

COMMENTARIES

New Examples of a Central Control of Bone Mass

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Commentary on:

- Baldock PA, Sainsbury A, Allison S, Lin EJ, Couzens M, Boey D, Enriquez R, During M, Herzog H, Gardiner EM. Hypothalamic control of bone formation: distinct actions of leptin and Y2 receptor pathways. *J Bone Miner Res.* 2005 Oct;20(10):1851-57.
- Bajayo A, Goshen I, Feldman S, Csernus V, Iverfeldt K, Shohami E, Yirmiya R, Bab I. Central IL-1 receptor signaling regulates bone growth and mass. *Proc Natl Acad Sci U S A.* 2005 Sep 6;102(36):12956-61.

Since the initial demonstration through the study of leptin that there was a central control of bone mass, this area of bone biology has generated a growing interest from both bone biologists and energy metabolism experts (1). Indeed, shortly after the initial publication it was shown that deletion in humans of MC4R, a receptor required for leptin regulation of appetite, led to an increase in bone density (2). The molecular basis of this phenotype has been recently elucidated (3). Slightly later it was shown in mice that deletion of the Y2 receptor, a receptor that can bind the neuropeptide NPY and other ligands, resulted in a high bone mass due to an increase in bone formation (4). In the last few weeks two studies have appeared that pursue the exploration of the leptin-independent neural regulation of bone mass (5;6).

The first paper is a continuation of the study of Y2-dependent signaling in the hypothalamus and its effect on bone formation. The increase in bone formation originally noted in Y2-deficient mice contrasted sharply with the normal bone formation parameters observed in NPY-deficient mice (7). This apparent contradiction could be explained if NPY is not the ligand of the Y2 receptor in the hypothalamus that is responsible for the reported high bone mass phenotype. Alternatively, and not exclusively, it could mean that Y2-deficient mice have low fat mass and therefore lower serum leptin

levels, a condition that increases bone formation in mice (8). That bone resorption was not affected in Y2-deficient mice as it is in leptin-deficient mice provided *in vivo* support for the second hypothesis. In an effort to address this question more thoroughly the Gardiner group examined a set of relevant mutants: Y2-deficient mice, leptin-deficient *ob/ob* mice, and NPY-overexpressing mice as well as Y2-deficient *ob/ob* double mutant mice and Y2-deficient NPY-overexpressing mice (5). Through a series of elegant experiments they show that NPY is not required for leptin regulation of bone formation. This body of work that spans several papers further suggests that the bone-regulating ligand of the Y2 receptor in the hypothalamus has not been identified yet.

The second study, from Bab and colleagues, studied the influence of interleukin-1 (IL-1) signaling on bone resorption (6). They noticed that mice lacking IL-1 receptor antagonist (IL-1ra) develop low bone mass, a phenotype for which there was no cellular explanation. Since IL-1 has been reported to modulate learning, memory and sleep pattern the authors suggest that lack of IL-1ra may disrupt the central mode of IL-1 action in the control of bone mass. To test this idea the Bab group over-expressed IL-1ra in glial cells. As expected their IL-1ra transgenic mice express IL-1ra at a high level in hypothalamic neurons and presumably in many other neurons. The IL-

1ra transgenic mice develop a more severe low bone mass phenotype than the IL-1-deficient mice; this phenotype appears to be due only to an increase in bone resorption parameters. This latter observation is somewhat surprising in view of the fact that IL-1 enhances bone resorption in wild type mice. There is no explanation yet for the fact that both increased and decreased IL-1 result in the same bone phenotypic abnormalities. This is certainly one aspect of the study that will need further investigation. One will need to establish *in vivo* that it is through hypothalamic expression that IL-1ra affects bone resorption. Lastly one will need to know if this involves sympathetic, CART (cocaine amphetamine regulated transcript) neuropeptide, or another type of signaling.

Conflict of Interest: The author has declared that no conflict of interest exists.

References

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