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Why It Hurts
The Mechanisms of Pain in Rheumatoid Arthritis

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KEYWORDS

• Rheumatoid arthritis • Pain mechanisms • Algogens • Central nervous system

KEY POINTS

- Rheumatoid arthritis-related inflammation can reduce the threshold for nociceptors to transmit action potentials, resulting in increased pain sensitivity or hyperalgesia.
- In addition to articular processes, spinal ,and supraspinal processes may play an important role in the modulation of pain in rheumatoid arthritis.
- Immune-mediated processes in rheumatoid arthritis may sensitize the nervous system even before joint inflammation is detected, and this may persist despite the resolution of joint inflammation.
- Quantitative sensory testing and neuroimaging are commonly used methods to study different pain mechanisms in rheumatoid arthritis.

INTRODUCTION

Pain is an important manifestation of inflammation, because inflammatory cytokines and mediators activate and sensitize primary afferent neurons.[1] It should thus not be surprising that pain is nearly a universal feature of rheumatoid arthritis (RA), particularly in those experiencing a flare of the disease. However, ongoing and/or severe inflammation may not suffice to explain pain in some patients with low disease activity who would otherwise be considered to be in remission. It has been noted that up to 40% of patients with RA are regular users of opioid medications,[2,3] with an increase noted in recent years.[2] Although targeted therapies have significantly improved our ability to treat the underlying inflammatory processes and their complications, pain management options have not increased proportionally.

Traditionally, pain in RA was presumed to be primarily driven by peripheral inflammation. One of the first mentions of inflammatory pain was suggested by a 1965 study conducted by Fremont-Smith and Bayles.[4] In this study, the anti-inflammatory effect of acetylsalicylic acid was of greater therapeutic importance than its concurrent analgesic effect in a study of 12 patients with RA who reported improvement in ring size,

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range of motion, grip strength, and finger volume when treated with high-dose acetylsalicylic acid. However, the recent literature suggests that there is likely a distinct contribution of central pain mechanisms that are in addition to and should be distinguished from that directly arising from peripheral inflammation.[5] When caring for patients with RA, physicians must be familiar with the myriad of contributors to pain. This point is particularly important, because many patients continue to report clinically significant levels of pain despite excellent control of peripheral inflammation.[6]

NOCICEPTION AND TYPES OF PAIN

Pain is a complex and multifaceted experience,[7] composed of both sensory and emotional components.[8] To understand pain, one must first understand nociception, which is the nervous system's process of encoding noxious stimuli owing to impending or actual tissue damage.[1] Nociception contributes to the pain experience but is not equivalent to pain,[7] which is a highly individualized experience that is impacted by multiple factors, including sleep, psychosocial distress, and past circumstances.[2]

Pain can be subdivided into 3 broad categories that may be particularly applicable for those with rheumatic diseases.[9] Nociceptive pain arises from actual or threatened damage to non-neural tissue and occurs as a result of the activation of nociceptors. In contrast, neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. More recently, a new descriptor of pain, termed nociplastic pain, was added to the taxonomy. Nociplastic pain is defined as pain that arises from altered nociception despite there being no clear evidence of actual or threatened tissue damage or a lesion of the somatosensory system.[10] Nociplastic pain may be relevant to certain patients seen in the rheumatology clinic, particularly those with nonspecific back pain, nonspecific peripheral joint pain, and fibromyalgia.[9] Some pain specialists also use the term mixed pain to define pain with an overlap of nociceptive and neuropathic symptoms.[11]

In this article, we discuss the current understanding of mechanisms that contribute to nociception and the experience of pain in RA.

PERIPHERAL MECHANISMS OF PAIN: INFLAMMATORY CYTOKINES AND MORE

Noxious stimuli are transmitted by rapidly conducting Aδ and slow conducting C fibers that innervate the joint and increase their firing rate in response to activation at nerve terminals. These fibers transmit impulses through the peripheral nerve up through the dorsal root and centrally into the dorsal horn of the spinal cord. The Aδ fibers relay first or fast pain and terminate in the superficial dorsal horn, whereas the C fibers relay second or slow pain and terminate predominantly in deeper structures in the spinal cord.

Inflammatory events in RA activate cells of both the adaptive and innate immune systems, producing a cascade of inflammatory mediators and attracting neutrophils, T cells, and B cells to the synovium, resulting in synovitis. The inflamed synovium generates multiple algogens, including bioactive lipids, kinins, cytokines (eg, tumor necrosis factor [TNF]-α, IL-1, and IL-6), neuropeptides (eg, calcitonin gene-related peptide), and neurotrophins (eg, nerve growth factor).[12–15] These signaling molecules can activate and sensitize nociceptors in the synovium, joint capsule, ligaments, subchondral bone, tendon sheaths, and muscles. Nerve growth factor, in particular, has received significant recent attention, because it promotes the proliferation of terminal nerves, upregulates the release of substance P, and contributes to the degranulation of mast cells leading to the release of histamine that activates nociceptor nerve terminals.[13]

In response to noxious inflammatory stimuli, ligand-gated and voltage-gated ion channels (eg, transient receptor potential V1 and Nav 1.7) are activated on the nociceptor nerve terminals.[16,17] Cytokines such as IL-1β, IL-6, TNF-α, and IL-17 act via signaling mechanisms to potentiate transient receptor potential and Nav channel activation, leading to the rapid sensitization of nociceptor neurons.[17] Neutrophils release neutrophil elastase, which cleaves proteinase-activated receptor 2, a G-protein–coupled receptor expressed on joint sensory nerves.[18] The activation of proteinase-activated receptor 2 results in the generation of joint pain and peripheral sensitization in rats and mice.[18–21] Nociceptors also actively release neuropeptides that modulate the activity of innate and adaptive immune cells,[22] suggesting bidirectional interactions between nociceptors and immune cells.[17] As a result of inflammation in RA, the threshold for nociceptor neurons to fire action potentials is decreased, leading to increased pain sensitivity or hyperalgesia.[22]

Animal models indicate that mechanical hypersensitivity often precedes and outlasts joint inflammation, suggesting the presence of additional noninflammatory etiologies for pain.[23] In a collagen antibody-induced arthritis model, mice developed transient joint inflammation, but pain-like behavior was observed before and outlasted the visual signs of arthritis. This finding may be the result of a greater concentration of nerve fibers in the synovium and the aberrant firing of afferent nerves. In a recent mouse study with the K/BxN model, researchers identified an increased density of nerve fibers in the synovium of arthritic ankles and also discovered that nerve fibers have a sprouted disorganized appearance that may lead to spontaneous discharges.[24] These observations suggest a potential role for sensory and sympathetic nerve fiber remodeling in the generation and maintenance of arthritic pain. A recent mouse K/BxN serum transfer model study also suggested that a decrease in the expression of proresolving lipid mediators may contribute to allodynia that persists after the resolution of joint swelling.[25]

CENTRAL MECHANISMS OF PAIN

Central sensitization was first described by Clifford Woolf in 1983 when he observed that enhanced, postinjury responses to sural nerve stimulation remained after blocking peripheral sensation with local anesthesia, indicating a role for then central nervous system (CNS) modulation of pain.[26] Since then, multiple mechanisms of central sensitization have been elucidated, which involve both spinal and supraspinal pathways. Although it is likely that these mechanisms play a role in the development and maintenance of chronic pain in RA, it is important to note that the majority of data discussed in this section are not specific to RA or other systemic inflammatory conditions.

Spinal modulation of pain perception occurs in the dorsal horn of the spinal cord, where primary nociceptive afferents terminate, and the incoming signals are transmitted to projection neurons for relay to the brain. At the dorsal horn, central sensitization can occur via multiple pathways, including (1) an increase in presynaptic excitatory neurotransmitter (eg, glutamate, substance P) release, (2) enhancement of the postsynaptic response (eg, at the *N*-methyl-D-aspartate receptor and/or G-protein–coupled receptors), (3) dampening of inhibitory neurotransmitters (eg, gamma aminobutyric acid and/or glycine), and (4) enhancement of membrane excitability (such that stimuli that would normally be subthreshold induce the propagation of action potentials).[14,27]

In addition, recent studies have implicated spinal microglia and astrocytes as important contributors to the CNS modulation of pain.[28] Spinal microglia express receptors for adenosine triphosphate and CX3CL1. Activation of these receptors upregulates the

production of TNF-α, IL-1β, IL-18, brain-derived growth factor, and cyclo-oxygenase.[29,30] In a collagen-induced rat arthritis model of inflammatory arthritis, reactive spinal microgliosis occurred with a similar time course as the development of mechanical hypersensitivity, at least 1 week before the onset of joint swelling and other clinical signs of arthritis.[31] Concurrent with the development of spinal microgliosis and mechanical hypersensitivity, increases in IL-1β levels were also observed in the cerebrospinal fluid. Intriguingly, there is also clinical evidence that proinflammatory cytokines, including IL-1β, are increased in the cerebrospinal fluid of patients with RA.[32,33]

Studies have also shown that spinal astrocytes are capable of synthesizing proinflammatory cytokines (eg, IL-1β), growth factors (eg, fibroblast growth factor 2), proteases (eg, matrix metalloproteinase 2), and chemokines (CCL2, CCL7, and CXCL1) that are important for the maintenance of chronic pain.[34–39] However, in the same rat model that showed reactive microgliosis in the early stages of collagen-induced arthritis, no increases in activated astrocytes were noted.[31] Additional studies are needed to clarify the role of astrocytes in the CNS modulation of pain in the setting of inflammatory arthritis.

From the dorsal horn, nociceptive signals are carried along the ascending pain pathways to the brain stem, hypothalamus, thalamus, and cerebral cortex by second-order dorsal neurons.[40] The spinothalamic tract plays an important role in transmitting information to the somatosensory cortex, thus providing information on the intensity and the location of the noxious stimulus. Other projection neurons engage the cingulate and insular cortices via the connections in the parabrachial nucleus and the amygdala, hence contributing to the pain experience.[41]

Descending pathways arise from areas in the brain located in the cortex (mainly the periaqueductal gray), hypothalamus, and brain stem (rostral ventromedial medulla), and modulate sensory input from the primary afferent fibers and projection neurons in the dorsal horn of the spinal cord.[42] Several descending pathways are activated in response to noxious stimuli and can cause a widespread decrease in pain sensitivity after exposure to acutely painful stimuli. These inhibitory pathways may be impaired in subgroups of patients with systemic inflammatory conditions like RA and might additionally contribute to the development of chronic pain.[43]

ASSESSING PAIN IN RHEUMATOID ARTHRITIS

The assessment of patients with pain in RA may use the following methods: patient-reported measures, quantitative sensory testing (QST), and functional neuroimaging (functional MRI [fMRI] and PET).

Measures Based on Patient Report

The most commonly used measure to assess pain is a rating of pain intensity, as assessed by a visual analog scale or numeric rating scale.[44] Other frequently used measures of pain assessment include validated assessments of pain and pain-related constructs using the Patient-Reported Outcomes Measurement Information System.[45,46] These instruments include item banks to assess pain interference, pain behavior, and pain quality.[47–49] Other legacy instruments commonly used to assess pain include the Brief Pain Inventory,[50,51] the McGill Pain Questionnaire,[52,53] and the Short Form-36 Bodily Pain Scale.[54]

In addition, measures to assess noninflammatory pain and, more specifically, the concepts of fibromyalgianess, central sensitization, and neuropathic pain, have been developed. To assess noninflammatory pain, McWilliams and colleagues[55] developed a measure that reflects the proportion of the Disease Activity Score in 28

joints (DAS28) attributable to patient-reported components (DAS28-P). The DAS28-P is calculated by dividing the portion of the DAS28 contributed by the tender joint count and the patient global assessment by the total DAS28 score. McWilliams and colleagues found that patients with high DAS28-P scores had a lesser likelihood of pain improvement. Based on this observation, the authors suggested that the DAS28-P may represent pain sensitization owing to central causes, such as fibromyalgia, rather than inflammation itself. A separate study found that the DAS28-P had very good discriminatory power for identifying patients with RA and secondary fibromyalgia compared with those with RA alone.[56]

To diagnose fibromyalgia, Wolfe and colleagues[57,58] developed the American College of Rheumatology 2010/2011 Preliminary Diagnostic Criteria for Fibromyalgia, which is composed of the Widespread Pain Index and the Symptom Severity Score. The Fibromyalgia Survey Questionnaire, which consists of the Widespread Pain Index and Symptom Severity Score, was subsequently evaluated as a measure of fibromyalgia severity.[59] Although not formally validated in patients with RA, this measure was developed in a population that included patients with RA, and several studies have shown that it is associated with poor outcomes, including disability, quality of life, and disease activity measures among patients with RA.[60–62] It should be noted that the Fibromyalgia Survey Questionnaire was originally termed the Polysymptomatic Distress Scale. Thus, several publications refer to it under the previous name.

The Central Sensitization Inventory (CSI) is another questionnaire-based method of assessing centralized pain.[63] Similar to the Fibromyalgia Survey Questionnaire, the CSI asks about symptoms associated with central sensitization (eg, headaches, feeling unrefreshed, depression), as well as pain in multiple locations (eg, pain all over the body, pain in the jaw, and pain in the pelvic area). Construct validity was established by comparing scores in patients with fibromyalgia, chronic widespread pain without fibromyalgia, work-related regional chronic low back pain, and a normative control group.[63] Compared with the Fibromyalgia Survey Questionnaire, the CSI has not been used as frequently in rheumatic disease populations. A study of 193 patients with 1 of 4 rheumatic conditions (RA, spondyloarthropathy, osteoarthritis, or fibromyalgia) reported that central sensitization, defined by the CSI, was identified in 41% of patients with RA, 45% of patients with spondyloarthropathy, 62% of patients with osteoarthritis, and 94% of patients with fibromyalgia.[64] However, the authors did not specify the thresholds used to define central sensitization in this study.

The painDETECT questionnaire has also been used to characterize pain in patients with RA. This questionnaire was originally developed to assess neuropathic pain in patients with back pain,[65] but has been applied in studies of multiple other conditions, including RA. A Rasch analysis of 900 questionnaires indicated acceptable psychometric properties among patients with RA, spondyloarthropathy, and psoriatic arthritis.[66] In several studies of patients with RA, the prevalence of neuropathic pain, defined by a painDETECT score of 19 or higher, ranging from 3% to 20%, with another 11% to 28% with painDETECT scores from 13 to 18.[67–69] In cross-sectional studies, painDETECT scores were associated with self-reported pain intensity and composite disease activity measures, but not with objective measures of inflammation, such as swollen joint count and C-reactive protein.[68,70] As a result, it was suggested that high painDETECT scores may indicate a noninflammatory or non-nociceptive mechanism. Longitudinal studies, however, have been conflicting. Two studies (one in early RA and one in established RA) reported that high painDETECT scores were associated with a lower likelihood of achieving disease remission.[71,72] In contrast, a study of 102 patients with RA starting a disease-modifying antirheumatic drug (DMARD) did not show any association between high painDETECT

scores and change in disease activity (measured by the DAS28), change in an MRI-based synovitis score, or change in pain intensity measured by visual analog scale.[67] However, the sample size of patients with high painDETECT scores was small (n = 17) and may have limited the ability to detect meaningful differences in outcomes.[67]

Although helpful in characterizing pain and pain-related constructs, these questionnaires have several limitations. First, although they can assess the symptoms of clinical conditions associated with central sensitization (eg, fibromyalgia), they ultimately do not provide information on the mechanisms underlying these symptoms. Few studies have examined the correlations between these measures and other assessments of central sensitization (eg, the QST).[73,74] Besides, most of these questionnaires were developed in noninflammatory pain conditions or heterogeneous populations that included both inflammatory and noninflammatory pain conditions. Thus, the applicability of these measures to patients with RA, particularly those with active inflammatory joint disease is unclear.

Quantitative Sensory Testing

The QST is a set of semiquantitative, noninvasive methods for the assessment of nervous system sensitization to nociceptive signaling by assessing response to quantifiable noxious stimuli.[75] Pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM) are the most widely used QST paradigms.

Pain threshold

The point at which a sensation first becomes painful is called the pain threshold. Higher pain thresholds reflect lower pain sensitivity. Several types of stimuli can be used to assess pain thresholds, including pressure, heat, cold, and vibration.

One of the most commonly modalities used stimuli to assess pain thresholds in RA is pressure, because it is thought to be most reflective of arthritis pain. An algometer probe is pressed against a predefined area of skin, and a series of ascending stimulus intensities are applied until pain is reported and the pressure pain-detection threshold (PPT) is identified. Low PPTs at joint sites are thought to indicate increased pain sensitivity as a result of local inflammation, whereas low PPTs at nonjoint sites are considered indicative of central sensitization.[76]

Studies assessing PPTs have provided evidence supporting the existence of peripheral sensitization at joint sites among patients with RA.[43,77,78] We and others have demonstrated that, compared with pain-free controls, patients with RA report lower PPTs at joint sites. Among patients with RA, PPTs at joint sites are consistently associated with tender joint count.[79,80] In a study of 59 patients with established RA, we also observed an association between PPT at the wrist and serum C-reactive protein levels, consistent with peripheral sensitization.[81] In contrast, we did not observe an association between PPTs at joint sites and swollen joint count in a larger study of 139 patients with active RA.[80] Similarly, Joharatnam and colleagues[79] did not observe an association between PPT at the knee and either swollen joint count or the erythrocyte sedimentation rate. The reason for this discrepancy is not clear. In these studies, PPTs were assessed at specific joint sites, irrespective of actual joint inflammation. Thus, it is possible that the joints assessed by QST were not inflamed and others were inflamed. Additional studies are needed to assess the association between peripheral inflammation and PPTs in patients with RA.

Studies assessing PPTs also suggest that patients with RA have abnormalities consistent with central sensitization.[43,82,83] The primary evidence for central sensitization is the observation that PPTs at nonjoint sites are diffusely lower among patients with RA compared with healthy controls. The clinical relevance of these data is

underscored by the observation that low extra-articular PPTs are associated with overall pain intensity, even after adjustment for C-reactive protein level and swollen joint count.[84] Low extra-articular PPTs are also associated with pain-related measures of RA disease activity (eg, a high tender joint count, a high patient global assessment, and a high Crohn's Disease Activity Index), but not objective measures of inflammation (eg, swollen joint count).[80] These studies point toward a role for pain centralization as a contributor to the pain experience in patients with RA. Given the assumption that pain in RA is related to inflammation, central sensitization also seems to contribute to higher composite measures of disease activity, despite the lack of association between extra-articular PPTs and objective measures of inflammation.

Temporal summation

TS occurs as a result of the summation of C fiber responses with brief intervals between stimuli. When the initial postsynaptic potential does not fully resolve before the onset of the next stimulus, there is a progressive increase in the perception of pain, even though subsequent stimuli are of the same magnitude as the first. This process mimics the initial wind-up process of dorsal horn neurons to peripheral stimulation and is an important mechanism of central sensitization.[85]

Two small studies have reported that patients with RA experience higher TS of pain than healthy controls. In a study comparing TS in 11 patients with RA, 10 patients with fibromyalgia, and 20 healthy, pain-free participants, Hermans and colleagues[86] reported that the TS was higher among the subgroups with RA and fibromyalgia, compared with healthy, pain-free participants. Additionally, Vladimirova and colleagues[87] noted a greater TS in 38 patients with RA with active disease compared with 38 healthy female control participants. In a study of 263 patients with RA, our research group reported a significant association between TS and patient-reported pain, with higher pain intensity in the most centrally dysregulated TS group compared with the least dysregulated group.[84] Greater central pain dysregulation was also significantly associated with more pain interference in unadjusted analyses, which was attenuated in the adjusted analysis. An analysis of a subset of these patients also revealed that high TS was associated with high tender joint counts, a high patient global assessment, a high evaluator global assessment, and a higher Crohn's Disease Activity Index.[80] Taken together, these studies suggest that an enhanced TS of pain may be a key pathway underlying the central pain dysregulation in RA.

Interestingly, however, TS has not been associated with poor treatment response in RA. Our research group did not see a statistically significant association between TS and European League Against Rheumatism response in a study of 182 patients.[88] Similarly, Christensen and colleagues[89] did not find a statistically significant association between TS and change in DAS28 at 4 months after DMARD initiation. Thus, although patients with RA seem to have an enhanced TS of pain, this mechanism does not seem to impact pain longitudinally. It is possible that the resolution of inflammation with DMARD treatment also leads to improvements in the TS. Additional studies are underway to explore this possibility.

Conditioned modulation

CPM refers to the concept that "pain inhibits pain."[90] Noxious input from peripheral C-fibers activates inhibitory pathways in the brain and spinal cord to diffusely inhibit incoming noxious stimuli.[91,92] In the laboratory, the initial noxious stimulus (test stimulus) is measured before and after the application of a second stimulus (conditioning stimulus), which activates the inhibitory pathways. In healthy individuals with properly functioning descending inhibitory pain pathways, the postconditioning test stimulus is

perceived as less painful than the preconditioning test stimulus because the conditioning stimulus activates the descending inhibitory pathways leading to a decrease in pain sensitivity. In individuals with chronic pain conditions, the descending inhibitory pain pathways may not function appropriately.[93] As a result, the decrease in pain sensitivity after exposure to the conditioning stimulus may be diminished.

Data regarding CPM in patients with RA have been conflicting. Hermans and colleagues[86] reported no difference in CPM between patients with RA (n = 11) compared with healthy controls (n = 20). However, in a study of 58 female patients with RA and 54 age-matched, female healthy controls, our research group reported that patients with RA experienced impaired CPM (median, 0.5 kg/cm^2) compared with healthy controls (median, 1.5 kg/cm^2).[43] Using mediation analyses, the same authors noted that low CPM levels in patients with RA may be attributed in part to sleep disturbances. This study was cross-sectional, so no causal inferences could be made.

Among patients with RA, impaired CPM has been associated with higher tender joint counts,[80] but not overall pain intensity.[84] The reason for this discrepancy is not clear, but may be related to differences in the measures of pain, with the tender joint count being a disease-specific measure and overall pain intensity reflecting multiple potential causes of bodily pain. Of note, our research group recently demonstrated that patients with RA with a low CPM were significantly less likely to have a good response to DMARD treatment.[88] These results suggest that inefficient CNS pain inhibition may contribute to a heightened assessment of disease activity, possibly by increasing subjective, disease-related, pain measures, such as the tender joint count.

Although it is still not clear how to improve CPM among patients with RA, a small study suggested that exercise does not improve CPM.[94] The same study also evaluated the effects of acetaminophen on CPM, but the results were inconsistent.[95] Additional studies are needed to identify efficacious interventions for improving CPM in patients with RA.

Neuroimaging Evidence

Recent advances in neuroimaging have identified differences in the structure and function of the brain in patients with RA compared with healthy, pain-free controls.[96,97] Wartolowska and colleagues[98] conducted an MRI study to investigate the brain correlates of pain in an RA population compared with healthy controls. They used a technique called voxel-based morphometry, which revealed larger gray matter volume in the caudate nucleus, putamen, and nucleus accumbens of patients with RA compared with controls. These structures are important in the cognitive, affective, and sensory discriminative processing of pain. These findings could represent chronic changes in the brain structures in response to long-term exposure to pain. Alternatively, these differences could also be attributed to other factors that differ between patients and controls (eg, inflammation, medications, and physical activity levels).

In addition, a growing body of evidence suggests that patients with RA may exhibit functional changes in the brain in response to pain.[99] Our research group used arterial spin labeling (ASL) to identify changes in the regional cerebral blood flow (rCBF) associated with pain provocations in patients with RA and pain-free control participants.[100] ASL is a noninvasive fMRI technique that enables quantifiable measurement of rCBF as a proxy for neural activation.[101] Joint pain was exacerbated by inflating a pressure cuff around the metacarpophalangeal joints for 6 minutes. In response to this stimulus, rCBF in the medial frontal cortex and the dorsolateral prefrontal cortex (dlPFC) increased among patients with RA. In contrast, no changes in the rCBF were noted in pain-free controls. These results suggest that the medial frontal cortex and the dlPFC may be areas of particular relevance to disease-related pain in RA.

Of note, the dlPFC was also highlighted as a region involved in RA-related pain in a recent study of 31 patients with RA and 23 controls.[102] In this study, participants underwent fMRI while being exposed to a series of painful and nonpainful pressure stimuli for 2.5 seconds each. Interestingly, this study showed deactivation (as opposed to activation) of the dlPFC in response to painful pressure. The authors postulated that the difference in results between this study and the ASL study mentioned elsewhere in this article may have been due to the duration of the noxious stimuli. When patients with RA are exposed to longer durations of noxious stimuli (as in the ASL study), the inhibition of pain through the dlPFC may be activated, whereas when participants are exposed to short pulses of noxious stimuli, the tonic inhibition of pain may be temporarily inactivated. Thus, patients may still feel acute increases in pain owing to acute noxious insults, thereby prompting the removal of the inflamed joint from potentially tissue-damaging situations, while simultaneously allowing the patient to acclimate to long-standing noxious stimuli. Additional studies are needed to clarify the role of the dlPFC in responding to noxious pain stimuli in patients with RA.

In addition to the differences in the rCBF and the neural activity in specific brain regions, recent studies suggest that patients with RA may exhibit differences in the way brain regions are connected functionally. Functional brain connectivity refers to the synchronization of neural activity displayed by 2 or more brain regions. It is assumed that this synchronization reflects communication between the brain regions.

Among patients with RA, systemic inflammation may be associated with changes in functional connectivity between the default mode network and other brain regions associated with pain. The default mode network is a group of interconnected brain regions that includes the medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobule, hippocampal formation, and lateral temporal cortex.[103] Functional connectivity between the default mode network and the insula has previously been identified as a neurobiological feature of primary fibromyalgia.[104–106] In a cross-sectional analysis of 54 patients with RA, Schrepf and colleagues[99] observed that erythrocyte sedimentation rate levels were positively correlated with functional connections between the inferior parietal lobule, medial prefrontal cortex, and several brain networks. Using data from the same population, Kaplan and colleagues[107] observed significant associations between erythrocyte sedimentation rate levels and the left inferior parietal lobule–insula functional connectivity, the left inferior parietal lobule–dorsal anterior cingulate functional connectivity, and the left inferior parietal lobule–medial prefrontal cortex functional connectivity among patients with RA with fibromyalgia, but not in patients with RA without fibromyalgia. A third report, also using data from the same 54 patients with RA, reported associations between functional connectivity between the default mode network and insula and the symptoms of fibromyalgia.[108] Taken together, these studies suggest that systemic inflammation may lead to changes in brain functional connectivity, which are associated with the development of a centrally sensitized state, that is, secondary fibromyalgia, among patients with RA. However, it should be noted that these analyses were all cross-sectional, and the study population consisted of patients with RA with an average disease duration of 11.5 years. Future studies involving longitudinal analyses in patients with a recent onset of the disease are needed to clarify the potential role of systemic inflammation in precipitating functional changes related to the acute to chronic pain transition in patients with RA.

In addition to understanding the neurobiological underpinnings of chronic pain in RA, fMRI studies have also provided evidence for how TNF-α inhibition can alleviate pain symptoms in patients with RA, even before changes in inflammation are observed. Rech and colleagues[109] conducted evoked pain fMRI in 10 patients with

RA before and after anti-TNF therapy with certolizumab and observed the differences in brain activation between responders and nonresponders. Compared with nonresponders, responders showed a significantly higher baseline activation in the thalamic, limbic, and associative areas of the brain. Brain activity in these areas decreased within 3 days after exposure to a TNF inhibitor in the responders, preceding clinical responses, and those noted on the anatomic hand MRI. This work again implies the possible existence of different neural signatures for different types of pain, because responders are more likely than nonresponders to have pain originating from inflammation. The lack of a control group and a small sample size are some of the limitations of these studies. Further studies are needed before conclusions can be made regarding the role of TNF-α inhibitors on the CNS regulation of pain.

FUTURE AREAS OF RESEARCH

Although the underlying mechanisms for pain in RA are beginning to be elucidated, the effect of treatment with DMARDs on the different types of pain in RA, the peripheral and central components of pain, and the role of centrally active antihyperalgesics on pain still needs to be identified. This work will be of great significance in the development of new analgesic therapeutics for RA.

CLINICS CARE POINTS

- In addition to peripheral joint inflammation, health care providers should consider other potential causes of pain, such as abnormalities in the CNS regulation of pain.
- Despite the perception of patients with RA being very stoic and resistant to pain, patients with RA are more sensitive to pain than healthy, pain-free individuals.
- To assess noninflammatory pain in RA in the clinic, health care providers could consider using measures based on patient-reported pain and symptoms, such as the DAS28-P, Fibromyalgia Survey Questionnaire, Central Sensitization Index, or painDETECT.
- If patients present with widespread pain but minimal joint inflammation, health care providers should consider treatments targeted at centralized pain mechanisms rather than aggressively increasing immunosuppressive therapies.

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