Pain in osteoarthritis: A review of literature

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SAJAA 2008; 14(3): 29-33

ABSTRACT
There is a vast body of evidence to suggest that osteoarthritis is a heterogenous condition that involves not only the articular cartilage but also an adaptive response of the bone and the synovium to a variety of environmental, genetic and biomechanical stresses.[5-11] There is also growing evidence pointing towards long term potentiation as the most likely mechanism for the transition of acute nociception to a chronic pain (CP) state.

The complexity and plasticity of the nociceptive system not only serve survival needs but also provide research opportunities for pharmacologic modulation of human suffering resulting from osteoarthritis.

Introduction

Osteoarthritis (OA) has been described "as a condition characterised by use-related joint pain experienced on most days in any given month, for which no other cause is apparent".[1] The pathological changes seen in OA are characterised by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and subchondral sclerosis) and thickening of the capsule.[1] Rehman and Lane[2] in 1999 described OA as a chronic, degenerative disease associated with joint pain and loss of function. The primary problem in OA is the damage to the articular cartilage, which triggers a series of other events that culminate in pain and loss/limitation of function in the affected joint.

In *The burden of musculoskeletal conditions at the start of the new millennium* and *The global burden of disease* published by the World Health Organization (WHO), OA is ranked fourth in health impact in women and eighth in men in the Western world.[1,3] OA is estimated to affect 70% to 80% of people older than 55 years. In England and Wales, between 1.3 and 1.75 million people have symptomatic OA.[4] Over half a million people in the UK have severe knee OA, while 80 000 hip or knee replacements were performed in 2000 in the UK at a cost of £405 million. Undoubtedly, pain, which is the most prominent and disabling presentation of OA, is an increasingly important public health problem especially within an increasing aging population.[3]

The aims of this review are firstly to evaluate in physiological terms the mechanisms involved in the initiation of pain in OA and the peripheral and central mechanisms involved in pain transduction, transmission, perception and modulation. Secondly, the mechanism involved in the progression of OA pain becoming chronic pain (CP) will be reviewed.

A literature search was conducted using the keywords arthritis, pain, economic impart, nociception, hyperalgesia and long-term potentiation.

Several research papers were published in the late 1990s and 2000s detailing the results of studies conducted to establish the possible mechanisms of the pathophysiology of OA and the methods involved in the destruction of the involved joints.[5-11] In addition, several animal research papers were also published in the last decade aimed at understanding the pain processes in OA. Few human research papers are however available describing the possible physiological mechanism involved in the process of pain mechanism in OA.

This review was therefore based on a computerised search of relevant papers from 2000 to 2006 in the EMBASE/Medline database. Due to a lack of sufficient research papers on the mechanism of pain in OA and progression to CP, relevant papers outside these dates were included in the review to ensure the most up-to-date research available.

To ensure clarity and in keeping with the aims, this literature review will be divided into six sections. These include:

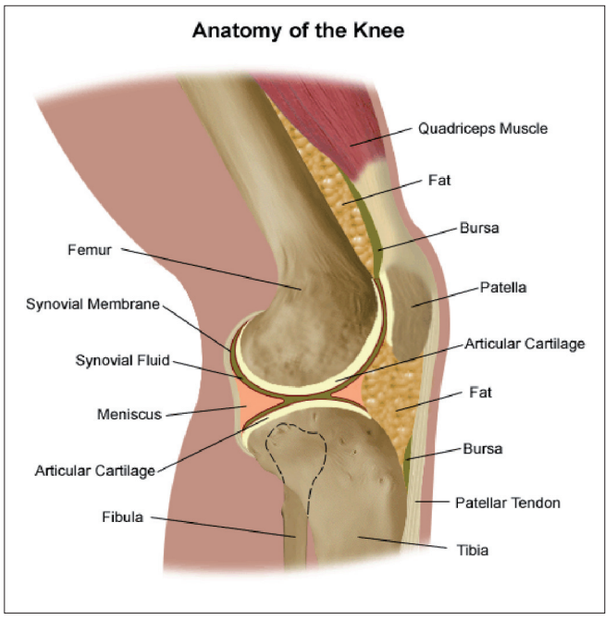
- Anatomy of the joint
- Sources of nociception in the joint
- Pathophysiology of OA
- Mechanism of pain in OA
- Progression of OA to CP
- Implications for practice

Anatomy of a joint

A brief review of the basic anatomy of a typical synovial joint is presented here to help understand the mechanisms involved in OA-induced damages of the involved joint which culminate in pain and other symptoms of OA.

A joint is where two bones meet. Articular cartilage covers the bone ends which are lubricated by synovial fluid. Seventy to eighty per cent of the cartilage is made up of water and a type II collagen with proteoglycans and glycosaminoglycans produced by chrondrocytes. The collagen fibres in the cartilage offer tensile strength to the cartilage because of its architectural makeup. The cartilage, however, contains no intrinsic blood vessels. It receives its nutrition from the synovial fluid. The synovial fluid, which is secreted by the synovial membrane lining the inner surface of the joint, facilitates not only movement but also provides nutrients, phagocytosis and other immunologic functions within the joint.[12-14] The integrity of a joint is therefore dependent upon its architecture, the cartilage, bone and the supporting structures enclosing the joint. OA in simple terms is a result of alterations in the aforementioned architectural structures within the joint with resultant pain, loss of function and instability in the involved joint. Figure 1 shows the diagram of a typical synovial joint.

Figure 1: A typical synovial joint



Sources of nociception in the joint

The term "nociception" was coined by the Nobel Laureate Sherrington to designate a physiological sensory phenomenon.[15] The term "nociception" is derived from "nocere", the Latin word for "to hurt". Nociceptors are peripheral sensory organs that are activated when nociceptive stimuli cause tissue damage. These nociceptors are unspecialised, naked nerve endings found close to small blood vessels and mast cells. The functional nociceptive unit is therefore made up of the structural triad of capillary, nociceptor and mast cell. This is the unit that is sensitive to tissue damage.[16-17]

Recent evidence[18-20] indicates that four different types of nerves innervate the joint and that there is a rich supply of myelinated and unmyelinated fibres innervating the joint capsule, subchondral bone, periosteum, ligaments and menisci. These four fibres include Type 1 (Aα), Type 2 (Aβ), Type 3 (Aδ) and Type 4 (C). A review of the neurology of joints from animal studies indicates that types 3 and 4 have been found in most joint structures, with the exception of articular cartilage.[18] Another study demonstrated that the periosteum, pad fat deep to patella, subchondral bone and joint capsule are made up of fibres containing substance P (SP).[21] SP was not demonstrated in the articular cartilage in this study. Two further studies using awake patients scheduled for arthrotomy or arthroscopy of the knee have shown that most pain-sensitive structures are located in the pad fat deep to patella, ligaments and synovium.[22-23] The cartilage was not tender in the subjects recruited for this study, suggesting that pain-sensitive fibres are not present in the articular cartilage.

In the anatomy of the joint described above, the cartilage does not contain blood vessels but derives its nutrients from the synovium. Therefore, whatever its role in the pathogenesis of joint damage, it cannot be in this tissue that OA pain originates. The subchondral bone, periosteum, synovium, ligaments, and the joint capsule contain nerve endings that could be the source of nociceptive stimuli in OA.[24-25] Irritation of the periostal as a result of remodelling, denuded bone, compression of soft tissue by osteophytes, microfractures of the subchondral bone, effusion and spasm of surrounding muscles has been shown to contribute to the pain that may be felt by patients with OA.[26]

Felson et al[27] in a cross-sectional observational study of 401 patients with demonstrable radiological knee OA found a significant ($p < 0.001$) bone marrow lesion in persons with a painful knee (77.5%) compared to 30% of persons without pain. Again large lesions were present almost exclusively in patients with knee pain compared to persons without pain ($p < 0.001$). They concluded that bone marrow lesions on MRI are strongly associated with the presence of pain in knee OA. Also, Sowers et al[28] in a study of women in their 40's with and without knee pain showed that, whereas tiny bone marrow lesions were not associated with pain, larger lesions similar to those identified by Felson et al[27] were strongly correlated with the presence of knee pain.

These two findings suggest that the bone in the periosteum and bone marrow is richly innervated with nociceptive fibres and represents a potential source of nociceptive pain in patients with OA.

Pathophysiology of OA

Significant advances have been made in understanding the pathophysiology of OA. A large body of clinical evidence has demonstrated the gradual proteolytic degradation of the joint cartilage matrix in OA. Metalloproteinases produced catalyse this process.

The synovium has also been shown to be inflamed in OA. Beside the inflammation of the synovium, the synovium has equally been linked with the production of high levels of interleukin-1 (IL-I), tumour necrosis factor-α (TNF-α) and cytokines. Cytokines and the other substances released from the cartilage, synovium and the bone invariably affect the chondrocyte function and when catabolism exceeds cartilage synthesis, OA develops. These complex series of events result in the early changes seen in OA as outlined in table I.below:

Table I: Stages of OA

Stage I	There is proteolytic breakdown of cartilage matrix
Stage II	There is fibrillation and erosion of cartilage surface, accompanied by the release of breakdown products into the synovial fluid
Stage III	Synovial inflammation begins when synovial cells ingest a breakdown product through phagocytosis and produce proteases and proinflammatory cytokines

(Martel-Pelletier, 2004)

Radiological changes in OA:
- Joint space narrowing
- Osteophytes
- Bony cysts
- Subchondral sclerosis

(Haq et al, 2003)

Inflammation pathway, which hitherto was not considered as contributory to the pathogenesis of OA, has been shown to be involved in OA. Advances in detection methods have made it possible to demonstrate that the inflammatory pathways are upregulated in OA.[29–31]

Recently, the role of nitric oxide (NO) in the pathogenesis of OA and in mechanical signal transduction has been described.[6,8,32]

Cartilage from patients with rheumatoid arthritis and OA spontaneously produces NO in vitro. In experimental OA, NO induces chondrocyte apoptosis, therefore contributing to cartilage damage. These findings suggest that unregulated NO production in humans plays a part in the pathophysiology of OA.

In addition to these structural damages in the involved joint, psychological factors, muscle weakness and comorbidities may play roles in the degree of the eventual pain felt by patients with OA.

Risk factors for OA include the following: (Kraus, 1997)
1. Age older than 50
2. Crystals in joint fluid or cartilage
3. High bone mineral density
4. History of immobilisation
5. Injury to the joint
6. Joint hypermobility or instability
7. Obesity (weight-bearing joints)
8. Peripheral neuropathy
9. Prolonged occupational or sports stress

(Kraus, 1997)

The classification of OA as primary and secondary is shown in table II. below.

Table II: Classification of OA

Primary OA	Has no known cause. Common. Related to aging and hereditary. May be localised or generalised. Commonly affects the distal interphalangeal joints of the hands, hip and the knee. The cervical and lumbar spine may be affected.
Secondary OA	Causes include articular injury, obesity, Paget's disease, or inflammatory arthritis and aging process. May be localised or generalised. May affect any joint and can occur at any age.

(Birchfield, 2001)

Mechanism of pain in OA

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[33] Pain, as generally acknowledged, is mainly a signal that the body has been injured.[34]

The processes involved in pain perception are shown in Box 1.

Tissue injury results in the release of inflammatory mediators such as serotonin, bradykinin, calcitonin gene-related peptide (CGRP) and SP, which lead to nociceptor nerve fibre sensitisation in peripheral tissue. These damaged fibres release inflammatory agents causing a spread of increased sensitivity around the area of tissue damage. This is called primary hyperalgesia. The repeated depolarisation of primary afferent fibres leads to a continuous release of neurotransmitters onto the secondary neurons in the spinal cord, resulting in central sensitisation and secondary hyperalgesia.[28,33–34]

Recent evidence indicates that peripheral pain sensitisation is a feature of osteoarthritis in the joint.[35–36] Farrel et al[35] conducted a study aimed at establishing the presence of hyperalgesia at the thumb in subjects with OA of the hand and at exploring the relationship between sensitivities to extrinsic stimuli and the experience of clinical pain. They hypothesised that in groups

Box 1: Process of pain perception

- (Jenkins, 1998; Bonica, 1985; Raja et al, 1999; Levine & Reichling, 1999)A noxious stimulus causes stimulation of nociceptors (pain receptors) in the receptor organ (e.g. joint).
- This firing of primary afferent fibres at the site of tissue injury causes axonal release of substance P (SP). This stimulation leads to activation of cells in the dorsal horn of the spinal cord and transmission of the nerve impulse to the midbrain and cortex. Thus, impulses travelling along first-order neuron synapse on second-order neuron in the dorsal horn of the spinal cord. The axon crosses to the contralateral side and ascends to synapse on the third-order neurons. The third-order neurons send fibres to the cerebral cortex where conscious perception of the sensation occurs.
- Transmission of sensory information is modulated (inhibited or potentiated) throughout the nervous system by neurons from the midbrain and spinal cord that release endogenous opioids, catecholamines and other neurotransmitters.
- Peripheral nociceptor sensitisation, which is the transmission of impulses at subnormal threshold, occurs following the release of chemical mediators such as prostagladins and leukotrienes at the site of injury or damage.
  Continued stimulation by peripheral nociceptors then leads to sensitisation of neurons in the spinal cord. This is known as central sensitisation.

(Jenkins, 1998; Bonica, 1985; Raja et al, 1999; Levine & Reichling, 1999)

with painful OA of the first carpometacarpal (CMC) pain thresholds would be lower over the thumb relative to the forearm, a regional difference that would be absent in cases without pain. In addition they proposed that among cases with symptoms, greater sensitivity at the thumb would be associated with more intense clinical pain. The major findings in the 80 subjects that underwent the psychophysical evaluation were lower thermal and mechanical pain thresholds. These were evident over the thumb relative to the forearm in the groups with persistent pain, incident as well as movement pain. Patients with only incident pain, pain-free OA patients and pain-free controls did not show any regional differences in sensitivity to thermal and mechanical pain thresholds. The findings in this study indicate that hyperalgesia over the thumb could be a consequence of spinal sensitisation and that OA in the hand is associated with local hyperalgesia, which may be mediated through the dorsal root reflexes. The authors opined that this peripheral sensitisation may be dependent on reflexes that are in turn dependent on a spinal environment that is also sensitised.

In 2003 Kidd and colleagues,[37] in their study aimed at comparing the contribution of SP to behavioural responses and inflammatory markers at serial time points in two chronic complete Freund's adjuvant (CFA) models of inflammation using NK-1 receptor knockout mice, demonstrated that mechanical hyperalgesia was significantly reduced in animals with a selective deletion of the NK-1 receptor for SP. They opined that SP, which has been showed to have important influences on inflammatory and immune cell function, may exert its peripheral pain sensitisation through mediation by nerve growth factors or cytokines.

In another study, Lindh et al[38] demonstrated increased SP-like activity in the cerebrospinal fluid (CSF) in patients with painful hips or knee OA compared to controls from the analysis of CSF samples from 11 patients. This finding has also been reported by Russell et al.[39] These findings suggest a gradual transition in OA from uncomplicated nociceptive pain to secondary sensory disturbances having similarities with observed findings in fibromyalgia.

In addition to peripheral pain sensitisation, Melzack et al[40] in their study aimed at evaluating central neuroplasticity and pathologic pain concluded that central pain sensitisation at the spinal or cortical level can occur in osteoarthritis. They suggest that pain in osteoarthritis, therefore, could be due to local and central sensitisation of pain, pathways resulting in normal stimuli becoming painful with inflammation being an important feature in the process of OA.

Most of the substances involved in inflammation such as proinflammatory cytokines and bradykinins interact with the nociceptive fibres present within the joint and induce hyperalgesia and allodynia seen in patients with chronic inflammatory joint disease like OA. These mechanisms acting in concert could participate in the progression of hyperalgesia to chronicity.

Progression of OA to chronicity

Bonica[41] defines chronic pain (CP) as pain that persists for a month beyond the usual course of an acute disease or a reasonable time period for an injury to heal.

CP differs from the acute process not only in the duration of its course but also the different receptors involved in the mechanisms of action for acute pain and CP.

Those most involved in the acute process are a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors, while those of primary importance in the sensation of CP are N-methyl-D-aspartate (NMDA) receptors.[42] Activation of NMDA receptors causes the release of peptide neurotransmitter SP, which amplifies the pain by causing the spinal neurons carrying the pain to be easily stimulated. Elevated levels of SP in spinal fluids have been documented in patients with OA and fibromyalgia.[39] The progression of nociception from an acute to a chronic process has yet to be fully understood. However, recent evidence from animal experiments as well as human research suggests that peripheral mechanisms in acute pain and long-term potentiation (LTP) of neuronal sensitivity to nociceptive inputs in the dorsal horn of the spinal cord may underline the transition from acute to a chronic process.[43–48]

LTP in spinal nociceptive systems has been suggested as one of the mechanisms underpinning the transition of acute pain to CP.

The pioneering work of Bliss and Lømo[43] and Lømo[44] showed that brief high-frequency trains of electrical stimuli resulted in increased efficiency of transmission at the hippocampus of the rabbit that could last for hours. This phenomenon was described as LTP. Recently, this observation has been extended to humans by Klein et al,[45] who suggested that the generation of LTP may be one mechanism whereby acute pain may be transformed into a CP state. It seems possible that LTP may underlie some forms of afferent induced hyperalgesia and that simultaneous activation of NMDA, SP neurokinin-I (NK-I) and glutamate receptors are required for the induction of spinal LTP.

Therefore, it is likely that the conditioning stimuli that induce synaptic LTP in the superficial spinal dorsal horn are similar to those that trigger hyperalgesia. LTP is likely to occur in both the sensory and the affective pain pathways. Additionally, spinal LTP and injury-induced hyperalgesia share signal transduction pathways, which make use-dependent LTP an attractive model of injury-induced central sensitisation and hyperalgesia.[46–48]

Extensive studies have shown that wide dynamic range (WDR) neurons are present in the deeper laminae of the spinal cord (lamina IV-VI) where nociceptive specific neurons are prevalent.[49] Studies have also shown that the deep WDR cells have the ability to code noxious and innocuous stimuli and that these neurons may play a pivotal role in transmission of painful inputs.[50]

Furthermore, in 2002 Afrah et al,[51] while using microdialysis to analyse the cerebrospinal fluid in the spinal cord, demonstrated that the release of SP is increased during the high-frequency stimuli (HFS). The result of the study indicates that SP and NK-I receptors play a significant role in the induction of LTP in the deep WDR neurons.

Svendsen et al[52,53] demonstrated that AMPA and NMDA receptor antagonists blocked the induction of LTP and NMDA receptor blockade de-potentiated the established LTP respectively. It is therefore apt to conclude that the activation of glutamate, AMPA, NMDA and the NK-I receptors is crucial to the induction of LTP in the deep WDR neurons.

Taking these data into a wider context and given the fact that LTP is considered not only as a cellular and synaptic model for memory and learning but also that LTP can be induced throughout the central nervous system, it will not be simplistic to conclude that LTP in the spinal nociceptive systems constitutes one of the most likely single cellular mechanisms to explain how acute pain may progress to CP.[54]

While the search for a broader and comprehensive understanding of the mechanism of transition from acute pain to CP continues, Brookoff[42] submits that repetitive generation of pain signals alters the neural pathways, making them hypersensitive. This pain signal becomes incorporated into the spinal cord, replaying like a needle stuck on a record. This simplifies the proposed mechanisms of a simple nociceptive input becoming persistent pain.

Implication for practice

The vast body of data and research findings over the last decade has led to a better understanding of the neurophysiology of pain. This is invariably beginning to influence clinical practice. For instance, anti-inflammatory agents that prevent or reduce peripheral sensitisation cannot be neglected as an important adjunct in comprehensive pain management. The important role of peripheral mechanisms in CP associated with chronic inflammation is suggested by the efficacy of aspirin and nonsteroidal anti-inflammatory agents, whose action is predominantly peripheral.

Again pain medication is now prescribed and given as scheduled regimens instead of the hitherto clinical practice of ordering pain medication on an as-needed basis. Furthermore, the severity of chronic pain and its associated complications have been found to be greatly reduced when more potent analgesics are started earlier.

Therefore, substantial pain control for some patients has been achieved by using sustained-release opiate preparations aimed at reducing breakthrough pain and associated adverse effects.[55] Because of the present understanding of the neurophysiology of pain and because of the findings that opiates have both peripheral and central analgesic effects, opiates are now being used in conditions such as arthritis in which they had previously been avoided.

The use of gabapentin, an effective anticonvulsant for the treatment of neuropathic pain, is due to the fact that gabapentin can enhance GABA activity and possibly prevent glutamate release.[56] Further research may provide a spectrum of agents with glutamate receptor blocking activity in the near future.

As discussed above, the windup phenomenon has become the focus of recent research in pain management with the hope of

finding a drug that will modulate this phenomenon in order to prevent its long-term sequelae. CP has been known to be modulated by noradrenaline and serotonin reuptake blocking agents. The awareness that increased concentrations of these neurotransmitters in the central nervous system inhibit pain impulse transmission has led to a search for other agents with similar actions.

The tremendous strides that have been achieved in the search for better care of patients with pain should serve as a springboard for the jump from an animal research model to an integrated care model in humans. It is hoped that integrated care and effective therapy will mitigate the long-term sequelae of persistent nociception on the central nervous system.

Conclusion

It is clear from the foregoing that any simple unitary concept about the link between joint damage and symptoms in OA is untenable. We are faced with a complex interaction between local events in the joint, pain sensitisation, the cortical experience of pain, and what people are doing in their everyday lives.

There is a vast body of evidence to suggest that OA is a heterogeneous condition that involves not only the articular cartilage but also an adaptive response of the bone and the synovium to a variety of environmental, genetic and biomechanical stresses.[5-11] There is also growing evidence pointing towards LTP as the most likely mechanism for the transition of acute nociception to a CP state.

The complexity and plasticity of the nociceptive system not only serve survival needs but also provide research opportunities for pharmacologic modulation of human suffering. Pain relief must always be viewed as humane.

CP puzzles patients because they are unable to comprehend why modern medicine cannot find a solution to their problem. To the healthcare provider CP is a frustration because the aetiology is almost unclear and satisfactory treatment is elusive.[51-55]

Carron's assertion that "minimal pathology with maximum dysfunction remains the enigma of CP"56 epitomises the challenge facing healthcare providers. **SAJAA**

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