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Review

Innervation of bones. Sensory innervation. Part I: A literature review

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ABSTRACT

BACKGROUND: Bone remodeling is a complex multifactorial process regulated by endocrine, paracrine, and mechanical factors. Nearly two decades ago, research showed that the nervous system is also involved in regulating bone remodeling. However, very few Russian publications focused on bone innervation mechanisms.

AIM: This study aimed to review publications that address the role of sensory innervation in the regulation of bone metabolism and the pathophysiology of bone pain.

MATERIALS AND METHODS: Data were searched in English and Russian in PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary. Information was analyzed and synthesized for this review. Most studies were published within the last 20 years.

RESULTS: All structural parts of the bone are innervated by sensory nerve fibers that are receptive to nociceptive information. The type of bone pain depends on both the location and nature of the disease process. Pain signals from the bones to the central nervous system are transmitted by the A-delta and C-fibers, each with its conduction velocity, neurotransmitters, receptor characteristics, and functions. In addition, sensory nerves regulate bone homeostasis by expressing the calcitonin gene-related peptide and substance P as their major neurotransmitters. Sensory nerves play a key role in the development of primary and secondary ossification centers during endochondral and intramembranous ossification. Some studies have shown that nerve fibers are present in the articular cartilage at some point in time.

CONCLUSIONS: Sensory fibers are important in nervous regulation of bone and cartilage metabolism. Impaired sensory innervation leads to impaired bone remodeling and slows endochondral ossification and, consequently, bone growth and development. This should be considered, particularly in patients with early-onset bone innervation disorders. To prescribe the correct treatment, the pathophysiology of bone pain must be elucidated.

Keywords: bone innervation; sensory innervation of bone; endochondral ossification; pathophysiology of bone pain.

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Научный обзор

Иннервация костей. Сенсорная иннервация. Часть первая (обзор литературы)

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АННОТАЦИЯ

Обоснование. Регулирование ремоделирования костной ткани — сложный многофакторный процесс, который контролируется эндокринными, паракринными механическими факторами. Проведенные почти два десятилетия назад исследования показали, что в дополнение к этим механизмам метаболизм костной ткани контролируется нервной системой. Однако публикации, посвященные особенностям иннервации костной ткани, в отечественной научной литературе практически отсутствуют.

Цель — проанализировать публикации, посвященные вкладу сенсорной иннервации в контроль метаболизма костной ткани, а также некоторым патофизиологическим механизмам, лежащим в основе боли в костях.

Материалы и методы. Поиск данных осуществляли в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary на английском и русском языках. В процессе написания статьи использовали метод анализа и синтеза информации. Большая часть работ, включенных в данный обзор, опубликована за последние 20 лет.

Результаты. Сенсорные нервные волокна, восприимчивые к ноцицептивной информации, иннервируют все структурные отделы кости. Тип боли в костях определяется не только локализацией, но и характером патологического процесса. Болевые сигналы от костей в центральную нервную систему передают А-дельта- и С-волокна, каждые из которых имеет свою скорость проведения, нейротрансмиттеры, характеристики рецепторов и функции. Кроме этого, сенсорные нервы регулируют гомеостаз костей, экспрессируя кальцитонин-ген-родственный пептид и вещество Р в качестве своих основных нейротрансмиттеров. Сенсорные нервы выполняют важную функцию при формировании первичных и вторичных центров оссификации при эндохондральной оссификации, а также интрамембранозной оссификации. Ряд исследований доказывает существование нервных волокон в суставном хряще в определенный период времени.

Заключение. Сенсорные волокна — важное звено нервной регуляции метаболизма костной и хрящевой тканей. Нарушение сенсорной иннервации приводит к ухудшению ремоделирования костей, а также замедлению процессов эндохондральной оссификации и, следовательно, роста и развития костей. Это необходимо учитывать, особенно у тех пациентов, у которых нарушение иннервации костей произошло в раннем возрасте. Понимание патофизиологических механизмов, лежащих в основе боли, важно для назначения патогенетически обоснованного лечения боли в костях.

Ключевые слова: иннервация костей; сенсорная иннервация костей; эндохондральная оссификация; патофизиологические механизмы боли в костях.

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BACKGROUND

Despite the extensive body of literature on the role of peripheral nerves in the development and regulation of other organs and tissues [1, 2], few publications have focused on the function of peripheral nerves in bones. Early studies have shown that sciatic nerve neurectomy in rats slows the longitudinal growth of hind limb bones and impairs fracture healing [3, 4]. Furthermore, in newborn mice treated with capsaicin to chemically destroy sensory nerves, besides reduced pain sensitivity, bone structure was altered, with reduced trabecular bone compared with the control group [5]. These results obtained in rodents align with the observations in patients with nerve dysfunction, where delayed bone consolidation occurs after fractures [6, 7]. In addition, patients with sequelae of perinatal brachial plexus injuries were found to have shortening and delayed ossification of the segments in the affected limb compared with the unaffected limb [8, 9].

Bone remodeling regulation is a complex, multifactorial process controlled by endocrine, paracrine, and mechanical factors [10, 11]. Nearly two decades ago, animal studies have revealed that in addition to these mechanisms, bone metabolism is controlled by the nervous system [12].

Evidence of central nervous system regulation of bone metabolism emerged with the discovery that leptin—a hormone exclusively produced by adipose tissue [13]—affects bones [12, 14]. Leptin is secreted by adipocytes, suppresses appetite, and promotes energy expenditure primarily through its action on the arcuate nucleus of the hypothalamus [15]. Adipocytes and osteoblasts differentiate from mesenchymal stem cells, so a crosstalk between these two cell types is likely. Leptin functions as an osteogenic hormone by directly acting on leptin receptors on osteoblasts [16, 17], reducing osteoclast differentiation and proliferation either directly or indirectly by influencing the ratio of osteoprotegerin to RANK ligand [18].

Other central regulators of bone metabolism were also identified, including neuropeptide Y, serotonin, endocannabinoids, cocaine- and amphetamine-regulated transcript, adiponectin, melatonin, and neuromedin U, which control the differentiation, proliferation, and function of osteoblasts and osteoclasts [11, 19, 20].

Long before the identification of this "central control" of bone tissue, the nervous system was hypothesized to control bone development and integrity. In 1868, the French neurologist Charcot described the joint pathology with progressive degeneration of bones and soft tissues in patients with syphilitic spinal cord damage. This condition involved atrophy, sclerosis of the posterior spinal columns, and degeneration of the nerve fibers in the posterior roots. Charcot hypothesized that the nerves in the bones have a trophic function, suggesting that nerve destruction disrupts the delivery of growth factors to the bones and joints, leading to joint destruction. This laid the foundation for the neurotrophic theory of bone growth and development [21]. However, this theory was opposed by neurotrauma theorists led by Volkmann and Virchow, who argued that nerve damage leads to the loss of peripheral sensation, which, in turn, predisposes to repeated trauma that outpaces healing. This theory was supported by sensory denervation experiments in animals. Eloesser (1917) and Corbin and Hinsey (1939) concluded that loss of sensation alone was insufficient to cause neuropathic osteoarthropathy because denervated animals exhibited gait disturbances, leading to inadequate loading and, likely, bone and joint lesions in these animals [22]. In the 1980s, publications emerged supporting the neurovascular theory, which proposed that disrupted sympathetic innervation contributes to altered vascular tone, resulting in excessive blood flow to affected joints. This, in turn, causes bone resorption and increases bone susceptibility to minor trauma [23, 24].

The development of immunohistochemical methods led Bjurholm et al. to identify sensory nerve fibers in rat bones by detecting their secreted neuropeptides, predominantly found near growth zones and the periosteum—regions of high osteogenic activity [25]. Subsequent studies on nerve fibers in bone tissue have demonstrated that neuropeptides secreted by nerve fibers are significant in bone remodeling, potentially indicating their involvement in skeletal development and formation.

Currently, bones are believed to be innervated by the sensory, sympathetic, and parasympathetic nervous systems [19], and the conceptual understanding of the interaction between the skeletal and nervous systems integrates the neurotrophic, neurotraumatic, and neurovascular theories [11, 19, 26]. Indeed, trophic signaling, protective pain, and blood flow regulation are essential components of the nervous regulation of the skeletal system.

This study aimed to analyze publications addressing the contribution of sensory innervation to the formation and maintenance of bone metabolism, as well as the pathophysiological mechanisms underlying bone pain.

MATERIALS AND METHODS

The data search was performed in PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary. The article employed methods of analysis and synthesis of information. Most of the analyzed studies were published over the past 20 years. The following keywords were used: *иннервация костной ткани / bone innervation, and сенсорная*

иннервация костной ткани / sensory bone innervation in Russian and English.

RESULTS AND DISCUSSION

The sensory system, a part of the nervous system, is comprised of sensory receptors that perceive stimuli from the external or internal environment, neural pathways that transmit information from the receptors to the brain, and brain regions that process and analyze this information [19].

Sensory nerves express calcitonin gene-related peptide (CGRP) and substance P (SP) as their primary neurotransmitters, regulating bone homeostasis [27]. The efferent activity of sensory nerves is most evident during neurogenic inflammation following tissue injury, where the release of neuropeptides such as CGRP and SP promotes vasodilation and plasma extravasation, respectively. Neurogenic inflammation in bones is supported by studies using a rat model of spondylitis, where chemical denervation of sensory nerves suppressed vasodilation and inflammatory cell spectrum in the bone marrow [28]. CGRP exists in two main isoforms (α and β), influencing osteogenesis through the activation of CGRPα and CGRPβ receptors. This activation stimulates osteogenesis via cAMP or protein kinase C pathways and mitosis in mesenchymal stem cells. CGRP promotes bone formation by osteoblasts through Wnt signaling stimulation and apoptosis inhibition [29]. Furthermore, CGRP inhibits osteoclast differentiation and function [30, 31]. αCGRP-deficient mice exhibited reduced bone formation [31]. This correlates with findings by Yang et al. who demonstrated in an experimental rat study that sensory rhizotomy led to a decrease in CGRP levels, reduced osteoblast activity, activated osteoclasts, and consequently diminished bone formation compared with the control group after 8 weeks [32].

Sensory nerves also influence chondrogenesis. Although articular cartilage is traditionally considered non-innervated, chondrocytes express SP, αCGRP, and their receptors [33]. Several foreign scientific studies have shown that nerve fibers exist in the articular cartilage at specific developmental stages. Hedberg et al. demonstrated transient nerve fibers in cartilage canals during the onset of secondary ossification in the rat knee [34]. Similarly, Schwab and Funk observed nerve fibers in the periosteum and thin branches penetrating the outer layers of the articular cartilage in adult rats [35]. Indirect evidence of nerve fibers has also been found in the surface zone of the cartilage in the sacroiliac joint of adults and cartilage canals in fetal and neonatal joints [36, 37]. Schwab et al. revealed that periosteal nerve fibers near the articular cartilage not only enter the hyaline cartilage but also form close associations with adjacent chondrocytes at distances of <1 μm [38].

Wang et al. utilized immunofluorescence analysis and electron microscopy to examine the cartilage of the femoral bone in 1-day-old, 5-day-old, and 10-day-old rats, revealing myelinated nerve fibers in the extracellular matrix of the articular cartilage. Compared with the findings on the myelin sheath of nerve fibers in 1-day-old rats, a looser structure of the sheath was observed in 5-day-old rats, and by 10 days, signs of pronounced degeneration were noted. Wang et al. demonstrated that nerve fibers form synaptic contacts with chondrocytes in the articular cartilage at an early stage and then gradually degenerate with chondrocyte development. The production of SP and neuropeptide Y (a neuropeptide of sympathetic nerve fibers) significantly increased in the articular cartilage during this period. These findings indicate that nerve fibers and their released neuropeptides may play an important role in articular cartilage development [39]. This likely confirms the conclusion of Hedberg et al. [34] that nerve fibers can only be detected during the developmental period of the cartilage. Opolka et al. demonstrated in an in vitro study that exogenous SP dose-dependently increased the proliferation rate of chondrocytes in the rib articular surface of neonatal mice, concluding that SP modulates the metabolic activity of the chondrocytes [33].

Most researchers agree that bone innervation begins concurrently with endochondral ossification [25, 40]. De Castro was the first to identify nerve fibers in endochondral ossification loci in 1925 [19]. This aligns with the findings of Calvo and Haas, who also observed nerve fibers during endochondral ossification in experimental rat studies conducted in 1967 [41]. The mechanisms underlying sensory nerve–chondrocyte interactions became investigable only 30 years later with advancements in molecular biology techniques.

In bone tissue, nearly all thin myelinated and unmyelinated sensory nerves express the neurotrophic receptor tropomyosin receptor kinase A (TrkA). TrkA is a high-affinity receptor for nerve growth factor (NGF) [42]. NGF belongs to the neurotrophin family, which is essential for the normal growth, proliferation, and regeneration of neurons. It has pronociceptive functions, facilitating the sensitization of peripheral and central sensory neurons and potentially stimulating neuronal sprouting at injury sites [43]. Using a mouse model, Reichardt demonstrated that NGF produced by chondrocyte progenitor cell functions as a skeletal neurotrophin by activating TrkA [44].

In an experimental mouse study, Tomlinson et al. showed that in the developing femoral bone, sensory nerves expressing TrkA reach the perichondrial surface by embryonic day 14.5 in response to NGF produced by chondrocyte progenitor cells. By embryonic days 16.5 and 18.5, NGF was no longer limited to the perichondrial

region and was also detected on newly forming bone surfaces. Postnatally, the nerve density in the bone continues to increase, coinciding with the bone modeling and remodeling necessary for long bone formation [25]. Sensory nerve axons expressing CGRP and SP are present in the femoral epiphysis of rats within the first 24 h after birth [40]. Similar to the invasion of sensory nerves into the primary ossification center, TrkA-expressing sensory nerve fibers enter the secondary ossification center through cartilage canals in response to NGF production by chondrocytes in the epiphysis. Sensory nerves producing TrkA also contribute to the vascular invasion of both primary and secondary ossification centers [26]. This aligns with earlier publications by Mukouyama et al., who, in an in vitro experiment, demonstrated that sensory nerves provide a "template" guiding blood vessel branching patterns in the skin via localized secretion of vascular endothelial growth factor [45].

The inactivation of TrkA signaling during embryogenesis in mice disrupted bone innervation, delayed vascular invasion of primary and secondary ossification centers, reduced the number of Osx-positive chondrocyte progenitor cells, and led to shorter and less voluminous femoral bones at birth [26].

Sensory nerves also participate in intramembranous ossification and flat bone remodeling, although this process remains less studied. However, *in vivo* blockade of TrkA signaling in mice slowed the sensory innervation of developing cranial bones, resulting in premature cranial suture closure [46].

In humans, *TRK1* mutations cause congenital sensory neuropathy with anhidrosis, a rare hereditary disorder characterized by peripheral innervation defects and impaired sweating, which is associated with short stature, early tooth loss, and delayed fracture healing [47]. According to Tomlinson et al., sensory nerves expressing TrkA are crucial in bone development and growth throughout life [26].

Initial studies on sensory nerve function in bones were motivated by the need to understand the mechanisms of bone pain and its management.

Currently, acute, recurrent, and chronic bone and joint pain is primarily managed using nonsteroidal anti-inflammatory drugs and opioids [48]. However, the selection of these analgesics is based on the assumption that the pathophysiological mechanisms of bone pain are similar to those in other body tissues [49].

Two types of sensory nerve fibers are involved in transmitting nociceptive information in bones: A-delta and C-fibers, each with distinct conduction speeds, neurotransmitters, receptors, innervation patterns, and functions [50, 51]. A-alpha and A-beta fibers do not significantly contribute to pain conduction in bones [49].

In an experimental rat model of bone pain caused by fractures, nociceptive information was primarily conducted via the A-delta and C-fibers [52]. A-delta fibers are myelinated and express TrkA, NGF receptor, and 200-kDa neurofilament, an intermediate cytoskeletal filament [53]. C-fibers are unmyelinated and produce TrkA, SP, and CGRP [54]. Both C-fibers and A-delta fibers innervate the bone marrow canal, cortical bone, and periosteum [55].

The A-delta and C-fibers are predominantly (>90%) located in the cambium layer, organized as a network [52, 56]. This enables them to detect mechanical disturbances such as compression, tension, or pressure, which may occur during a bone fracture. The cortical bone is innervated by A-delta and C-fibers, which travel through the Volkmann and Haversian canals along with blood vessels [50]. Historically, sensory nerve innervation was considered most prominent in the periosteum, followed by the bone marrow and cortical bone in a ratio of 100:2:0.1 [54]. This supports the classical concept that periosteal involvement is necessary for bone pain development [51].

Sayilekshmy et al. reported that sensory innervation of the human bone was the most abundant in cortical pores, followed by the periosteum and bone marrow [57]; however, the prevalence of A-delta and C-fibers was not determined. Furthermore, the study was conducted on bones from patients with hyperparathyroidism; thus, the results cannot be generalized to the healthy population. However, Mach et al. indicated that the bone marrow and mineralized bone contain more sensory fibers than the periosteum [50]. This finding may explain why patients with bone marrow malignancies, which clearly do not extend to the periosteum, often complain of bone pain [58].

A-delta and C-fibers are normally activated only in response to mechanical deformation, local acidosis, or increased intraosseous pressure. These stimuli are transmitted from the bone to the dorsal horn of the spinal cord and specific brain areas, resulting in pain [59].

Owing to the high conduction speed of the A-delta fibers, they are thought to transmit sharp, acute pain experienced immediately after a fracture. This pain is short-lived, as it is confined to a small area of damage. The mechanosensitive A-delta and C-fibers continue to be stimulated after a fracture until the bone is realigned. Fracture reduction and fixation reduces mechanical deformation (e.g., periosteal stretching) and thereby alleviates A-delta fiber irritation and associated pain. After the immobilization of the fracture, the patient may experience a duller or burning pain, which lasts longer and is caused by unmyelinated C-fibers, as their conduction speed is lower than that of A-delta fibers [49]. Moreover, a few hours after the initial fracture, the dull pain transmitted by the C-fibers is likely maintained by inflammatory mediators released by osteoblasts, osteoclasts, and immune cells. These mediators include

bradykinins, prostaglandin E2, serotonin, tumor necrosis factor-α, colony-stimulating factors, and NGF [60], which increase the sensitivity of nociceptors to stimuli [49, 61]. NGF directly affects nociceptors by activating inflammatory response cells and enhancing the synthesis of pain and inflammation mediators [61].

Osteoclasts, which are rich in lysosomes containing acidic hydrolases involved in the breakdown of osteoid macromolecules, exhibit high H^+-ATPase and carbonic anhydrase activity and release isoforms of acid phosphatase into the environment. During bone resorption, osteoclasts secrete H^+ ions via plasma H^+-ATPase, lowering the pH and activating acid-sensitive ion channels on the A-delta and C-fibers [62]. Experimental studies in rodent models have shown that A-delta and C-fibers in bone express the acid-sensitive ion channels 1 and 3 (ASIC1 and ASIC3). These ion channels are activated when the local pH drops (approximately to 4) [63].

In bone malignancies or skeletal diseases associated with significant osteoclast activity, local acidosis occurs, contributing to bone pain. Bisphosphonates, widely used for the treatment of bone malignancies, osteogenesis imperfecta, and osteoporosis, suppress osteoclast activity, reduce bone resorption, increase pH, and thereby alleviate bone pain [62]. Similar to fracture stabilization, the activation of the A-delta and C-fibers can be reduced by normalizing the pH.

NGF may be released by immune cells following bone injury or by tumor cells, subsequently binding to nociceptors expressing TrkA. This interaction leads to the phosphorylation of ion channels and receptors [42]. Specifically, NGF binding induces the phosphorylation of transient receptor potential vanilloid 1 and ASIC3 ion channels, making A-delta and C-fibers more sensitive to pH changes [58]. The interaction of TrkA with NGF, which promotes the opening of various ligand-gated transmembrane channels, can cause delayed pain lasting hours or even days. The NGF–TrkA complex undergoes internalization and retrograde axonal transport to the neuron's nucleus, where it activates cytokines, neurotransmitters, receptors, and channel components. Three main intracellular signaling pathways are triggered by the NGF–TrkA interaction: phospholipase C-γ, mitogen-activated protein kinase/Erk, and phosphoinositide 3-kinase [61].

NGF activity blockade has been extensively studied in various animal models of skeletal pain. Anti-NGF antibodies significantly reduce bone pain in mice with osteosarcoma and tumor-induced nerve fiber proliferation in preclinical models of metastatic prostate cancer [64, 65]. Furthermore, anti-NGF antibodies alleviate "pain behavior" associated with bone fractures in mice [54]. Rapp et al. indicated that analgesia using anti-NGF antibodies could be achieved without affecting fracture consolidation outcomes [66]. However, Li et al. reported that suppressing TrkA activation impairs stress fracture healing in mice [67]. Experimental studies in rats have shown that the local application of NGF accelerates rib fracture healing [68], and in rabbits, NGF reduced the time required for distraction callus formation [69]. However, anti-NGF antibodies did not alleviate the pain associated with skin injuries [54], confirming that the skin and bone are innervated by different sensory fibers [70].

CONCLUSION

Sensory fibers are crucial in the neural regulation of bone and cartilage metabolism. Bone and cartilage cells contain receptors for sensory neurotransmitters, enabling them to respond to stimuli from sensory nerve fibers. The disruption of sensory innervation impairs bone remodeling processes and endochondral ossification, thereby hindering bone growth and development. This should be considered in patients in whom bone innervation disturbances occur at an early age.

Sensory nerve fibers that perceive nociceptive information innervate all structural components of the bone (i.e., bone marrow canal, cortical bone, and periosteum). The type of bone pain (acute, diffuse, or aching) is determined not only by the damage location but also by the nature of the pathological process. Understanding the pathophysiological mechanisms underlying bone pain is crucial for prescribing pathogenetically sound treatments for bone-related pain.

The mechanisms of interaction between the bone–cartilage and nervous systems are not yet fully understood. Further research is required to enhance our understanding of bone and cartilage metabolism and the pathogenesis of various bone and joint diseases.

ADDITIONAL INFORMATION

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