Osteoarthritis pain and inflammation – the new science

In part one of a two-part series, Duncan Lascelles BSc BVSc PhD FRCVS CertVA DSAS(ST) DECVS DACVS; Scott Knauer MS; Katherine Walker BS; and Cynthia North DVM MS explore the underdiagnosis of osteoarthritis in dogs, the impact of chronic pain, and treatment options available

Osteoarthritis (OA) continues to be a significant disease, both for humans and dogs alike. The lack of therapeutics based on new targets to help manage the pain associated with osteoarthritis has been a gap for over 20 years in both the human and veterinary professions. The toll taken on the patient and family has led to increased emphasis on translational medicine, and novel approaches to understanding the molecular and cellular basis of OA and OA-associated pain. New scientific approaches, especially at the 'omics' level, have been employed to understand gene expression and subsequent protein changes associated with osteoarthritis as the disease progresses. This scientific approach has broadened our appreciation for the familiar biological processes, such as prostaglandin pathways, and has expanded our knowledge to include new biological processes and mediators demonstrated to impact the disease. The aim of this article is to update veterinarians on our understanding of these emerging signaling pathways in osteoarthritis and how this emerging science may result in new therapies for the veterinary profession.

Osteoarthritis is a disorder involving movable joints characterised by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterised by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.[1]

PREVALENCE

OA is the most common musculoskeletal disease in both humans and dogs. It is currently estimated to affect over 600 million people globally, while estimates in the late 1990s indicated that ~20% of dogs over the age of one year were affected.[2] However newer information suggests that it is almost double that. In a recent study using a canine OA screening checklist, close to 40% of dogs screened

had clinical signs of OA.[3,4] OA is, in many respects, a quiet epidemic as it is often under-diagnosed. In dogs, the underlying aetiology is related to conformational abnormalities of the joint, obesity or joint injury. Because the impact of joint conformation is such a major driver of disease, the development of OA can begin much earlier in life for dogs than what is often expected.

Another under-evaluated group are small dogs. Although they often have similar joint changes to large-breed dogs, their physical changes may be compensated for by dog owners lifting or carrying them. However, they likely still have pain related to the OA.

Dogs hide signs of pain and pet owners often overlook signs, attributing them to 'old age'. This may lead pet owners only to recognise signs very late in the disease when the signs are obvious and dramatic.

As a progressive and currently incurable disease, early diagnosis and management of OA can help reduce pain, improve mobility and improve a dog's quality of life.

BROAD IMPACT OF CHRONIC PAIN

There is now a greater understanding of the negative impact of OA pain, both in humans and dogs. In 2017, the Pain in Animals Workshop (PAW) held at the national Institute of Health (NIH) focused on chronic pain in companion animals associated with osteoarthritis, cancer, and neuropathic pain. This meeting brought together leading advocates in the areas of government, academia, industry and pain management to discuss and work on improving our ability to recognise and measure chronic pain – a fundamental prerequisite to being able to treat OA pain.

An important focus of this meeting was to highlight the multiple dimensions impacted by OA pain. In a subsequent publication, the holistic consequences of chronic pain that extend beyond the impact on gait, movement and the ability to perform the activities of daily living to include affective, cognitive and the human-animal and animal-animal bond relationships were discussed.[5] In addition, the impact on sleep and sensitivity to environmental stimuli were highlighted, along with approaches to measuring the impact of OA pain on all these dimensions.

CURRENT TREATMENT OPTIONS AND GAPS

Current treatment options have some limitations. Pharmacological treatment of pain centres around non-steroidal anti-inflammatory drugs (NSAIDs). Globally, several NSAIDs are approved for use in dogs, including the newest NSAID grapiprant. NSAIDs are used to relieve pain and promote functional improvement.[6] For many years, patients suffering from OA have benefited from this class of drugs. Despite their widespread use and clear beneficial therapeutic effects, NSAIDs are not always adequately effective when used as a monotherapy.[7] Additionally, there are safety and tolerability concerns with their use in some dogs.[8-11] Daily-administered medications can have compliance issues, with pet owners not always remembering to administer the medication, and some

Figure 1: Adapted from Lascelles BDX et al. Measurement of chronic pain in companion animals: Discussions from the Pain in Animals Workshop (PAW) 2017. The Veterinary Journal (2019) 250; 71-78.

dogs are just hard to dose orally.[12] Pet owners also may not recognise signs of pain and may elect to skip doses, resulting in intermittent and inconsistent dosing.[12] Lastly, some are labelled for use at lowest effective dose which may cause confusion as to what this means in terms of practical administration leading pet owners to drop to subtherapeutic doses for lack of knowing what signs to monitor.

Beyond NSAIDs, effective pharmacological treatment options for the control of pain are very limited.[1] Even with orally administered medications, compliance can be an issue with pet owners not always recognising signs of pain and/or remembering to administer the medication.[12,14]

A variety of putative analgesic drugs have been used to help control OA pain, mainly as adjunctive drugs in addition to NSAIDs. However, evidence for efficacy of adjunctive analgesics is extremely limited.[7,15,16] In fact, a 2018 placebo-controlled publication demonstrated that Tramadol has no clinical impact on dogs suffering from osteoarthritis of the elbow or stifle.[16] Additionally, there are few proven non-drug therapies, and none that have been shown to provide rapid pain relief.

OA related-pain remains a challenging clinical entity to treat, and indeed, OA-associated pain is one of the most common reasons for euthanasia in dogs.[17,18]

THE NEW SCIENCE OF OA DISEASE

OA has traditionally been classified as a non-inflammatory arthritis. This was based on early work that evaluated synovial fluid, comparing the quantity of inflammatory proteins in various arthritidies. Such studies showed that OA fluid had significantly lower amounts of inflammatory proteins than rheumatoid arthritis (RA) or septic arthritis samples (see Figure 2).[19,20]

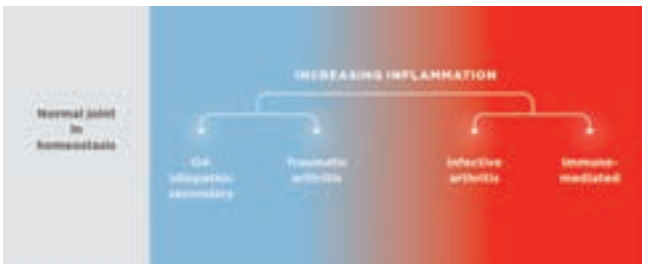

Figure 2.

It is now understood that the degree and characteristics of inflammation vary across the different arthritidies. Although largely overshadowed by the more pronounced histologic and biochemical inflammatory abnormalities in RA, studies from as early as 1959 revealed elevated levels of inflammatory plasma proteins in both the blood and synovial fluid of patients with OA20 compared to controls. More recently, the use of molecular, genomic and proteomic insights has expanded our understanding of the ongoing immune processes in OA.[21] Such research has uncovered a new molecule of interest, nerve growth factor (NGF). NGF is elevated in diseased joints,[22] it clearly plays a role in pain, and new science is emerging regarding its interactions with cells and tissues in the diseased joint.

The following section highlights new thinking in the science of OA disease: inflammation, including neurogenic inflammation, expanded understanding of the role of joint tissues, and the current understanding of the role of NGF in the osteoarthritic joint.

OA INFLAMMATION IS LOW GRADE AND CHRONIC

OA is associated with multiple risk factors, most notably conformation, joint trauma, and metabolic/obesity. These may be thought of as 'inciters' to the disease. Sokolove and Lepus (2013) have postulated that 'given its complex etiology, OA should not be thought of as a single disease, but rather as the clinical endpoint of numerous disorders leading to the eventual failure of one or more joints of the body. Even with different starting points, evidence suggests that the changes characteristic of OA share a common final pathway that operates to perpetuate joint destruction and eventual joint failure'.[21]

Once the joint faces an 'inciting factor', tissue damage occurs triggering the immune system to begin its traditional inflammatory role including the classic signs attributable to mechanical injury or infection. Acute inflammation persists for a couple of days or weeks and requires the presence of the external stimulus.

As time progresses beyond these initial weeks, the joint cells and tissues undergo transitions that ultimately lead to a state of low-grade, chronic joint inflammation that drives progression toward clinical OA.[23] It is interesting to note that this low-grade chronic inflammation is not what we typically think of when describing inflammation clinically. In clinical osteoarthritis, the normal remodeling and anti-inflammatory properties within the joint have been overcome and are in a pro-inflammatory, chronic catabolic state. Unlike RA, OA does not appear to be associated with a robust adaptive immune response. However, activation of the innate immune system is a central feature of both diseases.[21]

IMMUNE CELLS IN CHRONIC OA INFLAMMATION

The most frequent types of immune cells found in OA are macrophages, T lymphocytes and mast cells (MCs).[24] The involvement of many aspects of the immune response in OA, along with other mechanical and biochemical factors, makes OA a complex disorder.[25] Whereas the numbers of most immune cells (for example, macrophages and T cells) in synovial tissues are lower in OA than in RA, the number of mast cells in OA is as high as, or sometimes higher than, in RA.[26]

In this next section, we will discuss current theories and science related to selected cells and tissues associated with the joint, with an emphasis on how NGF affects function and responses of cells and tissues. This is not an all-inclusive examination. As stated at the beginning, this is an area of intense work and new information is coming forward at a rapid pace.

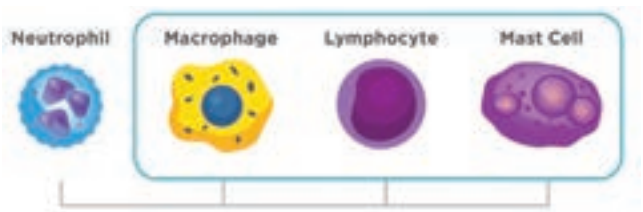

Figure 3: Cytokines (eg. TNF, IL-1β) and pain mediators (eg. NGF, PGE2, Histamine).

ROLE OF MAST CELLS IN CHRONIC OA

Mast cells are well known as effector cells of the innate immune system and are capable of producing cytokines and growth factors including NGF.[27,28] Research is emerging that dysregulation of the innate immune system, including mast cells, is likely involved in the pathogenesis of osteoarthritis.[29] Different activation stimuli lead mast cells to differentiate and respond in different ways[29], for example, a mast cell associated with allergy is different than a mast cell associated with OA joints. More research is needed to better understand mast cell's role in OA. At the synovial level, mast cells are located mainly in the synovial membrane and joint capsule, mostly along blood vessels and nerve endings of the joint.[28] Synovial mast cells interact with these blood vessels and sensory nerves. Alterations in their regulation can affect their function and physical nature.[28] Emerging evidence indicates mast cells help to orchestrate inflammation and neuroinflammation within the joint.[28,29]

Mast cells are a source of many types of growth factors. In addition to NGF, these also include vascular endothelial growth factor (VEGF) and angiogenin. It is thought that the release of angiogenin could contribute to the development of angiogenesis associated with OA.[28] The levels of these growth factors are altered in joints with chronic OA. NGF has been demonstrated to be elevated in the synovium and associated fluid of patients with osteoarthritis. This increase is correlated

with mast cell density.[28]
It has also been proposed that NGF may recruit more mast cells (acting as a chemoattractant). NGF may play an important role in mast cell's accumulation in non-allergic inflammatory conditions such as OA. It has been recognised for its ability to promote development and differentiation of immature mast cells.[24]
The dysregulation of mast cells in OA has also been implicated in the structural changes of cartilage, bone, synovia, matrix, nerve endings, and blood vessels.[28] The release of mast cell mediators, along with their proangiogenic and inflammatory effects, helps set the stage for joint inflammation.[28,29]

EMERGING ROLE OF NEURONS AND NEUROGENIC INFLAMMATION

It has long been known that there is extensive cross talk between nerves and the immune system. However, more recently this interaction is emerging as an important factor in multiple tissues effected by osteoarthritis. Neurogenic inflammation refers to the role of sensory nerves within inflammatory disease.
NGF, interacting with its two types of receptors on sensory nerve endings, induces changes to the nerves' structure, anatomy and activity. NGF binds to the high-affinity receptor tropomyosin receptor kinase A (TrkA) – see Figure 4 – and the complex is internalised and moves to the cell nucleus in the dorsal root ganglion (DRG).

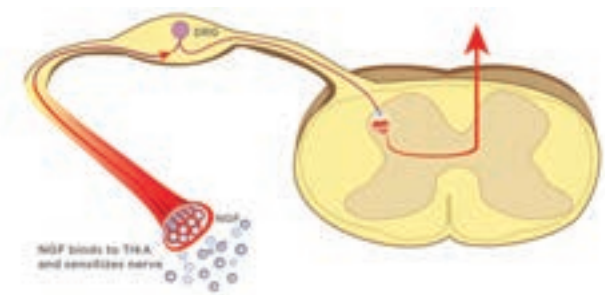

Figure 4. Image: Dr Duncan Lascelles.

There, the complexes alter the production of different proteins (through changing transcription) including upregulating the production of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) – see Figure 5.

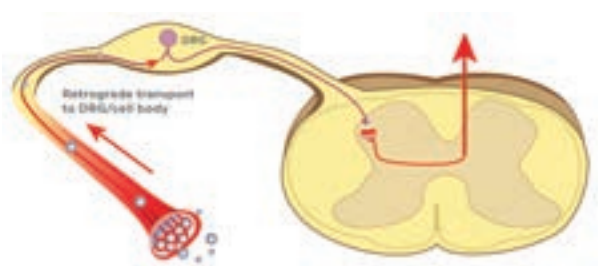

Figure 5. Image: Dr Duncan Lascelles.

SP and CGRP are then released back at the peripheral nerve ending in the joint when the nerve is stimulated, increasing local inflammation – see Figure 6.

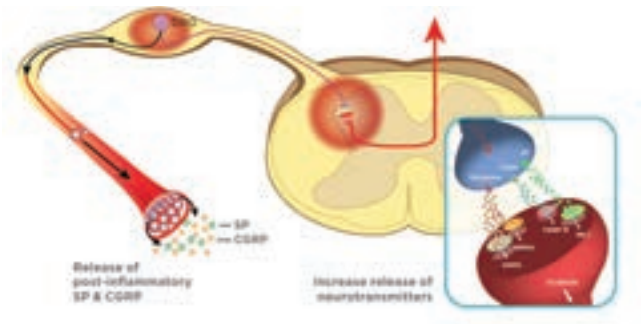

Figure 6. Image: Dr Duncan Lascelles.

This NGF-mediated increase in SP and CGRP release at the periphery means that NGF-affected sensory nerves play a greater role in neurogenic inflammation than those not affected by NGF. The action of NGF is supplemented by its binding to the low-affinity neurotrophin p75 receptor (P75NTR), which enables release of these neuropeptides.[13,28]
The changes to protein production also result in an increase in neurotransmitter release at the junction between the peripheral nerve ending (first order neuron) and the second order neuron, facilitating transfer of the signal towards the brain.[13]
By linking all of these processes together, NGF is released from the damaged cells in the osteoarthritic joint and binds to TrkA receptors on local sensory nerves inducing sensitisation of the nociceptor. In the longer term, the retrograde migration of the NGF/TrkA complexes induces the production of pronociceptor substances that may go to both the periphery and/or the junction between the first order neuron and second order neuron. This one-two punch results in increased nociceptor signaling. In addition, NGF binding to TrkA receptors on immune cells results in inflammatory mediators such as histamine, PGE and NGF itself being released. This additional NGF may bind to other immune cells and/or the nociceptor resulting in more sensitisation and inflammatory mediators.[30]

References available on request.

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