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COMMENTARY

More on bone and nerves

Marie Christine de Vernejoul

Department of Rheumatology, U 606 Bone and Joint, Paris Diderot University and INSERM 606, Paris, France.

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Commentary on: Bajayo A, Bar A, Denes A, Bachar M, Kram V, Attar-Namdar M, Zallone A, Kovács KJ, Yirmiya R, Bab I. Skeletal parasympathetic innervation communicates central IL-1 signals regulating bone mass accrual. *Proc Natl Acad Sci USA* 2012;**109**:15455–15460

Previous studies have demonstrated that the sympathetic nervous system decreases bone formation via the β_2 adrenergic receptors expressed in osteoblasts.[1] Bajayo *et al.*[2] now report that bone remodelling is controlled by the parasympathetic nervous system. They have reported observing the parasympathetic system, which uses the neurotransmitter acetylcholine in the bone marrow, next to the trabeculae. Nicotinic receptors for acetylcholine have been identified on both osteoblasts and osteoclasts. However, these authors show that acetylcholine increases osteoclast apoptosis, and that its main function in the skeleton is to decrease resorption. Indeed, Bajayo *et al.*[2] also show that mice invalidated for the α_2 subunit of the nicotinic receptor have a low bone mass and increased bone resorption. Interestingly, centrally acting Interleukin 1 is the main mechanism inducing activation of the parasympathetic system in bone. Inhibiting central parasympathetic system by decreasing Interleukin 1 signalling in the brain impairs parasympathetic activity in bone and induces bone loss with the same high resorption phenotype as that seen in mice deficient for the acetylcholine receptor. Deregulated autonomic activity is observed in several neurological and psychiatric disorders, suggesting that low parasympathetic tone could have a role in the decreased bone density observed in these disorders. These data add a new organ, bone, to the list of the known targets of the parasympathetic nervous system.

This elegant study adds to our knowledge of the role of the central nervous system in the control of bone remodelling. This sympathetic tone is controlled centrally by leptin and serotonin[3] and also by acetylcholine. Muscarinic receptor for acetylcholine have been identified in the brain and decreases the sympathetic tone. The parasympathetic nervous system therefore increases indirectly the bone formation and decreases bone resorption.[4] Taken together, these experiments suggest that sympathetic system controls mainly bone formation, whereas parasympathetic controls mainly bone resorption directly through its receptors on bone cells and indirectly through inhibition of the sympathetic system.

Besides leptin, other hypothalamic neuropeptides, Nuromedin U and Neuropeptide Y2, that are leptin-regulated, also control bone formation. The peripheral relay of these central peptide is based mainly on the sympathetic and parasympathetic innervations and on two neurotransmitters, noradrenalin and acetylcholine. Bone is also densely innervated by afferent sensory nerve fibres and several other neurotransmitters are also present in bone.[5] These neurotransmitters include vasoactive intestinal peptide, calcitonin gene-related peptide, neuropeptide Y, substance P and glutamate. Receptors for these neurotransmitters are expressed on bone cells. These neuromediators are released by nerve fibres and/or are synthesised by the bone cells themselves. Other cells in the bone micro-environment, such as adipocytes and immune cells, could make important contributions. Although experiments have shown that these mediators have a role in bone cells *in vitro*, their impact in bone physiology is not clear. It is likely that neuromediators participate to the paracrine regulations of bone remodelling that modulate locally the signals from hormones and mechanical loading.

Sometimes these mediators have opposed central and peripheral roles on bone remodelling. The clearest example of this is leptin. Osteoblasts express leptin receptor and leptin is synthesised in the bone micro-environment by adipocytes and systemic administration of leptin increases bone formation in several models.[6,7] In contrast, the opposite effect is observed when leptin is injected directly in the central nervous system and activates the sympathetic nervous system signalling.[1] Is for bone, this peripheral leptin more important than the central leptin? Opinions diverge on this point, and it is possible that the doses administered or anatomical differences of the bone studied could account for the discrepancies. For serotonin, Ducy and Karsenty[8] suggested that central control of the sympathetic system by serotonin is more important than peripheral serotonin. However, there are some controversies about the peripheral role of serotonin that we will not go into here.[9]

The influence of the sympathetic tone in the bone is regulated at the cell level. It was shown recently that isoproterenol, a sympathetic ligand, reduces osteoblastic function by increasing the expression of ostepontin.[10] Osteoblasts from

mice invalidated for osteopontin no longer respond to the adrenergic signal. Intracellular osteopontin is necessary to the down stream signalling of the β_2 adrenergic receptor in osteoblasts, which means that bone cells can modulate the signals received from the brain. The receptor of this neurotransmitter has also been demonstrated to have a specific role in osteoblasts. The presence of the β_2 adrenergic receptor induces control of the parathyroid hormone (PTH) osteoanabolic action. In absence of the β_2 adrenergic receptor, there is no longer anabolic signal of PTH in the osteoblasts, whereas it is expected that the lack of this receptor increases the osteoblast proliferation. This shows a functional interaction of the two G protein-coupled receptors at the cell level that overcomes the negative action of sympathetic tone.[11]

Neurological influence on bone remodelling is a good example of the regulation of a local system, bone, by multiscale influences ranging from central to paracrine and finally to cell levels. In the light of our current knowledge, none of them can be dismissed as trivial. It is important not to attempt to establish a hierarchy among these regulations, but rather to understand how they interact to control bone mass in physiological states and their role in various diseases that induce bone loss and, finally, to see whether they could in the future become target for the development of drugs that increase bone formation.

Conflict of Interest

The author declares no conflict of interest.

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