BONE DISEASES

Central control

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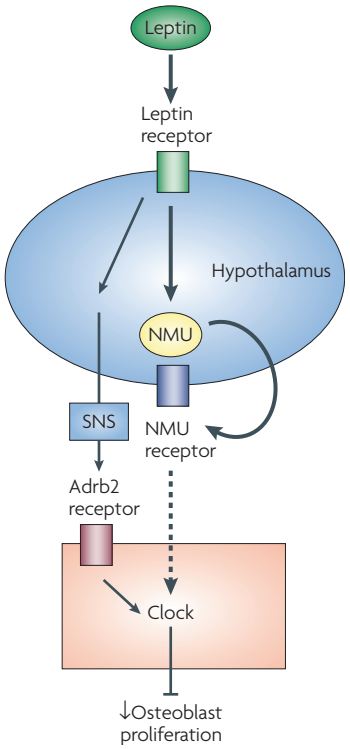
Bone remodelling is known to be regulated by the hormone leptin, and this has stimulated interest in other anorexigenic neuropeptides such as neuromedin U (NMU) that might also be involved in this process. Sato and colleagues, writing in *Nature Medicine*, show that NMU is a central mediator of the leptin-dependent regulation of bone mass, and so could play a part in diseases such as osteoporosis.

To investigate the role of NMU on bone mass, the authors used knockout mice (*Nmu*$^{-/-}$). When assessed at 3 and 6 months of age, male and female *Nmu*$^{-/-}$ mice showed a high bone-mass phenotype, which was more pronounced in males. *Nmu*$^{-/-}$ mice had a greater bone volume and an increased number of bone-forming osteoblasts in vertebrae and tibiae, but no change in the number of bone-reabsorbing osteoclasts. The effects of NMU on bone mass occurred independently of the regulation of energy metabolism. Several lines of experimental evidence suggest that NMU does not act directly on osteoblasts. NMU and its receptors were barely detectable in bone, and in NMU-treated osteoblasts, markers of osteoblast activity were unaffected. Moreover, *in vitro*, wild-type and *Nmu*$^{-/-}$ osteoblasts proliferated normally in response to NMU treatment, but *Nmu*$^{-/-}$ mice displayed greater osteoblast proliferation than wild-type mice.

Because NMU had no direct action on osteoblasts, the authors investigated the involvement of a CNS relay. When NMU was infused into the CNS of *Nmu*$^{-/-}$ mice, the high bone-mass phenotype was eliminated. To test the involvement of leptin — which is known to inhibit bone formation through a hypothalamic pathway — NMU or leptin was infused into leptin-deficient obese mice (*Lep*$^{ob/ob}$). NMU decreased bone mass in *Lep*$^{ob/ob}$ mice as efficiently as leptin did, indicating that NMU inhibits bone formation in a leptin-independent manner. Leptin decreased bone volume and bone formation in wild-type mice, but paradoxically increased bone volume and osteoblast number in *Nmu*$^{-/-}$ mice. This suggests that NMU acts downstream of leptin to regulate bone formation.

Next, the authors explored whether NMU and sympathetic tone are in the same pathway that regulates bone formation by using mice deficient in β_2-adrenergic receptors (*Adrb2*). *Nmu*/*Adrb2* double heterozygote mice had a higher bone mass than *Adrb2* single heterozygote mice. In addition, infusion of leptin — a potent stimulator of sympathetic nervous system (SNS) activity — or injection of isoproterenol, a sympathomimetic, did not reduce bone mass in *Nmu*$^{-/-}$ mice. Thus, *Nmu*$^{-/-}$ mice were resistant to the anti-osteogenic effects of both leptin and SNS activity.

These observations led the authors to suggest that NMU affects only the negative regulator of bone remodelling by leptin, that is, the molecular clock. Indeed, the molecular clock genes *Per1* and *Per2* were downregulated in *Nmu*$^{-/-}$ mice.



A model of how NMU controls leptin-dependent regulation of bone mass. Adapted from Sato, S. *et al.* © (2007) Macmillan Publishers Ltd.

Last, wild-type mice treated with a naturally occurring NMU receptor subtype 2 (NMUR2) agonist had decreased bone mass. This result, together with the predominant expression of *Nmur2* in the hypothalamus, suggests that NMU regulates bone remodelling through NMUR2.

Collectively, these results suggest that NMU acts via a central relay — an as yet undefined pathway — to modulate leptin-SNS regulation of bone formation (see figure). Therefore, an NMU antagonist might have therapeutic potential for the treatment of bone-loss disorders.

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ORIGINAL RESEARCH PAPER Sato, S. *et al.* Central control of bone remodeling by neuromedin U. *Nature Med.* **13**, 1234–1240 (2007)