FEBS Letters 528 (2002) 40–42 FEBS 26404

Feature

Role of leptin in bone growth: central player or peripheral supporter?

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Received 24 June 2002; revised 25 July 2002; accepted 26 July 2002

First published online 22 August 2002

1. Leptin and its receptor

Maintenance or gain of bone mass is associated with hormone and/or heavy mechanical load, either due to obesity or physical activity [1]. Amongst the many hormones that might account for the link between energy and bone metabolism is leptin. In this respect, much attention has focused on the effects of leptin as a central satiety agent, although in vitro studies provide evidence for direct effects on specific tissues and metabolic pathways. The debate related to central and/or peripheral regulation of bone metabolism by leptin has been ongoing during the last 2 years. The article by Lee and colleagues [2] in this issue further addresses this topic, and provides evidence that functional leptin receptors are expressed in rat osteoblasts. These results point towards a more direct role of leptin in bone growth.

Since its discovery in 1994 [3], leptin has been acknowledged as an adipocyte-derived signaling molecule, which may limit food intake and increase energy expenditure via specific receptors located in the central nervous system. However, the picture is becoming more complicated, and leptin is now looked upon as a multi-potent cytokine with both indirect central and direct peripheral effects in different organs, tissues and cells. Circulating leptin in adult individuals is mainly secreted from adipose tissue [3,4], although leptin polypeptide and mRNA are detected in other tissues like muscle [5], gastric epithelium [6], bone [7], and in breast epithelial cells [8]. Leptin expression has also been found in arterial wall cells [9] and in normal pituitary and different types of pituitary adenomas [10]. In pregnant women, leptin is synthesized and secreted from placental trophoblasts into the maternal and fetal circulation [11].

Leptin binds to receptors in the hypothalamus [4] which leads to reduced appetite and increased energy expenditure. The leptin receptor (OB-R) exhibits considerable homology with the interleukin-6 (IL-6) receptor and belongs to the cytokine class I receptor family [12]. At least six forms of the leptin receptor have been found, of which the long signal-transducing form, OB-R_L, presumably mediates most of leptin's signaling events. It is also the isoform most abundantly expressed in the hypothalamus [12]. However, the leptin receptor is expressed in various areas of the central nervous system, and in many other organs and cell types [13].

The cytokine receptor superfamily is a rapidly growing family of receptors. An early and most likely pivotal event for all subspecies is the activation of one or more members of the Janus (or JAK) family of tyrosine kinases. The activated JAK kinases, which form a complex with the cytokine receptor subunits, induce autophosphorylation as well as phosphorylation of the receptor. These phosphorylated tyrosines form binding sites for various signaling molecules that are themselves thought to be phosphorylated by JAK kinases, including signal transducers and activators of transcription (STATs) [14], which regulate transcription by adapter proteins like SH2-containing protein tyrosine phosphatase [15] that recruit Grb2 complexes thereby initiating the mitogen-activated protein kinase (MAPK) pathway, and insulin receptor substrate (IRS) proteins that, through phosphate inositol pathway, are thought to regulate metabolic events in the cell [16].

2. Central effect

It has been demonstrated in mutant leptin (*ob*/*ob*) and leptin receptor (*db*/*db*) mouse models that bone formation, like other homeostatic functions, is systemic regulated. Ducy et al. [17] found that intracerebroventricular injections of leptin in obese *ob*/*ob* mice decrease bone density. They were not able to demonstrate leptin receptor expression in osteoblasts from *ob*/*ob* mice, and claimed that leptin does not act directly on bone cells. Rather, leptin acts through a central pathway following binding to its receptor(s) in hypothalamic nuclei. The signal downstream of the hypothalamus to the bone is hitherto unknown. Bone tissue serves as a target of the nerve system. From birth on, the growth of nerves parallels the mineralization process, and sympathetic nerve fibers comprising neuropeptide Y (NPY) have been observed in bone [18]. NPY is known to be a potent stimulator of energy intake under OB-Rb control [19]. However, NPY causes bone loss, not growth, when infused intracerebrally [16], indicating that leptin may in fact use two different pathways regulating body weight and bone mass. NPY signaling, through binding to the Y2 receptor, restrains bone growth, as evidenced by the observation that $Y2^{-/-}$ mice display more and larger femoral trabeculae than normal mice. However, such animals exhibit a normal number of osteoblasts which are metabolically more productive than osteoblasts from normal littermates [20]. Interestingly, the high bone mass found in *ob*/*ob* mice was also proven to be a result of a normal number of osteoblasts making twice as much bone matrix as the osteoblasts produced in normal animals [17,21–25].

Endocrine mechanisms are involved in reproduction, as well as in control of body mass. In this context, leptin might also regulate bone growth through indirect control of ovarian cycling and estrogen production by promoting release of the hypothalamic gonadotropin-releasing hormone. Leptin may further prevent ovariectomy-induced bone loss in rats by suppressing the production of RANK (receptor activator of nuclear factor κB) ligand by osteoblastic stromal cells [26].

Key words: Leptin; Bone; Central effect; Peripheral effect

PII: S0014-5793(02)03161-7

3. Direct effect

The fact that bone is resorbed by osteoclasts and subsequently replaced by the osteoblasts at multiple skeletal locations indicates, within a remodeling cycle, direct link between osteoblasts and osteoclast activity [27]. This paracrine and/or autocrine regulation of bone turnover may be evoked by osteoblast-derived factors like transforming growth factor (TGF), insulin growth factor (IGF)-I and -II, tumor necrosis factor (TNF) and interleukins [28].

Recently, leptin was demonstrated to induce differentiation of marrow stromal cells into osteoblasts, and not to adipocytes [29]. Leptin receptor mRNA [7] and protein [30] expression has been demonstrated in human osteoblasts, strongly indicating a direct effect of leptin on bone metabolism. The article by Lee and colleagues in this issue of the journal clearly shows that osteoblasts express a functional leptin receptor capable of conducting an active signal through the Jak/Stat pathway, a convincing evidence for a direct action of leptin in these bone cells.

Leptin has been found to elicit important osteoblastic functioning, by inducing mineralized nodules in primary osteoblasts and osteosarcoma cells [7,17,22–25]. Leptin has also been demonstrated to have direct effects on proliferation, differentiation, mineralization, and to induce prolonged life span of human primary osteoblasts by inhibiting apoptosis [31]. The generation of cultured osteoclasts differentiated from peripheral blood mononuclear cells (PBMCs) and murine spleen cells is inhibited by leptin [32], indicating that leptin acts locally to increase bone mass and may contribute to the well-known linkage of bone resorption and formation.

Maor et al. [33] found that chondrocytes in the growth centers contain specific binding sites for leptin. Leptin stimulated the width of the chondroprogenitor zone at low concentrations, whereas higher concentrations had an inhibitory effect. They also found that leptin induced both proliferation and differentiation activities in the mandibular chondyle. Finally, it was demonstrated that leptin increases the abundance of the IGF-I receptor and IGF-I receptor mRNA within the chondrocytes and the progenitor cell population [33]. These results indicate that leptin acts as a skeletal growth factor with a direct peripheral effect on skeletal growth centers.

4. Central or peripheral action of leptin in bone growth – or both?

Steppan et al. [30] demonstrated shorter femurs in *ob/ob* mice, and that intraperitoneal injections of leptin increased bone area. Does the locus of leptin injection play a role in its effects on bone metabolism?

We have presented data showing that leptin is expressed in mature primary cultures of human osteoblasts and secreted to the surrounding media [7]. However, we know nothing about the local leptin concentration within the bone marrow, and little of the complex interactions between leptin and other factors from stromal cells, chondrocytes, adipocytes, osteoclasts, mononuclear cells and osteoblasts at different stages of differentiation in the local bone environment.

Present information on leptin indicates that leptin is involved in at least two different bone-controlling mechanisms, a direct stimulatory effect on bone growth, and/or an indirect suppressive effect on bone through the hypothalamus. The regulation of bone growth is complex, and leptin adds more complexity to this picture. The local environment may provide bone cells with signals favoring constant growth, whereas the central negative signal determines the density and length regulated by energy metabolism and leptin. Central administration of recombinant leptin in obese *ob/ob* mice [17] and normal mice causes a decrease in bone mass, whereas peripheral administration [30] and in vitro studies in cultured cells [31–33] indicate an increase in bone growth.

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