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News on current events in osteoporosis and rheumatology

Leptin: in search of a hormonal regulation of bone formation

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Two major features of osteoporosis are that osteoporosis invariably follows gonadal failure, and that obesity protects from it. These two observations suggest the existence of a common regulation of body weight (or appetite), reproduction, and bone mass. Since appetite and reproduction are governed by the hypothalamus, this hypothesis implies that the control of bone remodeling may also, in part, originate from the hypothalamus.

Searching for a common endocrine control of appetite, reproduction, and bone mass focused the attention on leptin [1, 2]. Mice lacking either leptin (*ob/ob*) or its receptor (*db/db*) are obese and sterile. The sterility (or hypogonadism) of *ob/ob* and *db/db* mice should increase their bone resorption.

Indeed, osteoclast number and bone resorption parameters are increased in leptin signaling-deficient (*ob/ob* and *db/db*) mice. Despite this, leptin signaling-deficient mice display a higher bone mass than wild-type mice. This high bone mass, affecting all bones in the body, is due to a massive increase in bone formation parameters. To date, leptin signaling-deficient mice are still the only animal models in which hypogonadism and high bone mass coexist. High bone mass was also observed in a patient harboring an inactivating mutation of the leptin gene.

The high bone mass of *ob/ob* or *db/db* mice cannot be explained by their obesity since mice lacking adipocytes ("fat-free" mice) display the same phenotype and since a leptin transgene can correct the high bone mass of fat-free mice, indicating that leptin is the adipocyte-derived gene product responsible for their bone phenotype. In addition, intracerebroventricular (ICV) infusion of leptin in leptin-deficient mice, at a rate that does not result in any detectable leak of leptin in the general circulation, completely corrects their high bone mass. This demonstrates that leptin uses a central (presumably hypothalamic) relay to control bone mass and rules out a direct effect of leptin on osteoblasts.

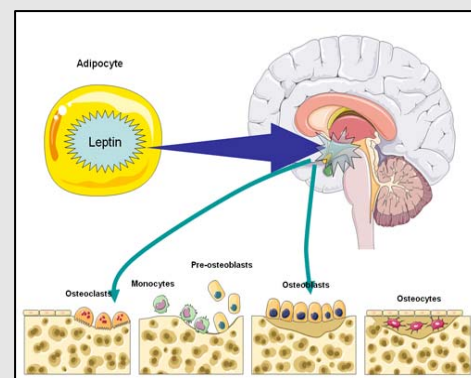
How and where does leptin act on the central nervous system is the next question to be answered?

1. Ducey P et al. *Cell*. 2000;100:197-207.
2. Karsenty G. *Cell Metabolism*. 2006;4:341-349.

How does leptin affect bone mass?

Leptin is a hormone secreted by adipocytes. In the absence of leptin or of its receptor, bone mass increases because of a stimulation of bone formation.

Leptin does not act directly on bone cells. Instead, leptin acts on the central nervous system which is a mandatory relay for the action of leptin on bone.



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