Uncovering the Sources of Osteoarthritis Pain

As osteoarthritis (OA) researchers from different specialties join forces, there has been rapid developments in the field of pain neurobiology, which is shedding light on OA pain as well.
By Anne-Marie Malfait, MD, PhD [1] and Kristin Della Volpe [2]

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An interview with Anne-Marie Malfait, MD, PhD *[1]*

Pain is the hallmark symptom of osteoarthritis (OA) and the most common reason why people with arthritis seek medical care. Osteoarthritis pain is associated with functional impairment, reduced quality of life, and a host of psychological comorbidities, including depression, anxiety, pain catastrophizing, and sleep disorders [3].[1-5]

Unfortunately, pain and global estimates of OA burden are often underestimated by physicians (see related article [4]), suggesting the need for a greater awareness of the causes and assessment of OA pain, as well as guidelines for treatment of OA pain [5].

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[6]

Studies indicate that joint damage is not the only factor correlated with OA pain, leading investigators to search for other mediating factors. Recent research supports the idea that OA pain is generated and maintained by continuous nociceptive input from the joint and that changes in the central nervous system lead to sensitization in OA.[6]

To uncover the latest findings on pain processing in osteoarthritis and how these discoveries may lead

to novel mechanism-based treatment approaches, *Practical Pain Management* spoke with Anne-Marie Malfait, MD, PhD [1]. Dr. Malfait is professor of medicine and biochemistry at Rush University Medical Center in Chicago.

Q How has the field of OA research changed in the past 2 decades?

Dr. Malfait: The concept of OA has changed from a primarily cartilage-driven disease to a whole joint disease, with pathology in all articular tissues and associated skeletal muscle (Figure). Pain in OA may not only result from innervated tissues; sensory neurons activated by factors released from cartilage, which is aneural, also may play a role.[6] In fact, magnetic resonance imaging and molecular studies have demonstrated that different joint tissues may all contribute to OA pain and pathogenesis.[7,8] Whether one of these tissues is more important than others, we don't really know.

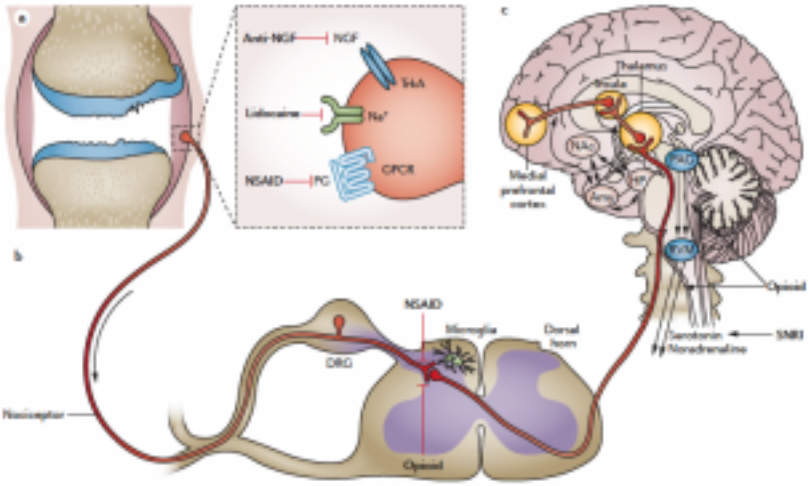

Figure. Neuroanatomy of the pain pathway and analgesic targets in OA. a) Pain signals are detected by nociceptors in the periphery and carried to the dorsal horn of the spinal cord. Various analgesics that are efficacious against joint pain act in the periphery by targeting receptors expressed at nociceptor peripheral terminals. b) The central terminals of the afferent nociceptors synapse with second-order neurons in the dorsal horn in a stratified pattern that is anatomically very precisely organized. Second-order neurons are either interneurons (not shown) or projection neurons that cross to the contralateral side and carry the signal up the spinal cord. Central sensitization can occur through the strengthening of synapses and through the loss of inhibitory mechanisms. In addition, the activation of microglia contributes to enhanced pain sensitivity. Prostaglandins can also have a sensitizing effect in the dorsal horn, and NSAIDs can thus exert central analgesic actions, in addition to their peripheral actions. Opioids can inhibit incoming pain signals in the dorsal horn. c) Projection neurons relay pain signals along the spinothalamic tract to the thalamus and along the spinoreticulothalamic tract to the brainstem. From there, the signals can be propagated to different areas of the brain, including the cortex. Descending pathways (black arrows), both facilitating and inhibitory, modulate pain transmission; descending inhibitory pathways release noradrenaline and serotonin onto the spinal circuits. SNRIs engage these descending inhibitory pathways. RVM neurons are opioid sensitive, and morphine has an analgesic effect through engaging descending inhibition.
Amy, amygdala; **DRG**, dorsal root ganglion; **GPCR**, G-protein-coupled receptor; **HP**, hippocampus; **Na**, sodium; **NAc**, nucleus accumbens; **NSAID**, nonsteroidal anti-inflammatory drug; **NGF**, nerve growth factor; **PAG**, periaqueductal gray; **PG**, prostaglandin; **RVM**, rostral ventromedial medulla; **SNRI**, serotonin–noradrenaline reuptake inhibitor; **TrkA**, tropomyosin receptor kinase A

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Another marked change is that, previously, there was little collaboration between researchers who studied joint pain and those who studied joint disease. We wouldn't go to their pain meetings, and they would not often come to our OA meetings. Researchers who studied pain used a model that OA investigators would think is irrelevant because, while it was good at inducing pain, it was more of an acute inflammation model.

For example, an irritating substance like CSA would be injected into the hind paw of a mouse, causing inflammation and subsequent pain. This would enable study of pain pathways but did not have bearing on the progressive nature of OA. Conversely, we would develop animal models of cartilage degradation, and the animals would develop joint damage and osteophytes. But rarely did we ask the question "are these animals in pain?"

Now there is a lot more collaboration between pain and joint disease researchers, and we have better models of OA that can be used to study pain mechanisms.

Q What has your research uncovered about the possible mechanisms behind pain in OA?

Dr. Malfait: We have applied a mouse model that mimics the slow progressive degeneration of OA, by destabilizing the medial meniscus, to the study of pain. We have developed many tools to see if these mice are becoming sensitized and if they are in pain. We are very carefully looking at the different stages of this mouse model (ie, early versus late OA) to determine what happens in the cartilage, bone, and synovium during disease progression. We want to study the relationship between pain and structural changes, but also are trying to determine which specific subsets of sensory neurons are involved in the beginning versus the later stages of OA. We hope to determine if we can block disease progression in any of those tissues and what effect that will that have on OA pain. Ultimately, we hope that our research will lead to stage-dependent management of OA.

While current clinical trials do not stratify by OA stage, we are now finally starting to learn from animal models that the beginning and end stage of OA might be so fundamentally different that you might as well be studying different diseases. It might be that we need to characterize or profile patients using a set of indicators or serum biomarkers to indicate if a patient is still in a mainly peripheral state, or if that patient is already centrally sensitized, so that we can start predicting which type of management patients would most benefit from.

By the time an X-ray detects joint space narrowing in a patient with OA, 10 years of pathological processes may have already occurred in the cartilage that would never be detected on an X-ray. It might be that there are signs of synovitis or, on a molecular level, subtle changes in the cartilage that current imaging methods do not detect.

Clearly, there is a structural disconnect between joint OA and pain, as patients with marked joint destruction may not feel pain while patients without radiographic evidence of OA may feel joint pain. In addition, a minority of patients still feels pain after joint replacement. This determination of whether a person with OA experiences pain may be dictated by various factors, including what stage of OA the patient is in, gender, a patient's overall metabolism, systemic inflammation in patients with obesity, or by genetic polymorphisms, as has been demonstrated in several genetic association studies by our team and others.[9-14]

In addition, research by our team and others suggests that cytokines (eg, tumor necrosis factor-α, interleukin (IL)-1, IL-6, IL-15, IL-10) and chemokines (monocyte chemoattractant protein-1) are present in the OA joint and may promote synovitis and joint destruction as well as directly activate innervating nociceptors.[15,16]

Q What has your research on potential disease-modifying agents for OA shown?

Dr. Malfait: The holy grail in OA research is to find a disease-modifying OA drug, which the US Food and Drug Administration defines as a lack of progression of joint space narrowing on radiographic imaging. Investigations into disease-modifying agents have targeted enzymes that are involved in cartilage breakdown or subchondral bone loss.[17]

We recently published research suggesting the therapeutic efficacy of blocking a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-5 with a neutralizing monoclonal antibody (mAb) in a mouse model of OA.[18] The mice were treated or untreated with anti-ADAMTS-5 mAb or IgG2c isotype control mAb starting 4 weeks after surgery to destabilize the medial meniscus. By 4 weeks, the

mice demonstrated mild cartilage degeneration, small osteophytes, and subchondronal bone sclerosis.

Progression of the degeneration was found at 16 weeks in untreated mice. However, in mice treated with ADAMTS-5 mAb from week 4 to 16 after surgery, cartilage degeneration and osteophyte growth was slowed; no effect of subchondral bone sclerosis was found. In addition, treatment with ADAMTS-5 mAb was linked to temporary reversal of mechanical allodynia, which was correlated with decreased monocyte chemoattractant protein (MCP)-1 production—a marker of sensitization in dorsal root ganglion neurons.

Q Where do you think the field of OA research is headed in the next 5 to 10 years?

Dr. Malfait: I think it is very exciting that pain and OA researchers are joining forces, and the rapid developments in the field of pain neurobiology will hopefully shed light on OA pain as well.
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