



Review

Osteoarthritis is a neurological disease – an hypothesis

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SUMMARY

Objective: This commentary aims to summarise the importance of the joint nervous system in maintaining joint homeostasis and the role of nerves in contributing to degenerative diseases such as osteoarthritis (OA).

Methods: Pertinent scientific literature was evaluated and summarised to form the hypothesis that OA is a neurological disease.

Results: Joint nerves regulate a constant blood supply to maintain joint homeostasis and sustain tissue health; however, in OA this neurovascular control system is compromised and joint tissue integrity declines. Similarly, a decrease in joint proprioceptors and nociceptors with age and during arthritis interferes with position sense and pain transmission so that the body is unable to correct abnormal loading and this alteration in joint biomechanics can lead to joint destruction. Finally, brain morphology and activity are altered in OA patients but can be rectified by total joint replacement.

Conclusions: Joints possess a complex nervous system that controls multiple physiological functions such as tissue blood flow, position sense, and pain. Damage or dysfunction of the joint nervous system can affect joint health and promote degenerative diseases such as OA. Drugs that are used to treat neurological diseases such as epilepsy and depression have been found to be effective at ameliorating the symptoms of OA. Thus, in addition to age, obesity, joint instability, and sex, neuronal impairment could be considered an additional risk factor for the development and pathogenesis of OA.

1. Introduction

Diarthroidal joints were once considered to be passive hinges that allow animals to move in response to loads being transmitted from muscles to bones. In fact, joints are complex organ systems consisting of diverse tissues, intricate physiological processes, and tightly regulated homeostatic feedback mechanisms. The maintenance of joint health is predominantly under the control of an extensive and elaborate nervous system that meanders throughout the joint innervating multiple tissues. For example, a constant and regulated blood supply is vital to sustain tissue function and allow a rapid vascular response to injury. Sensory and sympathetic nerves play a major role in controlling this vascular tone. Joint tissues which are subjected to abnormally high loads are likely to fail and the resulting injury is a major risk factor for the future development of osteoarthritis (OA). Again, joint afferents are able to sense this impending or actual tissue damage and alert the body to respond to these excessive forces by altering gait and minimise catastrophic loading. Finally, locomotion requires fluid, coordinated movement of the joint and these processes are under the auspices of the articular nervous

system. It is evident, therefore, that any damage to or dysfunction of joint nerves could have a devastating effect on normal joint function and health.

2. The nervous joint

The majority of nerves innervating diarthroidal joints are nociceptors highlighting that joints are exquisitely sensitive to pain [1]. These small diameter fibres have a relatively slow conduction velocity (<20 m/s) and a high threshold of activation [2]. The greatest density of joint nociceptors is located in the synovium which could be considered the nerve centre of the joint. Small diameter fibres are also found in the sub-chondral bone, the outer third of the menisci, the superficial layer of ligaments (epiligament), and the infrapatellar fat pad. The endings of these nerves are “free” and are rich in vasodilator neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) [3–5], and the vasoconstrictor opioid peptide endomorphin-1 [6].

In addition to afferent fibres, joints are innervated by postganglionic

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sympathetic efferents whose terminals occur in close proximity to arterioles. Electrical stimulation of joint sympathetic fibres leads to a reduction in synovial blood flow [7] while guanethidine-induced sympathectomy increases synovial perfusion [8]. The inability of synovial joints to autoregulate [7] means that blood flow to the organ, and therefore the health of the articular tissues, is entirely controlled by the joint innervation. Any disruption to this neurovascular control system would alter tissue blood flow resulting in joint tissue breakdown and disease.

3. Neurogenic drivers of joint inflammation and disease

Joint disease is typically bilateral in so much as the clinical manifestation of arthritis in a single joint ultimately develops in the contralateral joint. While the preponderance of the evidence for symmetrical arthritis relates to inflammatory joint disease [9], there is increasing evidence to suggest that OA can be bilateral [10,11] and has an inflammatory component [12]. This mirror imaging of joint disease is believed to be driven by the actions of the peripheral nervous system since patients with hemiplegia do not present with disease in the joint ipsilateral to the paralysis [13,14]. Known deficiencies in OA joint proprioception can lead to altered gait and abnormal loading in the contralateral joint which can initiate tissue destruction [15]. In addition to a sensory function, afferent nerves can fire in an antidromic direction (*i.e.* away from the spinal cord) leading to the peripheral release of inflammatory neuropeptides (*e.g.* SP, CGRP, VIP). Experimental studies have shown that electrical antidromic stimulation of joint afferents can cause joint hyperaemia, increased leukocyte chemotaxis, and oedema formation [16–18]. These pro-inflammatory events are primarily mediated by the peripheral release of inflammatory neuropeptides from afferent nerve terminals innervating the joint since the concentration and release of sensory neuropeptides is increased in arthritic joints [19–21]. Other neurotransmitters which have been found to cause synovitis include nitric oxide [22] and acetylcholine [23]. Neurotoxic destruction of small diameter nerve fibres by capsaicin treatment or by surgical denervation can profoundly reduce experimentally-induced inflammation [24,25] reinforcing a link between joint nerves and arthritis pathogenesis. Neurovascular bundles consisting of sympathetic and sensory nerves have been found to invade articular cartilage and bone in OA patients [26]; however, the functional significance of these complexes is unclear. The vasodilatory effect of various neurotransmitters are diminished in joints with early OA [25,27], while sympathetic vasoconstriction is abolished in arthritic joints due to a loss of alpha-adrenoceptor function [28,29]. These observations strongly suggest that neurovascular control is altered in arthritic joints which would impair joint homeostasis and contribute to disease progression.

In addition to this neurogenic component of arthritis, the nervous system has also been found to promote joint destruction by other means. Large diameter, myelinated afferents have specialised endings that are highly sensitive to mechanical stimuli. These nerves are located throughout the joint and are involved in position sense. Their rapid conduction velocities serve to warn the body of any abnormal or excessive joint movements and set up muscle reflexes that serve to stabilize the joint. Thus, these proprioceptors help to protect the joint from damage and possible development of future degenerative diseases. Experimental studies have found that deafferentation of the mammalian hindlimb can exacerbate post-traumatic and age-related development of OA [30,31]. It is hypothesised that the loss of large diameter fibres uncouples the neuroprotective effect of proprioceptive reflexes rendering the joint vulnerable to abnormal loading and accelerating joint deterioration. Age-related loss of large diameter joint fibres and the accompanying reduction in joint position sense correlate with degenerative joint disease severity [32,33]. Thus, joint proprioceptive nerves are important regulators of joint mechanical integrity and loss or damage to these nerves can lead to the development and exacerbation of joint diseases such as OA.

Joint small diameter peptidergic fibre density has also been found to decline as a function of age and OA in humans and in animal models. In the collagenase model of OA, for example, the number of SP and CGRP-containing neurones was dramatically reduced or even absent in arthritic joint soft tissues [34,35]. Loss of neuropeptidergic fibres has also been reported in human synovial samples taken from OA patients undergoing total knee replacement [3,36]. Finally, nociceptor density has been shown to be reduced in the joints of old animals with OA suggesting an age-related decline in joint afferents [37–39]. Taken together, these observations highlight neurosensory attrition in OA joints which could lead to altered pain perception and flawed neurovascular control.

4. Peripheral sensitization and pain

Shear and compressive forces generated during locomotion are conveyed throughout the joint and sensed by primary afferent neurones located in the joint capsule, ligaments, menisci, and subchondral bone. Mechanogated ion channels located on the exposed terminals of these sensory nerves open in response to this movement leading to the generation of action potentials [40]. This electrical activity is conveyed to the central nervous system and interpreted as normal movement. If joint displacements become overt, more mechanogated ion channels open resulting in a bombardment of action potentials which the brain now interprets as pain. In degenerating and inflamed joints, the activation threshold of these mechanosensitive nerves is dramatically reduced and the neurones now fire in response to normally innocuous movements [37, 41,42]. Nociceptor-specific sodium channels (NaV1.7 and NaV1.8) are also more likely to open in arthritic joints thereby contributing to nociception even when the joint is at rest [43,44]. This process of peripheral sensitization primarily occurs following the local release of inflammatory chemicals into the joint, although damage to the peripheral nerves themselves can also induce this phenomenon.

Sensory neuropeptides are produced in DRGs, transported peripherally and stored in afferent nerve terminals. In arthritis, the formation of these neuropeptides increases and upon release into the joint causes sensitization of articular nociceptors. Neuropeptides that have been shown to sensitize joint afferents include nociceptin [45], vasoactive intestinal peptide [42], substance P [46], and galanin [47]. Other inflammatory mediators that have been shown to reduce the firing threshold of joint mechanosensory afferents include prostaglandins [48, 49], cytokines [50], serine proteases [51], and serotonin [52]. The mechanism by which these algescic molecules sensitize peripheral nerves is uncertain but is likely due to an alteration in the gating properties of nociceptor cation channels. Pharmacological blockade of these receptors could be an exciting means of targeting nociceptor firing and inhibiting the neurotransmission of joint pain.

Nerve growth factor (NGF) has recently come under scrutiny for its potential role in OA pain. In addition to its neurotrophic properties, NGF can sensitize nociceptors and cause pain [53,54]. Preclinical studies using rodent models of OA found that synovial NGF levels increase and joint pain can be reduced by treating the animals with biologics directed towards NGF or its receptor [55–57]. These fundamental findings sparked a series of clinical trials which confirmed that targeting the NGF pathway was effective at reducing pain in OA patients [58]. Unfortunately, these trials were temporarily suspended when it transpired that some patients developed osteonecrosis and accelerated OA, even in joints that were not previously arthritic [59]. The reason for this heightened pathology was thought to be due to excessive doses and concurrent use with NSAIDs. Clinical trials have resumed with the proviso of dose limitations of the NGF therapy and strict exclusion of NSAID co-treatment.

The opioid peptide endomorphin-1 has been localised in joint nerves and upon release can reduce joint inflammation and nociceptor firing [6, 60]. Interestingly, in a model of chronic arthritis, mu-opioid receptors are downregulated and endomorphin-1 can no longer exert its anti-inflammatory or anti-nociceptive effects [60,61]. This phenomenon could also explain the poor efficacy of exogenously administered opioids

for treating chronic pain. Cannabinoid receptors have also been identified on joint sensory nerve endings where their activation by selective agonists reduces nociceptor firing [62,63]. The neuropeptide somatostatin when given locally into arthritic joint reduces inflammation, mechanonociception and pain [46,64]. The source of the somatostatin in these joints was determined to be capsaicin-sensitive sensory nerves [65]. Thus, articular nerves are a rich source of analgesic neurotransmitters which if damaged could deprive the joint of effective, endogenous pain relief. Promoting the production and maintenance of these endogenous analgesics is another possible strategy for controlling nociception locally in the joint.

5. Evidence that OA may have a neurological component

Complete loss of sensory innervation in a diarthroidal joint can lead to Charcot arthropathy, the histological and symptomatological features of which are similar to OA [66,67]. Clinical features that are comparable between OA and Charcot arthropathy include peripheral neuropathy, osteophytes, and heterogeneous levels of synovitis. Charcot joints, however, appear to have greater soft tissue hypertrophy and more profound bone erosion. The destruction of joint tissues is likely due to loss of proprioception and the generation of dyesthesias and subsequent abnormal joint loading. Following joint trauma, articular nerves become truncated and distorted and loaded with pro-algesic neuropeptides [5, 68]. The nerve damage biomarker activated transcription factor-3 (ATF-3) has been shown to be expressed in the sensory nerves of OA rat joints suggesting a neuropathic component to this disease [69]. The molecules responsible for OA nerve damage are unknown, but the lipid mediator lysophosphatidic acid (LPA) has recently been shown to cause demyelination, increased ATF-3 expression and induce joint nociception [70]. Furthermore, synovial fluid LPA concentration was found to increase in proportion to the severity of joint disease in a cohort of OA patients [70]. Since LPA is released during inflammation [71], it may be postulated that LPA could be a common link between joint injury, nerve damage, pain, and OA.

Neuropathy is associated with changes to the number and properties of cation channels present on sensory nerve terminals. These channelopathies lead to abnormal nerve signalling and the development of neuropathic pain. Voltage-gated sodium channels (Nav1.7 – Nav1.9) are primarily expressed on small diameter peripheral neurones and are involved in the generation of normal and pathological pain [72]. Gain of function in these ion channels results in symptoms of intense, burning pain in the extremities, while loss of function causes a congenital insensitivity to pain. In a rodent model of OA, local administration of the selective Nav1.8 ion channel blocker A803467 was able to block joint nerve sensitization and reduce OA pain [44]. Miller et al. developed a designer receptor exclusively activated by a designer drug on Nav1.8 expressing neurones and found that inhibiting these nociceptors reduced post-traumatic OA pain [73]. Interestingly, in the LPA model of joint neuropathy, blockade of articular Nav1.8 ion channels was found to be more effective in female rats than in males [74] indicating that peripheral pain mechanisms are different between the sexes and should therefore be treated differently.

The transient receptor potential vanilloid-1 (TRPV1) ion channel has also been studied as a potential target for OA pain relief. Synovium harvested from OA patients revealed a high level of TRPV1 expression, but these cation channels were found predominantly on infiltrated macrophages rather than on nerves [75]. Blockade of TRPV1 ion channels on OA joint afferents reduced peripheral sensitization and pain in an animal model [75]. While these preliminary data look promising, clinical studies to date using TRPV1 antagonists have shown limited efficacy and unwanted side-effects such as hyperthermia [76].

Drugs that have been classically used to treat neuropathic pain have shown analgesic efficacy in OA. For example, anti-convulsant gabapentinoids can reduce joint nociceptor hypersensitivity [77], OA pain in rodents [69,78], and OA pain in humans [79]. Duloxetine, which is

typically used to treat diabetic neuropathy, has also been found to be analgesic in OA patients [80] reaffirming that at least some of the pain of OA is neuropathically driven. Another intriguing observation has recently been made with the non-psychoactive cannabis derivative cannabidiol (CBD) in the monoiodoacetate model of OA [81]. Prophylactic treatment of OA rats with an acute regimen of CBD attenuated nerve demyelination and neuropathic pain in end stage joint disease. In another study, daily administration of CBD to collagen-induced arthritic rats slowed the progression of joint destruction and inflammatory cytokine production [82]. Whether the protective effect of CBD on joint damage could be due to a neuroprotective property of the cannabinoid requires further interrogation.

Functional imaging studies have revealed morphological changes in specific brain regions of chronic OA pain patients. The thalamus, for example, is a central processing region which integrates and relays nociceptive signals to specific regions of the brain responsible for engendering the cognitive and affective characteristics of pain. Thalamic volume was found to be less in chronic pain patients with hip OA compared to normal control subjects [83]. Similarly, in knee OA patients, deeper brain structures associated with the affective aspect of pain and nociceptive processing were found to be smaller than normal indicating morphological impairment to neural substrates in these individuals [84]. Interestingly, this brain atrophy was reversed in these OA patients following total joint replacement suggesting that the central neurodegeneration observed in the brain was primarily driven by peripheral joint disease.

Evidence is emerging which shows that joint disease causes structural and functional alteration to the central nervous system in animal models of arthritis. In a preclinical model of post-traumatic OA, neural connectivity between brain regions involved in pain processing were enhanced as determined by functional magnetic resonance imaging [85]. Treatment of these animals with a non-selective peripherally-restricted matrix metalloproteinase inhibitor reversed this enhanced functional connectivity. Descending inhibitory pathways have also been shown to be compromised in OA animals, while descending facilitation was found to be enhanced via a serotonergic pathway [86,87]. While these data are preliminary, they point to the fact that disease activity in the joint can lead to neuroplastic changes in the pain pathway in higher centres of the nervous system.

Altered central processing of joint pain results in gait shifts which on the one hand aim to limit joint loading, but these changes can also generate motor reflexes that alter muscle tone and exacerbate joint damage. Motor cortical representation of the knee joint is shifted in patients with knee OA which could account for some of the motor deficits observed in these patients [88]. Hyperactivity of central nociceptive circuits either by continuous peripheral bombardment or structural reorganisation can also have profound consequences on motor activity. Persistent pain suppresses motor output at the spinal and cortical levels [89] by activating inhibitory connections between the somatosensory and motor cortices [90]. In the periphery, stimulation of high threshold joint afferents inhibits the firing frequency of type II joint afferents suggesting that crosstalk exists between joint nociceptors and proprioceptors [2]. The maintenance of nociceptor firing in OA joints would therefore reduce joint position sense and inhibit corrective muscle reflexes leading to anomalous loading and expedited tissue damage.

6. Conclusion

While age, sex, obesity, and abnormal biomechanics are clear risk factors for the development of OA, a significant proportion of these elements are under the control or are directly influenced by the nervous system. As summarised in Fig. 1, I hypothesize that following a traumatic injury, joint nerves become hyperexcitable and signal pain. By a neurogenic mechanism, sympathetic and sensory neurovascular control is compromised which can gradually lead to hard and soft tissue destruction in the joint. Over time, joint afferents can themselves become

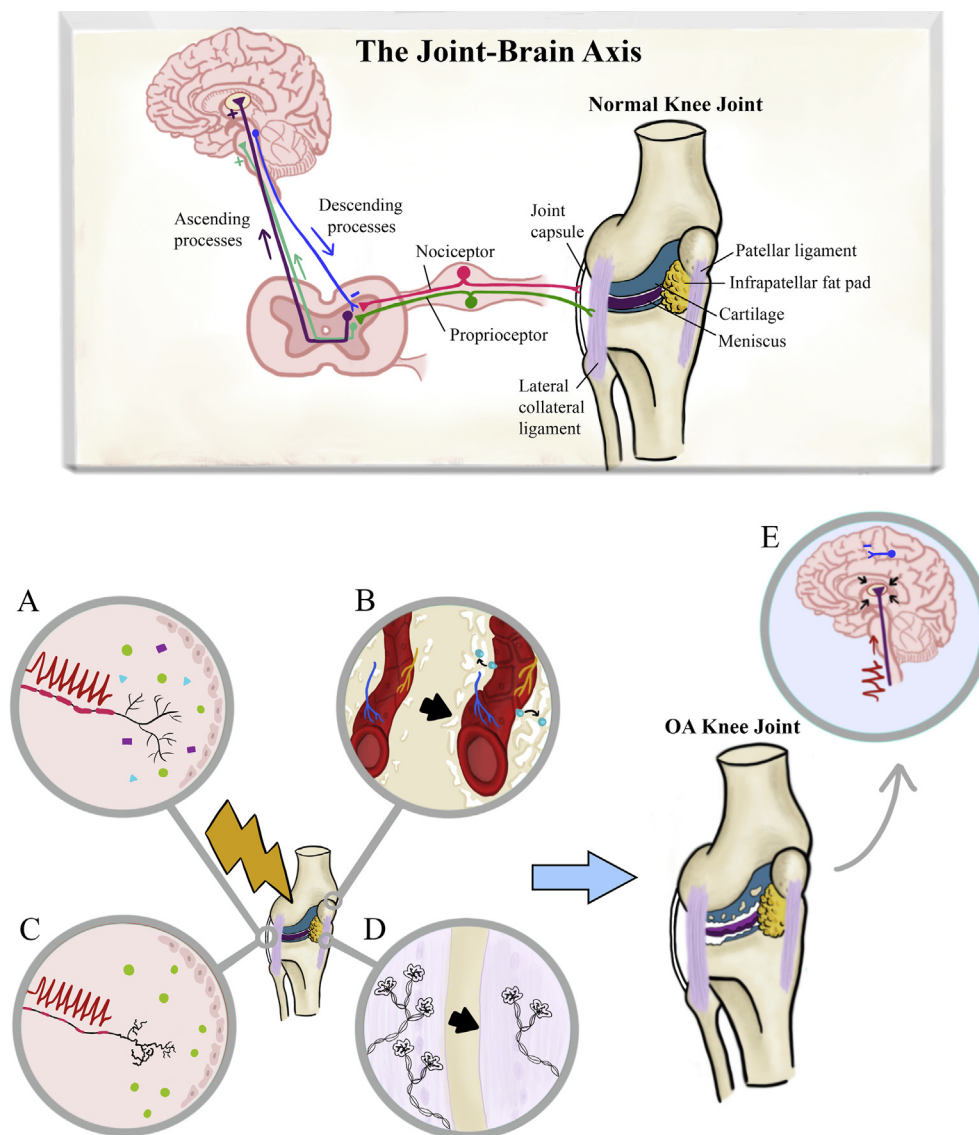


Fig. 1. A neurological basis for osteoarthritis and the joint-brain axis. (Top): Nociceptive (red nerve) and proprioceptive (green nerve) signals are transmitted from various tissues in the joint to specific regions of the brain where they are deciphered as pain and position sense respectively. Descending processes (blue nerve) originating in the periaqueductal grey can inhibit pain transmission in the superficial layers of the dorsal horn of the spinal cord. Following joint injury, (A): Various algogenic mediators are released into the joint where they sensitize small diameter afferents leading to increased neuronal firing and nociception. (B): Hyperexcitability of joint afferents can trigger local axon reflexes which causes the peripheral release of inflammatory mediators into the joint culminating in vasodilatation and protein extravasation. Altered sympathetic control in the damaged joint also leads to an inflammatory state which can initiate destruction of joint soft tissues and bone. (C): Chemical mediators released into the joint can cause progressive deterioration of peripheral nerves leading to neuropathic pain. (D): Loss of proprioceptors due to age or disease will compromise position sense in the joint and jeopardise corrective motor reflexes. The resulting deterioration in joint biomechanics and gait would alter normal joint loading and exacerbate disease progression. (E): Persistent nociceptive input into the central nervous system can cause neuroplastic changes in the brain such as thalamic atrophy and inhibition of motor cortex activity.

damaged leading to the generation of neuropathic pain symptoms in OA patients. This loss of sensory integrity will have proprioceptive consequences culminating in abnormal joint loading and mechanical instability, both of which would contribute to OA progression. Finally, constant neurosensory bombardment into the central nervous system leads to morphological and physiological changes in the brain which may manifest as centralised pain, fatigue, and psychological distress. Pharmacological and non-pharmacological therapies which are used to treat neurological diseases have proven to show symptomatological efficacy in OA patients which could slow the progression of joint degeneration.

Conflicts of interest

There are no conflicts of interest.

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