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A Mechanism-Based Approach to the Management of Osteoarthritis Pain

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Abstract

Pain from osteoarthritis (OA) affects millions of people worldwide, yet treatments are limited to acetaminophen, NSAIDs, physical therapy, and ultimately, surgery when there is significant disability. In recent years, our understanding of pain pathways in OA has developed considerably. Though joint damage and inflammation play a significant role in pain generation, it is now understood that both central and peripheral nervous system mechanisms exacerbate symptoms. Evolving management strategies for OA address central factors (e.g., sleep difficulties, catastrophizing, and depression) with treatments such as cognitive behavioral therapy and exercise. In addition, emerging data suggest that antibodies against peripheral signaling neuropeptides, such as nerve growth factor-1 (NGF-1), may significantly alleviate pain. However, concerns regarding potential adverse effects, such as rapidly progressive OA, still remain. A nuanced understanding is essential if we are to make headway in developing more effective treatments for OA.

Keywords

Osteoarthritis; NGF; Musculoskeletal pain; Pain mechanisms; Central sensitization

Introduction

Osteoarthritis (OA) is the most common form of joint disease in the USA, affecting nearly 12.1 million Americans [1]. OA leads to pain and disability and is responsible for an estimated cost of $89.1 billion annually in the USA for medical expenditures alone [2]. In a claims database analysis, indirect costs of OA (including lost wages, lost productivity, and

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent All studies by Dr. Lee involving animal or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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need for childcare) amounted to $4603 per person affected [3]. According to a survey-based study, individuals with OA were nearly three times as likely to report difficulty acquiring a job as the general population [4]. Along with back pain, OA accounts for the two most commonly reported causes of chronic pain in the USA [5].

Pain Mechanisms in OA

Pain in OA comes from several sources, both peripheral and central. Peripheral pain refers to pain arising in the tissues, nerves, or nerve roots, whereas central pain refers to the modulation of pain perception by the central nervous system (CNS) (e.g., brain and spinal cord).

Peripheral Pain Mechanisms

OAwas initially thought to be a disease primarily of cartilage. As a result, many studies investigated the correlation of joint space narrowing, a radiographic assessment of cartilage loss, with clinical measures of pain. These studies yielded conflicting results, likely due to differences in study design. One of the most sophisticated studies was done by Neogi at al. In this study, the authors performed a matched set analysis, comparing two knees, within each person, which were discordant in clinical measures of pain. This technique enabled the authors to minimize confounding by variables that differed between individuals. They concluded that structural abnormalities correlated strongly with self-reported pain, with joint space narrowing being most predictive of pain [6].

However, a puzzling question remained: how is pain generated in OA if cartilage is a tissue without nerves? Other studies have attributed peripheral sources of pain to nerves in the synovium and bone. A study of knee OA by Torres et al. concluded that significant synovitis, meniscal tears, bone marrow lesions, and bone attrition (flattening of articular surfaces) on magnetic resonance imaging (MRI) were all correlated directly with pain severity [7].

Stoppiello et al. compared patients who had undergone total knee replacement (TKR) with postmortem synovial samples from individuals who were asymptomatic in their last year of life [8]. They found that those with advanced OA (those who had undergone TKR) exhibited higher levels of staining for nerve growth factor (NGF) in the synovium and had a greater degree of synovitis and loss of cartilage integrity. NGF is a protein that promotes axon growth and survival of peripheral neurons. It is elevated in a variety of pain conditions, including OA, and it has been implicated in the development of peripheral sensitization [9, 10]. NGF decreases the firing threshold of vanilloid receptor 1, a cation channel which depolarizes nociceptive neurons in response to heat and pain. In mouse models of OA, intra-articular injections of NGF produced prolonged weight-bearing asymmetry. NGF is also upregulated in the synovial fluid of dogs with OA secondary to other conditions [11]. Pecchi et al. showed that in a culture of human OA chondrocytes, mechanical stress and exposure to interleukin (IL)-1β increased expression of NGF [12]. NGF is overexpressed at the osteochondral junction in individuals with OA, leading to disorganized innervation of previously aneural cartilage and peripheral sensitization [13]. An injection of NGF intramuscularly leads to increased pain scores and hyperalgesia [14].

The local production of inflammatory cytokines is thought to be critical to the generation of peripheral pain impulses. 'Dolor' is one of the first described features of inflammation and makes evolutionary sense as a signal to avoid danger in one's environment. TNF-α has been persistently implicated in the development of peripheral pain generation. In mice, intra-articular TNF-α injections augmented pain responses to mechanical stimulation while intra-articular injection of anti-TNF antibodies attenuated them [15]. In patients with OA, Orita et al. found that synovial TNF-α levels correlated directly with Western Ontario and McMaster Universities Arthritis Index (WOMAC) measures of pain, stiffness, and functional disability in 47 samples. In addition, a study of 149 older adults showed that total knee pain was correlated with high-sensitivity C-reactive protein (CRP), while IL-6 and TNF-α levels were associated with pain while standing [16]. A study by Takeshita et al. demonstrated immunoreactivity for TNF-α in patients undergoing hip reconstruction for OA but not in controls (patients with femoral neck fracture), supporting a role for TNF-α in nerve growth and pain expression in individuals with hip OA [17].

Central Pain Mechanisms

In contrast to peripheral pain, which is characterized by pain localized to specific sites (e.g., joint sites in OA), CNS pain mechanisms are characterized by widespread pain sensitivity. Multiple studies have shown that individuals with OA have lower pressure pain thresholds at multiple body sites [18, 19].

Specific mechanisms of central pain dysregulation include central sensitization in the spinal cord and dysregulation of the ascending and descending pathways from the brain through the spinal cord. Central sensitization occurs by a number of mechanisms, including enhanced glutamate receptor sensitivity and the formation of close synaptic connections [20]. A consequence of these processes is that the receptive field enlarges, so that areas not directly affected by noxious stimuli are interpreted as painful. Central sensitization may be assessed using the experimental paradigms of temporal summation, when individuals are asked to rate the severity of pain caused by a repeated stimulus, and spatial summation, when pain thresholds are assessed in response to stimuli provided over a small area compared to the same stimulus provided over a large area. Studies have shown that individuals with OA experience both enhanced temporal summation and enhanced spatial summation [19, 21]. Among individuals with knee OA, those who report higher pain levels have more enhanced temporal summation than those with low levels of pain [22••].

Ascending pathways arise from the dorsal root ganglion and make synaptic connections in the thalamus, from which they travel to different areas of the brain. MRI studies of chronic low back pain patients indicate that these pathways are regulated by cortical and subcortical areas, such as the medial prefrontal cortex and nucleus accumbens [23]. It is likely that these areas also play a role in the establishment of chronic pain in OA, though additional studies are needed to clarify these pathways in OA.

Descending pain pathways arise from the anterior cingulate cortex, hypothalamus, and amygdala and travel through the periaqueductal gray and rostral ventromedial medulla to the dorsal horn of the spinal cord. These pathways include mechanisms that facilitate pain, as well as those that inhibit pain. The inhibitory pathways are mediated by serotonin,

norepinephrine, and endogenous opioids, and these pathways are often impaired in individuals with OA. One experimental method of assessing the descending inhibitory pathways is via the paradigm of conditioned pain modulation. In this paradigm, pain thresholds are assessed before and after the descending inhibitory pain pathways are activated by a strong noxious stimulus (the conditioning stimulus). The difference between pain thresholds before and after application of the conditioning stimulus is an assessment of activity of the descending inhibitory pain pathways. Studies have shown that both individuals with knee OA and individuals with hip OA have impairments in conditioned pain modulation compared to controls [19, 24].

Abnormalities in pressure pain thresholds and conditioned pain modulation may improve after knee OA patients undergo TKR, suggesting that impairments in CNS pain processing are reversible after removal of painful peripheral triggers [19, 24]. However, the reversibility of these processes may differ depending on preoperative pain levels. A study by Petersen et al. showed that pressure pain thresholds only improved among those who had mild pain at baseline [22••]. Individuals who continued to have chronic pain after TKR had lower pressure pain thresholds, enhanced temporal summation, and lower conditioned pain modulation compared to those who did not have chronic pain after surgery [22••].

Recent advances in neuroimaging have yielded opportunities to assess neural activity in response to clinical and experimentally induced pain. A study by Kulkarni et al. compared the neuroimaging of arthritic knee pain to thermally induced pain in 12 subjects with knee OA. They found that arthritic pain was associated with increased fDG-PET activity in the limbic system and areas associated with fear and emotion [25]. A later study by Monfort et al. found that individuals with OA and clinical features of sensitization responded to non-articular pressure both with increased self-report ratings of clinical pain and sensory cortex enhancement on fMRI [26]. They also noted enhancement in fronto-subcortical structures, associated with pain-related learning and behavior. These studies suggest that neuroimaging of pain will be useful not only for better understanding pain pathways but also for predicting response to therapies.

Impact of Sleep and Psychosocial Factors

Sleep difficulties contribute to central pain processing by a variety of means [27]. Not only does chronic pain lead to sleeping difficulties, but sleep disturbances also induce hyperalgesia. Vitiello et al. showed that in older adults with OA and insomnia, short-term improvements in sleep predicted long-term improvements in pain, fatigue, and sleep [28]. Another study by Petrov et al. found an association between insomnia severity and experimental pain responses [29]. Disruption of sleep continuity was associated with impaired conditioned pain modulation, whereas sleep restriction was associated with increased circulating levels of CRP, TNF-α, and IL-6, acute phase reactants, and inflammatory cytokines which may play a role in central sensitization [30, 31].

In addition to sleep problems, psychological factors, such as pain catastrophizing, may alter CNS regulation of pain in OA. Pain catastrophizing is the mental process of magnifying pain sensations, perseverating, and feeling helpless in the face of pain. In a cluster analysis of 216 individuals with knee OA, individuals with high pain catastrophizing were noted to have

lower pain thresholds in a widespread distribution, higher measures of temporal summation, and lower levels of conditioned pain modulation, suggesting abnormalities in CNS pain regulation [32•]. Consistent with these results, a recent study of 208 individuals with knee OA and/or insomnia showed that pain catastrophizing was significantly associated with higher scores on a composite measure of abnormalities in CNS pain regulation [33]. In the same study, pain catastrophizing was also noted to be an effect modifier of the relationship between sleep efficiency and CNS pain regulation. In individuals with high levels of pain catastrophizing, low levels of sleep efficiency were strongly associated with impairments in CNS pain regulation, whereas sleep efficiency was not associated with measures of CNS pain regulation among individuals with low levels of catastrophizing.

Depression and negative affect may also contribute to alterations in CNS modulation of pain. In a study of 194 individuals with knee OA, Cruz-Almeida et al. reported that subjects with the highest levels of psychological distress (depression, negative affect and anger) had the lowest pressure pain thresholds, highest measures of temporal summation, and lowest measures of conditioned pain modulation, indicative of abnormalities in CNS pain processing mechanisms [34]. Interestingly, a separate study of 150 individuals with knee OA did not find any association between negative affective and temporal summation, but positive affect was associated with lower measures of temporal summation (better CNS regulation of pain) [35].

Treatments for Pain in OA

For organizational purposes, this manuscript divides the treatments for OA into three categories: (1) those which inhibit peripheral mechanisms of pain and inflammation, (2) those which treat central pain mechanisms, and (3) those which affect progression of joint destruction (peripheral pain generators). It is important to note that some drugs may have more than one mechanism of action, and the exact mechanism for some agents is not well-elucidated. For example, acetaminophen is the first-line treatment for OA, as recommended by the America College of Rheumatology clinical guidelines [36]. In some studies, acetaminophen had comparable efficacy to NSAIDs in OA, reducing mean pain scores by approximately 40 % [37]. A more recent meta-analysis showed a more modest benefit in pain reduction of 5 % [38]. Historically, acetaminophen has been assumed to work via peripheral pathways by inhibiting cyclooxygenase (COX) enzymes. However, its anti-inflammatory effect is largely neutralized in humans by the presence of hydroperoxides. More recent data suggest that acetaminophen acts centrally via the descending serotonergic pathways [39]. Studies in mice indicate that acetaminophen is metabolized to a compound called AM404, an endogenous cannabinoid that acts by desensitizing central vanilloid (TRPV-1) receptors [40]. Additional studies are needed to further characterize the mechanisms of action of acetaminophen in humans.

Treatments Primarily Targeting Peripheral Mechanisms of Pain

NSAIDs are regarded as one of the first-line treatments for OA [36]. NSAIDs work by inhibiting COX enzymes, which are involved in the synthesis of prostaglandins peripherally. Non-selective NSAIDs inhibit both COX-1 and COX-2 pathways, whereas selective NSAIDs preferentially inhibit the COX-2 pathway. Despite the wide use of NSAIDs for the

treatment of chronic pain conditions, a large meta-analysis examining NSAIDs for knee OA pain showed an effect size of 10.1 mm (out of 100) on the Visual Analog Scale (VAS), a reduction which may not be clinically significant [41]. In a large Cochrane review, there was no significant difference in efficacy between selective and non-selective NSAIDs [42]. Toxicities from NSAIDs are numerous, including rash and hypersensitivity, increased risk of cardiovascular disease, renal dysfunction, GI complications, and increased bleeding risk. Selective NSAIDs are associated with a lower risk for symptomatic GI ulcers and ulcer-related complications but are associated with a trend towards increased cardiovascular events. Naproxen had the lowest association with cardiovascular events [43].

Topical NSAIDs and salicylates have also been used extensively for OA in individuals with contraindications or lack of efficacy from oral NSAIDs. These treatments target local, peripheral mechanisms of pain and inflammation. Topical NSAIDs act on peripheral COX inhibition in the skin and soft tissue. According to a review by Altman and Barthel, diclofenac is the most commonly used prescription-strength topical NSAID [44]. While diclofenac can significantly impair platelet aggregation in oral form, topical diclofenac reaches 40–150-fold lower levels in the blood than its oral counterpart (depending on whether high or low dose oral dosing was used) [45]. Topical diclofenac did not reach clinically significant levels in the synovium when applied to the knee but did when applied to the hand [46, 47]. In clinical trials, topical NSAIDs demonstrated efficacy similar to oral NSAIDs with fewer adverse events [48–51]. The only exception was topical piroxicam, which carried higher risks compared to oral ibuprofen [52]. The most common adverse events of topical NSAIDs were site reactions. Topical aspirin had limited efficacy [44].

Capsaicin, the active ingredient in chili peppers, is a naturally occurring compound which is used mainly for neuropathic pain but also has some efficacy in OA. Capsaicin stimulates unmyelinated C-fiber afferents, resulting in the release of substance P. Over time, prolonged stimulation depletes neurons of substance P and impairs pain transmission [53]. Other studies suggest a more nuanced role, described as defunctionalization, whereby capsaicin neutralizes neuronal membrane potentials, alters expression of TRPV-1 receptors, and impairs transport of growth factors [54]. Unsurprisingly, burning at the site of application is the most commonly reported adverse reaction. There are concerns as to whether capsaicin may be carcinogenic in mice, but no clear associations have been noted in humans [55]. In a small randomized, controlled trial by McCarthy and McCarty, capsaicin reduced pain and tenderness in patients with RA and OA but did not improve function [56]. A larger study of individuals with OA involving multiple joints yielded similar results [57]. Based on these studies, capsaicin may play an adjunctive role in patients with pain from OA, with minimal systemic risk.

Given NGF’s role in promoting hyperalgesia, a number of anti-NGF antibodies have been tested in clinical trials. These antibodies are thought to act peripherally and do not cross the blood-brain barrier. Schnitzer et al. reviewed the efficacy and safety of anti-NGF antibodies (tanezumab, fulranumab, and fasinumab) in treating knee and hip OA [58]. All three antibodies demonstrated efficacy compared to placebo, and tanezumab had a larger impact on WOMAC pain scores than opioids or NSAIDs alone. At higher doses, all three antibodies had a greater number of adverse events than the placebo, consisting mainly of dysesthesias

and paresthesias, which were generally reversible. At lower doses, adverse event rates were similar to the placebo, but the impact on pain and function was more modest. In another study by Schnitzer comparing tanezumab monotherapy to combination therapy with NSAIDs, combination therapy did not provide a significant improvement in pain or function and was associated with a higher incidence of adverse events [59••]. Rapidly progressive OA and all-cause total joint replacements were higher in all tanezumab groups compared to the placebo. As a result of these concerns, the FDA placed a partial hold on studies examining NGF inhibitors for OA in 2012. The hold was lifted in 2015 after non-clinical data on the safety of these agents were presented to the FDA.

Treatments Targeting Central Mechanisms of Pain

Of pharmacologic treatments for central pain in OA, serotonin norepinephrine reuptake inhibitors (SNRIs) have been the most extensively studied. In a placebo-controlled randomized controlled trial (RCT) of knee OA, duloxetine significantly improved function and diminished pain scores [60]. Other studies have confirmed these results, and duloxetine is now an FDA-approved treatment for pain associated with OA [61, 62]. A pooled analysis by Brunton et al. of placebo-controlled studies of duloxetine showed a significantly increased incidence of nausea, constipation, hyperhidrosis, and fatigue compared to placebo. In addition, rarer, more severe side effects, such as serotonin syndrome, were reported, particularly when duloxetine was used with other drugs that modulate serotonin levels [63].

Exercise is a cornerstone of treatment for chronic pain in OA. Exercise may work by stimulating beta-endorphin release from the pituitary and hypothalamus [64]. A large systematic review by Uthman et al. concluded that there were significant benefits of exercise over no exercise in lower limb OA, mainly in improved physical functioning and reduction of pain and disability [65]. There are theoretical risks to exercise, however, including worsening of joint destruction. These concerns have been extensively studied, and in the absence of overt trauma, these concerns have not been borne out [66].

Cognitive interventions also hold great promises for pain conditions, including OA. A study by Smith et al. found that cognitive behavioral therapy reduced both sleep maintenance insomnia and clinical pain in OA [67•]. Interestingly, neither conditioned pain modulation nor temporal summation was altered by improvements in sleep. However, this study may have been underpowered to detect modest changes in these parameters.

Treatments Targeting Progression of Joint Damage (Peripheral Pain Generators)

Many attempts have been made to slow the progression of OA and restore joint integrity. Glucosamine and chondroitin are two supplements that have been extensively studied for treatment of OA, with mixed results. Glucosamine is a precursor to glycosaminoglycan synthesis. Oral ingestion of glucosamine may increase synthesis of native cartilage, thereby slowing progression of OA. Chondroitin is a glycosaminoglycan which is orally absorbed and works by a similar mechanisms to glucosamine. A large multicenter, double-blind trial led by Hochberg recently demonstrated that the combination of glucosamine and chondroitin was not inferior to celecoxib in ameliorating pain and stiffness in individuals with symptomatic knee OA [68]. Additional studies are needed to confirm these results, as they

differ from previous studies, including a large retrospective analysis which concluded no effect of glucosamine and chondroitin on symptom relief or disease progression in OA [69].

Other more invasive attempts have been tried to slow the damage caused by OA. Hyaluronic acid is a naturally occurring glycosaminoglycan administered in the form of intra-articular injections. Hyaluronic acid may work by many mechanisms, including promotion of chondrocyte hyaluronic acid synthesis and mitigation of matrix metalloproteinase and cytokine production. A large meta-analysis of viscosupplementation trials concluded that the available data were of a poor quality. While there was little evidence for clinical benefit, there was an increased risk for both local adverse events (e.g., flares in the injected knee and other local effects) and serious adverse events [70]. An earlier meta-analysis by Arrich et al. reached similar conclusions. In this study, hyaluronic acid injections were not associated with improvements in OA pain at rest. There was a small improvement in pain with movement, but the clinical importance of this finding was questionable [71].

The use of platelet-rich plasma has also been proposed as an adjunct therapy for OA. One proposed mechanism of action is the delivery of a high concentration of growth factors to the joint, leading to proliferation of chondrocytes and increased hyaluronic acid secretion [72]. The largest RCT of platelet-rich plasma in OA concluded benefit, with effects waning at 6 months, but overall evidence is scant [73].

Many major groups have made recommendations for the treatment of OA, but consensus has been elusive. A European League Against Rheumatism (EULAR) task force recommended that treatment of knee, hip and hand OA should account for patient age, comorbidity, and presence of inflammation [74–76]. They recommended that both pharmacologic and non-pharmacologic means be used. Acetaminophen was the medicine of choice for long-term treatment, and education and exercise were the preferred non-pharmacologic means. NSAIDs were recommended in patients unresponsive to acetaminophen, and intra-articular steroids were recommended for acute exacerbations. Glucosamine and chondroitin were thought to be relatively safe options, but the magnitude of clinical efficacy was noted to be small. Opioids were also recommended as a potential treatment option for hip OA when other treatment options, such as NSAIDs were contraindicated or ineffective [76]. American College of Rheumatology recommendations for knee and hip OA are similar, except they recommend against glucosamine, chondroitin, and capsaicin, and state that there is not sufficient evidence to comment on intra-articular hyaluronan or duloxetine [36].

Conclusions

OA is one of the most common conditions in the USA and can be debilitating. Pain in OA comes from multiple sources, both central and peripheral. Although mechanical factors and ‘wear and tear’ contribute significantly to pain in OA, our understanding of OA has become more nuanced over time, invoking peripheral inflammatory mediators and central pain processing mechanisms. We have discovered how psychosocial factors and sleep and pain behaviors influence OA, and the old dogma that exercise hastens joint destruction and worsens pain has been overturned. Despite advances in our understanding of specific

mechanisms of pain, our treatments lag far behind our understanding. Much work needs to be done to facilitate the development of new, effective therapies for pain in OA.

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