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Review

Fracture pain—Traveling unknown pathways

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ABSTRACT

An increase of fracture incidence is expected for the next decades, mostly due to the undeniable increase of osteoporotic fractures, associated with the rapid population ageing. The rise in sports-related fractures affecting the young and active population also contributes to this increased fracture incidence, and further amplifies the economical burden of fractures. Fracture often results in severe pain, which is a primary symptom to be treated, not only to guarantee individual's wellbeing, but also because an efficient management of fracture pain is mandatory to ensure proper bone healing. Here, we review the available data on bone innervation and its response to fracture, and discuss putative mechanisms of fracture pain signaling. In addition, the common therapeutic approaches to treat fracture pain are discussed.

Although there is still much to learn, research in fracture pain has allowed an initial insight into the mechanisms involved. During the inflammatory response to fracture, several mediators are released and will putatively activate and sensitize primary sensory neurons, in parallel, intense nerve sprouting that occurs in the fracture callus area is also suggested to be involved in pain signaling. The establishment of hyperalgesia and allodynia after fracture indicates the development of peripheral and central sensitization, still, the underlying mechanisms are largely unknown. A major concern during the treatment of fracture pain needs to be the preservation of proper bone healing. However, the most common therapeutic agents, NSAIDS and opiates, can cause significant side effects that include fracture repair impairment. The understanding of the mechanisms of fracture pain signaling will allow the development of mechanisms-based therapies to effectively and safely manage fracture pain.

Contents

Abbreviations: ASIC3, Acid-sensing ion channel 3; BDNF, Brain-derived neurotrophic factor; BMP, Bone morphogenetic proteins; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; CRPS, Complex Regional Pain Syndrome; DRG, Dorsal root ganglia; GAP43, Growth-associated protein 43; GDF8, Growth and differentiation factor 8; GDNF, Glial cell line-derived neurotrophic factor; IB4, Isolectin B4; IL, Interleukin; Mrgprd, Mas related G protein-coupled receptors; NGF, Nerve growth factor; NPY, Neuropeptide Y; NSAIDs, Non-steroidal anti-inflammatory drugs; PACAP, Pituitary adenylate cyclase activating peptide; Sema3A, Semaphorin 3 A; SP, Substance P; TGF-beta, Transforming growth factor-beta; TNF-alpha, Tumor necrosis factor-alpha; TrkA, Tropomyosin receptor kinase A; TRPV1, Transient receptor potential vanilloid 1; VIP, Vasoactive intestinal peptide.

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1. Introduction

The rapid population ageing and the associated intrinsic high incidence of osteopenia and osteoporosis are expected to cause an increase in the number of fractures in the coming decades [1]. It is estimated that 40 to 50% of women and 13 to 22% of men will suffer an osteoporotic fracture at some point in their life [2–4]. Also, the spectrum of fractures in the older population is changing [1,5]. Alterations in lifestyle, with older people being more active, are suggested to contribute to an increase in incidence and a change in the type of fracture in the elderly [6]. It has been recognized that osteoporotic fractures are becoming a major health problem, accounting for a significant fraction of healthcare costs [7,8].

Regarding the young population, the incidence of sports-related fractures is a serious concern [6,9]. In fact, sports activities are the third most common cause of fractures in the population as an all, after falls in the elderly and direct blows or assaults [6,9]. The growing practice of sports activities [10,11] is likely to increase the incidence of sports-related fractures in young and active population, thus amplifying the healthcare costs.

Fracture often results in severe pain. By inhibiting the use and load of the fractured bone, pain may delay or prevent its repair, and conversely, the early use and load of the fractured bone were shown to enhance the probability of successful bone repair [12,13]. Therefore, pain management is essential, both to improve quality of life of the patients and also for the success of bone healing. Nevertheless, the commonly used analgesic therapies have limited efficacy and impose significant side effects, which may include impairment of bone repair [14,15].

The major reason why fracture pain persists a medical and social burden is the present narrow understanding of the mechanisms that generate and maintain fracture pain. Bone is known to be innervated by sensory nerve fibers, as will be discussed in the next section. However, how these nerve fibers respond to fracture and the subsequent activation of nociceptive pathways is yet largely unknown. Although some overlap may occur in the pain signaling pathways in different disorders, the knowledge of the specific pain signaling mechanisms in fractures would potentially allow the design of safe and effective targeted therapies.

In this review, the available data on bone innervation and its response to fracture is discussed, and putative mechanisms of fracture pain signaling are presented. The available therapeutic approaches to treat fracture pain and their limitations are also discussed.

2. Bone innervation

Unequivocal evidence has been provided on the intense innervation of bone, and both sympathetic and sensory nerve fibers were shown to innervate the periosteum, the mineralized bone and the bone marrow, being frequently associated with blood vessels [16–22].

Adding to the recognized role of the sympathetic nervous system in bone homeostasis, whose activation promotes bone loss [for review see 23], a regulatory role for bone metabolisms has been attributed also to the afferent sensory nerve fibers. Indeed, capsaicin-induced reduction of peripheral sensory innervation results in significant bone loss in rat [24] and in mouse [25]. This role of the sensory nervous system is further supported by the study of Fukuda et al. (2013) showing that Semaphorin 3A (Sema3A), recently implicated in the regulation of bone metabolism, exerts its regulatory function through modulating bone sensory innervation [26]. It was shown that osteoblast-specific Sema3A-deficient mice had normal bone mass, regardless of the decrease in expression of Sema3A in bone. However, a low bone mass phenotype was observed in neuron-specific Sema3A deficient mice, similar to Sema3A(−/−) mice, and in both cases this phenotype was associated with a decrease in bone sensory innervation [26]. In addition to the recently demonstrated important role of primary afferent nerve fibers in bone metabolism, bone sensory innervation is long known to be involved in processing sensory information, mainly in pain signaling.

Electrophysiological, immunohistochemistry and imaging techniques have enabled the definition of the nature and distribution of bone nerve fibers. Thinly myelinated fibers, most probably A-delta, and unmyelinated peptide-rich C-fibers have been largely reported to innervate bone [16,27–29]. These nerve fibers express neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP) [16,27,29], and the majority are nerve growth factor (NGF)-sensitive expressing tropomyosin receptor kinase A (TrkA) [29]. In general, these nerve fibers are known to be responsive to noxious chemical and mechanical stimuli, and have a preponderant role in inflammatory pain signaling [30,31].

Despite some authors claiming that non-peptidergic C-fibers are mostly absent from bone, the presence of non-peptidergic C-fibers in bone has been also suggested. Ivanusic (2009) reported that 20% of the fast blue retrogradely labeled sensory neurons innervating rat tibia were isolectin B4 (IB4) positive (a marker of non-peptidergic unmyelinated neurons) [27]. The study by Castaneda-Corral el al. (2011) may also support the presence of IB4 positive nerve fibers in bone [29]. Although in this study the presence of IB4 positive fibers was not investigated, a portion of nerve fibers detected did not stain for peptides or for TrkA, so it most likely corresponds to non-peptidergic nerve fibers. Additionally, the study by Jimenez-Andrade et al. (2010) reported only a lack of Mas related G protein-coupled receptors (Mrgprd) positive fibers (Mrgprd positive nerve fibers were shown to represent 75% of the IB4 population of fibers in skin [32]), failing to investigate other non-peptidergic fibers that do not express Mrgprd. Therefore the authors did not confirm the absence of non-peptidergic nerve fibers [33]. The non-peptidergic C-fibers are sensory neurons that generally lack neuropeptide expression, bind IB4, are not sensitive to NGF, but are glial cell line-derived neurotrophic factor (GDNF)-sensitive neurons, and described to be involved in neuropathic pain [30,34,35].

Bone innervation by thickly myelinated A-beta fibers, associated with tactile or kinaesthetic sensation, has been considered absent or restricted to a few nerve fibers. Previous studies on the nerve fiber population supplying the canine tibia, report the presence of large fibers [36,37]. However, in these studies the nerve was sampled proximal to the point at which branches leave it to innervate muscle or aggregations of Pacininan corpuscles, resulting in the inclusion of nerve fibers supplying the bone-surrounding muscle or Pacininan corpusculus [36,37]. More recently, the study by Ivanusic et al. (2006) in the cat humerus supported the absence of large diameter afferent fibers in the sections of the nerve that supplies both the periosteum and the nutrient foramen [38]. Conversely, a study using retrograde tracing suggests the presence of a few large diameter neurons in bone, namely in the epiphysis of the rat tibia [27]. However, the fact that more large nerve fibers were observed following injections into the epiphysis than into medullary cavity or periosteum, supports the possibility that the visualization of large nerve fibers following injection into the epiphysis may result from the labeling of large neurons innervating the joint capsule, which is intimately associated with the epiphysis, as discussed by the authors [27]. The current lack of evidence for large neurons innervating bone, is consistent with the view that innocuous mechanosensation may be absent from the bone, or at least may not be significant. Therefore, the sensory nerve fibers that innervate bone will signal mostly noxious stimuli.

Several neurotransmitters, from neuropeptides to classical neurotransmitters, have been identified in the bone. In addition to CGRP and SP, which have been largely shown to be expressed in the population of peptidergic sensory nerve fibers [16,17,21,27,29], other neuropeptides, such as Neurokinin A [39] and Pituitary adenylate cyclase activating peptide (PACAP), were also suggested to be expressed by nerve fibers that innervate bone [40]. Vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) were shown to be expressed in bone typically by sympathetic nerve fibers [18,21,22,41]. Among the classical neurotransmitters, the expression of catecholamines, glutamate and acetylcholine has been suggested [20,29,42].