CPD article

Understanding and managing pain in the arthritic synovial joint: an update

Osteoarthritis is a very common cause of chronic pain in dogs and cats. Great progress has been made in the last 2–3 decades in unravelling the molecular mediators of joint pain. Now we are starting to see the benefits of this research in terms of new targets to block joint pain and new medicines reaching our pharmacy shelves. This review summarises the progress that has been made in understanding why and how arthritic joints cause pain. This will help readers understand novel medicines and provide insight into the others that might follow in the future.

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Osteoarthritis is an incurable condition that is slowly progressive and a cause of chronic pain. Chronic joint pain is a real challenge for veterinary teams to manage, a source of considerable anxiety for pet owners and a welfare issue for dogs and cats. Estimates suggest that 7–20% of adult dogs have osteoarthritis, although case definitions vary in the literature (O'Neill et al, 2014; Pettitt and German, 2015). For cats, it is estimated that over 70% of older cats have radiographic osteoarthritis (Hardie et al, 2002; Godfrey and Vaughan, 2018; Monteiro, 2020). Some studies have highlighted the negative impact that osteoarthritis has not only on an affected pet, but also on the wellbeing of pet owners (Belshaw et al, 2020). The author has frequently witnessed the extreme disappointment that owners feel when they realise that their dog has a problem that might limit their mobility and ability to exercise. After all, taking the dog for a walk is beneficial for the physical and mental health of both dogs and owners alike (Westgarth et al, 2019).

While some dog owners may be able to recognise signs of joint pain in their dog, such as lameness or joint stiffness, for many dogs, and most cats, the signs of joint pain may go unnoticed or dismissed as 'slowing down' because of age. Therefore, veterinary teams have a major role to play in educating clients, not only in the clinical signs of osteoarthritis, but also in guiding clients as to the best ways to manage the condition. Accordingly, a thorough understanding of the reasons why synovial joints may become painful is a prerequisite to providing informed advice to clients.

For the last three decades, non-steroidal anti-inflammatory drugs have been the mainstay of managing chronic pain in dogs and, to a lesser extent, cats. Classic non-steroidal anti-inflammatory drugs act by inhibiting cyclooxygenase, thereby reducing levels of prostaglandin E_2, and their properties have been extensively discussed elsewhere (Innes et al, 2010; Innes, 2018). More recently, a non-steroidal anti-inflammatory drug of the piprant class (grapiprant) was licensed for dogs. This is a prostaglandin EP4 receptor antagonist which blocks the action of prostaglandin E_2 in a more targeted way, providing some theoretical safety advantages (Rausch-Derra et al, 2016). While classic non-steroidal anti-inflammatory drugs undoubtedly provide significant pain relief for millions of animals, there are issues in managing osteoarthritis pain with only non-steroidal anti-inflammatory drugs, such as insufficient efficacy, adverse events, fear of adverse events and compliance issues from pet owners.

In recent years there has been considerable progress in the understanding of the pathophysiology of pain in the arthritic joint (Vincent, 2020). These advances have been made through three broad approaches: careful molecular interrogation of animal models of osteoarthritis, correlative clinical studies in human patients interrogating peripheral and central pain outcomes using magnetic resonance imaging, and molecular studies on tissues from human and animal patients with osteoarthritis. These scientific discoveries have led to the identification of new therapeutic targets. This article discusses the modern view of synovial joint pain as a basis for colleagues to understand the new therapies which have recently entered the market.

Factors that can incite joint pain

It is well-recognised that synovial joints are innervated by pain-transmitting nerves (nociceptors). These nociceptors are

thinly myelinated Aδ-fibres or unmyelinated C-fibres, with their cell bodies are located in the dorsal root ganglia. It is not yet fully understood which algogenics are responsible for stimulating these nociceptors. It is certainly true to say that a strong biomechanical influence underpins the aetiopathogenesis of osteoarthritis. For example, in dogs, hip dysplasia associated with joint laxity, or cranial cruciate ligament rupture leading to stifle joint instability, are two obvious common scenarios where these biomechanical changes initiate osteoarthritis and pain.

Nerve growth factor is a molecule that has been implicated to play a key role in neuronal development since its discovery nearly 60 years ago. Nerve growth factor plays a critical role in the development of the peripheral nervous system by promoting the survival of some neural crest-derived cells in developing embryos, in particular sensory and sympathetic neurons. However, in the developing organism, nerve growth factor has a key role in messaging neuronal development, and in the adult animal, it is recognised that nerve growth factor is a central player in the signalling of pain (*Figure 1*). Nerve growth factor acts through two highly specific cell-surface receptors, namely tropomyosin-related kinase A (TrkA) and p75, although it is the former that seems to be of greater significance in joint nociception. Interestingly, selective mutations in nerve growth factor or TrkA genes cause congenital insensitivity to pain in human beings, or loss of pain behaviours in genetically altered mice. Four broad subtypes of primary sensory neurons have been characterised within the dorsal root ganglion, of which three broad categories are known to be important in nociceptive transmission:

- Thin myelinated Aδ-fibres
- Peptidergic unmyelinated (C-) fibres
- Non-peptidergic unmyelinated (C-) fibres.

Peptidergic C-fibres and the majority of Aδ-fibres express TrkA, and are responsive to nerve growth factor. These TrkA-positive fibres innervate skin, viscera and musculoskeletal tissues. In contrast, non-peptidergic C-fibres lack TrkA or p75 receptors and are thus unresponsive to nerve growth factor; these fibres innervate skin but not the skeleton. Hence, nerve growth factor appears to be a logical target for the relief of musculoskeletal pain.

Studies in rodent models of osteoarthritis clearly implicate nerve growth factor in post-surgical and chronic osteoarthritis pain behaviours. In their experiments, McNamee et al (2010) used a surgically-induced murine model of osteoarthritis to demonstrate that nerve growth factor mRNA is increased after surgery, but then declines before increasing again as the osteoarthritis progresses over time. The authors also showed that blocking the action of nerve growth factor at its receptor significantly reduced pain behaviours in treated mice. Their evidence suggested that postsurgical pain is dependent on classical tumour necrosis factor-driven inflammation, but chronic osteoarthritis pain is not.

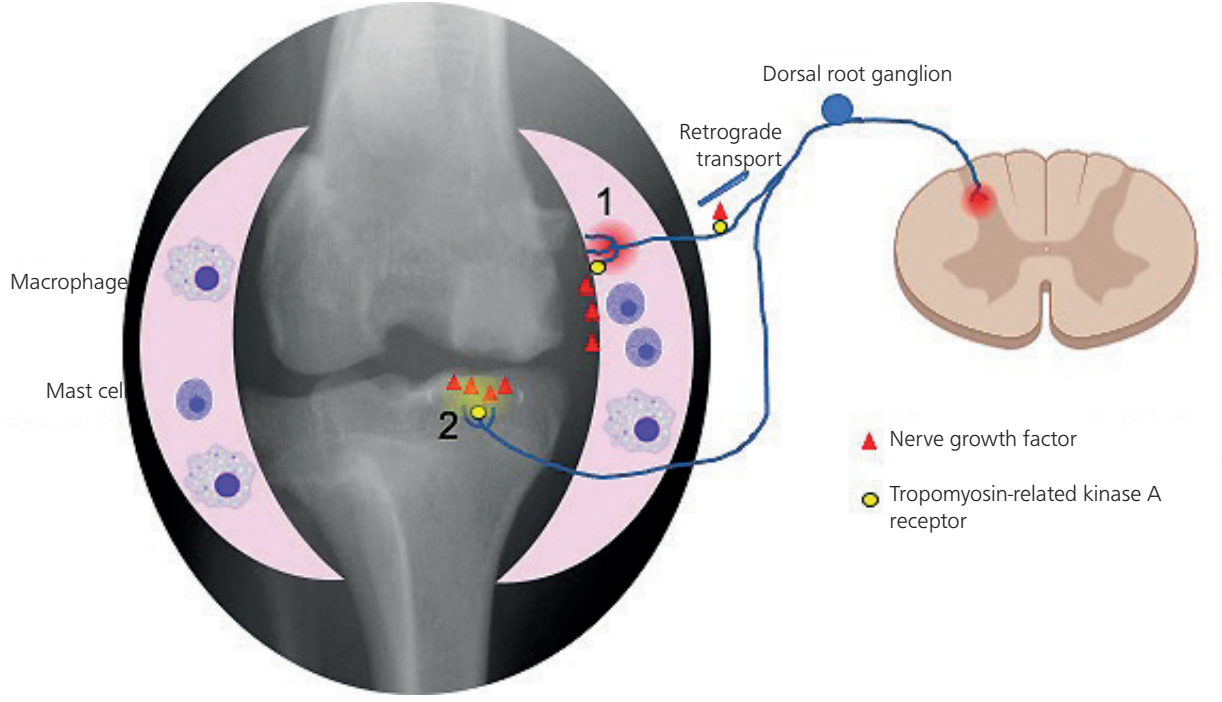

Figure 1. Proposed pain mechanisms in the osteoarthritic joint. 1) Inflammatory mediators, including nerve growth factor, are produced by inflammatory cells, including mast cells. Binding of nerve growth factor to the tropomyosin-related kinase A receptor on nociceptors results in the internalisation of the nerve growth factor-tropomyosin-related kinase A complex, causing sensitisation of the nerve ending (peripheral sensitisation). Angiotensin converting enzyme is also likely involved with angiotensin II triggering the angiotensin type II receptor and lowering the threshold for action potentials. Nerve growth factor-tropomyosin-related kinase A complex is transported retrogradely to the cell body in the dorsal root ganglion and initiates transcriptional changes. The resultant neurotransmitters (such as substance P, calcitonin gene-related peptide and brain-derived neurotrophic factor are transported both anterograde and retrograde to the nerve ending, and to the synapse in the dorsal horn respectively. 2) Chondrocytes in damaged cartilage can also produce nerve growth factor and this drives neoinnervation at the osteochondral junction.

A question remains as to the source of nerve growth factor in the arthritic joint. The synovium is often implicated as the source of joint pain since it is richly innervated and responds rapidly to an altered mechanical or biological environment within the joint. Evidence for the role of an activated innate immune system in osteoarthritis is strong and widespread (Orlowsky and Kraus, 2015; Miller et al, 2020; Vincent, 2020), but there have been surprisingly few studies that have identified the immune cells specifically driving this process and contributing to pain. One exception to this is the established role of mast cells in osteoarthritis pain by de Lange-Brokaar et al (2016). In arthritic joints, the number of mast cells is increased and these can express TrkA and secrete nerve growth factor. Therefore mast cells have a potentially important role in the pain mechanisms of osteoarthritis.

There is also evidence that chondrocytes can produce nerve growth factor and other inflammatory mediators in response to mechanical damage (so-called mechanoflammation). Furthermore, cartilage damage, particularly towards the basal layer adjacent to the osteochondral junction, causes the upregulation and release of nerve growth factor and other pain-inducing molecules to sensitise local pain fibres and induce neuronal sprouting and neoinnervation of the tissue. This aligns with the observed neoinnervation of the osteochondral junction documented in late human osteoarthritis, which relates to pain severity (Walsh et al, 2010; Aso et al, 2019, 2020). It seems likely that the source of nerve growth factor may vary at different stages of the evolution of osteoarthritis, which may explain the variable pain phenotypes that are well-documented in human patients, but less well characterised in canine or feline osteoarthritis.

Sensitisation of the peripheral sensory nerve and 'neurogenic inflammation'

Along with other pro-inflammatory cytokines, nerve growth factor can lower the threshold for nociception through TrkA-mediated sensitisation of peripheral neurons. Another key molecule thought to be involved in this process is angiotensin-converting enzyme, which is involved in the conversion of angiotensinogen to angiotensin II. This can activate the type II receptors present on pain fibres, ultimately reducing the threshold needed to fire action potentials.

After nerve growth factor binds to the TrkA receptor, the nerve growth factor–TrkA complex is internalised and retrogradely transported to the cell body where it induces transcriptional changes in the nucleus, resulting in enhanced afferent and efferent pain signalling of the sensory neuron through the production of neuropeptides such as substance P, calcitonin gene-related peptide and brain-derived neurotrophic factor. The neuropeptides are packaged in vesicles and transported in an anterograde and retrograde direction from the soma. Substance P is released at the nerve terminal, which stimulates neurokinin-1 receptors and activates macrophages, driving inflammation and forming one part of the 'neurogenic inflammation' process. In addition, when a nociceptor is triggered and an action potential is initiated, it travels in an afferent direction along the branch of the afferent axon. When the action potential meets a junction in the branched afferent axon, as well as travelling towards the cell body, it will travel in a retrograde manner towards other branches of the nerve endings causing the release of pro-inflammatory mediators. This adds a further dimension to neurogenic inflammation.

Angiogenesis and neuronal sprouting

Another phenomenon noted in various painful conditions, such as arthritis and neoplasia, is that of neuronal sprouting. Sprouting of nerve fibres has been observed in chronic skeletal pain states in human beings and animals, and likely has a role in maintaining hypersensitivity (Eitner et al, 2017; Schmelz et al, 2019). Reports suggest that during progressive disease in musculoskeletal tissues, significant sprouting of TrkA-positive nerve fibres can occur. There is evidence that endogenous stromal, inflammatory and immune cells play a significant role in this phenomenon through the release of nerve growth factor. Evidence indicates that neuronal sprouting in subchondral bone also occurs in osteoarthritis and this process is dependent on the secretion of netrin-1 from osteoclasts (Zhu et al, 2019). Nerve growth factor from basal layer chondrocytes is likely to be the directional cue for these new nerves in subchondral bone. Blocking nerve growth factor in progressive conditions, such as osteoarthritis, may therefore have the added advantage of limiting the process of neuronal sprouting in the synovium and in subchondral bone.

Angiogenesis is noted in the histopathological examination of osteoarthritis synovium and peripheral areas of the articular cartilage, as well as in the subchondral bone in late stage disease. Angiogenesis promotes neuronal sprouting and nerve growth factor may also be a mediator of angiogenesis. This may be another way in which nerve growth factor inhibition may be of value in the pathology of chronic osteoarthritis and its associated pain.

Anti-nerve growth factor therapies

For over a decade, the efficacy of blocking nerve growth factor to relieve pain in osteoarthritis in a variety of species has been recognised (Lane et al, 2010; McNamee et al, 2010; Lascelles et al, 2015; Gruen et al, 2016; Enomoto et al, 2019; von Loga et al, 2019). There are now licenced monoclonal antibodies to block nerve growth factor in dogs (bedinvetmab, Librela, Zoetis) and cats (frunevetmab, Solensia, Zoetis), which are given by monthly subcutaneous injections.

Two field studies were conducted to demonstrate the effectiveness of Librela (European Medicines Agency, 2021a). The first placebo-controlled study involved 287 dogs with osteoarthritis. The main measure of efficacy was the change in the Canine Brief Pain Inventory (Brown et al, 2008) score at 28 days post-treatment, which had to reach a certain threshold to be classified as a 'success'. Additionally, veterinarians assessed the weight-bearing ability of the dogs, the pain when dogs' limbs were touched or moved, and the general condition of the dogs in terms of mobility. The results showed an improvement in pain score in 43.5% of dogs treated with Librela, compared with 16.9% in dogs given placebo. The examinations by veterinarians also showed significant improvements in the Librela-treated group compared to the placebo group. In the second field study, 135 dogs were treated with Librela and 137 dogs received placebo. Treatment 'success' was achieved in 47.4% of Librela-treated dogs compared with 36.6% of dogs given placebo.

Solensia was investigated in three field studies (European Medicines Agency, 2021b). The pivotal field trial included 275 otherwise healthy cats with clinical signs of osteoarthritis and pain in at least two joints or spinal segments. The cats received either Solensia or placebo once a month for 3 months. The main measure of treatment success was a pain score assessed by owners, using a standard rating scale known as Client-Specific Outcome Measures (Lascelles et al, 2007). Of the cats that received Solensia, 76% had a successful treatment (defined as a reduction of at least two points in the total Client-Specific Outcome Measures score and no increase in any individual score), compared with 65% of cats that received placebo. Other studies also support the efficacy of Solensia in cats (Gruen et al, 2016; 2021).

These two agents provide veterinary surgeons with new options for the management of pain in osteoarthritis. The next few years will be interesting as veterinary surgeons come to understand the efficacy, safety and utility of these agents in patient populations.

Monitoring and measuring osteoarthritis pain in affected dogs and cats

Translating knowledge of the pain pathways in osteoarthritis allows us to target it with medical interventions, including both small molecules and monoclonal antibodies. The author strongly recommends staging the severity of osteoarthritis before commencing treatment, then using repeat staging to monitor the response to treatment. The face validity of an osteoarthritis staging tool (Canine Osteoarthritis Staging Tool) to be used by veterinary professionals has been published, but further work is required to validate this tool (Cachon et al, 2018). This staging tool uses a client-reported outcomes measure (clinical metrology instrument) such as the Liverpool Osteoarthritis in Dogs questionnaire (Hercock et al, 2009; Walton et al, 2013), or instruments such as the Canine Brief Pain Inventory (Brown et al, 2008, 2013b) or the Helsinki Chronic Pain Index (Hielm-Bjorkman et al, 2009). These client-reported outcomes measures are increasingly used in arthritis clinics, in clinical studies (Forster et al, 2012; Lascelles et al, 2015) and in regulatory clinical trials (Brown et al, 2013a). Using such instruments allows for disease staging, improved clinical records, tracking of disease progression and response to interventions, as well as better client education and engagement. The reader is referred to other sources for further information (Walton et al, 2018).

KEY POINTS

- Osteoarthritis is a common disorder of dogs and cats associated with chronic pain.
- Staging the disorder is useful to guide appropriate interventions.
- The mechanisms of pain in osteoarthritis are not fully elucidated but there is compelling evidence to implicate prostaglandins, nerve growth factor and other inflammatory mediators.
- Damage to articular cartilage can result in the production of inflammatory mediators from chondrocytes, including nerve growth factor, in a process termed 'mechanoflammation'.
- Peripheral and central sensitisation result in structural changes including neoinnervation at the osteochondral junction and in the synovium, and inflammatory changes in the dorsal root ganglion and dorsal horn of the spinal cord.
- There are now a range of therapeutic strategies that can be used to control chronic pain including non-steroidal anti-inflammatory drugs, piprants and monoclonal antibodies against nerve growth factor.

Conclusions

It is well-recognised that osteoarthritis is invariably a progressive disorder, although the rate of progression can vary markedly. The inflammatory processes described above produce a continuous cycle of degradation driven by catabolic cytokines and degradative enzymes that leads to cartilage matrix degradation. Damage to cartilage can continue to fuel the inflammatory response and induce structural changes in the synovium and subchondral bone. Along with instability, inflammation is one of the key drivers for osteophyte formation. Osteophytosis can also eventually lead to a reduction in the range of motion and have an impact on surrounding soft tissues such as the joint capsule, ligaments and tendons.

To date, there are no proven disease-modifying medicines for osteoarthritis, so once the disorder has commenced, it is expected to continue. Therefore, attention to managing chronic pain is very important for the welfare of affected animals. For these reasons, controlling pain is at the centre of strategies to limit the impact of osteoarthritis on patients. There is now a range of licenced pharmaceuticals, including classic non-steroidal anti-inflammatory drugs, piprants (dogs only) and biologicals (anti-nerve growth factor monoclonal antibodies) to manage osteoarthritis in dogs and cats (bedinvetmab and frunevetmab respectively).

Conflicts of interest

In the last 2 years, the author has performed consultancy for Altius (Romania and Bulgaria), Elanco and Zoetis.

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