Review

Arthritis and pain: Neurogenic origin of joint pain

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Abstract

Arthritis pain affects millions of people worldwide yet we still have only a limited understanding of what makes our joints ache. This review examines the sensory innervation of diarthroidal joints and discusses the neurophysiological processes that lead to the generation of painful sensation. During inflammation, joint nerves become sensitized to mechanical stimuli through the actions of neuropeptides, eicosanoids, proteinase-activated receptors and ion channel ligands. The contribution of immunocytes to arthritis pain is also reviewed. Finally, the existence of an endogenous analgesic system in joints is considered and the reasons for its inability to control pain are postulated.

Introduction

According to a recent report released by the World Health Organization [1], musculoskeletal disorders are the most frequent cause of disability in the modern world, and the prevalence of these diseases is rising at an alarming rate. The most prominent reason for loss of joint mobility and function is chronic or episodic pain, which leads to psychological distress and impaired quality of life. Current therapies to help alleviate joint pain have limited effectiveness and certain drugs produce unwanted negative side effects, thereby precluding their long-term use. In short, millions of patients are suffering from the debilitating effects of joint pain for which there is no satisfactory treatment. One of the reasons for this lack of effective pain management is the paucity in our knowledge of what actually causes joint pain. We are only now starting to identify some of the mediators and mechanisms that cause joints to become painful, allowing us to develop future new targets that could better alleviate arthritis pain. This review summarizes what is known about the origin of joint pain by describing the neurobiological processes initiated in the joint that give rise to neural signals and that are ultimately decoded by the central nervous system into pain perception.

Joint innervation and nociception

Knee joints are richly innervated by sensory and sympathetic nerves [2,3]. Postganglionic sympathetic fibres terminate near articular blood vessels, where they regulate joint blood flow through varying degrees of vasoconstrictor tone. The primary function of sensory nerves is to detect and transmit mechanical information from the joint to the central nervous system. Large diameter myelinated nerve fibres encode and transmit proprioceptive signals, which can be interpreted as being either dynamic (movement sensations) or static (position sense). Pain-sensing nerve fibres are typically less than 5 μm in diameter and are either unmyelinated (type IV) or myelinated with an unmyelinated 'free' nerve ending (type III). These slowly conducting fibres typically have a high threshold and only respond to noxious mechanical stimuli, and as such are referred to as nociceptors [4]. In the rat and cat, 80% of all knee joint afferent nerve fibres are nociceptive [5-7], suggesting that joints are astutely designed to sense abnormal and potentially destructive movement.

Nociceptors are located throughout the joint, having been identified in the capsule, ligaments, menisci, periosteum and subchondral bone [8-13]. The most distal segment of type III and type IV afferents is devoid of a myelin sheath and perineurium, and it is believed that this is the sensory region of the nociceptive nerve. Transmission electron microscopy revealed an hour glass shape repeating pattern along the length of type III and type IV nerve terminals, and the multiple bulbous areas exhibit the characteristic features of receptive sites [14]. It is within these 'bead-like' structures on the terminals of 'free' nerve endings that joint pain originates.

The question of how a painful mechanical stimulus is converted into an electrical signal that can then be propagated along sensory nerves to the central nervous system is still unclear. The exposed nature of sensory 'free'

CGRP = calcitonin gene-related peptide; COX = cyclo-oxygenase; N/OFQ = nociceptin/orphanin FQ; NSAID = nonsteroidal anti-inflammatory drug; PAR = proteinase-activated receptor; PG = prostaglandin; SP = substance P; TRP = transient receptor potential; TTX = tetrodotoxin; VIP = vasoactive intestinal peptide.

nerve endings means that the axolemma of these fibres is probably subjected to significant stretch during joint movement. The recent identification of mechanogated ion channels on type III and type IV knee joint afferents by electrophysiological means provided the first insight into the physiological mechanisms responsible for mechanotransduction in joints [15]. The present theory is that movement of the joint generates shear stresses on the axolemma of the 'free' nerve endings, resulting in the opening of mechanogated ion channels. This leads to a depolarization of the nerve terminal and the generation of action potentials, which are subsequently transmitted to the central nervous system where they are decoded into mechanosensation. If a noxious movement is applied to the joint, the firing rate of the afferent nerve increases dramatically and the central nervous system interprets this nociceptive activity as pain [16-18].

Peripheral sensitization and joint inflammation

During inflammation, major plasticity changes occur in the peripheral and central nervous systems that lower the pain thresholds, giving rise to allodynia (pain in response to a normally innocuous stimulus) and hyperalgesia (heightened pain intensity in response to a normally painful stimulus). One means by which pain is generated in arthritic joints is via the stimulation of so-called 'silent nociceptors'. These afferent nerve fibres are quiescent in normal joints; however, following tissue injury or induction of inflammation these nociceptors become active and start to send nociceptive information to the central nervous system [18-20]. This supplementary input from the periphery by the 'silent nociceptors' is one of the contributing factors responsible for the generation of arthritis pain.

An additional process that initiates arthritis pain is peripheral sensitization wherein the activation threshold of joint nociceptors is reduced and afferent nerves become hyperresponsive to both normal and noxious types of movement [18-21]. The pioneering work of Coggeshall and coworkers [21] as well as Schaible and Schmidt [19,20,22] showed that chemical induction of an acute synovitis by intra-articular injection of kaolin and carrageenan reduced the activation threshold of type III and type IV knee joint afferents. The firing frequency of these mechanosensory nerves was dramatically enhanced during normal joint movements as well as during hyperextension and hyperflexion of the knee. It is believed that this augmentation in neuronal firing rate is interpreted by the central nervous system as joint pain and that this process is the neurophysiological basis for joint allodynia and hyperalgesia in these acutely inflamed joints. Decreased mechanical threshold and heightened afferent discharge rate have also been noted in adjuvant-induced chronic arthritis [23,24] as well as in an animal model of osteoarthritis [25]. Resting neuronal activity in the absence of any mechanical stimulation was also described in these arthritis models, which is consistent with an awakening of 'silent nociceptors'. This spontaneous firing of joint sensory nerves accounts for the resting joint pain commonly described by arthritis patients.

Factors contributing to joint peripheral sensitization

The evidence presented thus far clearly indicates that peripheral sensitization of joint afferents is the origin of arthritis pain. Hence, a greater understanding of the mechanisms and mediators responsible for the generation and maintenance of joint sensitization could lead to development of novel drug targets that could alleviate or even abolish arthritis pain. The factors that alter joint mechanosensitivity and promote nociception can be divided into two separate groups: mechanical factors and inflammatory mediators.

Mechanical factors involved in joint nociception

Diarthroidal joints are enveloped by a fibrous capsule that contains synovial fluid, the volume of which in normal human knee joints is between 1 and 4 ml. Following joint injury or during inflammation, synovial blood vessels become increasingly permeable to plasma proteins, which can leak out of the vasculature and accumulate in the intra-articular space. The subsequent shift in Starling forces promotes fluid exudation into the joint with subsequent oedema formation. Because the joint is an enclosed space, this effusion causes a dramatic increase in intra-articular pressure. In normal joints, intra-articular pressure is subatmospheric, ranging from −2 to −10 mmHg [26,27]; however, in rheumatoid arthritic knees synovial fluid volume can rise to 60 ml or more, with a concomitant increase in intra-articular pressure to approximately 20 mmHg supra-atmospheric [28]. A study in which a solution of dextrose and saline was infused into the knee joint revealed that intra-articular pressure rose more steeply in arthritic patients than in normal control individuals [28], probably due to a loss of capsular viscoelasticity and the occurrence of an invading pannus. As intra-articular pressure increased, the participants reported greater tightness around their knee and ultimately moderate pain was experienced. Animal studies [29,30] have shown that an elevation in intra-articular pressure results in burst firing of articular afferents, and the frequency of these neuronal discharges correlates with the level of pressure incurred. Thus, the increased intra-articular pressure associated with oedema formation in arthritic joints likely activates joint nociceptors, leading to pain.

Acute trauma and repetitive stress injuries are major causes of joint pain and disability. Acute joint trauma, such as sport-related injuries, typically involves damage to multiple soft tissues in the joint with varying degrees of damage. A large body of research has found that rupture of articular ligaments leads to joint instability and consequently abnormal loading patterns in the joint [31-34]. The relatively poor healing capacity of joint ligaments means that, over time, chronic instability results in focal erosion of the articulating surfaces,

ultimately leading to joint degeneration and possibly osteoarthritis [35-40]. Inflammatory mediators released into the joint following trauma as well as the accumulation of cartilage degeneration products over time are probably the major contributors to peripheral sensitization in acute and repetitive joint injury, although the identity of these chemical agents is currently unknown. Altered joint biomechanics is also a likely candidate for initiating and maintaining joint pain; however, the processes that link loss of joint function and nociception have never been fully investigated. In one of the few reports on this matter, transection of the anterior cruciate ligament was found to cause increased electrical activity in the medial and posterior articular nerves in response to passive movement of the knee [41]. Again, it is unclear whether this heightened mechanosensitivity is due to local release of chemical sensitizers into the joint following surgery or whether abnormally high forces now act on the remaining uninjured articular tissues, leading to a rise in afferent firing rate. It is entirely feasible that both mechanical and chemical processes occur simultaneously in these unstable joints to generate pain, but further research is required to test this hypothesis.

Inflammatory mediators and peripheral sensitization

Following injury or pathogenic infection, joints typically exhibit a natural inflammatory response that mainly affects the synovium (synovitis). This process is necessary for the innate repair of damaged tissues, allowing the joint to recoup normal function. Inflammatory mediators released into the joint from such sources as nerves, immunocytes, synoviocytes, and vascular endothelium help to orchestrate these healing responses. These same inflammatory mediators also act on joint sensory nerves, leading to either excitation or sensitization. Indeed, local application of various compounds to normal joints elicits a frequency and burst profile of joint afferents that is similar to recordings made in arthritic knees. Identification of the inflammatory agents that evoke nociception is currently underway, and results from these studies will be of major therapeutic value in revealing novel targets that could inhibit peripheral sensitization and hence pain. The following is an overview of some of the better characterized inflammatory mediators that are associated with joint nociception.

Neuropeptides

Neuropeptides are a family of chemical mediators that are stored and released from the terminals of autonomic nerves and slowly conducting joint afferents. Local axon reflexes are responsible for the peripheral release of neuropeptides from sensory nerves, leading to neurogenic inflammation.

The inflammatory neuropeptides substance P (SP), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP) have all been immunolocalized in joint tissues and their levels increase during arthritis [13,42-46]. Electrophysiological recording from knee joint primary afferents found that although local administration of SP had no direct effect on neuronal firing properties, it did cause peripheral sensitization of the nerves in response to normal and noxious joint movements [47]. Ionophoretic application of CGRP close to spinal cord neurones that have an input from knee joint afferents caused an increase in firing rate of these spinal, wide dynamic range neurones [48]. Furthermore, the hyper-responsiveness of these neurones following acute synovitis could be blocked by the selective antagonist $CGRP_{8-37}$ [48], indicating that CGRP plays an important role in the central neurotransmission of painful mechanosensory information arising from the knee. The ability of CGRP to alter joint afferent activity peripherally has not yet been demonstrated. VIP is a 28-amino-acid neuropeptide that is contained in postganglionic sympathetic as well as capsaicin-sensitive sensory nerve fibres innervating the joint capsule [49-51]. Treatment of rat knee joints with exogenous VIP results in mechanonociceptive responses, as demonstrated by enhanced afferent firing frequency during joint rotation [25]. Animal behavioural studies confirmed that this elevation in sensory input to the central nervous system would translate into a pain response, because intra-articular injection of VIP causes a negative shift in hindlimb weight bearing as well as a reduction in hindpaw reaction thresholds to a tactile mechanical stimulus [52]. Interestingly, treatment of osteoarthritic knees with the VIP antagonist VIP_{6-28} reduced nociceptive and pain levels in these animals, highlighting the potential benefits in using this neuropeptide blocker to control arthritis pain [25,52].

A further sensory neuropeptide called nociceptin/orphanin FQ (N/OFQ) is also known to alter joint mechanosensitivity and modulate arthritis pain. N/OFQ is an opioid-like neuropeptide that has been immunolocalized in the peripheral and central nervous systems [53-55], where it controls central pain mechanisms [56-58]. In the knee joint, N/OFQ was found to have a dual effect on sensory nerve activity depending on dose of peptide, on level of mechanical manipulation of the knee, and on whether the joint was inflamed [59]. With normal rotation of control and acutely inflamed rat knees, N/OFQ had a sensitizing effect on joint afferents; however, high doses of N/OFQ desensitized joint mechanosensory nerves during hyper-rotation of inflamed knees. It was later found that the sensitizing effect of N/OFQ was due to the secondary release of SP into the joint because the selective NK_1 receptor antagonist RP67580 blocked N/OFQ-mediated nociception [60]. The ability of N/OFQ to induce hyperalgesia and allodynia in the joint was recently demonstrated in experiments in which peripheral injection of N/OFQ produced a deficit in ipsilateral hindlimb weight bearing and increased von Frey hair mechano-sensitivity [61].

Taken together, these studies clearly show that the sensory neuropeptides SP, CGRP, VIP and N/OFQ are all involved in the generation and promotion of knee pain.

Eicosanoids

Eicosanoids are lipid membrane derived metabolites of arachidonic acid that include the prostaglandins, leukotrienes, lipoxins, thromboxanes and endocannabinoids. The most heavily studied eicosanoids with respect to joint inflammation and pain are the prostaglandins, which are extensively reviewed elsewhere [62-64]. Prostaglandins are formed via a complex enzymatic pathway in which arachidonic acid released from membrane phospholipids is oxygenated by cyclo-oxygenases to produce cyclic endoperoxide prostaglandins. Tissue specific synthases and isomerases then transform these chemically unstable intermediates into the prostaglandins, thromboxanes and prostacyclins.

The pain field has generally focused on the activity of the cyclo-oxygenases, of which there are two isoforms: cyclo-oxygenase (COX)-1 and COX-2 (for review, see Smith and coworkers [65]). COX-1 is constitutively expressed in most cells, where its function is to maintain normal physiological processes in the tissue such as blood flow. Conversely, COX-2 is primarily upregulated during inflammatory situations by various inflammatory mediators such as cytokines [66], and it is therefore often referred to as the inducible isoform of the enzyme (although COX-2 is constitutively expressed in the central nervous system and kidney). In joints, COX-2 is not normally expressed but has been found to occur in significant amounts in the synovium, macrophages and endothelial cells of rheumatoid arthritis patients [67,68]. Because COX-2 is the predominant cyclo-oxygenase present at the site of inflammation, drugs that selectively inhibit COX-2 activity (the coxibs) were believed to have better therapeutic value than the nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). It was initially thought that another advantage to coxib use was that it produced less gastrointestinal toxicity compared with traditional NSAIDs [69]. Although the anti-inflammatory and analgesic capacity of coxibs in arthritis is convincing, a number of these agents produce severely hazardous side effects such as myocardial infarction, hypertension and chronic renal failure. Clearly, a peripherally acting NSAID or intra-articular treatment with either selective and/or nonselective prostaglandin inhibitors could prove to be beneficial in treating joint pain while minimizing systemic side effects.

Peripheral intra-arterial injection of prostacyclin (prostaglandin [PG]I_2), PGE_1 and PGE_2 have all been found to sensitize joint afferents in the rat and cat [70-72]. The sensitizing effect of these prostanoids was rapid in onset and led to an augmentation in afferent firing rate in response to mechanical as well as chemical stimuli. Furthermore, the sensitization of joint nociceptors by acute and chronic inflammation can be inhibited by the nonselective NSAIDs indomethacin and acetylsalicylic acid [73-75]. A recent study demonstrated that systemic administration of the COX-2 inhibitor meloxicam reduced pain evoked vocalization and joint favouring in adjuvant monoarthritic rats [76], although a direct antinociceptive effect of the drug on joint nociceptors was not definitively shown. Further study is necessary, therefore, to test the effectiveness of highly selective coxibs on joint nociception using animal models of arthritis.

The endocannabinoid anandamide is enzymatically synthesized from free arachidonic acid and ethanolamine [77]. Anandamide is a nonselective ligand that binds to both CB_1 and CB_2 cannabinoid G-protein-coupled receptors. CB_1 receptors are mainly found on central and peripheral nerves, whereas CB_2 receptors are associated with immunocytes [78-82]. The location of neuronal central and peripheral CB receptors indicates that activation of these receptors could modulate pain generation and perception [78,82-85]. In joints, high doses of anandamide actually caused excitation of polymodal sensory nerves, indicating a pro-nociceptive effect of the endocannabinoid [86], although the authors did suggest that low doses of anandamide could elicit an anti-nociceptive effect. An alternative explanation is the fact that anandamide acts on both CB receptor subtypes, and the net effect of the cannabinoid is an excitatory action. Experiments are currently underway to test the role of selective CB_1 and CB_2 agonists on joint mechanosensitivity to determine whether a differential response exists between these two receptor subtypes. An interesting aspect of the anandamide study was that its stimulatory effect on joint nociceptors was attained by activating the transient receptor potential (TRP) vanilloid channel 1 ($TRPV_1$). This pathway was reaffirmed by joint blood flow experiments that showed that the vasomotor effects of a selective CB_1 agonist in rat knees could be blocked by $TRPV_1$ antagonism [87]. Zygmunt and coworkers [88] deduced that anandamide activation of $TRPV_1$ channels on sensory nerves causes the secondary release of CGRP. It is possible, therefore, that the excitatory action of anandamide on joint afferents could be due to the secondary release of CGRP or other inflammatory neuropeptides into the joint.

Ion channel ligands

Multiple different types of ion channels exist on the terminals of nociceptors, and their activation either directly or via receptor coupling is necessary for nociceptive processing to occur. Opening of voltage-gated sodium channels permits depolarization of the afferent nerve terminal and propagation of action potentials towards the central nervous system. Sodium channels are typically blocked by the puffer fish poison tetrodotoxin (TTX); however, a significant population of sodium channels present on small diameter sensory neurones are resistant to TTX, and their function is to modulate nociceptive neurotransmission [89,90]. Chronic inflammation with concomitant persistence in nociceptive input has been shown to upregulate sodium channel expression and sodium channel currents in various tissues [91,92], including the temperomandibular joint [93]. Inflammatory mediators such as PGE_2, adenosine and 5-hydroxytryptamine have all be shown to augment sodium channel kinetics and

TTX-resistant sodium currents [94,95]. Thus, blockade of sodium channels on nociceptors may be a viable means of inhibiting pain. Indeed, treatment of adjuvant monoarthritic rat ankle joints with the sodium channel blockers mexilitine and crobenetine inhibited joint mechanical hyperalgesia and alleviated restrictions in animal mobility [96].

Calcium channels have also been implicated in pain processing (for review, see Yaksh [97]). Opening of voltage-gated calcium channels on primary afferent nerves leads to an increase in intracellular calcium concentration and consequently neurotransmitter release into the extraneuronal space. As is described above, a large number of these neuromediators can have a sensitizing effect on the sensory nerve and thereby promote nociception. In addition to the secondary release of algogenic agents from sensory nerve terminals, activation of voltage-gated calcium channels can directly have a positive effect on neuronal excitability and hence firing rate [97]. The role of calcium channels in joint pain is largely unexplored. In one of the few studies to address this issue, the anticonvulsant gabapentin, which binds to the $\alpha 2\delta$ subunit of calcium channels, was shown to reduce the mechanosensitivity of normal and acutely inflamed knee joints [98]. The full relevance of this finding to calcium channel neurobiology is uncertain.

In addition to voltage-gated cation channels, knee joints were recently found to possess mechanogated ion channels that are sensitive to changes in shear stress forces being applied to the neuronal membrane [15]. The forces generated by physical movement of a joint are transmitted throughout the organ where they are perceived by the articular innervation. The shear stress causes a conformational change in the mechanogated ion channels present on the nerve terminal, which leads to channel opening and consequently nerve depolarization. If movement becomes noxious, then greater forces are applied to the joint and the probability of mechanogated ion channel opening is increased and depolarization events become more frequent [15]. This enhanced activity is the molecular basis of joint pain.

Another superfamily of ion channels that has received a lot of attention recently are the TRP channels. Of particular interest in pain research are the TRPM (melanostatin) and the TRPV (vanilloid) channel subfamilies. The eighth member of the TRPM channels (TRPM8) is activated by cooling temperatures (22-26°C) as well as by agents such as menthol that produce a cool sensation [99,100]. It is thought that pharmacological activation of TRPM8 channels could elicit an anti-nociceptive effect in much the same way that applying ice packs to an injured joint can reduce pain sensation. Current research into this channel, however, has been hampered by the lack of efficacious and highly selective pharmacological tools. The use of heat to help control joint aches and pains has been appreciated for many years, but the molecular mechanism by which this is achieved has only recently been elucidated. The ion channel responsible for noxious thermosensation is TRPV1, which was first identified on rat sensory neurones by an expression-cloning approach [101]. In addition to being activated by temperatures above 43°C, TRPV1 is sensitive to protons, lipids, phorbols and cannabinoids. The CB_1 agonist arachidonyl-2-chloroethylamide, for example, exerts its physiological effects in joints via a TRPV1-dependent pathway [87]. Unlike other TRP channels, several agonists and antagonists have been developed that are selective for TRPV1, including the blocker SB366791, which has been shown to be effective in joint tissues [102]. Electrophysiological studies have revealed that capsaicin (the hot spicy component of chilli peppers) sensitizes joint afferents probably by causing secondary release of inflammatory neuropeptides into the joint (unpublished observations). The joint subsequently becomes insensitive to further noxious mechanical stimuli, although the precise mechanism underlying this process is unknown.

Other chemical mediators

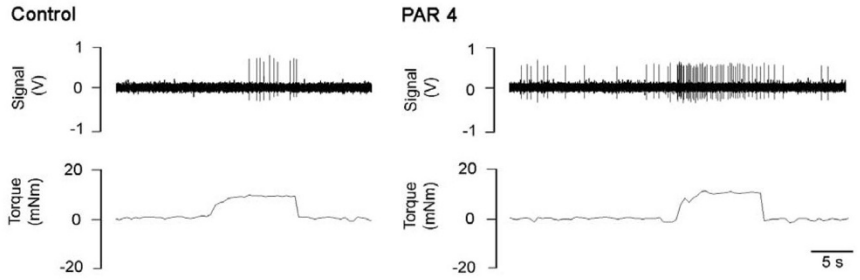
The preceding discussion has addressed the most commonly studied inflammatory mediators that are known to sensitize joint afferents, but it is far from exhaustive. Other chemical compounds that demonstrate peripheral sensitization in joints include bradykinin [103,104], histamine [105], 5-hydroxytryptamine [106], adenosine [107,108], and nitric oxide [109]. As the list of new potential targets continues to grow at a rapid rate, this exciting area of joint neurobiology will probably yield useful and beneficial pain control medicines that could act on one or a combination of these nociceptive pathways.

Neuroimmune pain pathways

The histological identification of synovial mast cells in close proximity to type III and type IV knee joint afferents [110,111], as well as the ability of neuromediators to stimulate leucocyte infiltration into joints [112,113] suggests an important involvement of immunocytes in neurogenic inflammation and pain. This concept is supported by the fact that mast cells and neutrophils can be activated by various sensory neuropeptides [114-123], resulting in explosive degranulation and subsequent release of inflammatory mediators into the local microenvironment. These immunocyte-derived factors can themselves cause joint inflammation and impart tissue hyperalgesia. For example, in acutely inflamed knees the vasomotor effect of N/OFQ is dependent on the presence of synovial mast cells and leucocytes [124], indicating a neuroimmune mode of action for this neuropeptide.

Another group of agents that recently have been found to activate mast cells leading to pain and inflammation are the serine proteinases. Proteinase levels are known to be augmented in patients with inflammatory joint disease [125-128], and it is believed that their enzymatic destruction of cartilage and other intra-articular tissues is a major contributing factor to the pathogenesis of rheumatoid

Figure 1



Specimen recording from a knee joint afferent fibre during rotation (torque) of the knee. Close intra-arterial injection of a PAR4 agonist caused spontaneous nerve activity as well as increased afferent firing rate during normal rotation compared with control. This PAR4 sensitization of the nerve would be decoded as joint pain by the central nervous system. PAR, proteinase-activated receptor.

arthritis. In addition to their classical proteolytic effects, proteinases were recently found to regulate cell signalling via specialized G-protein-coupled receptors. The unique characteristic of these proteinase-activated receptors (PARs) is the novel mechanism by which these receptors are triggered. Firstly, the proteinase hydrolyzes a specific arginine cleavage site located on the extracellular amino-terminus of the G-protein-coupled receptor, thereby exposing a new amino-terminal sequence. This modified amino-terminal sequence, while remaining tethered to the receptor, can now bind to a docking domain within the same receptor, leading to activation and cell signalling. Four PARs have thus far been identified (PAR1 to PAR4), and evidence is emerging that suggests that these receptors are involved in pain signalling [129,130]. In knee joint electrophysiology studies we found that administration of a PAR4-activating peptide can evoke spontaneous activity and sensitize joint afferents in response to mechanical manipulation of the knee (Figure 1). Inhibition of proteinase activity in diseased joints could have the dual benefit of reducing nociception as well as attenuating joint destruction through proteolysis. Thus, the PARs are an exciting new target for investigating joint pain modulation and for the potential development of disease-modifying drugs.

Endogenous anti-nociceptive ligands

In an attempt to offset peripheral sensitization responses, it is becoming evident that joints also possess anti-nociceptive capabilities. The endogenous μ-opioid receptor ligand endomorphin-1 has been immunolocalized in capsaicin-sensitive nerves innervating rat synovial tissue [131,132], where it acts to reduce inflammation and inhibit nociception following an acute synovitis [24]. Interestingly, the anti-nociceptive capacity of endomorphin-1 was lost during chronic arthritis due to a reduction in μ-opioid receptor expression in the joint. This observation could begin to explain why the endogenous opioid system is unable to ameliorate arthritis pain. Other substances that are tonically released into the joint to offset inflammation-induced peripheral sensitization include galanin [133] and somatostatin [134]. These peptides have been shown to reduce nociceptor activity during noxious movement of normal knees as well as during normal rotation and hyper-rotation of acutely inflamed joints. Future research is required to characterize other endogenous anti-nociceptive mediators and to elucidate the reasons for their limited effectiveness in controlling arthritis pain.

Central processes in joint pain

Action potentials are transmitted along nociceptors from the knee to the central nervous system and enter the dorsum of the spinal cord predominantly in the lumbosacral region. Joint nociceptors terminate in the dorsal horn of the spinal cord, where they synapse with spinal neurones. These neurones constitute either spinal inter-neurones that aim to modulate sensory input, or ascending processes that transmit nociceptive information to the brain via the spinothalamic, spinomesencephalic, spinoreticular and spinocervical tracts. Neurophysiological processes at the intraspinal level can either intensify (central sensitization) or dampen (inhibition) the nociceptor signals before they reach the sensory cortex. As such, the intensity of the nociceptive information originating from joint primary afferents can undergo significant modification before leaving the spinal cord. The complex mechanisms and chemical mediators involved in these central processes are outside the scope of this review.

An initial attempt to determine the regions of the brain to which joint nerves project was recently reported in the rat. By measuring evoked potentials in the cerebral cortex in response to electrical stimulation the knee joint innervation, it was determined that joint afferents project to areas SI and SII of the somatosensory cortex [135]. By mechanisms that are not clearly understood, the brain interprets these high-intensity signals as joint pain. In addition to this cognitive aspect of arthritis pain, there is also an affective or emotional component to the disease. Patients who suffer from chronic arthritis pain exhibit clinical signs of depression and anxiety that appear to have a physiological basis [136]. In one of the few studies to try to discern the neurophysiological pathways

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responsible for the negative affect of arthritis pain, Neugebauer and Li [137] recorded from neurones located in the amygdala, an area of the brain that is synonymous with pain and emotion [138]. They found that noxious mechanical stimuli applied to acutely inflamed joints had an excitatory effect on the firing rate of neurones in the central nucleus of the amygdala. These data provide the first electrophysiological evidence that the amygdala is involved in transforming nociceptive information arising from arthritic joints into an emotional, painful experience.

Conclusion

Recent advances in molecular technology and the development of selective and efficacious pharmacological tools have enabled us to piece together the complex processes involved in the generation of arthritis pain. Nevertheless, as this review consistently reminds us, there are still very large gaps in our knowledge of what is occurring in the nociceptors to maintain this chronic pain state. For example, why is some arthritis pain episodic whereas other patients complain of chronic persistent joint pain? Why is there a disconnect between the degree of joint deterioration and the level of joint pain reported? As we get older, our peripheral nerves degenerate and as such some patients may be experiencing neuropathic pain rather than arthritis pain *per se*. Indeed, gabapentin (a drug commonly prescribed to relieve neuropathic pain) shows some promise in controlling arthritis pain [98]. Although analgesia could be achieved by intervening at different levels in the pain pathway, the possibility of reducing pain in the periphery is very appealing because drug doses can be titred to a lower level and there is less scope for negative systemic side effects. The fact that pain and inflammation are inherently linked indicates that interventions that relieve the symptoms of arthritis may also moderate the severity of the underlying disease. Carefully planned studies using multiple arthritis models and relevant methodological approaches are therefore imperative to further our understanding of the origin of joint pain.

Competing interests

The author declares that they have no competing interests.

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