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Regulation of bone resorption by leptin

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The assumption that identical classes of molecules might regulate the two aspects of bone remodeling, formation, and resorption, prompted the investigators to look for neural regulation of bone resorption.

The answer came from mice lacking the adrenergic receptor [1]. These mutant mice not only present an increase in bone formation, but also a decrease in bone resorption. This latter abnormality, which contributes to the *Adrb₂*-deficient mice high bone mass, cannot be corrected by leptin ICV infusion, indicating that leptin regulates bone resorption via the sympathetic tone.

The differentiation of osteoclasts is determined by osteoblasts which produce two main regulators: M-CSF, a survival factor for osteoclast progenitor cells, and RANKL, a true osteoclast differentiation and activation factor. Culture of osteoblasts and osteoclast precursors revealed that sympathetic signaling regulates osteoclast differentiation by regulating expression of RANKL in osteoblasts. Following gonadectomy, a situation that usually increases bone resorption and decreases bone mass, bone resorption parameters and bone mass remained unaffected in *Adrb₂*-deficient mice, indicating that the integrity of the sympathetic nervous system is required for the bone loss that follows gonadal failure.

The ability of leptin to regulate the expression of gene(s) controlling osteoclast differentiation was then tested. One gene, whose expression is increased by leptin and decreased in *ob/ob* mice, is *Cart* (cocaine amphetamine regulated transcript). *Cart*-deficient mice display an osteoporosis phenotype due to an isolated increase in bone resorption. The importance of CART in osteoclast differentiation is shown by the fact that mice with increased hypothalamic *Cart* expression have a high bone mass with an isolated decrease in bone resorption parameters, a phenotype corrected by simply deleting *Cart*.

In summary, as in the control of bone formation, leptin regulates bone resorption through two antagonistic pathways. On the one hand, leptin favors resorption through the sympathetic nervous system; on the other hand, it inhibits this function through CART. The absence of CART probably explains the increased bone resorption observed in *ob/ob* mice [2].

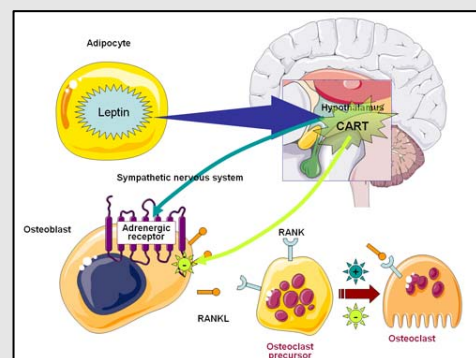
1. Elefteriou F et al. *Nature*. 2005;434:514-520.
2. Karsenty G. *Cell Metabolism*. 2006;4:341-349.

Leptin controls bone resorption

Leptin acts on hypothalamic neurons, which results in sympathetic activity. Stimulation of β -adrenergic receptors on osteoblasts induces RANK ligand (RANKL) synthesis. RANKL favors osteoclast differentiation and activation.

On the other hand, leptin activates CART, a gene expressed in the hypothalamus. CART reduces the expression of RANKL and thus reduces bone resorption.

The overall effect of leptin on bone resorption is most likely an inhibitory one.



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