RHEUMATOLOGY

Rheumatology 2011;50:2157–2165
doi:10.1093/rheumatology/ker283
Advance Access publication 27 September 2011

Review

What makes osteoarthritis painful? The evidence for local and central pain processing

Nidhi Sofat[1], Vivian Ejindu[2] and Patrick Kiely[1]

Abstract

OA is a chronic arthritic disease characterized by pain, local tissue damage and attempts at tissue repair. Historically, cartilage damage was believed to be the hallmark of OA. However, since cartilage is an avascular, aneural tissue, the mechanisms of pain are likely to be complex and influenced by non-cartilaginous structures in the joint including the synovium, bone and soft tissue. Imaging studies reveal the presence of synovitis and bone marrow lesions that may mediate pain. The presence of local joint inflammation and altered cartilage and bone turnover in OA implicates a potential role for a range of molecular mediators in OA pain. Mechanisms of pain perception may include the activation and release of local pro-inflammatory mediators such as prostaglandins and cytokines accompanied by the destruction of tissue, which is mediated by proteases. However, clinically, there is often disparity between the degree of pain perception and the extent of joint changes in subjects with OA. Such observations have prompted work to investigate the mechanisms of central pain perception in OA. Functional MRI has identified multiple areas of the brain that are involved in OA pain processing. These data demonstrate that pain perception in OA is complex in being influenced by local factors and activation of central pain-processing pathways. In this review, we will discuss current concepts underlying the pathophysiology of pain perception in OA and suggest possible directions for the future management of pain in this condition based on recent clinical studies.

Key words: Osteoarthritis, Cartilage, Bone, Synovium, Brain, MRI, Ultrasonography, NSAIDs, Intra-articular agents, Pain assessment and management.

Introduction

OA is the commonest form of arthritis worldwide, affecting growing numbers of people in our ageing populations. The commonest joints affected are large weight-bearing joints, such as the hip and knee, and smaller peripheral joints, including the hands [1]. OA affects at least 50% of people >65 years of age, and occurs in younger individuals following joint injury. This figure is set to rise with increases in obesity and the ageing of our population. The disease is characterized initially by cartilage degradation, which often precedes changes in the underlying bone. Patients largely present with pain and disability after significant loss of cartilage has occurred, but it is estimated that up to 40% of individuals with radiological damage have no pain [2]. There are currently no disease-modifying agents for OA, hence management is by physical approaches, pain relief and surgical joint replacement in suitable individuals. Pain is the main reason for presentation of OA patients to clinical services. However, despite treatment with conventional analgesic drugs, most subjects with OA continue to experience pain. There is, therefore, an unmet need to gain a deeper understanding of pain pathways in this condition.

Historically, OA has been described as a primary disorder of cartilage. Although there is loss of tissue components in OA, there is also production of new tissue, including fibrocartilage and attempts by the cartilage to regenerate as evidenced by increased protein synthesis by chondrocytes, especially in the early stages of disease. Such changes are accompanied by joint remodelling. Therefore, OA has been regarded as a hypertrophic arthritis (with RA as an atrophic arthritis), emphasizing that new tissue production and remodelling are characteristic features. Imaging studies in OA joints have shown that joint inflammation occurs in OA and is influenced by local structures including ligaments, bones, tendons and effusions [3]. Studies using US and MRI have demonstrated that synovitis and bone marrow oedema are

[1]Department of Rheumatology and [2]Department of Radiology, St George's Hospital, London, UK.

Submitted 2 June 2011; revised version accepted 8 July 2011.

Correspondence to: Nidhi Sofat, Department of Biomedical Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, UK. E-mail: nsofat@sgul.ac.uk

important factors contributing to pain in OA. More recently, neuroimaging has provided evidence of the contribution of the central brain network to pain perception in OA.

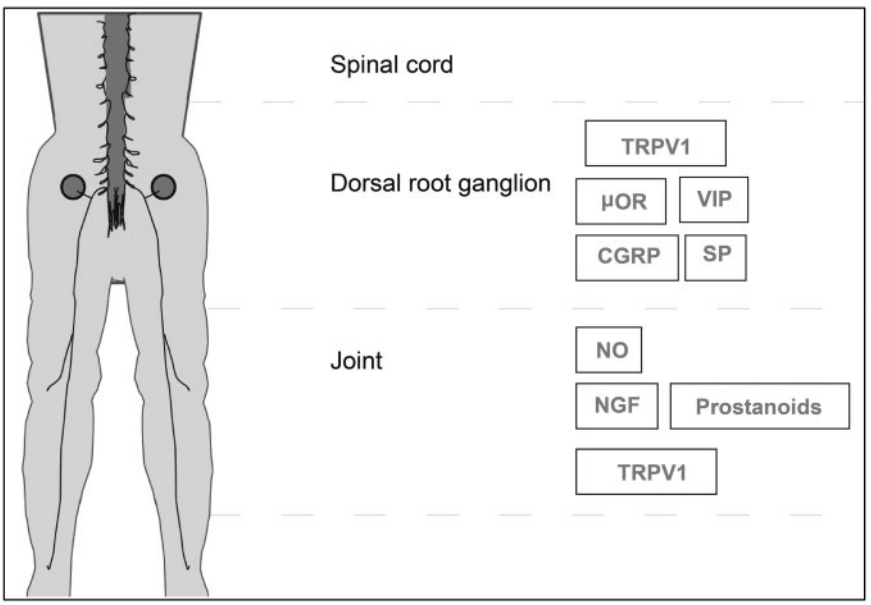
The main factors that we will consider with respect to OA pain in this review are: current understanding of the molecular pathways for pain mediation; how imaging techniques including MRI and US have helped to understand pain perception; and a review of the emerging data for central pain processing from clinical studies. Finally, we will relate how the data available can be applied to understanding potential therapeutic targets for the treatment of OA pain in the future.

Molecular pathways in OA pain

Recent developments have led to an improved understanding of pain pathways at the molecular level [4]. There is undoubtedly activation of local pain perception phenomena in the most common arthritides including OA and RA. An important consideration is that the pain experience in OA is probably no different from many other chronic conditions that are associated with peripheral tissue injury and repair. In this review, we will review the physiology of pain in OA and highlight how it is characterized by ascending processes and descending inhibition, often mirrored in other inflammatory and non-inflammatory joint conditions. Such observations emphasize that such features observed in OA are likely to be generalized to other joint conditions.

Historically, cartilage loss with accompanying bone changes such as osteophytes, sclerosis and cysts have been described as the hallmark lesions in OA [7]. More recent work has shown that not only do changes in cartilage in the OA joint include chondrocyte cell death and loss of cartilage extracellular matrix [8], but also there is production of new tissue including fibrocartilage and attempts by tissue to regenerate, e.g. increased protein synthesis and attempts at cartilage matrix repair by chondrocytes [8]. In normal physiology, cartilage is an avascular and aneural tissue, and thus pain mediation may well be arising from other joint structures. As ongoing joint destruction occurs in OA, features observed in the surrounding bone include osteophyte formation, which may impair joint mobility and induce pain by impinging on other local joint structures. Additional potentially relevant features include bone sclerosis and subchondral cysts. Physiological mechanisms of pain operate at the local joint level, the dorsal root ganglion (DRG) level and higher brain processing centres. Several pro-inflammatory mediators may be recruited into the OA joint associated with damage, including nerve growth factor (NGF), nitric oxide (NO) and prostanoids [11, 12] (Fig. 1). These inflammatory mediators cause localized damage to tissues, such as synovium, as well as activating peripheral nociceptors. During chronic disease, the nociceptive system can become sensitized, leading to a heightened sensitivity to noxious stimuli (hyperalgesia) [5], and to pain in response to non-noxious stimuli (allodynia) [6]. The activation of these nociceptors is subsequently transmitted via the DRG, up through the spinothalamic tract to higher cortical centres where signals are processed and perceived as pain. Mediators of pain at the DRG level in OA are believed to include NGF, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), vanilloid receptor 1 (TRPV1) and opioid receptors (ORs). Transient receptor potential cation channel subfamily V member 1 (TRPV1) is also known as vanilloid receptor 1 and the capsaicin receptor. Chemical mediators of pain in the brain include

Fig. 1 Molecules implicated in pain mediation in OA at the joint and DRG level. SP: substance P; μOR: μ class opioid receptor.



agents such as substance P, serotonin and glutamate [15]. These are illustrated in Fig. 1.

Recent reports have also suggested that growth factors are implicated in neovascularization in the OA joint. Specifically, VEGF and PDGF are important mediators of blood vessel growth. Previous literature describing observations that cartilage is entirely avascular and aneural has recently been challenged, suggesting that modifications occur during OA disease. Walsh *et al.* [13] have shown VEGF expression in OA chondrocytes and increased osteochondral angiogenesis in OA subjects. It has been suggested that molecules expressed by sensory nerves, e.g. NGF, may be associated with neovascularization, thereby linking osteochondral angiogenesis to pain in OA.

In addition in the joint, molecules such as prostaglandins, bradykinin and CGRP may stimulate primary sensory neurones by activating ion channel-linked receptors on the sensory afferent neurone [16]. TRPV1 can be activated in the primary sensory neuron and is heat sensitive [17]. Thus, changes in the local joint temperature may activate this receptor during chronic inflammation. Stimuli for the TRPV1 include capsaicin and acidic conditions, which can induce pain by activating polymodal nociceptive neurons [17]. Since these neurons contain VR1 (or VR1 variants) they may act as integrators of nociceptive stimuli. Upon prolonged exposure to capsaicin, TRPV1 activity decreases, a phenomenon called desensitization [18].

The CNS is an organ demonstrating plasticity in a system that has the capacity to change, e.g. following peripheral tissue damage. For example, receptor expression may be up- or down-regulated and new synapses may form within the dorsal horn. Neurones may also alter their threshold of firing. Inflammation may lead to hypersensitivity of peripheral afferent neurones. In central sensitization, there may be persistent activation of primary afferent neurons that is believed to be mediated by the *N*-methyl-D-aspartic acid (NMDA) receptor at the dorsal horn level [22]. Activation of such neurons may be influenced not only by localized noxious stimuli associated with inflammation, but structural and biochemical changes also seem to occur in the systems that perceive pain. This theory has been demonstrated by Ivanavicius *et al.* [23], who showed the variable efficacy of NSAIDs over time in a rat model of OA with the peak effect at 14 days post-injury. Beyond this time, the analgesic effect became minimal. However, throughout the time course of the experiment, amitriptyline and gabapentin remained efficacious. These results give weight to the theory that although inflammation and joint damage cause the initial trigger for pain, sustained exposure to noxious stimuli can cause neuronal plasticity and a subsequent abnormal sensation of pain, unrelated to the inflammation.

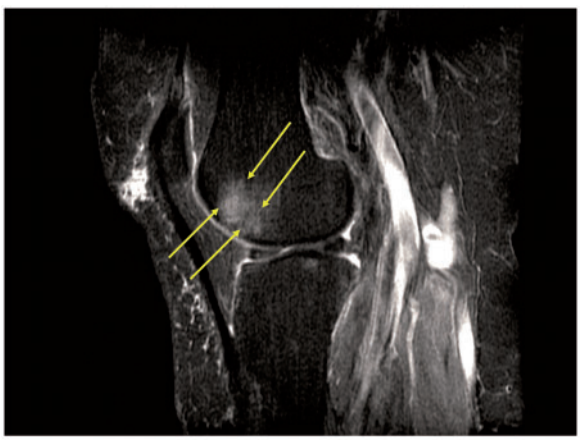
Radiological evidence for local inflammation in OA

Imaging techniques have recently provided new information to help understand mechanisms of pain perception in the OA joint. In this section, the evidence from imaging-based studies demonstrating that bone marrow lesions (BMLs) and synovitis mediate pain in OA will be discussed.

MRI is a sensitive technique, which allows the evaluation of several soft tissue structures including synovium, cartilage and subchondral bone. BMLs can often be visualized on MRI in subjects with OA (Fig. 2). For example, in one of the largest studies of its kind, BMLs were found in 272 (77.5%) out of 351 people with painful knees compared with 15 (30%) out of 50 with no knee pain ($P < 0.001$) [28]. BMLs are alterations in signal intensity, which are adjacent to the subchondral plate [24], and include bone marrow necrosis, bone marrow fibrosis, trabecular abnormalities and bone marrow oedema [25]. BMLs may appear after acute injury as a result of impact collision between the femoral condyle and tibial plateau [26]. However, BMLs can also occur in joint regions, which are subjected to chronic excess focal loading including when joints are malaligned [27]. Felson *et al.* [28] reported a study of 401 knee OA participants, 50 of whom had no knee pain. Subjects had coronal T_2-weighted fat-suppressed MRI scans and BMLs were graded 0–3 according to their size. The frequency of BMLs increased with radiographic grade of OA: 48% of Kellgren–Lawrence (KL) Grade 0 had BMLs compared with 100% of those with KL Grade 4. Additionally, BMLs were found in 78% of painful knee group compared with 30% of the non-painful knee group ($P < 0.001$). In another study of BMLs in OA subjects analysed by painful and non-painful OA groups, larger lesions ($>1\ cm^2$) were more frequent in the painful *vs* non-painful knee OA group ($P < 0.05$) [29]. In this study of women with knee OA, the participants with larger BMLs were more likely to have full-thickness cartilage defects, adjacent subcortical bone abnormalities and painful knee OA with an odds ratio of 3.2 [29].

Although much attention has been focused on BMLs, MRI studies of subjects with OA also have a number of other joint changes, which include knee effusions,

FIG. 2 MRI sagittal knee imaging showing severe OA with cartilage loss and femoral bone oedema (→ in yellow).



meniscal lesions, hyaline cartilage loss and synovitis, all at the same time (reviewed in [30]). It is, therefore, not entirely clear as to which lesions come first and whether there is a temporal sequence to the development of lesions that influence pain in OA. These issues have been addressed by the Multicenter Osteoarthritis Study (MOST) study [31, 32], which is a large prospective, longitudinal study to assess the temporal relation between MRI-detected BMLs, full-thickness cartilage loss and subchondral cysts (SCs) in the same subregion of the knee, for the evaluation of the pathogenesis of SCs in light of SF intrusion and bone contusion theories. The findings of the MOST study have demonstrated that mensical pathology is strongly associated with incident and enlarging BMLs [32] and BMLs also predict SC formation in the same region [31], thereby supporting the bone contusion theory of SC formation. Previous studies have demonstrated that BMLs and full thickness cartilage loss predict SC formation longitudinally [33]. BMLs appear to represent focal bone remodelling due to overloading, and enlarging BMLs are predictors of pain and progression of cartilage damage in OA [34]. They are, therefore, potential targets for treatment of pain in OA.

Taljanovic *et al.* [35] compared MRI features with histological findings in 19 subjects after hip replacement, demonstrating microfractures in different stages of healing and bone marrow necrosis in 100% of patients of whom 85% had bone marrow fibrosis. In contrast, only 40% of patients had small amounts of oedema. This study concluded that the amount of bone marrow oedema in the OA hip, as measured by MRI, correlates with the severity of pain, radiographic findings and microfractures.

Synovitis in OA

Synovitis is an under-appreciated phenomenon in OA, which may explain the perception of pain. Various imaging modalities including US (Fig. 3) and MRI have demonstrated that synovitis is a common subclinical phenomenon in OA-affected hands, hips and knees [37–39]. Roemer *et al.* [37] semi-quantitatively assessed synovitis using contrast-enhanced MRI and showed that 89.2% of OA-affected knees showed Grade >2 synovitis. The most common sites of detection included the posterior cruciate ligament and the suprapatellar region. Synovitis has also been shown to have a strong correlation with knee pain severity [assessed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scale] in a contrast-enhanced MRI study [39]. For knee pain, synovitis conferred a 9.2-fold increased odds ratio compared with those without synovitis (Table 1).

Evidence of central pain processing from neuroimaging studies

Recently, functional MRI (fMRI) studies have been used to investigate how the brain processes noxious stimuli in OA and the cortical location to which perception of pain is mapped (Fig. 4). fMRI measures changes in relative oxygenation of the blood in the brain during dynamic imaging

Fig. 3 US scan of the first CMC joint of a subject with OA showing evidence of synovial thickening and increased vascularity on power Doppler imaging.

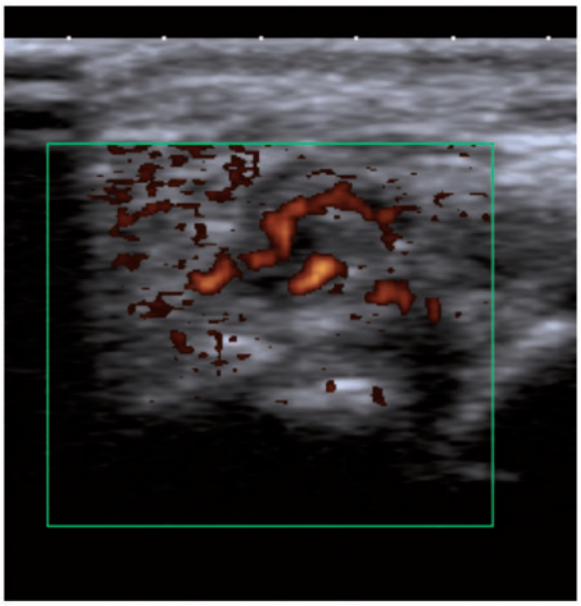
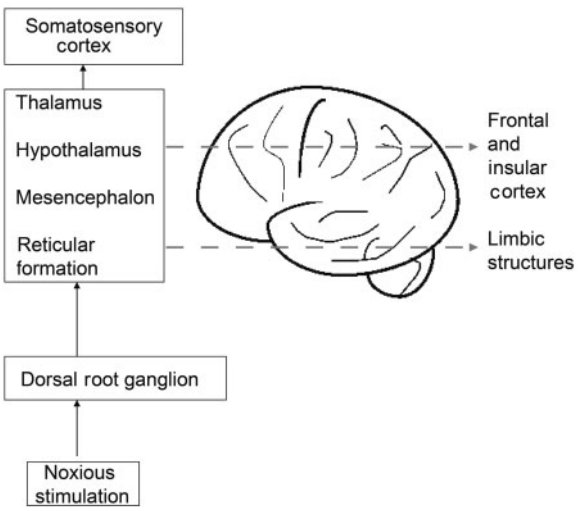


Table 1 Correlation of imaging changes with knee pain in OA

Radiological change	Odds ratio	Reference
BMLs	3.2	[29]
Synovitis	9.2	[37]

Fig. 4 Schematic diagram of central pain-processing pathways implicated in OA pain processing.



after performing functional tasks while patients are being scanned. Blood oxygen-level dependence (BOLD) is the MRI contrast of blood deoxyhaemoglobin, first discovered in 1990 by Seiji Ogawa at AT & T Bell laboratories [41]. The principles and problems of fMRI are well known [42], but it is worth highlighting a few points in relation to the experimental difficulties with regard to pain studies by fMRI. Such studies involve the use of a fast MRI method (less than a second per image slice) for which the image intensity is sensitive to the variations in magnetic field created in tissue by the presence of paramagnetic deoxyhaemoglobin. A regional increase in metabolic activity associated with performing a task or processing a stimulus, initiates a localized increase in blood flow that leads to reduced deoxyhaemoglobin levels and a small signal increase, which is a maximum of 10% even in a modern 3T clinical MRI scanner. fMRI is, therefore, a low-sensitivity measurement that generally requires that image data are averaged over several repeat measurements in individual patients, or over several patient data sets, to get reliable results. The use of paradigms with reproducible and quantifiable levels of pain stimulus are thus of great importance. fMRI data are temporally and spatially separated from the neuronal activation itself. In fMRI, the maximum blood flow change is being imaged, which occurs typically at ~5 s after the task or stimulus is initiated, and may relate to blood flow changes in arterioles displaced from the activated neurones, although this activation displacement is likely a small effect at the typical 3-mm spatial resolution of fMRI. As with all fMRI, careful paradigm design on how the pain is delivered and the data analysed and the use of appropriate control measurements are thus essential [43].

Recent work by Baliki *et al.* [44] has reported that painful mechanical knee stimulation in OA was associated with bilateral activity in the thalamus, secondary somatosensory, insular and cingulate cortices, with unilateral activity in the putamen and amygdala. These data suggest that painful stimulation in subjects with OA of the knee engages with many brain regions commonly observed in acute pain. Local treatment of the knee with lignocaine resulted in reduction of brain activity detected on fMRI in the regions described previously, suggesting that central activation of the brain mediates pain during OA. Such results also help to disentangle pain responses from anxiety or other emotional, non-painful responses. In the same study, patients who had spontaneous back pain in a cohort of patients with low back pain showed activity by fMRI in the medial prefrontal cortex, with reduced brain activation after treatment with lignocaine [44]. The regions activated in these studies of OA subjects show patterns in brain regions similar to those in touch-evoked pain (allodynia) [45] and acute pain [46].

Recent work by Gwilym *et al*. [47] using fMRI has also suggested that patients with hip OA who experience referred pain may have specific central components of activation to explain their symptoms when they are associated with neuropathic features. In their study, 20 right-handed subjects with hip OA were compared with 12 right-handed control subjects. They were assessed using recognized scales for behavioural testing, including the Beck Depression Inventory (BDI), the Pain Catastrophizing scale and the PainDETECT scale, which has been used to assess neuropathic elements of a patient's pain. Correlation of high PainDETECT scores was found with higher ratings of hyperalgesia on sensory testing and higher activation in the periaqueductal grey region compared with patients with less neuropathic symptoms and signs.

Other techniques, including PET, have been used in analysing central pain processing in OA. Using this technique, 2D or 3D images of blood flow or metabolic brain processes can be acquired. A variety or radioisotopes (e.g. ^{18}F, ^{11}C, ^{124}I) decay with the emission of a positron (a positively charged electron) and radiopharmaceuticals carrying these isotopes can be designed with specific biological activity. In tissue, the emitted positron will only travel by up to a few millimetres before encountering an electron and the two particles will annihilate and yield two high-energy photons that travel in opposite directions. A ring of scintillation detectors around the patient are designed to detect these annihilation pairs in coincidence and so reconstruct an image representing the tissue distribution of the radionuclide. ^{18}F fluorodeoxyglucose (FDG), an analogue of glucose, is commonly used for measuring tissue energy metabolism, ^{15}O in agents for perfusion measurements and other tracers have been designed to target dopamine receptors and serotonin transporters.

Kulkarni *et al.* [48] were one of the first groups to demonstrate activation of selective brain regions using FDG-PET in a cohort of patients with knee OA. The brain activity of 12 patients with OA was compared in three different states: arthritic knee pain; experimental knee pain (pin applied on an occasion when the patients were not experiencing arthritic pain); and pain free. Measurements of regional cerebral metabolic rate of glucose metabolism ($rCMR_{Glu}$) were measured in the three scenarios described. In a comparison of arthritic *vs* pain-free conditions, $rCMR_{Glu}$ was bilaterally enhanced in all areas of the brain implicated in pain processing, which included the posterior cingulated cortex, anterior midcingulate cortex, prefrontal cortex, orbitofrontal cortex and primary somatosensory cortex. In addition, unilateral activations were seen in the left thalamus, left periungal cingulated cortex, left amygdala and right supplementary motor area. In comparison, different regions of activation were observed in arthritic pain *vs* experimental pain. As the results from this study in Fig. 4 show, when compared with experimental knee pain, arthritic pain in the same knee was associated with increased activation of several areas in the limbic and motor areas. Bilateral activation was observed in the periungal cingulate, anterior midcingulate, posterior midcingulate, subungal cingulated and posterior cingulated, the amygdala and orbitofrontal cortex. The most statistically significant activations were observed in the anterior cingulated cortex, where the activation spanned from the anterior to the posterior midcingulate region. This study proposed that although arthritic pain and experimental pain activate

similar areas of the brain, arthritic pain is also associated with areas of the brain implicated in affect, aversive conditioning and motivation. These findings have important potential implications for the management of patients with long-term OA pain. The brain imaging studies described above provide deeper insights into the mechanistic processes of treatment effects, and have potential use as an anatomic and functional model for future analgesic drug development.

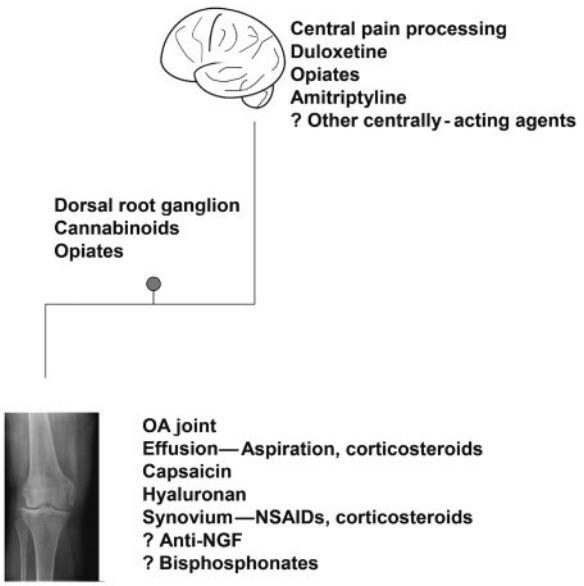
Implications for treatment of OA pain and future directions

In this review, we have outlined current understanding of the mechanisms of pain mediation locally in the OA joint based on molecular pathways and imaging studies. A number of features in the OA joint implicated in mediating pain have been outlined and include BMLs, effusions and synovitis. A summary of a logical approach for treatment of pain in OA is illustrated in Fig. 5.

Current treatments for pain continue to be focused on both the use of topical agents including NSAIDs [21] and capsaicin [19] and systemic agents including NSAIDs and opiate drugs [21]. Physical approaches, such as the application of heat or cold packs, transcutaneous electrical nerve stimulation (TENS) and capsaicin may affect molecular pathways; for example, desensitization of TRPV1 is thought to underlie the paradoxical analgesic effect of capsaicin.

The first reports of blockade of a specific molecular target with anti-NGF mAbs (in a study of knee OA) suggested that although promising analgesic effects were achieved in the short term, significant side effects were an important consideration, including paraesthesia, peripheral neuropathy and worsening arthritis [14]. There were also worsening rates of joint replacement in the treatment group, questioning whether anti-NGF therapy is viable in OA subjects in the long term. In a patient population with a chronic disease, this approach will need to demonstrate efficacy with minimal side effects in the long term, if it is to be adopted in routine care. Such results are awaited from ongoing studies of other NGF-directed therapies in development.

Fig. 5 Therapeutic options for targeting pain at different levels of the pain-processing pathway.



Therapeutic approaches targeting BMLs may include pharmacological intervention or alteration of loading. Emerging studies have demonstrated the use of bisphosphonates to target pain related to BMLs. For example, Laslett *et al.* [36] recently reported the use of a single zoledronic acid infusion for the treatment of knee pain in OA subjects associated with BML. The authors reported that participants had reduced VAS pain scores at 6 months, but not 12 months post-infusion. There was also a reduction in BML size compared with placebo, which was maintained at 12 months. It remains to be seen whether such therapies could have a sustained analgesic effect, and whether reduction of BML in the long term could influence structural progression of OA.

Data have also emerged that synovitis is a significant factor influencing pain in OA and recent work has proposed use of CSs in reducing such effects [39]. Evidence has also shown that exacerbations of OA can be associated with a synovial reaction [9]. Such changes may be amenable to treatment with anti-inflammatory drugs [10]. In hand OA, Keen *et al.* [39] showed that grey-scale hypertrophy and power Doppler synovitis are reversible with IM CS therapy [39] for up to 12 weeks. Other studies have demonstrated that in hip OA, with US-detected synovitis, treatment with CS injections had higher efficacy than saline or hyaluronan injections [40]. However, long-term CS use is not without toxicity and it may be preferable to consider trials aimed at inhibiting synovitis with disease-modifying drugs. For example, a recent open-label study reported the use of MTX for treatment of painful knee OA in subjects with radiological evidence of synovitis [49]. Further, large-scale randomized controlled trials are justified to assess the effects of DMARDs and other synovitis-directed therapies on pain and structural progression in the long term in OA.

Evidence for central pain processing in OA provides a rationale for the use of therapeutic agents that target central pain mediation pathways. For example, duloxetine, a selective noradrenaline and serotonin reuptake inhibitor, which is licensed for the treatment of neuropathic pain, has recently been shown to be effective in the treatment of OA knee pain as early as 4 weeks post treatment [50]. The analgesic effect of duloxetine was sustained at 13 weeks and associated with improvement in function [50]. These findings have also been replicated in an Egyptian population of 188 subjects with knee OA, where duloxetine resulted in a statistically significant reduction in pain compared with placebo, with additional improvement in WOMAC scores at 16 weeks [51]. Further work is warranted to investigate the effects of other centrally acting agents for the treatment of pain in OA.

At the dorsal horn level, descending inhibitory mechanisms arising from the frontal cortex and hypothalamus can alter pain stimuli [22]. This system of pain control that is endogenous to the body is mediated by opioids and cannabinoids produced within the body [20]. The production of these endogenous mediators can be enhanced by interventions such as relaxation, meditation and hypnosis and may also be accentuated in the placebo response. A number of randomized controlled trials in OA report significant improvements in outcome in placebo groups [52]. The mechanism of such placebo effects warrants further investigation and is currently not fully understood, but may be related to the observation that the process of engaging with patients themselves regarding a painful condition such as OA can have beneficial effects. Other non-pharmacological interventions including aerobic exercise have proven benefits in improving pain in OA by activating descending inhibitory pathways, and therefore should always be considered as part of multidisciplinary care in OA [53]. Many of these interventions are proposed as therapeutics, and are reflected in the National Institute for Health and Clinical Excellence guidelines for the treatment of OA [21]. Treatment of underlying depression and anxiety are also considerations, which are stated in NICE guidelines for OA management. However, although psychosocial factors cause significant comorbidity in OA [54], there are limited studies that have examined what happens to OA pain when these are treated. Such studies would provide useful information for future OA management.

In this review, we have highlighted the various steps at which intervention might occur in OA pain management based on basic science, clinical and imaging data (Fig. 5). A deeper understanding of the pain pathways involved should lead to the development of rationalized care pathways for the management of pain in OA.

In summary, this review has outlined current concepts of pain mechanisms in OA, based on molecular pathways, structural changes and the role of the peripheral and CNS. This complex pathway (Fig. 5) provides a range of potential therapeutic targets to improve pain in OA. As our understanding of the interactions in this system improves, so will the use of existing and novel therapeutic agents. Rational care pathways that make a substantial difference to pain management in OA may, therefore, not be too far away.

Rheumatology key messages

- BMLs and synovitis are associated with pain in OA.
- Pain management in OA could target BMLs, synovitis and centrally mediated pain processing.

Acknowledgements

Funding: This work is supported by the Rosetrees' Trust and St George's Charitable Trust.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Hochberg MC, Hunter DJ, Felson DT. Osteoarthritis. Br Med J 2006;332:640–2.

2 Kidd BL. Osteoarthritis and joint pain. Pain 2006;123:6–9.

3 Conaghan PG. Structural correlates of osteoarthritis pain: lessons from magnetic resonance imaging. In: Felson DT Schaible H-G, eds. Pain in osteoarthritis. New Jersey: Wiley-Blackwell, 2009.

4 Scholz C, Woolf CJ. Can we conquer pain? Nat Neurosci 2002;5:1062.

5 Bolay H, Moskowitz MA. Mechanisms of pain modulation in chronic syndromes. Neurology 2002;59:S2–7.

6 Andrew D, Greenspan JD. Peripheral coding of tonic mechanical cutaneous pain: comparison of nociceptive activity in rat and human psychophysics. J Neurophysiol 1999;82:2641–8.

7 Roy S, Meachim G. Chondrocyte ultrastructure in adult human articular cartilage. Ann Rheum Dis 1968;27: 544–58.

8 Sofat N. Analysing the role of endogenous matrix molecules in the development of osteoarthritis. Int J Exp Pathol 2009;90:463–79.

9 Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson Imag 1995;13: 177–83.

10 Sawitzke AD, Shi H, Finco M *et al*. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2 year results from GAIT. Ann Rheum Dis 2010;69:1459–64.

11 Fitzcharles MH, Almahrezi A, Shir Y. Pain: understanding and challenges for the rheumatologist. Arthritis Rheum 2005;52:3685–92.

12 Ji RR, Befort K, Brenner GJ, Woolf CJ. Erk MAP kinase activation in superficial spinal cord neurons induces prodynorphin and NK-1 upregulation and contributes to persistent inflammatory pain hypersensitivity. J Neurosci 2002;22:478–85.

13 Walsh DA, McWilliams DF, Turley MJ *et al*. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. Rheumatology 2010;49:1852–61.

14 Lane NE, Schnitzer TJ, Birbira CA *et al*. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Eng J Med 2010;363:1521–31.

15 Niisalo S, Hukannen M, Imai S, Tornwall J, Konttinen YT. Neuropeptides in experimental and degenerative arthritis. Ann N Y Acad Sci 2002;966:384–99.

16 Kidd BL, Urban LA. Mechanisms of inflammatory pain. Br J Anaes 2001;87:3–11.

17 Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a

heat-activated ion channel in the pain pathway. Nature 1997;389:816–24.

18 Tominaga M, Caterina MJ, Malmberg AB *et al*. The cloned capsaicin receptor integrates multiple pain-prodcuing stimuli. Neuron 1998;21:531–43.

19 Deal CL, Schnitzer TJ, Lipstein E *et al*. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383–95.

20 Desroches J, Beaulieu P. Opioids and cannabinoids interactions: involvement in pain management. Curr Drug Targets 2010;11:462–73.

21 NICE. http://www.nice.org.uk/nicemedia/live/11926/39557/39557.pdf (22 July 2011, date last accessed).

22 Dickenson AH, Sullivan AF. Evidence for the role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following C fibre stimulation. Neuropharmacology 1987;26:1235–8.

23 Ivanavicius SP, Ball AD, Heapy CG, Westwood FR, Murray F, Read SJ. Structural pathology in a rodent model of osteoarthritis is associated with neuropathic pain: increased expression of ATF-3 and pharmacological characterisation. Pain 2007;128:272–82.

24 Bollet AJ. Edema of the bone marrow can cause pain in osteoarthritis and other diseases of bones and joints. Ann Intern Med 2001;134:591–3.

25 Felson DT, McLaughlin S, Goggins J *et al*. Bone marrow oedema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003;139(5 Pt 1):330–6.

26 Frobell RB, Le Graverand MP, Buck R *et al*. The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. Ostearthritis Cartilage 2009;17:161–7.

27 Felson DT, McLaughlin S, Goggins J *et al*. Bone marrow oedema and its relation to progression on knee osteoarthritis. Ann Intern Med 2003;139:330–6.

28 Felson DT, Chaisson CE, Hill CL *et al*. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541–9.

29 Sowers MF, Hayes C, Jamadar D *et al*. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray defined knee osteoarthritis. Osteoarthritis Cartilage 2003;11:387–93.

30 Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormailities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70:60–7.

31 Crema MD, Roemer FW, Zhu Y *et al*. Subchondral cystlike lesions develop longitudinally in areas of bone edema-like lesions in patients with or at risk for knee osteoarthritis: detection with MR imaging – the MOST study. Radiology 2010;256:855–61.

32 Englund M, Guermazi A, Roemer FW *et al*. Meniscal pathology on MRI increases the risk for both incident and enlarging subchondral bone marrow lesions of the knee: the MOST study. Ann Rheum Dis 2010;69:1796–802.

33 Roemer FW, Neogi T, Nevitt MC *et al*. Subchondral bone marrow lesions are highly associated with, and predict subchondral bone marrow attrition longitudinally: the MOST study. Osteoarthritis Cartilage 2010;18:47–53.

34 Felson DT, Niu J, Guermazi A *et al*. Correlation of the development of knee pain with enalrging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007;56:2986–92.

35 Taljanovic MS, Graham AR, Benjamin JB *et al*. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination. Radiographic findings, and histopathology. Skeletal Radiol 2008;37:423–31.

36 Laslett LL, Dore DA, Quinn SJ, Winzenberg TM, Boon P, Jones G. Zoledronic acid reduces bone marrow lesions and knee pain over one year. In: *EULAR international Congress 2011*; OP0205.

37 Roemer FW, Kassim Javaid M, Guermazi A *et al*. Anatomical distribution of synovitis in knee osteoarthritis and its association with joint effusion assessed on non-enhanced and contrast-enhanced MRI. Osteoarthritis Cartilage 2010;18:1269–74.

38 Baker K, Grainger A, Niu J *et al*. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann Rheum Dis 2010;69:1779–83.

39 Keen HI, Wakefield RJ, Hensor EM, Emery P, Conaghan PG. Response of symptoms and synovitis to intramuscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. Rheumatology 2010;49:1093–100.

40 Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011;70:110–6.

41 Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med 1990;14:68–78.

42 Turner R, Jones T. Techniques for imaging neuroscience. Br Med Bull 2003;65:3–20.

43 Harris RE, Sundgren PC, Pang Y *et al*. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum 2008;58:903–7.

44 Baliki MN, Geha PY, Jabakhanji R, Harden N, Schnitzer TJ, Apkarian AV. A preliminary fMRI study of analgesic treatment in chronic back pain and knee osteoarthritis. Mol Pain 2008;4:47.

45 Maihofner C, Handwerker HO, Birklein F. Functional lamging of allodynia in complex regional pain syndrome. Neurology 2006;66:711–7.

46 Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms in pain perception and regulation in health and disease. Eur J Pain 2005;9:463–84.

47 Gwilym S, Keltner JR, Warnaby CE *et al*. Psychosocial and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum 2009;61:1226–34.

48 Kulkarni B, Bentley DE, Elliott R *et al*. Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum 2007;56:1345–54.

49 Wenham CYJ, Grainger AJ, Hensor EM, Conaghan PG. Methotrexate to treat painful knee osteoarthritis - an open label study. In: *EULAR International Congress, 2011*; Abstract 0115.

50 Chappell AS, Dessaiah D, Liu-Seifert H *et al*. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11:33–41.

51 Abou-Raya S, Abou-Raya A. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomized placebo-controlled trial. In: *EULAR International Congress 2011*; OP0211.

52 Lim AY, Doherty M. What of guidelines for osteoarthritis? Int J Rheum Dis 2011;14:136–44.

53 Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hoip and knee. J Sci Med Sport 2010;14:4–9.

54 Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007; 29:147–55.