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Osteoarthritis pain mechanisms: basic studies in animal models

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SUMMARY

Objective: Osteoarthritis (OA) is a complex and painful disease of the whole joint. At present there are no satisfying agents for treating OA. To promote OA research and improved treatment, this review summarizes current preclinical evidence on the development of OA.
Methods: Preclinical OA research was searched and key findings are summarized and commented.
Results: Mechanisms of OA-associated pain have been studied in rodent knee OA models produced by intra-knee injection of the chondrocyte glycolytic inhibitor mono-iodoacetate (MIA), surgery, or spontaneous development in some species. These models are clinically relevant in terms of histological damage and functional changes, and are used to study mechanisms underlying mechanical, thermal, ambulatory, body weight supporting-evoked, and ongoing OA pain. Recent peripheral, spinal, and supraspinal biochemical and electrophysiological studies in these models suggest that peripheral pro-inflammatory mediators and neuropeptides sensitize knee nociceptors. Spinal cytokines and neuropeptides promote OA pain, and peripheral and spinal cannabinoids inhibit OA pain respectively through cannabinoid-1 (CB1) and CB1/CB2 receptors. TRPV1 and metalloproteinases contribute and supraspinal descending facilitation of 5-hydroxytryptamine (5-HT)/5-HT 3 receptors may also contribute to OA pain. Conditioned place preference tests demonstrate that OA pain induces aversive behaviors, suggesting the involvement of brain. During OA, brain functional connectivity is enhanced, but at present it is unclear how this change is related to OA pain.
Conclusion: Animal studies demonstrate that peripheral and central sensitization contributes to OA pain, involving inflammatory cytokines, neuropeptides, and a variety of chemical mediators. Interestingly, brainstem descending facilitation of 5-HT/5-HT3 receptors plays a role OA pain.

Introduction

Osteoarthritis (OA), is a complex disease of the whole joint, is characterized by structural degradation of the articular cartilage, peri-articular bone, synovial joint lining, and adjacent supporting connective tissue elements. It manifests as joint pain and loss of joint function. There are currently no satisfying treatments to this disease. The current standard of care is to manage and alleviate symptoms[1], but despite treatment with conventional analgesic drugs most individuals with OA continue to experience pain[2]. A recent study demonstrated that subjects with chronic back pain and complex regional pain syndrome had significantly less bilateral hippocampal volume compared to controls, while those with OA did not[3]. This suggests that OA-induced pain might be related to unique mechanisms and this has attracted researchers' attention in recent years. Since the most common joints affected by OA are large weight-bearing joints such as hip and knee[4], intra-knee injection of the chondrocyte glycolytic inhibitor mono-iodoacetate (MIA)-, surgically induced, and spontaneous knee OA models have been used to investigate mechanisms of OA-induced pain[5–8].

In the MIA model, histological examination shows chondrocyte degeneration/necrosis at days 1–7 post-MIA, increased osteoclasts and osteoblasts in subchondral bone by day 7, focal fragmentation and collapse of bony trabeculae with fibrosis by day 28, and large areas of bone remodeling by day 56[9,10]. *In vivo* microCT-arthrography clearly detects cartilage degeneration in the injected knee[11].

Tramadol, celecoxib, and diclofenac improve movement-induced pain behavior evaluated with compressive hind limb grip force in the MIA model[12], and subcutaneous morphine and gabapentin significantly decrease the mechanical and thermal sensitivity and ambulation-evoked pain[13]. MIA-induced articular cartilage loss, progressive subchondral bone lesions, and the efficacy of clinical analgesics in inhibiting MIA-induced pain indicate that this model is clinically relevant and will continue to be useful

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for the development of better therapeutic strategies and better understanding of the mechanisms of chronic OA pain.

Surgery-induced medial meniscal tear (MMT), partial medial meniscectomy (PMM), destabilization of the medial meniscus (DMM), and anterior cruciate ligament transection (ACLT) have been used to induce knee OA[14,15]. The MMT results in a progressive cartilage lesion[16]. The MMT plus ACLT-induced OA model presents bone and cartilage remodeling, infiltration of immune cells into joint tissues, and pain[17]. The ACLT + PMM model showed no hind-limb difference in gait analysis or mechanical allodynia over a period of a month[18], making it analogous to patients who show radiological changes but no pain. PMM in female C57BL/6 mice produces progressive degenerative joint damage and OA-related pain[19]. The DMM-induced OA model displays a time-dependent cartilage lesion between 2 and 12 weeks, including cartilage surface fibrillations, loss of superficial cartilage and ulceration of subchondral bone, and produces pain assessed 12 weeks after surgery[7]. In that model, opioid receptor antagonists led to pain onset 4 weeks earlier than in vehicle-treated animals, and opioid receptors increased in the peripheral nerves that innervate the joint in naloxone-responsive mice[7], suggesting that endogenous opioids might inhibit early-stage OA pain.

Guinea pigs, particularly the Dunkin-Hartley strain, STR/1N, STR/ort, and C57 black mice, and several transgenic and genetically altered strains of mice develop characteristics of arthritic joints, but rats rarely develop them spontaneously (for a review, see D'Souza *et al.*, 2011). In Duncan-Hartley guinea pigs, age-dependent cartilage degeneration can be assessed by T(1ρ) magnetic resonance imaging (MRI) from 3 to 9 months[20].

All three model types have been used to investigate the mechanisms of OA pain, which has been assessed with various methods, including mechanical, thermal, ambulatory, and body weight supporting-evoked methods (for a review, see D'Souza *et al.*, 2011). MIA has been reported to be differentially potent: weight-bearing ≥ von Frey filaments > running wheel[21]. Von Frey filaments are a set of calibrated filaments used to perpendicularly stimulate skin. Recently, the MIA model has also been used to study ongoing pain assessed with conditioned place preference [22,23]. Additionally, it has been reported that biglycan (BGN) and fibromodulin (FMOD) play roles in regulating chondrogenesis and extracellular matrix turnover[24] and that doubly deficient BGN/FMOD mice develop premature temporomandibular joint OA[25]. Peripheral, spinal, and supraspinal l mechanisms (Fig. 1) have recently been discovered using these rodent models.

Peripheral mechanisms

Cytokines

Synovitis is highly correlated to OA patients' pain[26,27] and plays an important role in such pain[2,28]. An intra-articular MIA injection significantly increased tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in the knee synovium and capsule between days 1 and 28 post-MIA; the levels of TNF-α and IL-6 peaked at day 4. The injection also induced mechanical allodynia of the ipsilateral hind paw, which was significantly mitigated by local application of nonsteroidal anti-inflammatory drugs (NSAIDs)[29,30]. A TNF-α injection into the normal knee joint caused significant and persistent sensitization of nociceptive sensory fibers to mechanical stimuli that was abolished by co-administration of etanercept, a TNF-α inhibitor; and TNF-α induced excitation of isolated dorsal root ganglion (DRG) neurons with C-fiber axons[31] and increased mechanosensitivity and peripheral receptive fields of DRG neurons[32].

An electrophysiological study demonstrated increased spontaneous activity in C-mechanosensitive fibers and increased mechanical sensitivity in A-mechanosensitive fibers of the knee in MIA-treated rats[33]. Furthermore, knee primary afferents, thinly myelinated type III and unmyelinated type IV fibers, showed significant mechanosensitivity in response to normal and noxious joint rotation as compared to saline controls in an MIA model[34,35]. This was reduced by local NSAID application[35]. Collectively, these studies indicate that increased TNF-α sensitizes primary afferents to facilitate joint pain and that NSAIDs can alleviate OA-induced pain by inhibiting TNF-α expression.

IL-6 increased intracellular calcium in cultured DRG neurons in calcium-imaging studies. Additionally, glycoprotein 130, to which the IL-6/IL-6R complex binds, was found in almost all DRG neurons cultured from adult rats. This suggests functional IL-6 receptors in

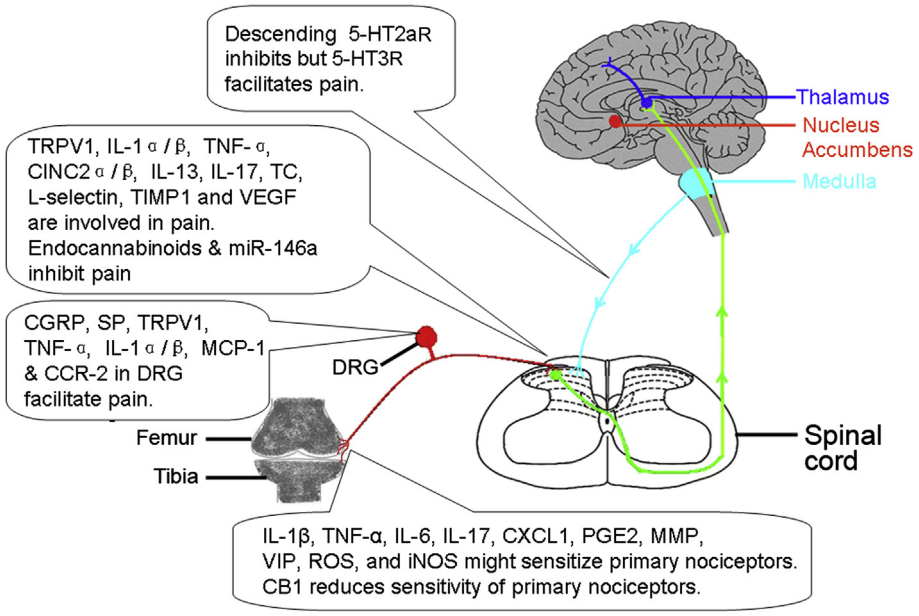

Fig. 1. Diagram illustrating mechanisms of OA-induced pain. Bioactive chemicals are involved in OA-induced pain at peripheral, spinal and supraspinal levels. IL-13, interleukin-13; IL-17, interleukin-17; IL-1α/β, interleukin alpha/beta.