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Towards a mechanism-based approach to pain management in osteoarthritis

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Abstract

Pain is the defining symptom of osteoarthritis (OA), yet available treatment options, of which NSAIDs are the most common, provide inadequate pain relief and are associated with serious health risks when used long term. Chronic pain pathways are subject to complex levels of control and modulation, both in the periphery and in the central nervous system. Ongoing clinical and basic research is uncovering how these pathways operate in OA. Indeed, clinical investigation into the types of pain associated with progressive OA, the presence of central sensitization, the correlation with structural changes in the joint, and the efficacy of novel analgesics affords new insights into the pathophysiology of OA pain. Moreover, studies in disease-specific animal models enable the unravelling of the cellular and molecular pathways involved. We expect that increased understanding of the mechanisms by which chronic OA-associated pain is generated and maintained will offer opportunities for targeting and improving the safety of analgesia. In addition, using clinical and genetic approaches, it might become possible to identify subsets of patients with pain of different pathophysiology, thus enabling a tailored approach to pain management.

Introduction

Pain is the defining clinical presentation of osteoarthritis (OA). Joint symptoms were responsible for 15 million visits to US physician's offices in 2004 and are closely corre lated with functional limitations, leading to decreased productivity and impaired quality of life.[1] Current management of OA pain falls short of patient needs both in terms of providing adequate and sustained pain relief and in terms of undesirable adverse events and health

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risks. Relief from pain is what drives people to seek out care, but available treatments provide modest relief at best. Inadequately controlled pain is the major reason for total joint replacement (TJR).[2] The efficacy of 'first-line' agents such as paracetamol is hard to distinguish from placebo, and our most common effective therapies, NSAIDs and opioids, when used to treat OA, generally have effect sizes of ~0.3, which is considered small to moderate.[3] The fact that placebo itself has been advanced as a possible therapeutic approach,[4] and the vast use of unproven over-the-counter remedies, speaks to the need for more effective approaches to pain manage ment in this condition. Safety concerns with the currently available drugs are legion. For example, NSAIDs have long been associated with gastro intestinal adverse events, both minor and life-threatening,[5] and have more recently been implicated in thrombotic cardio vascular disease.[6] With opioids, constipation, nausea, dizziness and confusion limit use, and the abuse potential when used chronically is serious.[7]

Recent efforts in OA management have largely focused on arresting or slowing structural disease progression;[8] how such interventions might affect pain, if at all, is not well understood. The demonstration that non-opioid agents that act on the central nervous system (CNS), such as serotonin–noradrenaline reuptake inhibitors (SNRIs), can modulate musculoskeletal pain,[9] coupled with the reports of efficacy of purely peripherally-acting antibody therapy against nerve growth factor (NGF),[10] provides important new insights into the patho physiology of OA pain and opens up avenues for the exploration of novel therapeutic approaches.

A careful look at the clinical presentation of OA pain offers additional appreciation of its mechanisms. Joint pain associated with OA has a strong mechanical component, triggered by specific activities (for instance, climbing stairs elicits knee pain) and relieved by rest.[11] The pain becomes more constant over time, and has been described as "dull, aching, throbbing, punctuated increasingly with shorter episodes of a more intense, often unpredictable, and emotionally draining pain".[12] In advanced disease, neuropathic traits can be present, such as a burning sensation and 'pins and needles'.[13,14] Mood changes, sleep disturbances and fatigue are all part of chronic pain states, and are present in OA as well.[15]

Clinical investigators have reported signs of central sensitization,[16] including reduced pain pressure thresholds,[17] in patients with OA. Moreover, knee OA is associated with loss of proprioception, and cross-sectional studies have suggested a correlation between loss of proprioception and pain severity.[18] Loss of proprioceptive acuity was a modest predictor of worsening of knee joint pain in a 30-month prospective study (n = 2,243).[19] Deficits in vibratory sensation can be associated with OA of the knee and hip, and in the latter scenario even vibratory deficits in the upper extremities have been documented.[20,21] Thus, an emerging clinical picture suggests that pain and complex somatosensory changes constitute an integral part of progressive OA.

This Review provides a mechanistic overview of how musculoskeletal pain in the context of OA can be generated and of the factors that are important for its chronification. A more thorough understanding of the pathophysiology of chronic OA pain, including its heterogeneity in clinical presentation and response to analgesic treatment, might lead to the

development of mechanism-based therapies. Selected representative agents are reviewed here to highlight progress with this rational approach.

Pain mechanisms in osteoarthritis

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.[22] Pain prompts behaviour to avoid situations that might lead to tissue damage (for example, withdrawal from a flame) and imposes immobilization of an injured tissue, which favours healing; thus, pain is vital to survival of the organism. In its most essential physiological form, pain equals nociception, occurring when afferent nociceptive neurons that innervate tissues are activated by a noxious (that is, high-threshold) stimulus of a mechanical, thermal or chemical nature (reviewed elsewhere[23]). Nociceptors are pseudo-unipolar cells, with an axonal stalk that extends from the cell body in the dorsal root ganglia (DRG) and splits into two terminals. The peripheral terminal innervates peripheral tissues and the central terminal extends to the dorsal horn of the spinal cord (Figure 1a,b). Thus, nociceptors can receive and send signals at both terminals. On the peripheral terminal, specific receptors—for example, heat receptors, chemoreceptors and mechanoreceptors—can detect specific stimuli. Activation of these receptors triggers a set of voltage-gated sodium and potassium channels that are essential for the generation and propagation of action potentials.[23] These action potentials carry the ‘painful’ information along nociceptor axons, which are either medium-sized thinly myelinated Aδ-fibres or small unmyelinated C-fibres, to the dorsal horn of the spinal cord. Other neurons then transmit the signals further cephalad, to the brainstem, thalamus and cortex (Figure 1b,c). Detection, transmission and decoding of noxious stimuli are subject to complex control mechanisms at many levels in both the peripheral nervous system and the CNS, and are characterized by tremendous plasticity. Next, we provide an overview of this process, and describe how these levels and their controls are thought to be operating in OA.

Activation and sensitization of joint afferents

The joint is a densely innervated organ, and its sensory innervation is geared predominantly towards proprioception and nociception, indicating how vital positioning sense and awareness of potentially injurious movement are to proper joint function. In rats and cats, reportedly 80% of all afferent neurons in the knee joint are nociceptors.[24] In humans, articular branches of the tibial nerve that innervate the posterior knee joint capsule contain 70–80% unmyelinated C-fibres and sympathetic nerves (which have also been associated with pain).[25] Nociceptors are abundant in the joint capsule, ligaments, periosteum, menisci, subchondral bone and synovium.[26–29] Thus, pain can originate from many articu lar tissues, and a study in 20 patients demonstrating that an intra-articular local anaesthetic abolishes OA knee pain suggests that these structures are in contact with the intra-articular environment.[30] A fascinating experiment was reported by researchers who consciously mapped the pain sensation of intra-articular structures in the knee of an intrepid co-author.[31] They found that the most sensitive areas were the anterior synovium, fat pad and joint capsule. Cartilage surfaces transmitted no pain, which is in line with cartilage being aneural.[31]

The fast-growing literature exploring the relationship between pain and structural changes in the joint is shedding more light on which structures in the OA joint might generate pain. The documented discordance between radiographic severity and pain, particularly for knee OA,[32,33] has underscored the poor correlation between structural changes in the joint and the severity of pain.[34] Several studies, however, are reporting stronger associations than previously proposed. For example, one study reported that in individuals with knee pain and symptoms, those with worse pain and disability were more likely to have radiographic OA.[35] Another study showed that radiographic OA and individual radiographic features of OA were strongly associated with knee pain. Specifically, joint space narrowing was more strongly associated with pain than were osteophytes.[36] Moreover, painful knees display greater rates of medial cartilage loss, as assessed longitudinally by MRI, than knees without pain, with or without adjustment or stratification for radiographic disease stage.[37] Specific MRI-detectable features that have been related to knee pain include bone marrow lesions (BMLs), subarticular bone attrition and synovitis (reviewed elsewhere[38,39]). Patients with chronic symptomatic OA of the knee experi ence fluctuations in the presence and intensity of knee pain, and changes in BMLs and synovitis, as demonstrated by MRI, are associated with these fluctuations.[40] A randomized placebo-controlled clinical trial of intravenous zoledronic acid in patients with knee OA (n = 59) demonstrated significant reduction of BML size after 6 months (−175.7 mm^2, 95% CI −327.2 to −24.3), with a trend after 12 months (−146.5 mm^2, 95% CI −307.5 to +14.5), and of pain, as assessed by a visual analogue scale (VAS) score, after 6 months (−14.5 mm, 95% CI −28.1 to −0.9) (although not after 3 or 12 months).[41] Histological evidence of synovitis has also been correlated with symptoms in patients with early knee OA undergoing arthroscopic meniscectomy.[42]

It is now fully appreciated that OA is a disease of the entire joint, not just the cartilage.[43] This fact implies that, during the course of progressive OA, nociceptors are exposed to the changing biochemical environment in the different joint tissues. These changes might contribute to their activation and sensitization, as discussed below.

Mechanical stimulation—Mammalian molecular mechanisms of mechanosensation—the process by which a cell converts a mechanical stimulus into an electrical signal—are poorly understood.[23] Only a few studies have addressed how mechanical pain is sensed in the joint. One such study used an electrophysiological approach to demonstrate the presence of mechanogated ion channels on rat knee joint nociceptors, suggesting that these channels might have a role in pain sensing.[44] In addition, experiments in the rat monoiodoacetate (MIA) model, which is frequently used to model OA pain pathways,[45] have found a role for the voltage-gated sodium channel Nav1.8 in noxious mechanosensation in the joint.[46] Nav1.8 is restricted in its expression to small primary afferent neurons[47] and has been implicated in noxious mechanosensation in mice.[48] Approximately 50% of C-fibres and 10% of Aδ-fibres in normal rats express Nav1.8,[49] and expression levels were shown to be increased in afferent neurons that innervate inflamed rat knees.[50]

Inflammatory mediators in the joint—Nociceptors express a broad range of receptors for ligands that can change the properties of these neurons, such that they require lower thresholds to fire action potentials or even fire spontaneously when the receptors are

engaged. These ligands include cytokines, chemokines, neuropeptides and prostaglandins,[51] which can all form part of the biochemical milieu in the OA joint. As a result of this peripheral sensitization, joint movement within the normal range becomes painful (a phenomenon known as mechanical allodynia).

It has long been known that injecting proinflammatory agents into the joint cavity sensitizes afferent neurons.[52,53] Now being established is how specific cytokines can sensitize neurons following intra-articular injection; such cytokines include TNF[54] and IL-6,[55] which cause prolonged mechanical hypersensitivity,[56] and IL-17, which sensitizes joint nociceptors to mechanical stimuli.[57] The proinflammatory cytokines IL-1β and TNF can directly affect sensory neurons and can also trigger hyperalgesia via downstream mediators such as other cytokines, chemokines, prostanoids, neurotrophins, nitric oxide, kinins, lipids, ATP and members of the complement pathway (reviewed elsewhere[51]). Nonetheless, how these processes operate in OA is still unclear.

In addition to increasing cytokine levels, inflammation enhances local levels of NGF, a major contributor to peripheral hypersensitivity.[58] Indeed, NGF has been shown to elicit a pain response following injection in humans.[59] The binding of NGF to its high-affinity receptor, TrkA, on peripheral nociceptors causes rapid potentiation of the thermosensitive ion channel TRPV1 (transient receptor potential cation channel, sub family V, member 1).[60] TRPV1 is present in a subpopulation of primary afferent sensory neurons and is activated by noxious heat and by certain chemicals, including capsaicin.[61] Sensitization of TRPV1 contributes to pain hypersensitivity associated with tissue injury.[62] In addition, NGF taken up by peripheral nerve terminals is retrogradely transported to the cell body in the DRG, where it activates the mitogen-activated protein kinase p38[63] and promotes expression of pronociceptive proteins, including substance P, TRPV1 and Nav1.8.[63,64] Mast cells also express TrkA, and NGF binding to this receptor promotes mast-cell-mediated production of a range of additional proinflammatory molecules that can potentiate its activity.[65]

NGF can be produced by articular cartilage, meniscus and synovium, and increased levels have been reported in synovial fluid from patients with inflammatory arthritis.[66–69] In a widely used surgical mouse model of OA, induced by destabilization of the medial meniscus (DMM),[70] *Ngf* mRNA was present in joint extracts immediately after surgery (day 3) and again 16 weeks post-DMM, when the mice showed signs of pain, as assessed by hindlimb weight bearing.[71] Injection of a soluble recombinant form of the NGF receptor, known as TrkAd5, suppressed pain in both phases.[71] Blockade of NGF has been shown to be efficacious in many preclinical models of pain, including joint pain in rat autoimmune arthritis.[72] However, results from studies with anti-NGF antibodies in preclinical models of OA are not available in the public domain.

Tissue damage and remodelling—Degradation and remodelling of joint tissues is the hallmark of OA pathology. In human OA and in animal models, blood vessels grow from the subchondral bone into the articular cartilage.[73,74] Fine, unmyelinated nerves (C-fibres and sympathetic nerves) accompany these vessels.[75] Moreover, this vascular and nerve growth has also been observed in the meniscus.[76] Osteochondral and meniscal

vascularization might thus be a source of arthritic pain and constitute a target for analgesic therapy.[73]

Unravelling the molecular mechanisms of nociceptor activation and sensitization in the OA joint will require more studies in animal models and patient cohorts. Scant data are available regarding the spatial and temporal changes in receptor expression on joint afferent neurons in OA. Furthermore, information on the expression and source of putative ligands that might sensitize these afferent neurons in the OA joint is also scarce. It is often noted that cartilage, as an aneural and avascular tissue, probably does not directly 'hurt'. However, degrading cartilage is potentially a major source of factors that feed into the pain machinery, including cytokines, other mediators (such as H^+ ions and adenosine) and possibly extra cellular matrix fragments. Nociceptors have been reported to express Toll-like receptors (TLRs), which are pattern-recognition receptors that recognize a variety of damage-associated molecular patterns (DAMPs) released during tissue injury and that contribute to pain generation.[77–79] In OA, no information on the role of TLRs in pain generation is available, but it has been proposed that TLRs have a role in synovitis in OA.[80,81] Thus, TLRs might contribute to pain in OA indirectly by activating synovial fibroblasts and macrophages,[80] and potentially directly by sensitizing nociceptors.

Modulation in the DRG—Neuronal cell bodies in the DRG reside alongside small satellite glial cells and macrophages, and their interactions may promote the transition from acute to chronic pain (reviewed elsewhere[82]). In the slowly progressive mouse DMM model, the expression of the chemokine CCL2 (CC-chemokine ligand 2; also known as MCP1) and its receptor, CCR2 (CC-chemokine receptor 2), was increased in DRG neurons 8 weeks after surgery, but not at an earlier time point.[83] This increase was accompanied by the infiltration of macrophages into the DRG and by the onset of pain behaviours.[83] *Ccr2*-null mice did not develop these pain behaviours, and showed no macrophage infiltration in the DRG.[83] DRG infiltration by macrophages also correlated with pain-related be haviours in rats with antigen-induced inflammatory arthritis.[84] Evidence is growing that in the DRG, glial cells, neurons, and immune cells form an integrated network in which reciprocal signals dynamically modulate pain.[82] However, in the context of OA or preclinical OA models, very little is known about the contribution of these DRG phenomena to chronic pain.

Central sensitization: spinal mechanisms

Central termini of afferent neurons enter the dorsal horn of the spinal cord and make their first synapse with interneurons or projection neurons (Figure 1b). Continued nociceptor input can lead to prolonged hyperexcitability of pain circuits in the CNS, a phe nomenon known as central sensitization.[16] Many mechanisms contribute to central sensitization (reviewed in detail elsewhere[85]). Cellular processes involved are increased neuronal membrane excitability, synaptic facilitation, and disinhibition.[85] Glial cells (microglia and astrocytes) also have a role in this process.[86] Overall, central sensitization is the result of tremendous plasticity of the CNS, and it leads to increased spontaneous neuronal activity, reduced activation thresholds, and expansion of the receptive field, and is manifested as hyperalgesia (increased sensitivity to noxious stimuli) and allodynia (the interpretation of non-noxious stimuli as painful), even in areas outside the initial trigger zone.[16]

Central sensitization thus contributes to the lack of direct correlation between nociceptor activation and the pain experience, and this phenomenon is characteristic of chronic pain. Mounting evidence suggests that central sensitization phenomena are integral to OA pain. Indeed, several papers have reported tactile allodynia and lowered pain thresholds in OA.[87–89] More recently, quantitative sensory testing has been more systematically explored in patients with OA. Findings have been extensively reviewed by Suokas *et al.*,[17] who concluded that patients with OA display reduced pressure pain thresholds in both affected and unaffected sites.

Thus, central sensitization might contribute to the apparent disconnect between structural changes and pain. Indeed, a study reported that central sensitization in knee OA is especially apparent among patients with high levels of clinical pain in the absence of moderate-to-severe radiographic evidence.[90] The exact mechanisms of central sensitization in OA are not known. However, as discussed, central sensitization occurs through plasticity of the CNS. Abnormalities in somatosensory perception are reversible after successful surgery or joint replacement, as reported for hip OA[89] and knee OA.[91] This reversibility further underlines the plasticity of the CNS and, mechanistically, implies that central sensitization is maintained by peripheral input from the joint.

Ascending pathways and supraspinal processing

From the dorsal horn, projection neurons relay pain signals to the thalamus and the brainstem, and onwards to higher brain centres (Figure 1c). The manner in which these signals are then processed differs substantially not only between acute and chronic pain but also among different chronic pain states. Indeed, neuroimaging studies of conditions such as chronic back pain, OA, post-herpetic neuropathy and pelvic pain all show distinct patterns of brain activity to either evoked or spontaneous pain; these conditions are particularly distinguished from acute pain by enhanced activation of the prefrontal cortex, an area of the brain engaged in emotional behaviour.[92] A study in 14 patients with knee OA and 9 healthy controls revealed a dissociation between mechanically induced and spontaneous OA knee pain, the latter engaging brain regions involved in emotional assessment of the self.[93] Thus, it can be concluded that spontaneous chronic pain involves emotional (affective) conditioning, and this verdict applies to chronic knee OA pain too.[93,94] Brain anatomical changes, including loss of regional brain grey matter, have also been defined in chronic pain states.[95,96] Interestingly, in OA, these anatomical changes have been shown to be reversible,[96] reflecting brain plasticity. Associated with these anatomical changes are alterations in established brain functional networks (for example, the default mode network), which might reflect the importance of the alterations in functional connectivity observed in chronic pain states.[97] Using these techniques, it might become possible to identify brain circuitry that identifies patients who are more prone to developing chronic pain, permitting better targeting of therapeutic interventions.[98]

In the past few years, attention has focused on a number of cortical and subcortical areas for their role in pain processing and the development of chronic pain states. In addition to the well-described anatomical changes in regional brain grey matter volume associated with chronic pain, changes in functional connectivity between cortical and subcortical areas have

been defined that are important for pain chronification. In a longitudinal study of people with subacute lower back pain, which compared those whose pain persisted after 1 year with those who recovered, brain functional reorganization was shown to be coupled with grey matter changes and the persistence of pain.[99] In this setting, functional connectivity between the nucleus accumbens and the medial prefrontal cortex was increased in individuals with persistent pain and, when assessed independently, was a predictor at baseline for the development of chronic pain. The nucleus accumbens is part of the mesolimbic system involved in emotion-driven reinforcement learning, and this learning circuitry is known to have a role in pain chronification.[99] Thus, agents that target this and related pathways might provide an effective approach to pain management.

Descending pathways

In addition to the ascending pain pathways, descending pathways operate in the CNS, and these pathways can either facilitate or dampen pain.[100,101] Descending signals come from the hypothalamus, amygdala and rostral an terior cingulate cortex, and radiate to the peri-aqueductal grey (PAG) in the midbrain and the rostral ventro medial medulla (RVM) in the brainstem. Neurons project from the RVM to the dorsal horn of the spinal cord and directly or indirectly enhance or dampen nociception. Descending inhibitory pathways modulate the response to pain through the release of noradrenaline and serotonin (also known as 5HT) (Figure 1c). RVM neurons are opioid sensitive, and engagement of descending inhibition by morphine accounts for a part of its analgesic effects (Figure 1c).

Conditioned pain modulation (CPM; formerly known as diffuse noxious inhibitory control) is a serotonergic mechanism, active in healthy individuals, whereby applying a noxious stimulus at a remote site inhibits pain at the initial site of pain.[102] In patients with OA, as in many chronic pain sufferers, CPM is defective.[103,104] However, this mechanism seems to be restored after successful surgery, when patients are in a pain-free state,[103,104] which provides further evidence that chronic peripheral input maintains chronic pain-associated changes in the CNS.

Management options

Guidelines and/or recommendations for the management of OA have been updated and published by a number of professional groups, including the ACR,[105] American Geriatrics Society,[106] EULAR,[107,108] UK National Institute for Health and Clinical Excellence,[109] American Academy of Orthopaedic Surgeons[110] and Osteoarthritis Research Society International (OARSI),[3] among others. All of these sets of recommendations are based on results from existing clinical trials, which vary greatly in methodological rigour and quality, and they also include expert opinion to varying degrees. None of these recommendations is mechanism-based or gives substantial consideration to which part of the pain pathway might be modulated by treatment.

A wide variety of interventions have been evaluated in the management of OA, with greatest attention focused over the years on the effects of weight loss, exercise, acupuncture, nutraceuticals, paracetamol, NSAIDs, opioids and other centrally-acting drugs (such as antidepressants, and particularly SNRIs), as well as intra-articular therapy with

glucocorticoid and hyaluronan preparations. The following discussion focuses on clinical data and pathophysiological correlates for three therapeutic approaches—NSAIDs, SNRIs and antibodies to NGF—to highlight how study of these agents has improved our understanding of pain mechanisms in OA.

NSAIDs

Clinical studies of NSAIDs have repeatedly demonstrated their efficacy, compared with placebo, in relieving pain and increasing function in people with OA.[111,112] Their dose–response curve seems to be reasonably flat with regard to pain relief, such that only numerical and not statistically significant differences can be demonstrated for different doses of the same NSAID.[113] Nevertheless, high doses are generally regarded as more efficacious and in clinical practice tend to be used to treat greater degrees of pain. However, only low doses of NSAIDs (specifically naproxen, ibuprofen and ketoprofen) are approved for sale without prescription in the USA to treat musculoskeletal pain for limited periods of time. Despite the widespread use of these drugs, their overall efficacy is remarkably limited. The effect size for NSAIDs in a recent OARSI meta-analysis (n = 14,523) was reported as 0.29 (95% CI 0.22–0.35),[3] which signifies a small-to-moderate effect. More clinically meaningful is the evaluation of responders; that is, the percentage of patients meeting a pre-specified threshold of pain relief, often in the range of a 20–50% decrease in pain from baseline.[114–116] This analysis permits the determination of the number-needed-to-treat (the number of patients who need to be treated for one to benefit), which can be more easily translated to the clinical setting than other measures of efficacy, such as effect size, mean change in WOMAC (Western Ontario and McMaster Universities Arthritis Index) or VAS pain scales. For NSAIDs, the number-needed-to-treat has not typically been reported in OA studies, but the values available are in the range of 3–5.[117]

Difficulty tolerating NSAID treatment owing to adverse effects including dyspepsia, nausea, vomiting, diarrhoea and rash is a common reason to discontinue use of these drugs, surpassing lack of efficacy in many reports.[3] Serious NSAID-related adverse events—namely gastrointestinal bleeding and an increased incidence of myocardial infarctions—have resulted in a reassessment of how extensively, with which co-therapies and in which populations these drugs should be used. Individuals with a history of gastrointestinal ulcers or pre-existing cardiovascular disease should be treated with NSAIDs only if other therapies are not effective or appropriate, and only then with caution.[105] The concomitant administration of gastroprotective agents has been shown to be effective at reducing the incidence of peptic ulcers.[118] Whether aspirin co-therapy has a clinically meaningful effect on the thrombotic risk associated with NSAID use is not clear;[119] however, data support a specific pharmacodynamic interaction between aspirin and ibuprofen, such that the beneficial anti-platelet effect of aspirin is significantly inhibited.[120] This interaction is not seen with some other types of NSAID, namely selective cyclooxygenase 2 (COX2) inhibitors and diclofenac.[121] These findings have led to the recommendation by the FDA that individuals on cardioprophylactic doses of aspirin requiring NSAID treatment carefully time the administration of both these drugs or consider treatment with either an analgesic that does not interfere with the anti-platelet effect of low-dose aspirin or a non-NSAID

analgesic.[122] Nevertheless, NSAIDs in general are and can be used safely in large numbers of individuals with OA, providing meaningful clinical benefit.

How do NSAIDs reduce pain in OA, and can our understanding of these mechanisms help to explain the limited efficacy reported? NSAIDs are potent inhibitors of the COX enzymes in humans, and thereby reduce the production of prostaglandins.[123] Prostaglandins effectively sensitize peripheral nociceptors to painful stimuli, resulting in increased sensitivity to pain.[124] In OA, considerable evidence shows that inflammatory processes known to result in prostaglandin production occur in the synovium, bone and surrounding joint tissues.[125] Hence, in OA, NSAID activity might be based on the ability of these drugs to downregulate the peripheral production of neural sensitizers. In addition, it is now recognized that COX2 expression is upregulated in painful states not only in the periphery but also in spinal cord neurons;[126] thus, NSAIDs, which can cross the blood–brain barrier, might also have a role centrally in modulating the pain response. Indeed, pilot data have demonstrated a relation ship between cerebrospinal fluid COX2 inhibitor levels and change in pain after NSAID treatment in patients with OA.[93] Thus, NSAIDs might have dual sites of action, inhibiting the sensitization of peripheral nociceptors as well as acting centrally at the level of the spinal cord and brain (Figure 1a,b).

SNRIs

In contrast to early antidepressant drugs, which were selective serotonin reuptake inhibitors (SSRIs), newer antidepressants, including duloxetine, venlafaxine and milnacipran, inhibit both serotonin and noradrenaline reuptake in the CNS and have shown efficacy in the treatment of major depressive disorder and general anxiety disorder.[127] Subsequent clinical trials with duloxetine also demonstrated its efficacy in reducing pain levels in patients with diabetic peripheral neuropathy as well as in individuals with fibromyalgia.[128,129] Most recently, duloxetine has been shown to reduce pain in individuals with chronic back pain and in those with OA,[130–132] leading to its approval in the USA by the FDA for the treatment of chronic musculoskeletal pain. In these OA and back pain studies, duloxetine at 60 mg twice daily resulted in statistically significant pain relief when used as either a monotherapy or an adjunctive therapy to existing analgesics, and titration to a higher dose did not result in greater efficacy.[130–132] The magnitude of pain relief reported was similar to that observed for NSAIDs, and use of duloxetine in the OA study population resulted in the expected, known adverse effects of the drug, including an increase in blood pressure and heart rate, elevated liver function tests, nausea, dry mouth, fatigue, constipation, dizziness and increased sweating.[133] Duloxetine offers an alternative to opioids for patients who are not able to take NSAIDs or who have a sub optimal response to NSAIDs and require adjunctive therapy. No head-to-head trials of duloxetine versus opioids or NSAIDs have been reported, so the relative efficacy, tolerability and safety of these drugs are not known.

As described above, duloxetine is thought to work by increasing local brain levels of serotonin and noradrenaline. The reduction in pain observed with duloxetine treatment has been ascribed to an increase in the tonic activity of the descending inhibitory pain pathways in the CNS (Figure 1c).[100] Data on the pain-relieving effects of other SNRIs are sparse, although venlafaxine and milnacipran have been reported to be effective in some studies of

fibromyalgia and neuropathic pain.[134,135] No studies with these agents in musculoskeletal pain have been reported. The efficacy of duloxetine, a drug with activity in the CNS, in patients with OA supports the concept that OA pain pathways can respond to modulation within the CNS. This concept thus provides the rationale for targeting central pain pathways in the t reatment of OA pain.

Antibodies to NGF

Early clinical studies with antibodies to NGF in patients with OA, first reported in 2005,[136] demonstrated the potential efficacy of this approach to treatment and led to a larger and more definitive phase II study of tanezumab (n = 450).[10,136] This study provided clear data regarding the efficacy of this novel approach for reducing pain levels in OA, with a dose-dependent response evident for both efficacy and safety. Mean knee pain on walking was reduced by 45–62% with various doses of tanezumab as compared with 22% with placebo (P <0.001). The OMERACT–OARSI responder rate ranged from 74% to 93% in the tanezumab-treated groups versus 44% with placebo (P <0.001). The most common adverse effect possibly related to tanezumab treatment was paresthesias, reported in 7% of those treated. Several large phase III studies were then initiated with tanezumab,[137–141] which confirmed the phase II efficacy data but also found an unexpected incidence of what seemed to be an accelerated OA process. This adverse event was much more common in study participants taking concomitant NSAIDs and was primarily limited to joints already affected by OA, leading to TJR in some patients.[141] Because such findings were reported not only with tanezumab but also with other anti-NGF monoclonal antibodies in development,[141] all clinical studies were put on hold by the FDA to allow further evaluation. An FDA advisory panel met in 2012 to review the data and concluded that additional clinical trials were warranted and could be undertaken with appropriate risk evaluation and mitigation programmes in place.[141]

A role for NGF in the pain pathway has been clearly demonstrated (see above) and, hence, reducing NGF levels is a rational approach to modulating pain. The mechanism(s) involved in NGF activity in pain have been extensively studied (see discussion above and elsewhere[142,143]). From a mechanistic perspective, what is important to note is that antibodies to NGF do not cross the blood–brain barrier and therefore function entirely in the periphery. The fact that a substantial subset of individuals report complete or almost complete pain relief after treatment with tanezumab, whereas others have little relief, supports the possibility that differing pain mechanisms are important in different individuals. Thus, further study of pain phenotypes might enable a more rational use of such targeted interventions.

Unresolved issues and clinical challenges

The clinical presentation of OA is heterogeneous, affecting different types and numbers of joints to varying degrees and resulting in pain that can be intermittent or persistent and can fluctuate with activity and in response to other external factors. The question arises as to whether, despite this heterogeneity of clinical presentations, it might be possible to define specific subsets of patients with OA on the basis of the pathophysiology of their pain, leading to a more focused and rational approach to therapeutic intervention.[16] From the

evidence discussed above, a defined group of patients with OA exists in whom central sensitization can be identified and in whom, presumably, this process might have a considerable role in their pain. The obvious next step would therefore seem to be to ask whether such patients are differentially responsive to centrally acting agents (such as SNRIs) versus peripherally acting agents (such as anti-NGF antibodies). Furthermore, we know from clinical trials of both SNRIs[133] and antibodies to NGF[137] that some individuals show a marked decrease in pain in response to treatment, whereas others have little or no response. It could be presumed that those individuals who are SNRI responders are those in whom central sensitization plays a more prominent part in pain potentiation and maintenance, whereas the pain of non-responders might be a consequence of a more purely acute, nociceptive type of pain input. The opposite might be the case for the pain response to anti-NGF antibodies[137]: responders have pain that is primarily peripherally driven, whereas non-responders have more central sensitization, which might have become less dependent on peripheral input for its maintenance. Further studies using these pharmacological agents as tools will help to answer questions such as these.

Maintenance of central sensitization in the apparent absence of peripheral input might also explain the finding that some patients report continued pain after what is an apparently technically successful TJR. Persistent pain occurs in 10–20% of patients following such surgery,[144,145] with no explained aetiology. The magnitude of pain preoperatively is known to be a risk factor for poor outcome,[146,147] whereas an inverse relationship between preoperative radiographic severity and postoperative pain after TJR has been reported.[148] These data might point to the presence of a peripheral pain generator that is distinct from that typically observed in OA and that is not affected by joint replacement surgery. In addition, it is possible that, in a minority of indivi duals with long-standing chronic pain, irreversible changes in neural pain networks can occur. Whether such changes are related to the phenomenon that has been termed central sensitization is unknown. Variations exist in sensitivity to pain between individuals, and this variation might be genetically determined.[149] Several genetic association studies in patients with symptomatic OA have been reported,[150–155] but information on the genetic effect on OA pain is rather limited so far (Table 1). Nonetheless, in addition to potentially enabling the stratification of patients with OA, future genetic studies might shed light on molecular pathways of pain genesis in OA.

Conclusions

Current evidence supports the idea that OA pain is generated and maintained through continuous nociceptive input from the arthritic joint. During the progression of OA, chronic pain is modulated at different levels in the periphery and the CNS. Future research in human OA and in disease-specific animal models should enable us to elucidate how these cellular and molecular mechanisms operate at different stages of OA. This understanding should offer tremendous opportunity for targeted and safer analgesic intervention—perhaps tailored to subsets of patients depending on the stage of OA, the presence of central sensitization or the genetic makeup of the individual.

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Key points

- Current evidence supports the idea that osteoarthritis (OA) pain is generated and maintained through continuous nociceptive input from the joint
- Chronic OA pain is associated with changes in the central nervous system (CNS); these changes are reversible, reflecting the plasticity of the CNS and the requirement for continuous input from the periphery
- Antibodies to nerve growth factor, which do not cross the blood–brain barrier and therefore act entirely through effects in the periphery, are effective at relieving OA pain
- OA pain pathways can also respond to modulation centrally, as exemplified by data from OA pain trials with duloxetine, thus offering opportunity for the identification of new targets for pain relief
- Heterogeneity in the clinical presentation of OA pain and in the response to analgesic therapies suggests that, in the future, distinct mechanism-based therapeutic approaches could be tailored to specific subsets of patients

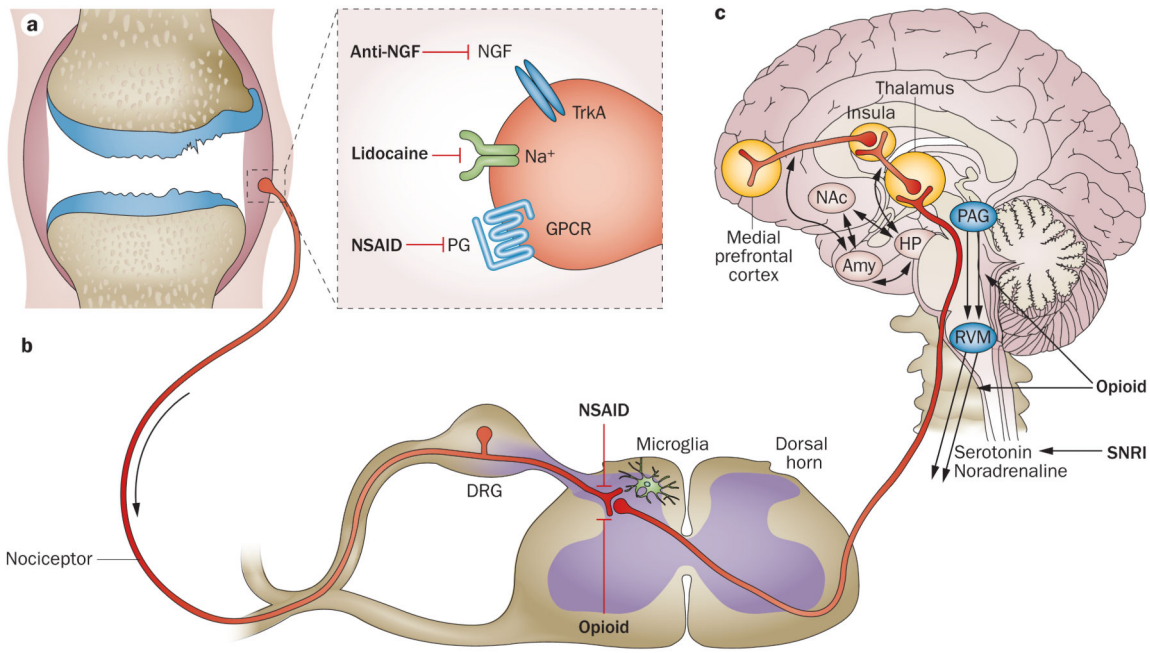

Figure 1.

Neuroanatomy of the pain pathway and analgesic targets in OA. **a** | Pain signals are detected by nociceptors in the periphery and carried to the dorsal horn of the spinal cord. Various analgesics that are efficacious against joint pain act in the periphery by targeting receptors expressed at nociceptor peripheral terminals. **b** | The central terminals of the afferent nociceptors synapse with second-order neurons in the dorsal horn, in a stratified pattern that is anatomically very precisely organized. Second-order neurons are either interneurons (not shown) or projection neurons that cross to the contralateral side and carry the signal up the spinal cord. Central sensitization can occur through the strengthening of synapses and through the loss of inhibitory mechanisms. In addition, the activation of microglia contributes to enhanced pain sensitivity. Prostaglandins can also have a sensitizing effect in the dorsal horn, and NSAIDs can thus exert central analgesic actions, in addition to their peripheral actions. Opioids can inhibit incoming pain signals in the dorsal horn. **c** | Projection neurons relay pain signals along the spinothalamic tract to the thalamus, and along the spinoreticulothalamic tract to the brainstem. From there, the signals can be propagated to different areas of the brain, including the cortex. Descending pathways (black arrows), both facilitating and inhibitory, modulate pain transmission; descending inhibitory pathways release noradrenaline and serotonin onto the spinal circuits. SNRIs engage these descending inhibitory pathways. RVM neurons are opioid sensitive, and morphine has an analgesic effect through engaging descending inhibition. Abbreviations: Amy, amygdala; DRG, dorsal root ganglion; GPCR, G-protein-coupled receptor; HP, hippocampus; NAc, nucleus accumbens; NGF, nerve growth factor; PAG, peri-aqueductal grey; PG, prostaglandin; RVM, rostral ventromedial medulla; SNRI, serotonin–noradrenaline reuptake inhibitor.

Table 1

Genetic association studies of pain responses in OA

Gene	Encoded protein	Variant	Cohort	Association	Reference
TRPV1	TRPV1	585 Ile–Ile*	Multiple OA cohorts (3,270 symptomatic knee OA cases, 1,098 asymptomatic cases, 3,852 controls)	This variant (which has also been associated with reduced thermal pain sensitivity) was associated with a reduced risk of symptomatic knee OA	Valdes *et al.*[150]
PCSK6	PACE4	Noncoding	Multiple OA cohorts (2,068 symptomatic knee OA cases, 674 asymptomatic cases)	Associated with protection against pain in knee OA	Malfait *et al.*[151]
P2RX7	P2X7	Hypofunctional Arg270His variant (impaired pore formation)	One OA cohort (743 cases, 586 controls)	Associated with reduced pain intensity	Sorge *et al.*[152]
COMT	COMT	Reduced activity Val158Met variant	One OA cohort (n = 171)	Associated with increased pain	van Meurs *et al.*[153]
SCN9A	Nav1.7	Arg1150Trp variant is predicted to have increased activity	One OA cohort (n = 578) Multiple OA cohorts (n = 1,854)	Associated with higher pain scores No association with OA pain‡	Reimann *et al.*[154] Valdes *et al.*[155]

*An amino acid variant, Ile585Val, of TRPV1 has been reported to be associated with thermal pain sensitivity, with the Ile–Ile genotype corresponding to lower sensitivity to cold pain.

‡This variant was significantly associated with an increased risk of chronic widespread pain (CWP), which might imply that different mechanisms operate in CWP and in OA.[155] Abbreviations: COMT, catechol O-methyltransferase; Nav1.7, voltage-gated sodium channel subunit α Nav1.7; OA, osteoarthritis; P2X7, P2X purinoceptor 7; PACE4, paired basic amino acid cleaving enzyme 4; TRPV1, transient receptor potential cation channel, subfamily V, member 1.