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Invited Plenary Abstract
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Central control of bone mass

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Bone remodeling is controlled by local and systemic factors, the latter including direct central neural inputs involving critical hypothalamic relays. The details of such neural regulatory mechanisms are emerging. In particular, two distinct but interacting pathways regulated by the adipocytic hormone leptin and neuropeptide Y (NPY) are the subjects of intensive ongoing investigations.

Genetic ablation of leptin function in mice leads to a high cancellous bone mass phenotype associated with increased bone turnover. Binding of circulating leptin to its receptor on specific hypothalamic neurons inhibits cancellous bone formation via the sympathetic nervous system (SNS) and stimulates osteoclast differentiation via the SNS and a hypothalamic circuit involving cocaine- and amphetamine-regulated transcript (CART). Leptin-dependent sympathetic control of bone formation acts via β2-adrenergic receptors on the osteoblast to control cell proliferation by two antagonistic pathways that are mediated, in turn, by circadian *Per* genes and the AP-1 transcription factor. Sympathetic control of bone resorption, also via osteoblasts, relies on the above mechanisms as well as CART-mediated control of RANKL expression[1].

NPY is a downstream mediator of leptin in the control of energy homeostasis, and hypothalamic NPY-ergic neurons express both leptin and Y2 receptors. Y2 acts as an inhibitory auto-receptor, modulating NPY secretion and thus the effects of leptin on energy metabolism. In both leptin- and Y2-deficient (Y2KO) mice, hypothalamic NPY levels are elevated, suggesting a shared pathway for leptin and NPY in the central control of bone physiology. Germline or conditional hypothalamic deletion of the Y2 gene leads to increased cancellous bone formation similar to that in leptin-deficient *ob*/*ob* mice. Importantly, cortical bone mass is also increased in mice lacking hypothalamic Y2 receptor, but is reduced in *ob*/*ob* mice, a clear difference arguing against a shared pathway. Viral over-expression of NPY in the hypothalamus caused increases in fat mass and thus circulating leptin levels in both *ob*/*ob* and Y2KO mice. Consequently, decreases in osteoblast activity were observed in both models, but the Y2-associated elevation of bone formation relative to wildtype mice was maintained under this circumstance[2]. Thus, the Y2KO pathway can act consistently to stimulate bone formation, even as leptin continues to provide an opposing stimulus as obesity becomes more marked. NPY and leptin therefore act through distinct pathways to regulate bone remodeling.

Central control of bone remodeling therefore involves antagonistic mechanisms at several levels. Greater understanding of these mechanisms, and particularly of the peripheral osteoblastic responses to these central circuits, may facilitate targeting of these circuits for therapeutic advantage.

[1]Fu et al. 2005 Cell 122:803, Elefteriou et al. 2005 Nature 434:514 and refs therein.
[2]Baldock et al. 2005 J Bone Miner Res 20:1851 and 2006 *in press* and refs. therein.