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Mechanisms for Joint Pain in Rheumatoid Arthritis (RA): from Cytokines to Central Sensitization

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Abstract

Purpose of review—Pain in rheumatoid arthritis (RA) may be due to different etiologies, ranging from peripheral inflammation to dysregulation of central nervous system (CNS) processing. This review evaluates relevant literature published on RA pain mechanisms in recent years.

Recent findings—Despite successes of disease-modifying anti-rheumatic drugs (DMARDs), pain persists for many RA patients. Studies involving patient-reported outcomes, quantitative sensory testing and neuroimaging indicate that, in addition to joint inflammation, abnormalities in CNS pain processing may contribute to pain. Some DMARDs (e.g., janus kinus inhibitors) may work via multiple pathways to decrease pain. Adjunctive treatments (e.g, antidepressants, antiepileptics) may also be useful in managing pain in RA patients with well-controlled disease.

Summary—Both peripheral and central mechanisms play key roles in the expression of pain in RA. To effectively manage pain, physicians need accurate assessment tools to identify the pathways involved in each patient so that treatments may be appropriately targeted.

Keywords

Pain; Rheumatoid Arthritis; Disease Activity; Inflammation

Introduction

Rheumatoid arthritis (RA) is one of the most common forms of arthritis, with prevalence rates between 0.3-4.2%, depending on the population studied [1, 2], Severe, chronic joint pain is a debilitating manifestation of RA and is often cited as a primary patient concern [3]. Pain classically occurs in the small joints of the hands, wrists and feet, and sometimes the elbows, shoulders, neck, knees, ankles, or hips. Because pain from RA is traditionally thought to be a direct result of peripheral inflammation, physicians have historically

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considered pain a marker of inflammation. Numerous randomized controlled trials have reported significant pain reduction associated with treatment with disease-modifying antirheumatic drugs (DMARDs), but many patients still experience clinically meaningful levels of remaining pain despite treatment [4]. A study from the British Society for Rheumatology Biologics Register reported that bodily pain scores improved in both RA patients started on biologic DMARDS, as well as RA patients started on non-biologic DMARDs [5]. However, after one year of treatment, pain scores in both groups continued to be greater than 1 standard deviation worse than the general population average. These patterns were noted even among individuals with moderate to good responses to DMARD treatment, assessed by the European League of Rheumatism (EULAR) response criteria, EULAR remission criteria, and absolute values of swollen joint count and erythrocyte sedimentation rate. In addition, many studies have shown discordance between physicians' assessments of inflammation and patient-reported pain [6, 7], and pain intensity is only weakly correlated with serum C-reactive protein levels [8]. Taken together, these results indicate the importance of evaluating pain, even among patients with well-controlled inflammation.

Pain Mechanisms in RA

RA pain arises from the interplay between joint pathology and the processing of pain signals by peripheral, spinal, and supraspinal pain pathways. The intensity, distribution and character of perceived pain ultimately depends on a combination of the direct activation of peripheral nociceptors, as well as modulation of the sensitivity of neurons throughout the nociceptive pathway, both peripherally and centrally. "Allodynia" is the term used to describe heightened pain sensitivity when stimuli that were previously not painful are perceived as painful. "Hyperalgesia" is the term used to describe heightened pain sensitivity when nociceptive stimuli that were previously perceived as mildly pain are now perceived as more painful.

Nociceptive pain and peripheral sensitization

Peripheral pain mechanisms include the direct activation of nociceptors, as well as sensitization of nociceptors by joint inflammation [9, 10]. Local immune cells secrete inflammatory cytokines along with additional molecular mediators that act on the peripheral nerve terminals of nociceptor neurons. In response to the inflammatory mediators, intracellular signaling pathways lead to a phosphorylation cascade, which reduces the threshold for nociceptor neurons to generate action potentials, ultimately leading to heightened pain sensitivity [11].

Several inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), interleukin-6 (IL-6) and interleukin-17 (IL-17), can directly alter the responses of nociceptive neurons [12]. In animal models, receptors for TNF-a, IL-1β, and IL-17 have been identified on sensory neurons [13–15], and dorsal root ganglion neurons express a transmembrane signal-transducing subunit that binds to the IL-6-IL-6 receptor complex [16]. Furthermore, injection of TNF-α, IL-6 and IL-17A into normal rat knees results in increases in C-fiber action potential frequency when the knees are rotated in

a non-painful manner (less rotation) and in a painful manner (more rotation) [17–19]. Injection of IL-1β also increases C-fiber action potentials frequency, but only in response to painful rotation [20]. A more nuanced understanding of how neuroimmune mechanisms produce peripheral sensitization may lead to more effective management strategies for pain.

Central nervous system regulatory mechanisms

Central causes of pain arise as a result of abnormalities in the central nervous system (CNS) pain regulatory mechanisms. Similar to peripheral sensitization, dysregulation of the CNS pain pathways (e.g., inactivation or over-activation) can lead to hyperalgesia and allodynia, and an imbalance between pain pathways that facilitate pain and those that inhibit pain may underlie conditions associated with chronic pain [21, 22]. Three primary categories of CNS pain regulatory mechanisms are: (1) descending facilitatory pathways, (2) descending inhibitory pathways, and (3) central sensitization. The descending facilitatory and inhibitory pathways travel from the brain through the brainstem to the spinal cord. Two key regulatory centers are the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). The PAG receives input from the frontal cortex, amygdala, and hypothalamus about factors, such as stress and mood, which influence pain perception [21]. The PAG integrates this information and transmits signals to the brainstem and RVM, resulting in the release of the neurotransmitter serotonin. The RVM can act to inhibit and/or facilitate pain, depending on the specific pathways that are activated. For example, studies suggest that proteins (e.g., brain-derived neurotrophic factor) and peptides (cholecystokinin) in the RVM are key players in the descending facilitatory pain pathways, whereas norepinephrine and the endogenous opioid peptides are important mediators of pain inhibition in the RVM [23]. The third CNS pain regulatory mechanism, central sensitization, occurs in the dorsal horn of the spinal cord, resulting in expansion of receptive fields and enhanced pain sensitivity. Two primary phases exist: 1) an acute phase mediated by the activation of N-methyl-D-aspartate (NMDA) receptors by glutamate, and 2) a chronic phase mediated by the transcription of pain-regulating peptides and activation of spinal microglia [24].

While numerous studies have assessed CNS pain mechanisms in fibromyalgia and research on the CNS pain mechanisms in osteoarthritis is increasing [25–27], research assessing central pain in RA is still in its infancy. Recent studies suggest that non-inflammatory factors may play just as much of a role as inflammation in maintaining pain. A deeper understanding of the non-inflammatory causes of chronic pain in RA is essential in improving treatment.

Animal Models of Rheumatic Pain

In numerous preclinical pain studies, arthritis animal models have been used to experimentally assess the inflammatory mechanisms that cause chronic pain [28]. Spontaneous arthritis models have primarily focused on the K/BxN and TNF-transgenic mouse model, while the leading inducible animal arthritis models include collagen-induced, adjuvant-induced, pristane-induced, and antibody-induced arthritis models [28, 29].

In a recent study by Wigerblad et al., researchers injected mice with murinised monoclonal autoantibodies against citrullinated proteins (ACPA), purified antibodies from human RA

patients, or antibodies from healthy individuals [30]. Mice were then treated with the CXCR1/2 (interleukin (IL) 8 receptor) antagonist reparixin. Mice injected with human or murinised ACPA developed increased sensitivity to mechanical, heat, and cold stimulation, which lasted at least 25-28 days, despite no physical signs of joint or systemic inflammation. The authors interpreted these results to indicate that ACPA may directly induce pain via a pathway separate from inflammation. If these findings can be replicated, they may lead to the discovery of new targets for novel analgesic drugs to treat pain in patients with RA.

Also using mice as a model system, Su et al. characterized neuropeptide expression levels in the dorsal root ganglia and spinal cord, after the induction of an inflammatory arthritis with an anti-collagen type II monoclonal antibody cocktail [31], Whereas arthritis was only evident through day 34, sensitivity to a mechanical pain stimulus remained for 48 days, indicating that factors beyond active peripheral joint inflammation are involved in the maintenance of pain. Specifically, the expression of the neuropeptides galanin, calcium channel subunit α2δ1, and growth-associated protein 43 were all elevated during the acute inflammatory phase as well as in the late stage, after arthritis had resolved but pain remained. These peptides have been associated with the development of neuropathic pain in previous studies [32–34] and may point towards a mechanism for the development of chronic, non-inflammatory pain in individuals with inflammatory arthritis.

Ghilardi et al. examined the effects of nerve growth factor (NGF) on sensory and sympathetic nerve fiber sprouting in the knee joints of mice injected with complete Freund's adjuvant (CFA) to induce inflammatory arthritis [35]. Twenty-eight days after CFA-injection, the density of macrophages ($CD68^+$), blood vessels ($CD31^+$), and nerve fibers ($CGRP^+$, $NF200^+$, $GAP43^+$, TH^+) was significantly increased. Anti-NGF treatment, given intraperitoneally, successfully blocked ectopic nerve fiber spreading and reduced pain behaviors. These results indicated that NGF may play a role in the development and maintenance of arthritis pain [35].

Humans Studies of RA Pain

In human studies, multiple assessment tools have been used to investigate the factors contributing to persistent pain in RA. These include questionnaire and physical exam-based measures, quantitative sensory testing (QST), and neuroimaging. Each of these methods is reviewed below.

Questionnaire and physical exam-based measures

Given the increasing recognition that pain persists despite effective inflammatory response to RA treatment, researchers have turned their attention to the development and use of assessment tools that can differentiate between inflammatory pain and pain due to other causes. In a study of 1,189 patients, McWilliams et al. proposed using the proportion of the Disease Activity in 28 joints (DAS28) attributable to patient reported components (e.g., VAS for patient global assessment of disease activity and tender joint count) as a measure of non-inflammatory contributors to disease activity assessment [36]. They found that a high proportion of DAS28 scores attributable to patient reported components was associated with lower likelihood for pain improvement. Based on this observation, the authors suggested that

the proportion of the DAS28 attributable to patient reported components may represent pain sensitization due to central causes, such as fibromyalgia, rather than inflammation itself.

In a study by Ahmed et al., researchers investigated the use of a survey combining the visual analog scale (VAS) for pain intensity and the painDETECT questionnaire [37]. Over 50% of patients reported pain levels ≥ 54/100, even though they were on stable DMARD therapy with well-controlled clinical disease activity (mean DAS28 2.07 ± 0.9). In addition, a large number of patients had symptoms consistent with possible or likely neuropathic pain, based on painDETECT scores. From these data, the authors concluded that many RA patients may be sensitized to pain, resulting in high overall pain scores, despite good control of inflammation with DMARDs. It should be noted, however, that the painDETECT questionnaire was originally developed to assess neuropathic pain in individuals with low back pain and other chronic pain conditions [38-39]. While some researchers have used the painDETECT questionnaire to represent pain due to central nervous system (CNS) sensitization [40 - 42], controversy still exists regarding the appropriateness of using an instrument developed for neuropathic pain as an assessment of central pain sensitization. Furthermore, neither of the above studies assessed pain sensitization using quantitative sensory testing (QST) or neuroimaging, as described below.

Quantitative sensory testing (QST)

QST is a method that identifies abnormalities in pain regulatory mechanisms by assessing pain in response to quantifiable noxious stimuli [43]. Three of the most commonly used QST paradigms are the assessment of pain thresholds, temporal summation, and conditioned modulation.

Pain thresholds—The pain threshold is defined as the point at which a particular sensation first becomes painful. Higher pain thresholds reflect lower pain sensitivity. Many types of stimuli can be used to assess pain thresholds, including pressure, heat, cold, and ischemia. One of the most commonly used stimuli to assess pain thresholds in RA is pressure, as it is thought to be most reflective of arthritis pain. Using the ascending method of limits, a probe is pressed against an area of skin and increasing pressure is applied at a constant rate (typically 1 kg/sec), until the pain threshold is achieved [44]. Utilizing this method, pressure pain-detection threshold (PPTs) may be measured to identify the intensity required for blunt pressure stimuli to induce pain.

In a study conducted by Joharatnam et al., investigators measured PPTs at the knee, tibia, and sternum for 50 patients with stable RA, all on DMARD treatment [45]. Enhanced sensitivity to pressure pain was observed at both joint and non-joint sites, and low PPTs (high pain sensitivity) were associated with higher tender joint counts, worse patient assessment of global health, greater severity of fibromyalgia symptoms, and more severe depression. Taken together, these observations points towards a potential role for pain centralization in RA.

Temporal summation—Temporal summation (TS) is a commonly used experimental paradigm that assesses pain sensitivity following repeated exposure to a noxious stimulus. TS is a natural neurophysiological phenomenon and is thought to reflect summation of C-

fiber responses as a result of short inter-stimulus intervals, such that the initial post-synaptic potential does not completely dissipate before exposure to the next stimulus. Thus, repetitive exposure to the painful stimulus results in increasing perceived pain intensity, even though the stimulus itself remains the same [46].

To date, studies comparing TS scores between RA patients and healthy controls have yielded conflicting results. While some studies have reported that RA patients have higher TS scores than healthy controls, consistent with heightened central sensitization [47], other studies have reported comparable TS scores between RA patients and healthy controls [48]. In a study by Christensen et al., 102 RA patients underwent evaluation of TS, as well as US Doppler assessment of synovitis prior to DMARD initiation [49]. These measures were then examined as predictors of treatment response at 4 months after DMARD initiation. Although higher baseline US Doppler scores predicted greater improvements in disease activity ($P < 0.05$), baseline assessments of TS were not associated with changes in disease activity. These results supported the authors' original hypothesis that subclinical inflammation, assessed by US Doppler, is a prognostic marker for response to DMARD treatment, but the data did not support a role for TS in predicting treatment response. As TS can be a highly variable measure and heightened TS may only be present in a subgroup of individuals, it is possible that this study was not sufficiently powered to see an association. More studies utilizing TS measures are needed.

Conditioned modulation paradigms—Conditioned modulation paradigms (CPMs) are used to assess descending inhibitory pain pathways. These paradigms involve 2 noxious stimuli: 1) the conditioning stimulus, which activates the descending inhibitory pathways, and 2) the test stimulus, which measures pain sensitivity pre- and post-conditioning stimulus. In healthy individuals with properly functioning descending inhibitory pain pathways, the post-conditioning test stimulus is perceived as less painful than the pre-conditioning test stimulus because the conditioning stimulus has activated the descending inhibitory pathways, decreasing pain sensitivity. In individuals with chronic pain conditions, the descending inhibitory pain pathways may not be functioning appropriately. As a result, the decrease in pain sensitivity following exposure to the conditioning stimulus may be diminished. In a study of 58 female RA patients, age-matched with 54 female healthy controls, Lee et al. reported that RA patients experienced impaired CPM (median = 0.5 kg/cm^2) compared to healthy controls (median =1.5 kg/cm^2). Using mediation analyses, the same authors noted that low CPM levels in RA patients may be attributed in part to sleep disturbances ($P = 0.04$) [50]. However, this was a cross-sectional study, so no causal inferences could be made.

Utilizing all 3 QST experimental paradigms described above, Lee et al. examined 139 subjects at 5 academic medical centers across the US, in the largest comprehensive study done to assess pain sensitization in RA [51]. PPTs at both joint and non-joint sites were inversely correlated with disease activity, measured by the Clinical Disease Activity Index (CDAI), a composite measure of tender joint counts, swollen joint counts, evaluator global assessment and patient global assessment of disease activity. High temporal summation at the forearm was also associated with high disease activity measures, whereas CPM was not associated with CDAI and only marginally associated with tender joint count. Based on

these data, Lee et al. concluded that pain sensitization may impact assessment of disease activity and/or vice versa. Longitudinal data are needed to elucidate the effect of pain sensitization on disease activity, particularly as an assessment of treatment response.

Neuroimaging

In addition to QST, a variety of neuroimaging techniques have enriched our understanding of pain in RA [52, 53]. The most commonly used technique is magnetic resonance imaging (MRI), which can assess both structure and function. Researchers use structural scans to measure the size of different brain regions, enabling comparisons of brain volume between different populations (e.g., individuals with chronic pain vs. those without chronic pain). Functional MRI (fMRI) scans are used to assess changes in blood flow, which can be used as proxies for neural activity. Together, these techniques have led to the identification of several brain regions and neural pathways that are activated among individuals with chronic pain.

To assess structural organization of the brain in 31 RA patients compared to 25 age- and sex-matched controls, Wartolowska et al. used a technique called voxel-based morphometry to measure the volume of different brain regions [54]. Compared to controls, RA patients had larger volumes of subcortical gray matter structures, including the caudate nucleus, putamen and nucleus accumbens. These regions are areas important in the affective, cognitive, and sensory-discriminative processing of pain [55]. These findings could represent chronic changes in brain structures in response to long-term exposure to pain. Alternatively, these differences could be due to other factors that differ between RA patients and healthy controls (e.g., inflammation, medications, physical activity levels). Studies examining correlations between the volume of brain regions and clinical characteristics (e.g., measures of pain intensity, inflammation and mood) may better delineate the cause of these differences, though examining correlations with current measures may not suffice, as these changes may evolve over long periods of time.

In contrast to structural changes in the brain, functional changes in the brain likely occur more rapidly and may be more amenable to assessment of correlations with clinical characteristics and outcomes. Schweinhardt et al. used fMRI to identify the effects of depressive symptoms on: a) neural activations in the brain, and b) pain distribution, measured by the tender-to-swollen joint ratio [56]. Depressive symptoms were significantly associated with both fMRI-assessed activation of the medial prefrontal cortex (MPFC), as well as the tender-to-swollen joint ratio. In addition, a post-hoc mediation analysis indicated that the effect of depressive symptoms on joint pain distribution was through MPFC activation. Based on these results, the authors suggested that the MPFC may be an important center for the emotional processing of pain in RA. This conclusion is consistent with other reports of the role of MPFC in pain processing in other chronic pain syndromes [57, 58].

fMRI studies have also revealed clues to understanding how TNF-α inhibition can quickly improve pain symptoms in RA patients, before changes in inflammation are detected. In a small study of five women with RA, Hess et al. reported that blood oxygen level-dependent signals, which serve as proxies for neural activity, were diminished in the somatosensory cortex, cingulate cortex and insula within one day of infliximab infusion [59]. Similarly,

pain intensity also decreased within 24 hours. However, measures of inflammation, including joint swelling, did not respond to TNF-α inhibition until day 14. Based on these findings, the authors concluded that TNF-α inhibition alters nociceptive brain activity before decreasing peripheral joint inflammation. This study, however, was small and did not include a control group of RA patients who did not receive a TNF-α inhibitor. Thus, these further studies are needed before conclusions can be made regarding the role of TNF-α inhibitors on CNS regulation of pain.

Treatment

To date, the treatment of pain in RA patients has mostly focused on treating inflammation to indirectly treat pain. Recently, however, it has been suggested that some DMARDs, notably janus kinase inhibitors, may also have direct effects on pain. In a clinical trial of the janus kinus inhibitor baricitinib versus the TNF inhibitor adalimumab versus placebo (RA-BEAM), pain intensity was significantly lower among RA patients in the baricitinib arm than RA patients in the control arm at 1 week, with significant differences seen through 52 weeks [60, 61]. A follow-up analysis of the same clinical trial data was presented at the 2017 American College of Rheumatology Annual Meeting, showing that factors beyond reductions in inflammation likely contribute to the pain-relieving properties of baricitinib, though the exact mechanisms are still unknown [62].

In addition to DMARDs, other types of medications may be needed to treat pain, depending on the underlying cause of pain. A study by Lee et al. evaluated the efficacy of milnacipran, a serotonin norepinephrine reuptake inhibitor (SNRI), for treating widespread pain in RA [63]. Milnacipran is FDA approved for the management of fibromyalgia, a chronic pain syndrome, characterized by abnormalities in central pain processing. However, it is not FDA approved for the treatment of pain in RA, and most studies examining the efficacy of milnacipran for pain treatment have specifically excluded individuals with systemic inflammatory conditions, such as RA [64-66]. This study was a double-blind, crossover study in which 43 subjects on stable RA medications were randomized to take milnacipran 50 mg twice daily or placebo for 6 weeks [63]. Participants then underwent a 3-week washout period and crossed over to the other treatment (placebo or milnacipran) for another 6 weeks. In the overall study cohort, milnacipran did not lessen pain compared to placebo. However, in the subgroup with well-controlled inflammatory disease (baseline swollen joint count ≤ 1), a significant reduction in pain was observed after 6 weeks of milnacipran vs. placebo. These results indicate that identifying the underlying origins of pain, specifically inflammatory vs. non-inflammatory pain, can have an important impact on identifying the most appropriate management plan for treating pain in RA.

Conclusions

With the development of increasingly effective DMARDs in recent years, pain due to active joint inflammation is becoming more treatable. However, as addressed throughout this review, many patients continue to have persistent pain, which may be related to non-inflammatory processes, such as joint damage and dysregulation of CNS pain regulatory

pathways. Additional research is needed in this area to further improve quality of life among individuals with RA.

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Compliance with Ethical Guidelines

Conflict of Interest

Yvonne Lee reports grants from National Institutes of Health grant (R01AR064850) during the conduct of the study; grants from Pfizer, and is an unpaid member of an advisory board for Lilly Angela Zhang declares no conflict of interest.

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