Chapter

Understanding the Mechanisms of Pain in Rheumatoid Arthritis

Kathryn Biddle and Nidhi Sofat

Abstract

Pain is a debilitating feature of rheumatoid arthritis (RA) and is often described by patients as their most important symptom. Rheumatoid arthritis pain has traditionally been attributed solely to joint inflammation, however despite the advent of increasingly effective disease modifying agents, patients continue to report pain at long term follow up. The cause for ongoing pain is multifactorial and includes joint damage and pain sensitisation. In this book chapter, we will describe the mechanisms underlying the distinct components of pain which are manifest in rheumatoid arthritis and discuss why a thorough assessment of pain is vital to target treatments appropriately.

Keywords: pain, rheumatoid arthritis, inflammation, pain sensitisation, nociceptors, rheumatology

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease with a prevalence of between 0.5 to 1% in different worldwide populations [1]. Inflammation predominantly affects the joints causing synovitis, pannus formation and if left untreated, joint destruction. Patients with RA classically present with tender and swollen joints, early morning joint stiffness and systemic symptoms such as fatigue. Severe pain is a particularly debilitating feature of RA that is commonly described as patients' most important symptom [2]. In addition to causing a significant impact on quality of life, studies have shown that RA pain is associated with psychological distress, impaired physical and social function and increased healthcare costs [3].

The pathogenesis of pain in RA is multifactorial. Traditionally, pain was entirely attributed to synovitis and consequent joint destruction. With the advent of increasingly effective disease modifying agents, joint inflammation has become a more treatable cause of pain and joint destruction is preventable. Indeed, the randomised controlled trials (RCTs) that supported the use of classical disease modifying anti-rheumatic drugs (DMARDs), showed statistically and clinically significant reduction in pain with treatment [4]. However, despite effective control of inflammation and disease remission, patients have continued to report troublesome pain at follow-up [5]. The same has been shown in patients taking biologic DMARDs [6]. This suggests that pain does not always fully resolve with the effective suppression of synovitis [7]. Observational studies have also highlighted the complex relationship between pain and inflammation in patients with RA. For example, large discrepancies between objective measures of inflammation such as acute-phase proteins and reported pain, have been shown in some patients with RA [8].

Taken together, this evidence suggests that inflammation and joint destruction alone cannot account for the total pain manifesting in RA. Indeed, increasing evidence supports a role for aberrant pain processing, including peripheral and central pain sensitisation, in the pathogenesis of pain in RA. Throughout this book chapter, we will explore the different mechanisms underlying the perception of pain in patients with RA.

2. Inflammation in RA

RA is a pathologically heterogenous autoimmune condition. The disease can broadly be divided into sero-positive and sero-negative subtypes. In sero-positive patients, the presence of anti-citrullinated peptide antibodies (ACPAs), is associated with more severe joint damage and increased mortality [9]. In these patients, ACPAs bind to citrullinated autoantigens including fibrinogen, vimentin, collagen type 4 and α-enolase, resulting in the formation of immune complexes (ICs) [10]. ICs activate the complement system and trigger inflammatory cell infiltration within the synovium [11].

The pathology of RA is characterised by the activation of cells of both the innate and adaptive immune system within the synovial matrix. The innate immune response consists of macrophages, mast cells and dendritic cells. These cells produce inflammatory mediators including cytokines, chemokines, lipids, proteases and growth factors. These mediators attract neutrophils and activate cells of the adaptive immune system, such as T cells, B cells and plasma cells. The inflammatory cytokines produced during the innate immune response shape the subsequent activation of the adaptive immune system. For example, cytokines produced in the early phases of inflammation regulate the differentiation of naïve T helper cells into T helper cell subsets and the subsequent T cell response.

In RA, the inflammatory milieu within the synovium is characterised by complex cytokine and chemokine interactions. Cytokines including TNF-α and IL-6 appear to be particularly important, and biologic agents targeting these mediators are well-established treatments for RA [12].

Inflammation results in a catabolic state within the joint. One of the pathognomonic features of RA is the synovial pannus, a hypertrophied area of synovium with tissue destructive properties [13]. Within the pannus, synovial fibroblasts assume an inflammatory phenotype resulting in enhanced cartilage catabolism and synovial osteoclastogenesis [14]. Cytokine-mediated chondrocyte activation results in the stimulation of catabolic pathways. Enzymes including matrix metalloproteinases (MMPs) are activated to degrade the cartilage matrix [15]. Bone erosion is stimulated by the interaction between RANK-L on fibroblasts, T and B cells and its receptor RANK on dendritic cells, macrophages and pre-osteoclasts [16]. Ultimately, this process can result in cartilage and bone destruction and joint deformity.

Therapies that target inflammation such as conventional DMARDs and biologic therapies are effective at suppressing synovitis and reducing joint destruction. The treat-to-target approach is widely recommended for the management of RA. This strategy involves regular monitoring of disease activity, using validated scoring measures such as the DAS28, and escalation of treatment if a target is not reached. RCTs have found that this approach substantially improves disease activity, radiographic progression, quality of life and physical function [17]. These immunomodulatory agents have been shown to reduce pain, albeit not completely [18]. Throughout the next section of this chapter, we will discuss the inflammatory basis of pain in RA.

2.1 Pain and joint inflammation

Inflammation has long been accepted to cause pain. Indeed, pain was one of the cardinal features of inflammation, as defined by Celsus in the first century [19]. Pain secondary to inflammation can be classified into acute or chronic pain. The neurotransmission of acute pain signals in response to noxious stimulation involves the activation of a specialised subset of sensory neurons called nociceptors. Nociceptors innervate peripheral tissues, including joints, and transmit painful stimuli to the dorsal root ganglion (DRG). There are many subsets of nociceptors, each responding to different types of noxious stimuli. Aδ and C fibres are the two main types of primary afferent nociceptors [20]. Whilst both Aδ and C fibres are found in superficial organs, such as the skin, C-fibres generally supply deeper structures such as joints [20]. C-fibres are activated by thermal, chemical or mechanical stimulation, resulting in poorly localised, dull pain sensation [20].

The activation of nociceptors involves the stimulation of ligand-gated and voltage-gated ion channels including transient receptor potential cation channel, subfamily A, member 1 (TRPV1), transient receptor potential cation channel, subfamily A, member 1 (TRPA1), $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ channels, which are expressed on peripheral nerve terminals [21]. Activation of these channels results in the stimulation of intracellular signalling pathways and the transmission of acute pain signals [21]. In the longer term, chronic inflammation results in long lasting changes in nociceptor signalling resulting in peripheral pain sensitisation, a phenomenon that we will discuss later in this chapter.

2.2 Synovial joint structures and pain

Arthritic pain is thought to be mediated by nociceptors that innervate the synovium and subchondral bone. In contrast, under physiological conditions, cartilage is an aneural and avascular tissue. This is illustrated in **Figure 1**.

In RA, chronic inflammation is thought to result in structural and functional changes in the peripheral innervation of joints. This has been shown in animal

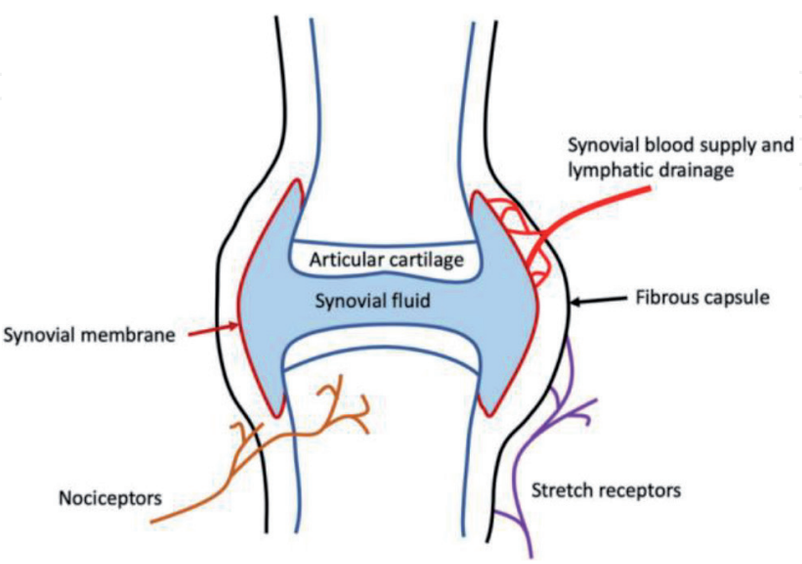

Figure 1.
Diagram of a synovial joint. A synovial joint consists of two articulating cartilage surfaces surrounded by a synovial membrane. Synovial fluid fills the synovium. Under physiological conditions, cartilage is avascular and aneural. Nociceptors innervating the synovium and subchondral bone are responsible for arthritic pain. In contrast, stretch receptors, innervating the fibrous capsule are responsible for proprioception.

models where chronic synovitis results in increased innervation of the synovium and increased spontaneous and mechanical-induced firing of articular primary afferents [22, 23].

2.3 Nociceptor pathways

Nociceptor pathways mediating acute pain perception in response to inflammation are well defined. In the periphery, local immune cells release inflammatory mediators, such as cytokines, that act on the peripheral nerve terminals of nociceptor neurons. This activates the nociceptors to transmit signals via the DRG through the spinothalamic tract to the higher cortical centres, resulting in the perception of pain. It is also well accepted that inflammation can result in heightened nociceptor sensitivity to both noxious and innocuous stimuli. In this case, the activation of nociceptors by inflammatory mediators triggers intracellular signalling cascades that reduce the threshold for nociceptor neurons to fire action potentials [21]. This results in heightened pain sensitivity which can manifest as allodynia; the sensation of pain arising from a non-painful stimulus, or hyperalgesia; a heightened sensation of pain in response to painful stimulation. Throughout the next section of this chapter, we will discuss the inflammatory mediators that stimulate nociceptor activation and sensitisation in RA.

2.4 Pain and innate immunity

Cells of the innate immune system, including neutrophils, mast cells and macrophages, release noxious inflammatory mediators and have been shown to stimulate pain and pain sensitisation in a wide range of models and systems. For example, in mouse models of carrageenan-induced inflammatory pain, neutrophils migrate to tissues and sustain pain through the production of cytokines and prostaglandin E2 [24]. In incisional wound injury, macrophages (CD11b + myeloid cells) have been shown to mediate acute pain and pain sensitisation [25]. Mast cell degranulation activates nociceptor firing acutely and may also contribute to pathology of chronic pain and mast cells have been shown accumulate in chronic inflammatory conditions such as complex regional pain syndrome [26, 27]. Throughout the next part of the chapter, we will discuss the noxious inflammatory mediators that are released by innate immune cells.

2.5 Lipid mediators of pain

Pro-inflammatory lipids include cyclooxygenase (COX) dependent molecules such as prostanoids (prostaglandins, prostacyclins and thromboxanes). COX-dependent molecules are well known to cause pain and pain sensitisation and inhibition of the COX enzyme, using non-steroidal anti-inflammatory drugs (NSAIDs), is used for the suppression of pain and inflammation. Indeed, NSAIDs are potent analgesic and anti-inflammatory medications which are effective for the treatment of acute inflammatory pain including synovitis [28].

Studies have investigated the mechanism of action underlying the noxious effect of prostaglandins. Prostaglandin E2 (PGE2) has been shown to activate nociceptors through the binding of EP1-EP4 receptors. This stimulates pain and pain sensitisation via multiple mechanisms. PGE2 stimulates proximal ion channels in nociceptive neurons. This sensitises the neurons to painful stimuli [29]. PGE2 activates more persistent pain sensitisation via PKA and PKC-mediated activation of NFκB in the dorsal root ganglion neurons [30].

Many other classes of pro-inflammatory lipids are thought to be involved in the activation of nociceptor activity. For example, lysophosphatidic acid and

sphingosine-1-phosphate are produced during inflammation and have been shown to activate nociceptors leading to increased TRPV1 activity [31]. Leukotrienes may also have an noxious effect and the injection of leukotriene B4 has been shown to activate C and Aδ-fibres in rat models and induce hyperalgesia in humans [21, 32].

More recent work has also demonstrated a role for anti-inflammatory and pro-resolving lipids in the silencing of pain. For example, pro-resolving lipids, including lipoxins, resolvins and protectins have generally been shown to have analgesic effects [33]. Further work is required to characterise the underlying molecular pathways but these mediators may represent targets for the future treatment of pain [33].

2.6 Neurotransmitters and pain

Innate immune cells release neurotransmitters capable of modulating pain transmission. For example, mast cells contain histamine and serotonin that are released on degranulation. Histamine triggers pain sensitisation through the activation of H1 and H2 receptors expressed on nociceptors [34]. This results in increased expression of Nav1.8 channels and increased sensitivity to noxious stimuli [34, 35].

2.7 Cytokines and pain

Inflammatory cytokines represent another important class of molecules that stimulate nociceptors and activate pain sensitisation. IL-1β was the first cytokine to be described as hyperalgesic [36]. This finding was seminal in the field of neuro-immunology and represented early evidence for the cross-talk between the immune system and pain sensitisation. Cytokines have now been found to play important roles in pain modulation in most painful conditions, including RA. Notably, pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, IL-17A and IL-5, have all been shown to active nociceptors directly [21].

IL-1β sensitises nociceptors through different intra-cellular signalling pathways. Firstly, IL-1β activates the p38 MAPK-mediated phosphorylation of Nav1.8 sodium channels resulting in increased action potential generation and an associated mechanical and thermal hyperalgesia [37]. Secondly, the activation of IL-1R1 by IL1-β, has also been shown to result in increased TRPV1 expression on nociceptors, resulting in thermal pain sensitisation in animal models [38].

IL-6 stimulates pain sensitisation directly and indirectly. Directly, IL-6 activates nociceptors via the signal transducer gp 130 leading to increased TRPV1 and TRPA1 expression [39]. Indirectly, IL-6 activates nociceptors via the production of prostaglandins [39]. TNF-α also induces pain sensitisation via TRPA1 and TRPV1, however TNF-α mediated inflammatory pain appears to be dependent on prostaglandins [40]. Indeed, COX-2 inhibitors have been shown to inhibit TNF-α induced capsaicin responsiveness in cultured nociceptors [41]. TNF-α also modulates nociceptor sensitivity through the activation of p38 MAPK mediated phosphorylation of Nav.18 and Nav1.9 sodium channels [42].

Increasing work suggests a role for IL-17 in pain sensitisation. Indeed, many painful autoimmune diseases, such as RA and psoriasis, are characterised by a Th17 immune response. IL-17A has been shown to be broadly expressed by nociceptors and IL-17 has been demonstrated to induce a rapid increase in neuronal excitability [43]. In animal models of RA, IL-17 has been shown to induce hyperalgesia, through a mechanism dependent on the amplification of TNF-α, IL-1B, CXCL-1, endothelin 1 and prostaglandins [44].

In summary, IL-1β, IL-6, TNF-α and IL-17 stimulate pain and pain sensitisation through the synthesis of prostaglandins and/or the activation of sodium or TRP

channels. The different cytokines appear to act via different intracellular signalling pathways, however it remains unclear whether different immune responses (e.g. Th1, Th2 or Th17) induce different pain characteristics through the activation of specific nociceptors and pain receptors.

2.8 Immune derived growth factors in pain

Innervation by nociceptors is a dynamic process affected by neurotrophic factors. These factors are often upregulated in response to inflammation or tissue injury and are important to restore the density of innervation post-injury [21]. If there is inappropriate or excessive release of neurotrophic factors, heightened pain sensitivity can occur [21]. Nerve growth factor (NGF) is an important neurotrophic factor that is secreted by innate immune cells during the acute phase of inflammation. NGF activates the receptor TrkA on nociceptors, stimulating the P13K/Src kinase pathway and the phosphorylation of TRPV1 and its translocation into the cell membrane [45]. This results in the rapid sensitisation of nociceptors in response to stimulation by NGF. In the longer term, NGF has been shown to stimulate axonal terminal sprouting, contributing to increased pain sensitivity [46].

2.9 A role for ACPAs in pain in RA

It is well established that arthralgia can precede overt joint inflammation and that joint pain is often one of the first symptoms of emerging RA. The mechanism underlying arthralgia preceding inflammation remains unclear but a role for ACPAs has been suggested. Observational studies have shown that ACPAs frequently occur in the preclinical phase of disease and can be detected months to years prior

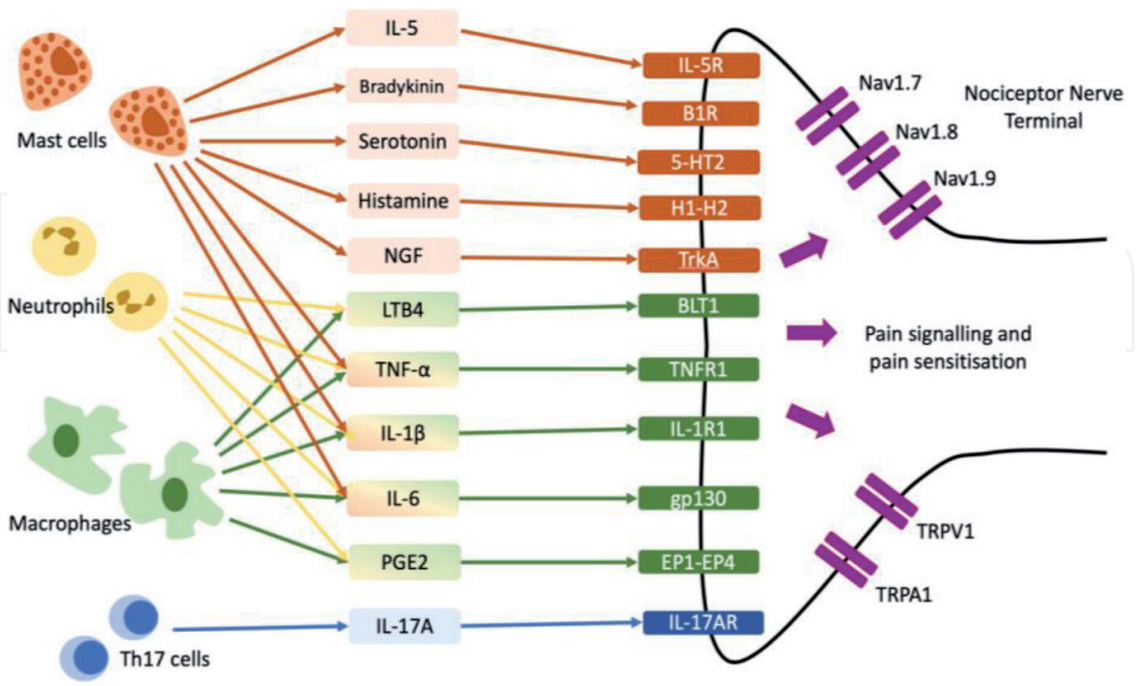

Figure 2.
*Inflammatory mediators and pain. **Figure 2** Summarises the inflammatory mediators that have been shown to activate and sensitise nociceptors[21]. As illustrated, innate and adaptive immune cells release inflammatory mediators that act on their respective receptors to activate nociceptors and sensitise pain signalling through Nav and TRP channels.*

to diagnosis [47]. Experimental studies have raised the possibility that ACPAs can induce pain via a pathway independent of joint inflammation. In one study, mice injected with human or murine ACPAs developed increased pain sensitivity, despite no signs of joint inflammation. In this study, ACPAs were shown to bind to osteoclasts in the bone marrow, and induce CXCL1/2 expression and release. Intra-articular injection of CXCL1/2 was shown to evoke pain-like behaviour and this was inhibited by an IL-8 inhibitor, reparixin [48]. Further work is required to confirm this hypothesis. If correct, it could alter the management of ACPA positive arthralgia and offer new therapeutic targets in the management of early RA.

In summary, inflammation is a well-accepted cause of pain in RA and many inflammatory mediators have been shown to stimulate nociceptor activation and sensitisation, as summarised in **Figure 2**.

Despite the important role for inflammation in pain in RA, the extent of inflammation does not always correlate with the severity of total pain reported RA patients. Indeed, observational studies have shown that changes in inflammation account for only 40% of changes in pain in RA patients [49]. Furthermore, factors associated with the degree of inflammation such as serology, acute phase response and joint damage correlate poorly with pain prognosis in RA patients [7]. Moreover, in common with other chronic pain conditions, psychosocial factors and female gender predict pain prognosis more accurately than the severity of inflammation [7]. Therefore, additional mechanisms must be responsible for the pain experienced in RA. These mechanisms include joint damage and aberrant pain sensitisation.

3. Joint damage and pain

The contribution of structural joint changes to the total pain in RA is controversial. In patients with advanced RA, erosions and joint space narrowing are associated with disability and make a small but significant contribution to total reported pain [50]. Moreover, patients with advanced disease show an improvement in pain following joint replacement surgery [51]. However, as more effective disease modifying protocols have been developed, structural joint damage in RA has decreased and corresponding rates of orthopaedic surgery have declined [52]. The prevention of joint damage has produced superior pain outcomes but it is not clear how much of this can be attributed to the prevention of structural damage versus the suppression of inflammation or prevention of pain sensitisation. In recent studies, radiographically assessed joint damage appears to make a small contribution to pain in RA patients [53]. However, some of this pain may be explained by coincident osteoarthritis (OA), which occurs in a similar demographic of patients.

The correlation between joint damage and pain severity appears weak, although investigation on this subject has primarily occurred in patients with OA and relatively little data exists for patients with RA. In OA, structural joint changes do not correlate well with joint pain [54]. The severity of radiographic OA has been shown to explain <20% of the variance in pain intensity [54]. Furthermore, post-joint replacement, many patients continue to report pain. 10% of patients post-total hip replacement (THR) and 20% post-total knee replacement (TKR) report unfavourable long term pain outcomes [55]. This suggests that structural joint damage alone cannot explain the total pain experienced in OA. Like in RA, central pain sensitisation has been proposed to explain the pain not accounted for by joint destruction [56].

4. Central pain sensitisation and RA

Processing by the central nervous system (CNS) can affect pain reporting, sensitivity, intensity and pain characteristics [57]. Aberrant pain processing can result in central pain sensitisation; an amplified response of the central nervous system to peripheral nociceptive input [58]. The term central sensitisation was coined in 1989 by Woolf and colleagues based on work in the rat model showing hyperexcitability of spinal cord neurons in response to peripheral tissue injury [58]. Physiologically, central sensitisation represents a state of hyperexcitability of spinal and supraspinal structures due to amplified neuronal signalling involving enhanced synaptic and neurotransmitter activities [59].

An increasing abundance of evidence supports the role for central pain sensitisation in RA and an understanding of central sensitisation is important to optimise patient treatment. Clinically, pain secondary to an inflammatory flare must be differentiated from pain secondary to central sensitisation as they require vastly different management approaches. Throughout the next part of this chapter, we will discuss the molecular basis of pain transmission from the periphery to the CNS, clinical evidence supporting a role for pain sensitisation in RA and some proposed mechanisms for pain sensitisation in the DRG and in the cerebral cortex.

4.1 Molecular basis of pain sensitisation

As discussed previously, A-δ and C nociceptive neurons are activated by inflammatory mediators in the periphery. These fibres converge at the DRG, along with non-noxious A-β fibres. Following activation, nociceptor fibres release substance P (SP), calcitonin gene-related peptide (CGRP), glutamate, aspartate and NGF at the afferent nerve endings into the synaptic cleft [60]. These neurotransmitters activate their corresponding receptors on post-synaptic neurons. Activation of post-synaptic receptors results in intracellular signalling changes. For example, activation of NMDA receptors results in increased membrane permeability, intracellular entry of calcium, activation of protein kinases and the expression of c-fos [61]. These signalling changes result in the hyperexcitability of the secondary neurons and amplification of the peripheral noxious stimulus. Post-synaptic neurons ascend in the spinothalamic tract to the thalamus, hypothalamus, limbic system and the somatosensory cortex [61]. These signalling pathways are summarised in **Figure 3**.

Animal models of RA have been used to investigate the molecular mechanisms underlying spinal pain sensitisation. In these models, molecular changes have been shown to occur in the DRG, spinal neurons and spinoreticular neurons. For example, in complete Freund's adjuvant (CFA) induced arthritis models, increased expression of SP, CGRP, NPY, c-fos, TRPV1, P2X3 and Trk-A receptors in the DRG have been demonstrated [62]. These changes are thought to result in hyperexcitability of spinal neurons and enhanced sensitivity to nociceptor signalling.

4.2 Clinical evidence for a role of pain sensitisation in RA

Patients with RA show widespread reductions in pain threshold and increased pain sensitivity, not only over inflamed joints but at distant, non-articular sites [62]. Evidence to support this has come from clinical studies using techniques such as quantitative sensory testing (QST). This technique involves the application of stimuli under standardised testing protocols and the quantification of the participants sensory experience. QST employs different tools for the assessment of the perception of vibration, touch, proprioception, pinprick or blunt pressure

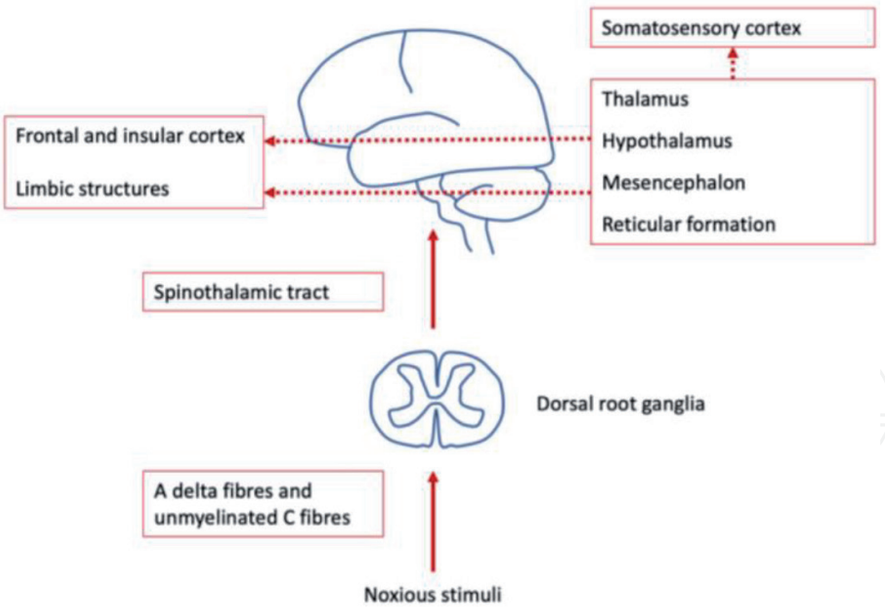

Figure 3.
A simplified diagram of pain signalling pathways. As illustrated, noxious stimulation activates A-δ and C fibres in the periphery. These fibres converge at the DRG and activate post-synaptic neurons that ascend to higher cortical centres via the spinothalamic tract.

sensitivity. RA patients have a lower pain threshold than healthy controls with QST [63]. Furthermore, sensitisation has been shown to affect a wide range of sensory modalities, including thermal and mechanical stimulation.

Studies have demonstrated that pain thresholds vary substantially between patients with RA. Multiple factors have been shown to correlate with differences in pain threshold. Importantly, these include high tender joint count and prolonged disease duration [64]. This suggests that the persistence of nociceptive stimulation results in long-term changes in pain processing resulting in central pain sensitisation. Other factors that have been shown to influence pain threshold include sleep quality, psychosocial factors and analgesic use [65].

Repetitive sensory stimulation, also known as temporal summation, is another experimental model that has been used to investigate central sensitisation in RA. Temporal summation occurs when the time between stimuli is short enough to prevent the dissipation of postsynaptic action potentials before re-activation [66]. This results in a higher membrane potential, increasing the probability that further stimulation will result in post-synaptic activation. In healthy controls, repetitive stimulation results in the reduction of pressure pain thresholds [62]. Studies have shown that this response is augmented in RA patients [67]. This has also been demonstrated electrophysiologically through the measurement of action potentials in response to repetitive stimulation. In healthy controls, there is an increase in the amplitude of action potential evoked from repetitive stimulation using noxious stimulation. This response is amplified in RA patients and has been shown to correlate with disease activity scores and high tender joint counts [68].

4.3 Neuropathic pain in RA

In addition to measuring pain thresholds, pain characteristics can be analysed to assess the possible contribution of pain sensitisation to overall pain experience. Specifically, pain questionnaires are commonly used to detect the presence of neuropathic-sounding pain. Neuropathic pain is the perception of pain in the absence of nociceptive input or peripheral tissue damage and is caused by pathology

of the peripheral or central nerves. A classic example of neuropathic pain is sciatica. This pain has distinct characteristics such as burning, radiation, shooting, tingling and sensitivity to non-painful stimuli (i.e. allodynia). RA can be associated with neuropathic pain through several mechanisms including compression neuropathy (e.g. carpal tunnel syndrome), co-morbidities (e.g. diabetes), vasculitis (resulting in mononeuritis multiplex) or drug therapies (e.g. gold or leflunomide). Nevertheless, emerging evidence suggests that RA itself can result in neuropathic pain through the induction of aberrant pain processing.

The painDETECT questionnaire enables the classification of pain into likely, possibly or unlikely to be of neuropathic origin. Patients with RA often describe pain with neuropathic features and painDETECT questionnaires can yield between 5 to 20% fulfilling criteria for "likely neuropathic pain" [62]. A significant proportion of these patients have no underlying evidence of neuropathy. One study demonstrated that only 33% of RA patients fulfilling clinical criteria for neuropathic pain had clinical evidence of neuropathy [69]. Of the remaining patients, 57% were shown to have subclinical or axonal neuropathy [70]. This left a significant number of patients with RA who reported neuropathic-sounding pain in the absence of objective nerve injury. It has been suggested that this pain occurs secondary to pain sensitisation however, this has not been proven. Nevertheless, neuropathic-sounding pain is an important clinical feature as it predicts inferior pain outcomes. Indeed, a positive correlation between VAS pain scores and painDETECT scores has been demonstrated and patients with probable or likely neuropathic pain have been shown to report significantly higher VAS scores than patients without neuropathic-sounding pain [71].

Although the painDETECT questionnaire is a useful tool for characterising pain, care must be taken to interpret results based only on questionnaires. Furthermore, confounding effects with pain severity may affect interpretation. Patients with fibromyalgia demonstrate high painDETECT scores, although evidence of pathology in the peripheral or central nervous system has been difficult to demonstrate. This raises the question of whether painDETECT scores identify pain with similar features to neuropathic pain rather than neuronal pathology itself. Further work is required to fully understand the significance of neuropathic sounding pain in RA.

4.4 Fibromyalgia-RA

The association between fibromyalgia and RA sheds light on the complex relationship between inflammation, pain and central pain sensitisation. Fibromyalgia (FM) is the prototypical central pain sensitivity syndrome. Clinically, FM is characterised by chronic widespread pain, sleep disturbance and impaired cognition [72]. Observational studies have shown that the prevalence of fibromyalgia in RA patients is much higher than in the general population with estimated prevalence of 18-24%, compared to 2-4% in non-RA cohorts [73, 74].

Two groups of fibromyalgia (FM) have been characterised. Patients with "primary" FM report pain in the absence of identifiable nociceptive input [72]. These patients generally report regional pain syndromes that progress to widespread pain phenotypes with time. "Secondary" FM occurs when aberrant centralised pain processing occurs in the context of identifiable nociceptive input, for example in inflammatory arthritis [72]. It is not yet clear whether these conditions represent the same or different diseases.

The co-existence of FM in RA patients is associated with increased pain scores, a poorer quality of life and worse patient-reported outcomes. In a meta-analysis of 18 studies, RA patients with co-morbid FM had significantly higher pooled DAS28 scores than those without FM [73]. When studies reported individual components

of the DAS28, patients with co-existent FM had significantly higher tender joint counts and higher patient global assessment scores than those without FM [73]. Objective measurements including swollen joints and inflammatory markers were not significantly different between RA patients with and without FM [73]. Other scoring systems including the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) were also higher in RA patients with comorbid FM [75]. A large study of 11,866 RA patients reported that those with comorbid FM had increased pain, poorer quality of life and greater functional limitation [76].

The recognition of FM in RA patients is important for multiple reasons. Firstly, both RA and FM commonly present with pain and fatigue. Differentiation of the conditions and diagnosis of co-morbidity is vital for patient management as different treatment approaches are required. In FM-RA patients, characterisation of the pain is imperative to manage patients appropriately. For example, inflammatory flares must be differentiated from painful flares secondary to FM. Secondly; recognition of patients with secondary FM offers an important insight into the pathogenesis of pain centralisation which is currently poorly understood. Nevertheless, caution should be used when interpreting the association between inflammatory arthritis and FM as the FM diagnostic tools have not been validated in RA. Furthermore, confounding factors including female sex and mental health problems are more prevalent in both FM and RA.

4.5 Central mechanisms of pain sensitisation

Central pain sensitisation is thought to occur at both spinal and supraspinal levels [62]. At the level of the DRG, spinal hyperexcitability occurs secondary to ongoing nociceptive input and pain transmission can be modified by inhibitory or facilitating neurones that can be modulated by descending signals from supraspinal levels [72]. Spinal pain facilitation is thought to be responsible for the spread of mechanical allodynia beyond the innervated field of cutaneous neurons. This has been shown in models using the intradermal injection of capsaicin [77]. Both ipsilateral and contralateral pain facilitation is thought to occur secondary to chronic inflammation and in RA patients, enhanced responses to noxious stimulation occurs at sites distal from inflamed joints [78]. Pain sensitisation is also thought to occur at supraspinal levels and brain imaging has demonstrated changes in cerebral activation secondary to chronic pain. Throughout the next section of the chapter, we will discuss the evidence of supraspinal pain sensitisation in RA.

4.6 Brain neuroimaging and pain

Imaging studies have attempted to characterise the neuronal circuitry resulting in cerebral sensitisation in RA. Structural MRI studies have shown increased grey matter density in the basal ganglia of RA patients compared to controls. This area is involved in both motor function and in pain processing [79]. Functional imaging has been used to investigate neuronal activation in response to pain. Functional MRI (fMRI) studies have demonstrated differences in resting state functional connectivity between RA patients and controls. In RA patients, there is increased connectivity between frontal midline regions that are implicated in pain processing, including the supplementary motor area and the mid-cingulate cortex, to sensorimotor regions [80]. Moreover, in RA patients, increased EEG activity has been reported in response to repetitive painful stimuli [81]. These studies suggest that aberrant pain cerebral pain processing may occur in RA and therefore, may result in augmented pain responses.

A further level of complexity is introduced when the biopsychosocial model of pain is considered. This suggests that cognitive and emotional processes are also critical contributors to the overall perception of pain. Indeed, the transmission of nociceptive information is influenced by multiple higher-level factors, such as mood, attention and cognitive factors, to form the resulting pain experience [82]. Mood is a particularly important cognitive factor in RA and meta-analysis has revealed that 16.8% of patients with RA meet the criteria for a major depressive episode [83].

In RA patients, depressive symptoms have been found to correlate significantly with tender joint count [84]. The medial prefrontal cortex has been suggested to play an important role in mediating the relationship between pain severity and depressive symptoms. Evidence has demonstrated an association between depressive scores (measured using the Becks depression index), tender joint count and MPFC activation during provoked joint pain. In the same study, MPFC activation co-varied significantly with limbic activation, an area involved in affective processing. This led the authors to suggest that the MPFC engages areas important for self-relevant processing to mediate the relationship between pain and affective symptoms [84]. In summary, pain processing by higher brain centres affects pain perception and the affective response to pain in RA. Although we are beginning to shed light on higher processing using functional imaging studies, more work is required to fully appreciate the complexities of central pain processing in RA.

5. Management of pain in RA

The cornerstone of RA treatment is the suppression of inflammation using the treat to target approach. However, disease remission will not lead to the complete resolution of pain in all patients and a multi-modal approach to pain management is very important. This approach has been recommended by rheumatology associations. For example, EULAR have recommended a patient centred approach to pain management where a biopsychosocial framework should be adopted [85]. Specifically, clinicians should differentiate between local and generalised pain and should be guided by patient needs, preferences, pain characteristics, inflammation and psychological factors. Treatments should include education, psychical therapies, orthotics, psychosocial interventions, sleep hygiene, pharmacological and joint-specific treatment options. Throughout this section of the review, we will discuss the different facets of pain management.

5.1 Pharmacological therapies

Pharmacological treatments include analgesic agents and immunomodulatory medications. Many analgesic agents are used in the management of RA pain although their use is rarely supported by high-quality RCTs [62]. Commonly used analgesic medications include paracetamol, NSAIDs, opioids and tricyclic anti-depressants. Optimal pain management should involve the characterisation of pain phenotype, in particular, differentiation of peripheral and central pain mechanisms. Pain phenotype could alter the choice of analgesic agent. For example, NSAIDs have been shown to reduce inflammatory pain in RA but not central pain in FM [86]. More work is required to define optimal analgesic use in different subsets of RA patients.

The cornerstone of RA management is the suppression of inflammation. Medications that reduce synovial inflammation are well known to reduce pain in RA patients. Immunomodulatory medications used in RA include glucocorticoids,

conventional synthetic DMARDs and biologic DMARDs. Glucocorticoids are commonly used to treat acute inflammatory flares and have been shown to provide significant pain relief [87]. Extensive evidence supports the efficacy of traditional DMARDs, including methotrexate, sulfasalazine and leflunomide, in reducing joint pain. The analgesic effect of cDMARDs parallels the suppression over a time course of weeks to months [62]. Combination therapy has been shown to be superior than monotherapy and the addition of a biologic agent has been shown to reduce pain even further [88, 89]. Nevertheless, pain improvement may plateau despite effective suppression of inflammation and studies have shown that this plateau is worse that the UK mean [7]. Persisting pain may result from centrally mediated pain hypersensitivity and may respond better to neuropathic agents or non-pharmacological treatments including education, exercise and cognitive behavioural therapy (CBT) than those treatments focusing on management on nociceptive triggers alone.

5.2 Neuropathic agents

Neuromodulatory medications used for the treatment of neuropathic pain include antidepressants such as tricyclic antidepressants (e.g. amitriptyline) and serotonin-noradrenaline re-uptake inhibitors (e.g. duloxetine) or anti-convulsants, e.g., pregabalin or gabapentin [90]. The clinical efficacy of these medications well well-established in conditions including neuropathic pain and generalised pain sensitisation syndromes such as fibromyalgia [91, 92]. Neuropathic agents are sometimes used for the treatment of pain in RA however evidence from high quality RCTs is lacking [93]. However, in other localised pain conditions such as hand OA, pregabalin has been shown to improve pain and function [94]. Further work is required to establish the role for neuropathic medications in RA patients.

5.3 Psychosocial therapies

Psychological pain management programmes, including cognitive behavioural approaches and mindfulness, have an important role in the management of chronic pain. An abundance of evidence supports the efficacy of psychosocial approaches to pain management in chronic pain conditions [95]. In RA, CBT has the best evidence base for the management of pain with multiple meta-analyses confirming efficacy [96, 97]. In addition to benefiting pain symptoms, CBT has been shown to improve other symptoms including fatigue in RA patients [98]. Psychosocial therapy may be most efficacious when offered early in the disease course however further work is required to determine which subset of patients should be offered psychosocial therapies and at which time-point in their illness [99].

5.4 Exercise based therapies

Exercise based therapies have an important role in the management of RA. Evidence has shown that resistance exercises decrease disability and functional impairment [100]. Furthermore, a meta-analysis of five studies revealed that resistance exercises resulted in a trend towards a small positive effect on VAS pain [100].

6. Conclusion

In conclusion, pain remains a significant problem for many patients with RA and is associated with psychological distress, fatigue and reduced quality of life.

In RA patients, pain results from a combination of joint inflammation, structural joint changes and pain sensitisation. In order to treat patients effectively, it is vital to differentiate between different types of pain, as each type should be targeted differently. Effective pain management approaches using a multimodal approach are vital to increase patient well-being, functioning and to reduce individual and societal costs [85].

List of abbreviations

ACPA	anti-citrullinated peptide antibodies
CBT	cognitive behavioural therapy
CDAI	clinical disease activity index
CGRP	calcitonin gene-related peptide
CNS	central nervous system
COX	cyclooxygenase
CXCL	chemokine (C-X-C motif) ligand
DAS	disease activity score
DMARDs	disease modifying anti-rheumatic drugs
DRG	dorsal root ganglia
EEG	electroencephalogram
EULAR	European league against rheumatism
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
IC	immune complexes
IL	interleukin
MAPK	mitogen activated protein kinase
MMP	matrix mellatoproteinase
MPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	nerve growth factor
NPY	neuropeptide Y
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
PI3K	phosphoinositide 3-kinases
PGE	prostaglandin E
PK	protein kinase
QST	quantitative sensory testing
RA	rheumatoid arthritis
RANK	receptor activator of nuclear factor kappa beta
RANK-L	receptor activator of nuclear factor kappa beta ligand
RCT	randomised control trials
SDAI	simple disease activity index
SP	substance P
THR	total hip replacement
TKR	total knee replacement
TNF	tumour necrosis factor
TrkA	tropomyosin receptor kinase A
TRPA1	transient receptor potential cation channel, subfamily A, member 1
TRPV1	transient receptor potential cation channel subfamily V member 1
VAS	visual analogue scale

DOI: http://dx.doi.org/10.5772/intechopen.93829

IntechOpen

Author details

Kathryn Biddle and Nidhi Sofat*
Musculoskeletal Research Group, Institute for Infection and Immunity, St George's, University of London, London, United Kingdom

*Address all correspondence to: nsofat@sgul.ac.uk

IntechOpen

References

[1] Y. Alamanos, P. V. Voulgari, and A. A. Drosos, "Incidence and Prevalence of Rheumatoid Arthritis, Based on the 1987 American College of Rheumatology Criteria: A Systematic Review," Semin. Arthritis Rheum., 2006.

[2] T. Heiberg and T. K. Kvien, "Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: Pain has highest priority," Arthritis Rheum., 2002.

[3] G. da Rocha Castelar Pinheiro, R. K. Khandker, R. Sato, A. Rose, and J. Piercy, "Impact of rheumatoid arthritis on quality of life, work productivity and resource utilisation: An observational, cross-sectional study in Brazil," Clin. Exp. Rheumatol., 2013.

[4] H. J. Williams et al., "Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A Controlled Clinical Trial," Arthritis Rheum., 1985.

[5] R. Altawil, S. Saevarsdottir, S. Wedrén, L. Alfredsson, L. Klareskog, and J. Lampa, "Remaining Pain in Early Rheumatoid Arthritis Patients Treated With Methotrexate," Arthritis Care Res., 2016.

[6] D. F. McWilliams and D. A. Walsh, "Factors predicting pain and early discontinuation of tumour necrosis factor-α-inhibitors in people with rheumatoid arthritis: Results from the British society for rheumatology biologics register," BMC Musculoskelet. Disord., 2016.

[7] D. F. McWilliams, W. Zhang, J. S. Mansell, P. D. W. Kiely, A. Young, and D. A. Walsh, "Predictors of change in bodily pain in early rheumatoid arthritis: An inception cohort study," Arthritis Care Res., 2012.

[8] S. J. Bartlett et al., "Identifying core domains to assess flare in rheumatoid arthritis: An OMERACT international patient and provider combined Delphi consensus," Ann. Rheum. Dis., 2012.

[9] D. Aletaha, F. Alasti, and J. S. Smolen, "Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials," Arthritis Res. Ther., 2015.

[10] L. Klareskog, K. Lundberg, and V. Malmström, "Autoimmunity in Rheumatoid Arthritis: Citrulline Immunity and Beyond," in Advances in Immunology, 2013.

[11] X. Zhao et al., "Circulating immune complexes contain citrullinated fibrinogen in rheumatoid arthritis," Arthritis Res. Ther., 2008.

[12] M. Feldmann and S. R. N. Maini, "Role of cytokines in rheumatoid arthritis: An education in pathophysiology and therapeutics," Immunological Reviews. 2008.

[13] C. M. Weyand and J. J. Goronzy, "Immunometabolism in early and late stages of rheumatoid arthritis," Nature Reviews Rheumatology. 2017.

[14] I. B. McInnes and G. Schett, "The pathogenesis of rheumatoid arthritis.," The New England journal of medicine. 2011.

[15] J. Martel-Pelletier, D. J. Welsch, and J. P. Pelletier, "Metalloproteases and inhibitors in arthritic diseases," Best Pract. Res. Clin. Rheumatol., 2001.

[16] K. Redlich et al., "Osteoclasts are essential for TNF-α-mediated joint destruction," J. Clin. Invest., 2002.

[17] C. Grigor et al., "Effect of a treatment strategy of tight control for

rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial," Lancet, 2004.

[18] E. Krock, A. Jurczak, and C. I. Svensson, "Pain pathogenesis in rheumatoid arthritis-what have we learned from animal models?," Pain. 2018.

[19] D. W. Gilroy and D. Bishop-Bailey, "Lipid mediators in immune regulation and resolution," British Journal of Pharmacology. 2019.

[20] M. F. Yam, Y. C. Loh, C. S. Tan, S. K. Adam, N. A. Manan, and R. Basir, "General pathways of pain sensation and the major neurotransmitters involved in pain regulation," International Journal of Molecular Sciences. 2018.

[21] F. A. Pinho-Ribeiro, W. A. Verri, and I. M. Chiu, "Nociceptor Sensory Neuron–Immune Interactions in Pain and Inflammation," Trends in Immunology. 2017.

[22] M. Shinoda et al., "Nerve terminals extend into the temporomandibular joint of adjuvant arthritic rats," Eur. J. Pain, 2003.

[23] Y. Yamazaki, K. Ren, M. Shimada, and K. Iwata, "Modulation of paratrigeminal nociceptive neurons following temporomandibular joint inflammation in rats," Exp. Neurol., 2008.

[24] T. M. Cunha et al., "Crucial role of neutrophils in the development of mechanical inflammatory hypernociception," J. Leukoc. Biol., 2008.

[25] N. Ghasemlou, I. M. Chiu, J. P. Julien, and C. J. Woolf, "CD11b+Ly6G- myeloid cells mediate mechanical inflammatory pain hypersensitivity," Proc. Natl. Acad. Sci. U. S. A., 2015.

[26] A. Aich, L. B. Afrin, and K. Gupta, "Mast cell-mediated mechanisms of nociception," International Journal of Molecular Sciences. 2015.

[27] W. W. Li, T. Z. Guo, D. Y. Liang, Y. Sun, W. S. Kingery, and J. D. Clark, "Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome," Anesthesiology, 2012.

[28] C. Gunaydin and S. S. Bilge, "Effects of nonsteroidal anti-inflammatory drugs at the molecular level," Eurasian Journal of Medicine. 2018.

[29] S. H. FERREIRA, "Prostaglandins, Aspirin-like Drugs and Analgesia," Nat. New Biol., 1972.

[30] G. R. Souza et al., "Involvement of nuclear factor kappa B in the maintenance of persistent inflammatory hypernociception," Pharmacol. Biochem. Behav., 2015.

[31] A. Nieto-Posadas et al., "Lysophosphatidic acid directly activates TRPV1 through a C-terminal binding site," Nat. Chem. Biol., 2012.

[32] H. A. Martin, A. I. Basbaum, G. C. Kwiat, E. J. Goetzl, and J. D. Levine, "Leukotriene and prostaglandin sensitization of cutaneous high-threshold C- and A-delta mechanonociceptors in the hairy skin of rat hindlimbs," Neuroscience, 1987.

[33] C. N. Serhan, "Pro-resolving lipid mediators are leads for resolution physiology," Nature. 2014.

[34] J. X. Yue et al., "Histamine Upregulates Nav1.8 Expression in Primary Afferent Neurons via H2 Receptors: Involvement in Neuropathic Pain," CNS Neurosci. Ther., 2014.

[35] C. A. Parada, C. H. Tambeli, F. Q. Cunha, and S. H. Ferreira, "The major

role of peripheral release of histamine and 5-hydroxytryptamine in formalin-induced nociception," Neuroscience, 2001.

[36] S. H. Ferreira, B. B. Lorenzetti, A. F. Bristow, and S. Poole, "Interleukin-1β as a potent hyperalgesic agent antagonized by a tripeptide analogue," Nature, 1988.

[37] A. M. Binshtok et al., "Nociceptors are interleukin-1β sensors," J. Neurosci., 2008.

[38] M. Ebbinghaus et al., "The role of interleukin-1β in arthritic pain: Main involvement in thermal, but not mechanical, hyperalgesia in rat antigen-induced arthritis," Arthritis Rheum., 2012.

[39] P. Malsch et al., "Deletion of interleukin-6 signal transducer gp130 in small sensory neurons attenuates mechanonociception and down-regulates TRPA1 expression," J. Neurosci., 2014.

[40] E. S. Fernandes et al., "A distinct role for transient receptor potential ankyrin 1, in addition to transient receptor potential vanilloid 1, in tumor necrosis factor α-induced inflammatory hyperalgesia and Freund's complete adjuvant-induced monarthritis," Arthritis Rheum., 2011.

[41] G. D. Nicol, J. C. Lopshire, and C. M. Pafford, "Tumor necrosis factor enhances the capsaicin sensitivity of rat sensory neurons," J. Neurosci., 1997.

[42] S. Gudes, O. Barkai, Y. Caspi, B. Katz, S. Lev, and A. M. Binshtok, "The role of slow and persistent ttx-resistant sodium currents in acute tumor necrosis factor-α-mediated increase in nociceptors excitability," J. Neurophysiol., 2015.

[43] F. Richter et al., "Interleukin-17 sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors in rodents," Arthritis Rheum., 2012.

[44] L. G. Pinto et al., "IL-17 mediates articular hypernociception in antigen-induced arthritis in mice," Pain, 2010.

[45] M. A. Eskander et al., "Persistent nociception triggered by nerve growth factor (NGF) is mediated by TRPV1 and oxidative mechanisms," J. Neurosci., 2015.

[46] L. S. Ro, S. T. Chen, L. M. Tang, and J. M. Jacobs, "Effect of NGF and anti-NGF on neuropathic pain in rats following chronic constriction injury of the sciatic nerve," Pain, 1999.

[47] W. H. Bos et al., "Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: A prospective cohort study," Ann. Rheum. Dis., 2010.

[48] G. Wigerblad et al., "Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism," Ann. Rheum. Dis., 2016.

[49] K. L. Druce, G. T. Jones, G. J. MacFarlane, and N. Basu, "Determining pathways to improvements in fatigue in rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register for rheumatoid arthritis," Arthritis Rheumatol., 2015.

[50] K. W. Drossaers-Bakker et al., "Long-term outcome in rheumatoid arthritis: A simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup," Arthritis Rheum., 2002.

[51] A. Judge et al., "Predictors of outcomes of total knee replacement surgery," Rheumatol. (United Kingdom), 2012.

[52] E. Nikiphorou et al., "Hand and foot surgery rates in rheumatoid arthritis have declined from 1986 to 2011, but large-joint replacement rates remain unchanged: Results from two UK inception cohorts," Arthritis Rheumatol., 2014.

[53] T. Sokka, A. Kankainen, and P. Hannonen, "Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores," Arthritis Rheum., 2000.

[54] S. L. Murphy, A. K. Lyden, K. Phillips, D. J. Clauw, and D. A. Williams, "Association between pain, radiographic severity, and centrally-mediated symptoms in women with knee osteoarthritis," Arthritis Care Res., 2011.

[55] A. D. Beswick, V. Wylde, R. Gooberman-Hill, A. Blom, and P. Dieppe, "What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of Prospective studies in unselected patients," BMJ Open. 2012.

[56] V. Wylde, A. Sayers, A. Odutola, R. Gooberman-Hill, P. Dieppe, and A. W. Blom, "Central sensitization as a determinant of patients' benefit from total hip and knee replacement," Eur. J. Pain (United Kingdom), 2017.

[57] D. A. Walsh and D. F. McWilliams, "Mechanisms, impact and management of pain in rheumatoid arthritis," Nature Reviews Rheumatology. 2014.

[58] C. J. Woolf, S. W. N. Thompson, and A. E. King, "Prolonged primary afferent induced alterations in dorsal horn neurones, an intracellular analysis in vivo and in vitro," J. Physiol. (Paris)., 1988.

[59] M. Yunus, "Editorial Review (Thematic Issue: An Update on Central Sensitivity Syndromes and the Issues of Nosology and Psychobiology)," Curr. Rheumatol. Rev., 2015.

[60] N. Sofat, V. Ejindu, and P. Kiely, "What makes osteoarthritis painful? The evidence for local and central pain processing," Rheumatology. 2011.

[61] A. I. Basbaum, D. M. Bautista, G. Scherrer, and D. Julius, "Cellular and Molecular Mechanisms of Pain," Cell. 2009.

[62] D. F. McWilliams and D. A. Walsh, "Pain mechanisms in rheumatoid arthritis," Clin. Exp. Rheumatol., 2017.

[63] A. S. Leffler, E. Kosek, T. Lerndal, B. Nordmark, and P. Hansson, "Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis," Eur. J. Pain, 2002.

[64] L. C. Pollard, F. Ibrahim, E. H. Choy, and D. L. Scott, "Pain thresholds in rheumatoid arthritis: The effect of tender point counts and disease duration," J. Rheumatol., 2012.

[65] Y. C. Lee et al., "The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: A cross-sectional study," Arthritis Res. Ther., 2009.

[66] S. D. Boyden, I. N. Hossain, A. Wohlfahrt, and Y. C. Lee, "Non-inflammatory Causes of Pain in Patients with Rheumatoid Arthritis," Current Rheumatology Reports. 2016.

[67] J. Wendler et al., "Patients with rheumatoid arthritis adapt differently to repetitive painful stimuli compared to healthy controls," J. Clin. Neurosci., 2001.

[68] M. Mms. C. O. B. I. M. R. R. E. P. Yvonne C. Lee et al., "Pain Sensitization is Associated with Disease Activity

in Rheumatoid Arthritis Patients: A Cross-Sectional Study," Arthritis Care Res (Hoboken), Feb-2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654691/. [Accessed: 30-Jun-2020].

[69] M. K. Sim, D. Y. Kim, J. Yoon, D. H. Park, and Y. G. Kim, "Assessment of peripheral neuropathy in patients with rheumatoid arthritis who complain of neurologic symptoms," Ann. Rehabil. Med., 2014.

[70] V. Agarwal et al., "A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis," Clin. Rheumatol., 2008.

[71] S. Ahmed, T. Magan, M. Vargas, A. Harrison, and N. Sofat, "Use of the painDETECT tool in rheumatoid arthritis suggests neuropathic and sensitization components in pain reporting," J. Pain Res., 2014.

[72] W. Häuser et al., "Fibromyalgia," Nat. Rev. Dis. Prim., 2015.

[73] S. S. Zhao, S. J. Duffield, and N. J. Goodson, "The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis," Best Practice and Research: Clinical Rheumatology. 2019.

[74] L. P. Queiroz, "Worldwide Epidemiology of Fibromyalgia," Curr. Pain Headache Rep., 2013.

[75] S. J. Duffield, N. Miller, S. Zhao, and N. J. Goodson, "Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis," Rheumatology (Oxford)., 2018.

[76] F. Wolfe and K. Michaud, "Severe Rheumatoid Arthritis (RA), Worse Outcomes, Comorbid Illness, and Sociodemographic Disadvantage Characterize RA Patients with Fibromyalgia," J. Rheumatol., 2004.

[77] V. H. Morris, S. C. Cruwys, and B. L. Kidd, "Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis," Pain, 1997.

[78] N. G. Shenker, R. C. Haigh, P. I. Mapp, N. Harris, and D. R. Blake, "Contralateral hyperalgesia and allodynia following intradermal capsaicin injection in man," Rheumatology, 2008.

[79] K. Wartolowska, M. G. Hough, M. Jenkinson, J. Andersson, B. P. Wordsworth, and I. Tracey, "Structural changes of the brain in rheumatoid arthritis," Arthritis Rheum., 2012.

[80] P. Flodin et al., "Intrinsic brain connectivity in chronic pain: A resting-state fMRI study in patients with rheumatoid arthritis," Front. Hum. Neurosci., 2016.

[81] T. Hummel, C. Schiessl, J. Wendler, and G. Kobal, "Peripheral and central nervous changes in patients with rheumatoid arthritis in response to repetitive painful stimulation," Int. J. Psychophysiol., 2000.

[82] P. Rainville, Q. V. H. Bao, and P. Chrétien, "Pain-related emotions modulate experimental pain perception and autonomic responses," Pain, 2005.

[83] F. Matcham, L. Rayner, S. Steer, and M. Hotopf, "The prevalence of depression in rheumatoid arthritis: A systematic review and meta-analysis," Rheumatol. (United Kingdom), 2013.

[84] P. Schweinhardt, N. Kalk, K. Wartolowska, I. Chessell, P. Wordsworth, and I. Tracey, "Investigation into the neural correlates of emotional augmentation of clinical pain," Neuroimage, 2008.

[85] R. Geenen et al., "EULAR recommendations for the health

professional's approach to pain management in inflammatory arthritis and osteoarthritis," Ann. Rheum. Dis., 2018.

[86] K. Kroenke, E. E. Krebs, and M. J. Bair, "Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews," Gen. Hosp. Psychiatry, 2009.

[87] J. R. Kirwan, "The effect of glucocorticoids on joint destruction in rheumatoid arthritis," N. Engl. J. Med., 1995.

[88] S. M. Van Der Kooij et al., "Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis," Arthritis Care Res., 2009.

[89] E. C. Keystone et al., "Radiographic, Clinical, and Functional Outcomes of Treatment with Adalimumab (a Human Anti-Tumor Necrosis Factor Monoclonal Antibody) in Patients with Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy: A Randomized, Placebo-Controlled," Arthritis Rheum., 2004.

[90] N. B. Finnerup et al., "Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis," Lancet Neurol., 2015.

[91] M. Kremer, E. Salvat, A. Muller, I. Yalcin, and M. Barrot, "Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights," Neuroscience. 2016.

[92] G. J. Macfarlane et al., "EULAR revised recommendations for the management of fibromyalgia," Ann. Rheum. Dis., 2017.

[93] B. L. Richards, S. L. Whittle, and R. Buchbinder, "Neuromodulators for pain management in rheumatoid arthritis," Cochrane Database Syst. Rev., 2012.

[94] N. Sofat et al., "The effect of pregabalin or duloxetine on arthritis pain: A clinical and mechanistic study in people with hand osteoarthritis," J. Pain Res., 2017.

[95] A. C. d. C. Williams, C. Eccleston, and S. Morley, "Psychological therapies for the management of chronic pain (excluding headache) in adults," Cochrane Database of Systematic Reviews. 2012.

[96] J. A. Astin, W. Beckner, K. Soeken, M. C. Hochberg, and B. Berman, "Psychological interventions for rheumatoid arthritis: A meta-analysis of randomized controlled trials," Arthritis Rheum., 2002.

[97] K. Knittle, S. Maes, and V. De Gucht, "Psychological interventions for rheumatoid arthritis: Examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials," Arthritis Care Res., 2010.

[98] S. Hewlett et al., "Reducing arthritis fatigue impact: Two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT)," Ann. Rheum. Dis., 2019.

[99] L. Sharpe, "Psychosocial management of chronic pain in patients with rheumatoid arthritis: Challenges and solutions," Journal of Pain Research. 2016.

[100] A. Baillet, M. Vaillant, M. Guinot, R. Juvin, and P. Gaudin, "Efficacy of resistance exercises in rheumatoid arthritis: Meta-analysis of randomized controlled trials," Rheumatology, 2012.