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Perspective Article

Hylonome

Role of innervation in the control of bone remodeling

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Abstract

During the last fifteen years, an increasing number of studies have examined the origin, the ontogeny, and the distribution of nerve fibers in bone. They have also investigated the nature of neuromediators conveyed by these skeletal nerve fibers. Experimental models of sensory and sympathetic denervation and clinical studies have shown that these two neuronal systems are involved in bone development, growth and remodeling. More recently, some new concepts regarding the role of nerve fibers in bone physiology have emerged with the demonstration of a leptin-dependent central control of bone formation via the sympathetic system. This new neural regulating pathway of bone cell functions could have enormous implications for human skeletal biology and treatment of bone pathologies.

Keywords: Innervation, Neuromediators, Bone Remodeling, Sympathetic Nervous System

Introduction

The traditional view is that bone modeling and remodeling are regulated by autocrine/paracrine and hormonal mechanisms. However, recent work suggests the influence of higher integrating neuronal pathways. The most striking evidence for a role of the nervous system in the control of bone remodeling is the demonstration that the fat-derived hormone leptin controls bone formation through a hypothalamic relay. Leptin-deficient mice have an increased bone formation leading to high bone mass, and leptin binding to its hypothalamic receptor is sufficient to induce bone loss by decreasing osteoblastic function[1]. Interestingly, these central effects of leptin on bone were recently shown to be mediated via the sympathetic nervous system[2]. Similarly, Y2 receptors-deficient mice have a two-fold increase in trabecular bone volume compared to control mice, and intracerebroventricular administration of neuropeptide Y also causes bone loss[3].

Skeletal innervation

Recent immunocytochemistry studies have shown a dense innervation of bone[4-6]. These nerve fibers are primary afferent sensory and sympathetic fibers that are frequently associated with blood vessels. Nerve fibers are present in periosteum, bone marrow and mineralized bone, the periosteum receiving the densest sensory innervation. In cortical bone, nerve fibers run within the Haversian and Volkmann's canals. Sensory and sympathetic nerve fibers are abundant along the epiphyseal trabecules facing the growth plate and in the metaphysis of long bones. They form dense parallel networks of thin nerve processes running along vessels at very close proximity to bone and bone marrow cells. Although no typical synapses were observed between nerve endings and bone cells, direct contact of nerve fibers and bone cells were demonstrated, strongly supporting a role of innervation in bone cells functions.

Neuromediators

Several neuromediators have been identified in bone by immunocytochemistry and quantitative assessments in extracts of bone tissues using radioimmunoassays[7,8]. They include a number of neuropeptides, such as vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase activating peptides (PACAP), neuropeptide Y, substance P (SP), as well as classical neuromediators such as noradrenaline, serotonin and glutamate. Immunolocalizations of these neurotransmitters in skeletal nerve fivers were demonstrated. For most of these neuromediators, receptors on bone cells have been identified and several *in vitro* studies have shown that these receptors are functional and can affect osteoclast and osteoblast activities[7,8].

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Bone modeling and remodeling are controlled by the nervous system

There is an increasing body of evidence that the nervous system participates in skeletal development and bone turnover. In addition to the demonstration of a leptin-dependent central control of bone formation, several denervation experiments have indicated that nerve fibers control bone cell functions. Those studies have shown that developmental skeletal growth in the rat foot is reduced after denervation[9], and that chemical and surgical denervations of sympathetic and/or sensory nerves modulate the number of bone-resorbing osteoclasts[10,11]. The role of the sympathetic nervous system in controlling bone resorption is not completely understood as sympathectomy may also induce changes in neuromediator-containing skeletal nerve fibers[12]. Clinical studies have also indicated that spinal cord injury is associated with the development of a rapid and severe osteoporosis that is not only due to a compromised biomechanical function but can have a neurological origin[13]. Changes in skeletal innervation were demonstrated in various skeletal pathobiological conditions, such as osteoarthritis, heterotopic bone formation and fracture repair, suggesting that nerve fibers are actively involved in situations of unbalanced bone resorption and formation. We have recently shown that ovariectomy-induced bone loss in rat tibiae is associated with a reduction of skeletal nerve fibers density, suggesting that neural regulation may play a role in the bone loss observed after ovariectomy[14].

Direct or indirect effects of the nervous system on bone cells

Signaling molecules in skeletal nerve fibers may be involved in the regulation of bone cell activity directly through receptors expressed by bone cells or indirectly through the regulation of the skeletal blood flow. Although blood vessels-unrelated nerves and free nerve endings are present in bone, nerve fibers are indeed frequently associated with blood vessels, and it is well known in many tissues that neuromediators conveyed by the sympathetic nervous system control blood flow. The studies that were conducted to investigate blood flow changes in bone and periosteum *in vivo* have however not shown any consistent effect of the sympathetic nerves on blood flow in this tissue[15]. It is also possible that neuromediators released by nerve fibers control bone cell functions indirectly though the regulation of cytokines expression by cells of the immune system.

Neural hypothesis of bone mechanical strain-adaptive response

There is an intriguing paradox between the central control of bone remodeling proposed by Karsenty's group[1,2] and bone adaptive response to its local mechanical environment. It is well known that the most important property of bone that controls its normal remodeling is its adaptation to the strain environment, increased mechanical loads stimulating bone formation while bone disuse inducing a rapid bone loss. The classical view is that bone adaptation to mechanical loading is only under local and systemic influences. Hert et al. have indeed demonstrated that innervated and denervated limbs react to intermittent loading in the same way[16], and other groups have shown that bone explants and isolated bone cells are sensitive to mechanical stimuli, excluding a role for central connections[17,18]. The demonstration that bone formation is centrally controlled challenges this view. The hypothesis that innervation may contribute to the bone response to mechanical stress is supported by a very dense innervation of the periosteum and trabecular surfaces[4] and by the demonstration that the areas of mineralized bone which receive the greatest mechanical stress and load display the highest density of nerve fibers[5]. Furthermore, recent preliminary work has shown that central sympathetic control mediates the unloading-induced bone loss[19]. Further studies are required to resolve this paradox and to determine whether bone adaptive remodeling is mediated by the nervous system, centrally through the hypothalamus and/or peripherally via the release of neurotransmitters.

Conclusion

Clearly, all these studies indicate an important role of the neural tissue in regulating bone cell functions, in addition to its previously described role in transmitting and modulating skeletal pain. The manipulation of the neuronal pathway in bone may present a major therapeutic impact for treatments of pathologies associated with modifications of bone remodeling.

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