

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Towards elucidation of the central nervous system network involved in leptin control of bone formation

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Once it was known that leptin acts on the central nervous system, the next step was to identify leptin-sensitive neurons controlling bone formation. This was achieved through chemical lesioning in wild-type and leptin signaling-deficient mice, and the use of other genetically modified mouse models. These experiments established that hypothalamic neural networks regulate bone formation. The final proof that leptin was the mediator came when *ob/ob* mice, which lack leptin, with destroyed arcuate or ventromedial hypothalamic (VMH) neurons received leptin ICV (intracerebroventricular) infusion. In this situation, leptin ICV infusion decreased body weight but did not affect bone formation parameters or bone mass. Thus, VMH neurons regulate bone formation under the control of leptin [1, 2].

What is the mediator of leptin-mediated regulation of bone formation? It has long been known that *ob/ob* mice have low sympathetic activity. This observation naturally led to the assumption that the sympathetic nervous system must mediate leptin regulation of body weight and/or reproduction. This supposition was challenged, however, by the fact that another mouse model, *Dbh*-deficient mice, unable to produce epinephrine and norepinephrine, were neither obese nor sterile. This is because the low sympathetic tone observed in *ob/ob* mice is not responsible for their obesity or their sterility, but rather controls bone mass. Indeed, patients with reflex sympathetic dystrophy, a disease characterized by localized high sympathetic activity, develop a severe and localized osteoporosis that can be improved by  $\beta$ -blockers. In support of this hypothesis, the following observations were made: *Dbh*-deficient mice have high bone mass; this high bone mass is resistant to leptin ICV infusion, whereas this infusion decreases fat and body weight. More importantly, restoring sympathetic activity in *ob/ob* mice had no measurable effect on food intake and body weight but led to a 45% decrease in bone mass.

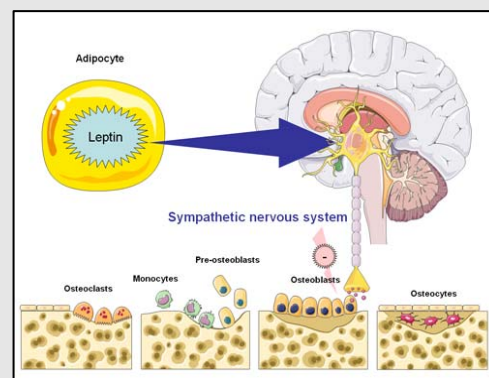
Taken together, these lines of evidence demonstrate that, at least in animals fed a normal diet, the sympathetic nervous system mediates selectively leptin regulation of bone mass.

1. Takeda S et al. *Cell*. 111: 2002;305-317.
2. Karsenty G. *Cell Metabolism*. 2006;4:341-349.

### How does brain mediate the effect of leptin on bone?

Leptin acts on ventromedial hypothalamic neurons. From there, a signal is sent through the sympathetic nervous system.

In the absence of leptin or of its receptor, sympathetic activity is low and the inhibitory effect of catecholamines on bone formation is relieved.



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