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EDITORIAL

Arthritis Pain: Moving Between Early- and Late-Stage Disease

David A. Walsh

Joint pain remains the main problem for people with arthritis, despite availability of an increasing range of analgesic medications acting through discrete molecular targets. Existing treatments can relieve pain for some but not all people with arthritis, some but not all of the time. There remains a pressing need for better treatments to reduce the distress and disability of arthritis pain. Pain, however, also importantly warns us about and protects us from injury, and painkillers therefore need to target pathologic pain in the right people at the right times. In this issue of *Arthritis & Rheumatology*, Miller et al (1) provide important evidence that different types of pain might respond differently to the pharmacologic manipulation of a single analgesic target at various stages in the development of experimental osteoarthritis (OA) in mice. These preclinical findings resonate with observations in people with arthritis, and they point the way to how animal models and sophisticated interventional and measurement techniques might lead to new treatments and to more effective use of existing treatments in the foreseeable future.

Miller et al chose to explore pain transmitted through the abundant subset of articular sensory primary afferents that express voltage-gated sodium channel 1.8 ($Na_V1.8$). Using designer receptors exclusively activated by a designer drug technology, they selectively stimulated $G_{i/o}$ protein signaling in order to reduce peripheral sensory nerve activity. They found that they could reduce pain behaviors at various time points after surgical destabilization of the medial meniscus (DMM) in mice, sometimes to an extent similar to the analgesic effects observed with morphine. Morphine also activates $G_{i/o}$ proteins, but across a wider range of nerve types in the peripheral and central nervous systems. All of this is as might have been expected. Perhaps more importantly, Miller and colleagues' carefully conducted studies reveal that the effects of pharmacologic activation of $G_{i/o}$ varied according to the type of pain behavior measured and the time since DMM surgery. Indeed, significant analgesic effects were only observed before 12 weeks after surgery, and not at 16 weeks, a time point generally considered to represent late-stage OA in humans. In contrast, an analgesic acting on both peripheral and central nerves was able to inhibit pain behaviors at all time points.

Pain is not a single and homogeneous experience, and people with arthritis describe different types of pain, including pain on weight bearing, joint movement, or at rest, as well as aching pains or burning pains. Different pain qualities might well reflect different underlying pain mechanisms (2). Pain quality is not measurable in animal models, but various pain behaviors have also been associated with different pathophysiologic mechanisms. A reduced threshold for paw withdrawal from a normally non-noxious punctate stimulus has been associated with evidence of central sensitization in rodents and is consistent with low pain thresholds to mechanical stimuli distal to an OA joint in humans (3). Reduced threshold to mechanical pressure on a mouse's knee might model increased joint line tenderness in human arthritis, a characteristic interpreted in rheumatoid arthritis as a sign of active synovitis. Miller and colleagues' data suggest that both of these types of pain might at least sometimes be dependent on $Na_V1.8$-expressing peripheral sensory nerves and suppressible by $G_{i/o}$ activation.

Unfortunately, many analgesic interventions that have shown great promise in animal models have failed to impress through randomized controlled trials in arthritis in humans. Many explanations have been proposed for this

David A. Walsh, PhD, FRCP: Arthritis Research UK Pain Centre, University of Nottingham, Nottingham, UK.
Address correspondence to David A. Walsh, PhD, FRCP, Arthritis Research UK Pain Centre, University of Nottingham Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK. E-mail: David.walsh@nottingham.ac.uk.
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lack of translational success from laboratory to clinic. Clearly, humans are different from mice, and pain mechanisms in humans might differ fundamentally from those in rodents. Animal models of arthritis pain are designed to minimize suffering of the animal, and the protracted time course of human arthritis is ideally avoided in experimental studies. Miller and colleagues' data highlight that findings in mouse models might also not translate to other time points within the same model. In the same way, effective analgesics in acute pain in humans might not provide benefit for chronic arthritis pain. Opiates, which also act through $G_{i/o}$ proteins, are effective in acute musculoskeletal pain but have limited and typically only very partial benefit for chronic pain in humans, for example, in OA or low back pain. Their underwhelming benefit might partly be attributed to tolerance with chronic use and to adverse events. It is also important to consider that they might not work simply because different pain mechanisms are at play.

So what additional mechanisms might contribute to chronic arthritis pain? Miller et al rightly draw attention to possible central pain mechanisms. Arthritis pain is probably not often centrally initiated, in contrast to chronic pain after cerebrovascular accident. Central mechanisms can, however, importantly augment evoked pain, both allodynia (pain in response to a normally non-noxious stimulus) and hyperalgesia (increased pain experienced with a standardized noxious stimulus). Evoked pain requires an intact peripheral sensory system, and therefore allodynia and hyperalgesia can be inhibited by peripherally acting analgesics as well as by agents targeting central pain processing. Inhibiting $Na_V1.8$-expressing neurons increased paw withdrawal thresholds during the early phases of the DMM model, again demonstrating that at least some centrally augmented pain might be improved by peripherally acting analgesics. Evidence of central sensitization is commonly observed in severe, late-stage OA in humans but does not preclude pain relief from joint replacement surgery, an intervention specifically designed to reduce peripheral nociceptive inputs. However, not all people undergoing arthroplasty experience adequate pain relief, suggesting that non-nociceptive inputs from the postsurgical joint might continue to be sufficient to activate central pain pathways (allodynia). With increasing chronicity, central pain augmentation might lose its dependence on peripheral nociceptive input, perhaps due to structural change within the central nervous system (4) or long-lasting functional change, as might be driven by epigenetic modifications (5). Identifying these mechanisms of chronicity could lead to novel interventions that maintain capacity for neuronal plasticity and permit reversal of chronic pain.

Another possibility is that peripheral pain mechanisms change during the progression of arthritis. Miller et al comment on a predominant role of inflammation in the early stages of the DMM model. Synovitis is also a characteristic of established OA in humans; it is associated with OA pain (6), and pain relief may be achieved at least in some patients through antiinflammatory medications (either delivered systemically or by intraarticular injection). The contribution of subchondral bone to OA pain might vary between early and late disease, when the osteochondral junction is breached and bone marrow lesions are associated with regions of cartilage defects (7). Sensory nerve terminals might eventually grow into articular structures that are not innervated in the normal joint, for example, in the inner regions of knee menisci or in noncalcified articular cartilage, becoming exposed to unaccustomed mechanical or chemical stimuli (8). Gene expression patterns in dorsal root ganglia also change through the development of arthritis (9,10), and $G_{i/o}$ activation might have less potential to inhibit nociceptive drive once different nerve types and signaling pathways become recruited. Better understanding of peripheral pain mechanisms might lead to novel treatments for chronic arthritis pain. If those mechanisms are specific for chronic (pathologic) rather than acute pain, analgesics might be developed that do not impair normal protective responses (and might even lack acute analgesic efficacy) despite offering relief to those with chronic arthritis.

Animal models are developed to mimic a particular human condition, and the DMM model was devised to resemble human OA. It reflects how internal derangement in human knees can lead to OA, although the time course for OA development in humans is usually much more protracted than that observed in mice. Indeed, by 16 weeks, the histologic, molecular, and behavioral characteristics of the DMM model closely resemble those of late-stage human OA. It is less clear, however, to what extent pathologic changes shortly after surgery reflect those in the more common, idiopathic forms of OA seen in humans. Despite these reservations, the early time points in the pathogenesis of the DMM model might give useful insights into other painful articular conditions, for example, sports injuries and inflammatory joint disease. Specific analgesic approaches might only be effective at specific times for specific symptoms in OA, but they might additionally be effective for other diagnostic groups that share discrete pain mechanisms.

Miller and colleagues are to be congratulated for their well-designed and thought-provoking research. Like much of the best research, it might raise more questions than are answered, but the direction of travel is clear. Each increment to our understanding is leading us to better explain why different people might respond differently to the same intervention and, ultimately, who will be most likely to benefit from which interventions and when. What can be seen by some as inconsistency or lack of

robust translational validity in animal models might better be seen as modeling the heterogeneity of the human experience of arthritis pain. Understanding this heterogeneity should lead us ever closer to a more effective and personalized approach to rheumatology.

AUTHOR CONTRIBUTIONS

Dr. Walsh drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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