice. Leptin treatment in young *ob*/*ob* mice increased both cancellous and cortical mineral content of the femora [6]. Leptin treatment also increased femur length, total body bone area, bone mineral content (BMC) and density (BMD) when compared to vehicle-treated controls. Similar results were observed in 15-week-old *ob*/*ob* mice treated with subcutaneous leptin infusion [11].

These apparently conflicting findings suggest differing effects of cortical and cancellous bone in *ob*/*ob* mice. Indeed, subsequent analysis has demonstrated 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 [6,8–10]. While leptin treatment increased whole body BMC and endosteal bone formation in the *ob*/*ob* mice, no differences were seen in wild-type mice [11]. These data indicate that the primary effect of leptin deficiency on the skeleton is a reduction in cortical bone formation, which comprises 80% of the murine skeleton. In addition, to envelope specific effects, *ob*/*ob* mice also display altered responses between the axial and appendicular regions. Leptin-deficient mice were found to have increased vertebral length, lumbar BMD and cancellous bone volume but shorter femur length, femoral BMD, cortical thickness, compared to lean wild-type mice [12].

A number of factors may influence the skeletal response to leptin deficiency, not the least being, the many endocrine changes associated with the loss of this pleiotropic hormone. One suggestion is that the sparing of cancellous bone during periods of diminished serum leptin may act to preserve mineral stores during periods of food restriction [13]. Consistent with such a notion, caloric restriction in mice reduces total bone mass but increases bone mass in the spine [14]. In addition, to caloric influences, the differential innervation of axial and appendicular bones may contribute to the regional differences observed. Differences in bone marrow composition are also suggested, which are illustrated by the high adiposity of *ob*/*ob* femurs compared to vertebrae [12]. A recent article suggested a bimodal threshold response to serum leptin levels, with low-dose leptin preventing bone loss, while high-dose leptin inhibiting bone growth [15]. However, despite the complexity of leptin's actions on bone, the mode of action proved a paradigm shifting discovery.

3. Central effects of leptin on bone

One of the critical developments in the area of bone metabolism in recent years has been the discovery of a central locus for the regulation of bone mass. The long form of the leptin receptor (*Ob-Rb*), which performs signal transduction, is found within the hypothalamus [16]. A shorter form of the leptin receptor (*Ob-Ra*) is co-expressed with *Ob-Rb* in the hypothalamus where it is thought to facilitate transport of leptin into the brain [17]. Critical to the notion of a central axis of leptin action, intracerebroventricular (icv) infusion of leptin, without detectable leakage in the blood stream, was able to correct the cancellous bone phenotype of ovariectomised *ob*/*ob* mice [5]. Moreover, in wild-type mice, the selective destruction of *Ob-Rb* positive hypothalamic neurons by gold thio-glucose increased cancellous bone mass, with icv leptin treatment no longer able to correct the cancellous phenotype [18]. Together, these results indicated, for the first time, that the central hypothalamic pathway is sufficient to exert leptin's effect on cancellous bone. Recently, the central leptin pathway was studied using a more targeted approach. A single hypothalamic icv injection of leptin producing adeno-associated virus in *ob*/*ob* mice resulted in normalization of body weight and recapitulation of wild-type skeletal phenotype [19]. Femoral and vertebral cancellous bone volumes were reduced to wild-type levels, while femur length and total femur bone volumes were increased to wild-type level. This reinforces the anti-osteogenic effect of leptin on cancellous and pro-anabolic actions on cortical bone as described previously, more importantly, originating from the same region of the brain. The study of leptin has firmly established the hypothalamus, as not only the seat of endocrine control of bone, but also critical in the direct neural control of this tissue.

4. Association of leptin and bone in humans

Epidemiological evidence shows that obesity is correlated with increased bone mass, and that a reduction in body weight may cause bone loss [20,21], while low body weight is a key risk factor for fracture and mortality post-fracture [22]. Taken together, these data suggest a protective effect of fat mass on bone [23] and as such a positive relationship between leptin and bone mass. However, correcting for the mechanical loading effect of body weight on bone mass has revealed both positive [24] and negative associations [25], suggesting further complexity in this relationship. One of the most likely sources of complexity in the relationship between leptin and bone mass in humans involves the development of leptin resistance, which increases markedly with increasing fat mass and age, involving the down regulation of leptin receptor expression [26,27]. A large meta-analysis of leptin and BMD in nearly 6000 postmenopausal women found that less than 1% of the variation in BMD was explained by leptin with no significant correlation with femoral neck or lumbar spine BMD [28]. Similarly, exogenous leptin supplementation has no significant effect on weight loss in humans [29]. In addition to leptin resistance, hormonal abnormalities associated with obesity, such as insulin resistance, hypogonadism and hypercortisolism further complicate the characterization of leptin's action on bone in obese patients.

While hypogonadism and hypercortisolism are also an issue, patients with anorexia nervosa have lower circulating leptin and thus lack leptin resistance. Anorexic patients have markedly reduced BMD, coincident with elevated (up to sevenfold) inci-