HHS Public Access

Author manuscript

Curr Osteoporos Rep. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Curr Osteoporos Rep. 2018 December ; 16(6): 763–771. doi:10.1007/s11914-018-0493-1.

Mechanisms underlying bone and joint pain

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Abstract

Purpose of Review.—The goal of this review is to provide a broad overview of the current understanding of mechanisms underlying bone and joint pain.

Recent Findings.—Bone or joint pathology is generally accompanied by local release of pro-inflammatory cytokines, growth factors and neurotransmitters that activate and sensitize sensory nerves resulting in an amplified pain signal. Modulation of the pain signal within the spinal cord and brain that result in net increased facilitation is proposed to contribute to the development of chronic pain.

Summary.—Great strides have been made in our understanding of mechanisms underlying bone and joint pain that will guide development of improved therapeutic options for these patients. Continued research is required for improved understanding of mechanistic differences driving different components of bone and/or joint pain such as movement related pain compared to persistent background pain. Advances will guide development of more individualized and comprehensive therapeutic options.

Keywords

Nociception; chronic pain; peripheral sensitization; central sensitization; spinal

Introduction

Bone and joint pain can occur in response to numerous conditions including trauma, infection, inflammation, autoimmune disease, genetic driven disease states, joint and bone pathology associated with aging, and cancer. Bone and joint associated pain can be acute (e.g. due to trauma), recurring, or chronic in nature. Indeed, musculoskeletal pain such as osteoarthritis is the most common form of chronic pain and disability worldwide. It is important to recognize that bone and joint pain is very complex, with multiple types of pain as well as multiple etiologies that may require different treatment strategies for complete pain management. Some patients also report development of persistent background pain

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and/or breakthrough pain episodes that are resistant to currently available medications [1–4]. This indicates a requirement for development of therapies targeting multiple mechanisms underlying the various aspects of bone and joint pain for more comprehensive pain management for these patients. Development of such therapeutic options requires better understanding of mechanisms underlying the multiple aspects of bone and joint pain needed for better care for these patients.

Overview of the Pain Pathway:

Signals from events that may damage tissue (e.g. twisted joint, stressful impact) or from actual damaged tissue activate specialized sensory neurons known as nociceptors. Both bone and joint tissue are innervated by these specialized neurons which allow for the transduction of painful stimuli to aid in preventing further damage to tissue and repeating potentially tissue damaging behaviors [5–8]. Multiple classes of nociceptors have been studied to date, differentiated by their cell body and axon size, their myelination patterns and electrophysiological characteristics such as conduction velocity and response thresholds, and the characteristics of stimuli that they respond to [9–12]. Recent RNA sequencing data indicate that multiple classes of nociceptors exist [13]. Distinct RNA transcription profiles and protein expression in conjunction with behavioral experiments demonstrate specific nociceptive responses from nociceptor populations that have distinct molecular characteristics [13–17, 11, 18, 19]. Studies such as these demonstrate that different fiber populations convey distinct sensory information depending on modality (thermal, chemical, mechanical) as well as areas of innervation (cutaneous vs deep tissue) as outlined in the labeled line hypothesis of sensory processing [15–17, 11, 18, 19].

Sensory fibers mediating pain and itch project to the spinal cord, where projections terminate in the superficial lamina of the dorsal horn, lamina I and II [20–25]. Upon activation by noxious stimulation, terminal endings of the nociceptors release small molecule (eg. glutamate) and peptidergic (e.g. substance P, CGRP) neurotransmitters into the synaptic cleft. These two populations are often referred to as the “non-peptidergic” and “peptidergic” populations of nociceptors respectively. These act on receptors located on interneurons within the spinal cord as well as projection neurons that project along specialized tracts (e.g. the anterolateral tract) to various regions of the brain such as the thalamus, periaqueductal grey, lateral parabrachial area and regions within the medullary reticular formation [20–25]. There has been a great deal of progress in gaining a better understanding of the circuitry mediating nociception within the spinal cord [20–25]. Within lamina I-II, most neurons are characterized as interneurons in lamina II, while 90–95% are interneurons in lamina I [25]. Interneurons that modulate pain signals intuitively consist of both inhibitory neurons that release GABA and glycine, and excitatory interneurons that are predominately glutamatergic [25]. Various studies examining the role of these interneurons indicate that they play a key role in processing the incoming signal, with several interneuronal populations responding to multiple modalities of input (e.g. chemical, mechanical, thermal, touch, itch) [20, 26–28]. Although studies have begun to explore the role of subpopulations of spinal inhibitory and excitatory interneurons in mediating pain, itch and mechanical allodynia, a full understanding of the complex interactions and circuitry is not complete [28]. Little is known regarding processing of sensory information from deep

tissues such as the joint and the bones. It is very likely that gaining a better understanding of the processing and integration of signals within the spinal cord will be essential in developing improved treatments that address the multiple components of bone and joint pain such as movement-associated pain, breakthrough pain, and persistent background aches and pains.

Of importance, multiple regions within the brain including cortical regions (e.g. anterior cingulate cortex, somatosensory cortex, prefrontal cortex, insula, parietal lobe), the diencephalon (thalamus), and the limbic regions (e.g. amygdala) are implicated in processing the incoming signal and contribute to the perception of pain [29]. Notably, these different brain regions may contribute to different components of the complex sensation of pain that includes both sensory and emotional components [30, 31]. Clinical and preclinical studies are making important gains in our understanding of how these different brain regions contribute to the affective (unpleasant) and sensory (intensity, location) aspects of pain [32]. How these and other regions interact and how they may be altered in the conditions of chronic pain (e.g. arthritis, low back pain) are under investigation [33, 34]. Moreover, key changes in brain volume, functional connections, and processing are observed using imaging studies [35, 36]. In patients with chronic back pain, studies have reported diminished cortical grey matter and impaired emotional decision making [37, 38]. This observation has been expanded to other chronic pain states including chronic osteoarthritis pain [35, 36].

Initiation of Pain Signals from the Bone and Joint:

Early studies in the cat demonstrated that the knee joint is innervated by sympathetic fibers as well as sensory afferent fibers, primarily fine myelinated (A-δ) fibers and unmyelinated (slow conducting C-fibers) sensory afferent neurons [39]. Both A-delta and C-fibers demonstrated responses to mechanical stimulation at higher thresholds compared to other tissues such as skin, with some fibers that respond only to stimulation in the noxious range [9]. Electrophysiological studies characterizing movement-induced activation of sensory fibers innervating the joint further classified these fibers into 4 subtypes: fibers activated by non-noxious movement; fibers activated both by non-noxious and noxious movement; fibers activated only by noxious movement, and fibers that failed to respond to movement [10]. These data led to the conclusion that the sensory afferent fibers innervating the joint contribute to deep pressure sensation and nociception, and likely signal that the joint is about to leave the normal working range [10]. Subsequent electrophysiological characterization of the A-delta and C-fibers innervating the knee joint in the setting of acute inflammation revealed altered firing properties in the context of injury. Fiber populations from inflamed knee joints demonstrated increased activity in the absence of any stimulation or joint movement (spontaneous activity). In addition, they demonstrated lower response thresholds to mechanical stimulation (hypersensitivity), and increased activity in response to mechanical stimulation from probing the joint with calibrated von Frey filaments and to joint movement [40–42]. In addition, silent sensory fibers that normally do not demonstrate activity during non-noxious movement of the joint, became active following exposure to knee joint injection of kaolin/carrageenan, a model of acute experimental arthritis in the cat [43]. Findings such as these have highlighted the potential of sensory neurons to undergo maladaptive change in their response to both natural and artificial stimuli.

Several studies examining innervation of the bone indicate that bone is well innervated by small-diameter peptidergic C-fibers, Aδ fibers, and sympathetic fibers [44, 45]. Several reports suggest key differences in patterns of innervation of the bone and other deep tissue compared to skin. Studies using an eGFP protein targeted to the mas-related G-coupled protein sub family D expressing (MrgD+) non-peptidergic population of C-fibers demonstrated that this population of non-peptidergic fibers selectively innervate the skin and is absent from other tissue [14, 44]. Studies that directly compared innervation of skin and bone using these mice and demonstrated that whereas skin is innervated by both peptidergic and non-peptidergic populations of C-fibers, bone shows evidence of innervation by peptidergic, but not by non-peptidergic C-fibers [46, 44]. This has led to the proposal that bone and joints are not innervated by the non-peptidergic population of C-fibers in mice [47]. However, evidence regarding the presence of non-peptidergic C-fibers innervating the bone has been reported in rat studies using retrograde tracers injected into the intramedullary space of the bone [6, 48, 49].

Such discrepant findings suggest the possibility that there may be a subpopulation of non-peptidergic fibers that innervate the bone that have not been directly assessed in previous studies. Alternative explanations include the possibility of differences in the methods used to examine innervation. The processes of decalcification of the bone may have altered binding sites for markers of non-peptidergic fibers such as isolectin B4 (IB4) or P2X3 diminishing potential visualization of fibers innervating the bone and leading to false negative findings [44]. However, IB4 binding has been reported in muscle that had been decalcified in the same manner as bone that did not show these markers of non-peptidergic fibers [44]. In addition, MrgD+ and IB4 binding were not observed in periosteum whole mount tissue that did not undergo decalcification whereas both were expressed in the skin [44]. These observations indicate that the decalcification process does not explain the absence of these markers of non-peptidergic fibers within the bone. Alternatively, as bone is a site of perfusion, it is possible that injection of the retrograde tracers may have leaked to other sites resulting in false positive findings.

Finally, it is possible that there are species differences in innervation that causes these discrepant findings. Indeed, differences between rats and mice related to expression of these specific molecular markers of neuronal subtypes have been reported [50]. In the mouse these populations have been demonstrated to be mostly non-overlapping in the DRG [51, 52, 15], whereas in the rat these populations show a ~45% overlap in expression in the DRG, and these expression profiles vary between DRG and trigeminal ganglia [50]. In addition to these differences between rats and mice, distribution of these fiber populations have been reported to differ across different strains of mice [53]. Future studies examining potential differences in innervation of bone and joint across multiple species is warranted to better understand whether patterns of innervation of bone is conserved.

In addition to these populations of nociceptors, some recent studies have implicated low threshold mechanoreceptors (C-LTMRs) in mediating mechanical pain to normally non-noxious stimuli in conditions of injury and chronic pain [54–56]. The C-LTMRs have been most studied within the skin. Whether this population innervates bone or joint or mediates pain associated with trauma or pathology that generates chronic pain is unknown and

difficult to assess due to the nature of joint and bone tissue accessibility. Improved understanding of subpopulations innervating the bone and surrounding tissues as well as how they may contribute to diverse aspects of bone and joint pain are needed to develop a more comprehensive understanding of mechanisms underlying the multiple components of bone and joint pain.

Site of injury or pathology:

Inflammation.

Tissue damage leads to an innate immune response that results in release of molecules including chemokines, cytokines, and growth factors from local tissue (e.g. fibroblasts, chondrocytes), blood, and local and migrating inflammatory cells [57, 47, 58, 59]. These factors may promote disease progression and pathology in disease states such as arthritis or cancer-induced bone pain. Pro-inflammatory cytokines such as TNFα, IL-6 and IL1β have been implicated in bone resorption by increasing osteoclast activity [60]. In addition, these cytokines produce peripheral sensitization of nociceptive fibers, resulting in decreased thresholds for activation and amplified signaling [61]. Growth factors such as nerve growth factor (NGF), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) are also implicated in development of bone or joint pathology in disease states such as arthritis and cancer-induced bone pain. VEGF has been implicated in angiogenesis associated with arthritis and skeletal metastases [62, 47]. NGF has been implicated in peripheral sensitization through mechanisms such as upregulation of key channels such as sodium channels and transducers that regulate neural activity and by phosphorylation of transducers such as TRPV1 within neurons leading to enhanced activity and increased neuronal excitability [63]. In addition, NGF has been shown to mediate pathological sprouting of nociceptive and sympathetic fibers within the bone and joint across various rodent models of bone and joint pain including cancer-induced bone pain [7], arthritis [64] and fracture [65, 66]. Building upon these preclinical studies, therapies such as anti-TNF α, anti-IL6 and anti-NGF antibody are in clinical use or in clinical trials for pain associated with bone or joint pathology.

Neuropathic Pain.

In addition to the development of inflammation, neuropathic changes have also been reported in animal models of bone and joint pain [67, 68, 47, 69, 70]. Studies in rat and mouse models of cancer-induced bone pain and chemical-induced osteoarthritis joint pain have demonstrated expression of ATF3, a neural marker of nerve damage, in cell bodies within the dorsal root ganglion innervating the bone or joint [71–73, 69]. Pathological changes to sensory and sympathetic nerve fibers within the bone and joint have been demonstrated across models of cancer bone pain, arthritis pain, and fracture pain [74, 64–66]. These studies describe development of neuromas and disorganized structures of fibers similar to those reported following traumatic nerve injury in patients and animal models of nerve-injury induced neuropathic pain. Finally, pharmacological studies in animal models of bone and joint pain have demonstrated that knee joint arthritis pain and cancer bone pain associated with markers of nerve damage are resistant to pain alleviating effects of anti-inflammatory drugs such as NSAIDs (e.g. ketorolac, diclofenac) [75, 76, 70]. In contrast,

these pain states were found to be responsive to drugs typically used to treat neuropathic pain within the clinical setting, duloxetine, pregabalin and gabapentin [77, 70]. Importantly, these studies demonstrate that anti-inflammatory drugs may be effective in some aspects of pain whereas they are ineffective on others. In a rat model of advanced osteoarthritis in which both evoked measures of joint pain and non-evoked ongoing pain are observed, the NSAID diclofenac effectively blocked weight asymmetry whereas it failed to block persistent ongoing joint pain [75] whereas duloxetine blocks both evoked and ongoing joint pain [77]. Similarly, in a rat model of cancer-induced bone pain, diclofenac was demonstrated to effectively block tactile hypersensitivity, a measure of referred evoked pain, but not ongoing pain [76]. Such observations indicate that there are mechanistic differences between different clinically important aspects of bone and joint pain. Such complexity highlights the need for more comprehensive analysis of the multiple aspects of bone or joint pain when examining potential molecular mechanisms of pathological chronic pain and for effectiveness of potential therapeutic targets.

Sensitization

Many animal and clinical studies have demonstrated that sensitization of peripheral and central neurons develops in the context of chronic bone or joint pain [5, 67, 78]. The international association for the study of pain (IASP) defines sensitization as “Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs”. They note that sensitization may include a decrease in activation threshold, increase in suprathreshold responses, spontaneous discharges of neurons, and increases in receptive field of neurons. They further clarify that sensitization is a neurophysiological term and can only be applied when both input and output of the neural system being studied (e.g. peripheral input, spinal signaling) are known. It is emphasized that clinically, sensitization may only be inferred indirectly from observations such as hyperalgesia or allodynia. Temporal summation is also used within the clinical literature as a sign of sensitization [78]. Sensitization can be measured in the periphery, termed peripheral sensitization defined by IASP as “Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields”. Sensitization can also be measured at sites within the central nervous system such as the spinal cord, termed central sensitization defined by IASP as “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.” This has been described in patients with moderate to severe knee osteoarthritis [78]. Further, in patients with knee osteoarthritis associated with spread of allodynia and temporal summation, functional magnetic resonance imaging demonstrated that whereas direct painful stimulation at the osteoarthritic site did not distinguish between sensitized and non-sensitized patients, stimulation at an area of spreading sensitization resulted in increased signals within brain regions associated with pain processing [79]. Stimulation of an area associated with spreading sensitization also produced activation of brain regions not associated with pain processing, extending to the auditory, visual, and ventral sensorimotor cortices [79]. Such studies will be critical in gaining a better understanding of changes associated with development of central sensitization that

contribute to worsening of pain and to medication resistant pain states associated with bone and joint pain.

There are many well written overviews of mechanisms contributing to development of peripheral sensitization [80, 58] and central sensitization [67, 68, 80, 81]. Much has been learned about the impact of many of the factors that are released by local tissues, such as ATP, ADP, endothelins, bradykinin, and growth factors [7, 12, 47, 58, 80]. These factors have been shown to act both directly on neurons to activate them and to alter the properties of the neurons. These actions including lowering of activation thresholds and increased in responses are key characteristics of peripheral sensitization [7, 12, 58]. Several factors including proinflammatory cytokines (e.g. IL-1β, TNFα, IL-6) have been shown to be catabolic and may enhance bone resorption promoting underlying pathology [82]. Mechanisms underlying peripheral sensitization include translation and trafficking of transducer channels as well as phosphorylation of transducer channels such as TRPV1 resulting in altered activation thresholds and increased transfer of cations allowing for enhanced depolarization of the neurons and amplified signaling [12, 7, 58]. Similarly, increased translation and trafficking of sodium channels resulting in amplified action potentials and increased numbers and phosphorylation of calcium channels result in enhanced neurotransmitter release from afferent terminals within the spinal cord [83, 84]. In addition, pathophysiological changes in neurons such as pathological sprouting and formation of neuromas may contribute to ectopic discharge and amplified signaling from the bone or joint [7].

Ongoing afferent input has been suggested to result in spinal sensitization [81, 85, 86]. Various studies in animal models of cancer-induced bone pain and osteoarthritis have demonstrated development of central sensitization including lowered thresholds for activation, amplification of signal, and widening of the receptor field [69, 70], as well as activation of spinal neurons in response to normally non-noxious stimuli such as movement of the tumor bearing hindlimb [87] or arthritic joint [77]. Various mechanisms have been implicated in mediating spinal sensitization, including activation of glia, upregulation and excitatory signaling by dynorphin, and diminished tonic inhibition by GABAergic interneurons [88–96]. Several studies have demonstrated a role for spinal microglia and elevated pro-inflammatory cytokines in mediating cancer-induced bone pain [97] and in animal models of osteoarthritis [98]. In addition to release of pro-inflammatory cytokines, spinal microglia mediated release of the brain derived growth factor (BDNF) has been implicated in mediating spinal changes resulting in disinhibition and spinal sensitization [91, 95, 96]. These changes have been described in animal models of nerve injury as well as opioid-induced hypersensitivity. Release of BDNF is proposed to increase chloride channels (KCCL) leading to disruption of the gradient balance of chloride ions [95, 96]. This is proposed to result in GABA activation of normally inhibitory channels become excitatory, thereby facilitating sensitization and hyperexcitability [26, 91, 90, 99]. Whether such changes are implicated in chronic bone and joint pain has not been well studied. The role of these changes in mediating evoked hypersensitivities compared to persistent ongoing pain has not been systematically studied. Upregulation of dynorphin has also been implicated in spinal sensitization in preclinical models of nerve injury-induced pain through activation of non-opioid receptors such as the bradykinin receptor [93]. Upregulation of dynorphin has

been reported in a mouse model of cancer-induced bone pain [87]. However, further investigation regarding the role of spinal dynorphin in mediating chronic bone or joint pain has not been further investigated.

Descending Pain Modulation

Another important aspect of pain processing is the ability for the brain to modulate the pain signal through descending pain pathways that can amplify (descending pain facilitatory pathways) or diminish (descending pain inhibitory pathways) the pain signal (reviewed by [100, 101]). Key sites implicated in descending pain modulation including the anterior cingulate cortex, the periaqueductal grey, and the rostroventromedial medulla (RVM) [101, 100]. In the uninjured/non-pain state, pain can be modulated in response to physical or psychological stress. Much has been learned about how stress can activate these descending pain modulatory pathways to dampen pain or induce analgesia through endogenous opioid and cannabinoid signaling within the brain [101]. Following injury, a time-dependent increase in net descending pain facilitation occurs, wherein descending facilitatory pathways promote enhanced spinal cord activity to noxious and non-noxious stimuli [67, 101] as well as behavioral responses showing enhanced responsiveness to noxious and non-noxious stimuli modeling hyperalgesia and allodynia, respectively [102, 103, 77, 104, 105].

Conclusion

Much has been learned regarding biological mechanisms contributing to bone and joint pain. The continued improvement and development of animal models that more accurately represent the human condition will continue to advance the field and allow basic researchers to identify translational proteomic, cellular and systems to better treat pain. In addition, the relatively recent advent of specific genetic tools including transgenic animals with alterations to “pain-specific” genes (i.e. knock-ins and knock-outs), reporter genes, and development of virally deliverable tools to induce genetic alterations allow dissection and analysis of molecular targets and microcircuitry underlying specific and distinct aspects of chronic pain. Optogenetic and chemogenetic tools offer increased ability for spatial and temporal precision of the investigation of key cell subtypes and circuits within the CNS. Fluorescent proteins that serve as a surrogate for neuronal firing/activity such as GCaMP6 and the continued incorporation of light sensitive ion channels and pumps that allow for selective activation or inhibition of cells are immensely powerful tools working their way to the forefront of the pain field. In addition, improvements in imaging techniques both at the site of pathology [62] and brain imaging assessing brain activity and changes in processing in chronic pain patients will guide future studies on molecular and circuit changes that are associated with chronic pain. Such analyses will open new potential targets as genomic and proteomic analyses reveal novel targets at the site of pathology or the neural circuitry driving chronic pain. In addition, brain imaging will allow for potential insights into development of comorbidities associated with chronic pain such as development of depression, anxiety and altered cognitive processing [106–111]. Beyond the development of exciting new tools there remain complexities that go beyond the scope of this review such as integral contributions by the immune system and the endocrine system. Continued and growing analysis of genetic susceptibility to increased or decreased pain sensitivity, and epigenetic modifications that

result from chronic pain will guide our understanding of the predisposition of different races/ethnicities/sexes to chronic pain and the potential effectiveness or insensitivity to specific pain treatments.

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