The hypothalamic control of bone mass, implication for the treatment of osteoporosis

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The goal of my laboratory is to uncover the molecular bases of degenerative diseases of the skeleton such as osteoporosis, and to use this knowledge to propose adapted therapy. To pursue this aim we used clinical observations to formulate hypotheses testable in vivo. In particular we were struck by the fact that osteoporosis invariably follows gonadal failure while obesity protects from it. We viewed these observations as suggesting that bone mass, appetite and reproduction may be regulated by the same hormone. To test this hypothesis we studied the role in bone of leptin, the only hormone regulating in a meaningful manner reproduction and appetite in vivo. Mice deficient in either leptin or its receptor are obese and hypogonadic, yet despite their hypogonadism leptin signaling-deficient mice have a high bone mass phenotype due to an increase in bone formation parameters. To date, leptin signaling-deficient mice are the only animal models in which hypogonadism and high bone mass coexist. In an effort to understand the regulation of bone mass by leptin we showed that the high bone mass of leptin signaling-deficient mice was due to the absence of leptin, not to their obesity, that the regulation of bone formation is a function of leptin conserved between mice and humans, and that infusion of leptin in the third cerebralventricle of ob/ob mice corrects, fully, their high bone mass. This latter finding not only established the existence of a central regulation of bone mass under the control of leptin but also suggested that this was the only anatomical route leptin could use, physiologically, to regulate bone mass. Next we identified in the hypothalamus a specific neuronal network regulating bone formation under the control of leptin, then provided genetic and clinical evidence that the sympathetic nervous system acting through the regulation of expression of c-myc and thereby cell cycle progression. The importance of leptin’s control of bone mass was further enhanced by demonstrating that it also regulates bone resorption. This was established by showing that Adrβ2-/- mice have, besides their increase in bone formation, a decrease in bone resorption parameters. This function of leptin and of the sympathetic tone occurs in osteoblasts through the regulation of expression of Rankl, the main osteoclast differentiation factor. This latter function also explains why gonadectomized Adrβ2-/- mice do not develop osteoporosis. The clinical relevance of this regulatory loop comes from retrospective and prospective studies showing that β-blockers protect from fracture in post-menopausal women. The conservation between mouse and human of the leptin and sympathetic functions in bone established the importance of this integrative physiology of bone and energy metabolism.

BIBLIOGRAPHY

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