Pain mechanisms in rheumatoid arthritis

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ABSTRACT

Understanding of the causes and underlying mechanisms of pain in people with RA is rapidly changing. With the advent of more effective disease modifying drugs, joint inflammation is becoming a more treatable cause of pain, and joint damage can often be prevented. However, the long-term prognosis for pain still is often unfavourable, even after inflammation is suppressed. Pain is associated with fatigue and psychological distress, and RA pain qualities often share characteristics with neuropathic pain. Each of these characteristics suggests key roles for central neuronal processing in RA pain. Pain processing by the central nervous system can maintain and augment RA pain, and is a promising target for future treatments. Inflammatory mediators, such as cytokines, may provoke central pain sensitisation in animal models, and both local and systemic inflammation might contribute to central pain augmentation in RA. Controlled trials of treatments that target central pain processing have shown some benefit in people with RA, and might be most effective in individuals for whom central pain augmentation plays a key role. For people with RA who experience persistent pain, identifying underlying pain mechanisms critically determines the balance between escalation of anti-inflammatory and disease-modifying treatments and other strategies to provide symptomatic analgesia.

The problem of RA pain

People with rheumatoid arthritis (RA) can expect many of their long-term outcomes to be much more favourable than they were for people in the past. However, they still often describe pain as constantly present, and often rate it, on average, as "moderate" (1). The randomised controlled trials (RCTs) that underpin current DMARD usage showed reductions in pain that were both statistically and clinically significant. However, participants still reported pain at final follow up. In observational cohort studies of people starting new treatment with DMARDs for early or established RA, the mean levels of pain remain troublesome at follow up (2, 3). After initial improvements in the average pain score, a plateau might be reached beyond which RA pain does not fully resolve.

Epidemiological studies can conceal heterogeneity and variability within populations. People with RA describe pain that changes during the day, and might flare from day to day, or month to month. Pain is a major component in RA flares, in addition to the inflammatory and psychological aspects of RA, and often prominent fatigue (4). The OMERACT initiative has defined flare in people with RA as 'a cluster of symptoms of sufficient duration and intensity that cannot be self-managed by the patient and require initiation, change or increase in therapy' (5). The unpredictable nature of RA pain can itself have substantially impact on quality of life, frustrating attempts to plan or commit to valued activities.

Self-reported flares in RA are reflected by increases in disease activity scores such as the 28 joint DAS28 (6). This might be expected given that DAS28 includes components both measuring inflammation and pain (3, 7). However, not all RA flares are associated with noticeable joint swelling or increases in erythrocyte sedimentation rate or C-reactive protein, and painful flares might sometimes be discrete from inflammatory flares (8, 9). People with OA (10), or with fibromyalgia (11) also report pain flares, although it is unclear whether these share mechanisms with RA flare. Initiation, change or increase in DMARD therapy might be desirable during a flare episode, although the heterogeneous nature of these events raise important questions about whether this will always be the ideal intervention.

Pain in people with RA might indeed

be caused by inflammation, but might also result from joint damage and from changes in how the central nervous system processes signals from the joint (Fig. 1). Pain relief following DMARD introduction might be partly attributable to inflammation suppression, but also from contextual factors that might be replicated in placebo arms of RCTs. Understanding the characteristics of pain, and its underlying mechanisms, is essential in deciding the most appropriate treatment. DMARD escalation in those whose pain is predominantly caused by factors other than inflammation might not only be ineffective, but exposes people unnecessarily to risks adverse events from treatment. Recognising potentially modifiable factors other than inflammation that contribute to RA pain opens the door to more effective treatment with existing therapies, and the development of new treatments that might benefit specific patient subgroups.

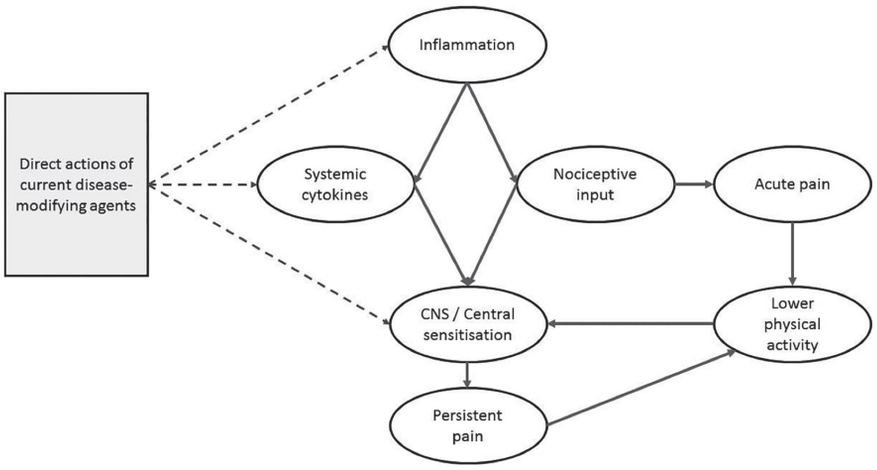

Fig. 1. Pathways towards persistent RA pain.
Each ellipse represents a physiological process and possible target for intervention. Solid arrows represent proposed mechanistic pathways. Dashed arrows represent possible mechanistic pathways by which current DMARDs might improve RA pain.

Pain predictors and prognosis in people with RA

In common with other chronic painful conditions, female gender and psychosocial factors including anxiety and depression predict pain prognosis in RA (3, 12). Other factors often thought of as predictors of successful long-term outcomes in people with RA, such as serology, joint damage and acute phase response, are less able to predict pain prognosis (3, 12). A key issue for healthcare providers and patients is that disease-modifying treatment provides less robust improvement in pain than in other outcomes such as inflammation, joint damage, deformity and even life expectancy. Persistent pain and fatigue despite effective suppression of inflammation can continue to impair quality of life.

While joint inflammation and disease activity contribute to current pain, one registry study of established RA found that changes in inflammation only explained approximately 40% of the changes in pain (13). Large observational cohorts have identified subgroups of people with early and established RA who display discordantly low levels of ESR and SJC, but high reported bodily pain, fatigue and worse mental health scores (14). One year after DMARD initiation or change, pain remained troublesome for 40–50% of participants despite "undetectable" residual inflammation, assessed as no swollen joints with normal ESR levels (2). Similar pain prognosis was found in people classified as displaying good treatment response, and those who remained on biologics for 1 year.

Additional pain mechanisms fill the gap of unexplained pain that is independent of disease activity measures. Discrete phenotypic subgroups, reflecting different pain experiences (15), or patient global assessments (16) distinguish between individuals with RA. Phenotypes characterised by widespread bodily pain are recognised amongst people with RA (17). If pain in people with RA is not uniquely linked to disease activity, then it may share common causes, and hopefully common treatments, with other chronic pain conditions.

Contributions of joint damage to pain in RA

Pain in people with advanced RA can be substantially improved following joint replacement surgery (18), suggesting that structural factors continue to influence RA pain. Arthroplasty might have effects on pain through mechanisms that are additional to directly reducing nociceptive drive from a damaged joint. For example, arthroplasty might permit increased physical activity or directly reduce synovitis. Augmented central pain processing in OA can be reversed following arthroplasty (19), although it remains unknown whether the same occurs in RA. As disease modifying treatment protocols have improved, progressive joint damage and radiographic structural change have decreased in RA (20). Correspondingly, rates of orthopaedic surgeries have declined (21), although those with persistent disease activity still experience worse structural outcomes (22). Early and intensive treatment with combination therapies offer benefits through long term pain reduction (23), although it is not certain how much this might be due to inhibition of joint damage, rather than changes in pain mechanisms or suppression of inflammation. Radiographically assessed joint damage or structural changes in people with RA now appear to only make small contributions to current pain (24-26). Pain in RA might also sometimes be due to coincidental osteoarthritis, given that peak incidence now occurs in similar demographic groups, albeit often affecting different joints. Some of the weak association between pain and radiographic joint space narrowing might be explained by coincidental osteoarthritis rather than RA pathogenesis (24).

Central mechanisms of RA pain

Pain processing by the central nervous system can affect pain reporting, sensi-

tivity, descriptive quality and intensity/severity. All types of pain and all chronic painful conditions can be influenced by central factors, whether pain is acute or chronic, widespread or definitively local and nociceptive. A recent systematic review concluded that central sensitisation is present in people with RA (27). In people with RA, fulfilling fibromyalgia classification criteria is highly suggestive of central pain augmentation. At RA presentation, fibromyalgia classification has similar prevalence to the population as a whole (28), but prevalence increases throughout the course of RA natural history (29). People with RA who satisfy fibromyalgia classification criteria display worse psychological health, poorer sleep, as well as greater pain sensitivity, report more widespread pain and display multiple tender points (7, 30-35).

Fibromyalgia classification also predicts worse functional prognosis (36). Seronegativity might be associated with fibromyalgia classification in RA (37). However, autoantibodies might also promote chronic pain in arthritis models (38), and the association between autoimmunity and central pain augmentation might therefore be complex and deserve further study.

Fibromyalgia classification is independent of the well-known measures of clinical inflammation in RA (31, 39), despite tenderness and pain increasing DAS28 scores through higher tender joint counts (TJC) and visual analogue scales for global health (VAS-GH) (39). Discordance between patient-reported and observed or measured disease activity components has inspired several attempts to derive novel indices that might distinguish inflammatory from non-inflammatory processes. A large difference between TJC and SJC (7), a high proportion of patient-reported components in DAS28 (so-called DAS28-P (2, 3, 39)) and the ratio between swollen and tender joint counts (40) have each statistically predicted pain (3). Each is also associated with fibromyalgia classification, and derived DAS28 indices might provide measures of central pain augmentation in people with `active' RA (7, 39). Assessment of people with RA plus fibromyalgia might suggest worse disease activity than objectively measured synovitis would indicate. Correspondingly, this subgroup displays less joint damage that would be expected from their disease activity scores (24, 34). Discordance between patient-reported and observed/clinical outcomes is a key factor in interpreting results of RCTs (41), or response to DMARD treatment in clinical practice. However, elevated markers of central sensitisation do not necessarily predict worse disease activity outcomes (42, 43).

Some studies of RA have attempted to measure specific pain mechanisms or pathways through psychophysical tests known as quantitative sensory testing (QST). The underlying mechanisms of pain sensitivity may be characterised through a variety of QST modalities, including blunt pressure, punctate, hot or cold temperature, or electrical stimulation. QST can measure the stimulus intensity corresponding to transition from painless (*e.g.,* pressure) to pain during a standardised stimulus ramp. Algometers, typically with a 1 cm diameter circular probe end, non-invasively applies pressure to deeper tissues than do punctate stimuli, for example using von Frey hairs or blunt needles. Punctate stimuli typically measure cutaneous sensation, whereas algometers elicit sensations for example in joint capsule, muscle or periosteum. Arthritis pain might derive from these deeper structures, but also from synovium and subchondral bone which are not amenable to non-invasive sensory testing by current techniques. This evoked pain response might reflect similar mechanisms to those underlying tender point or tender joint counts. These different measures certainly intercorrelate, although mechanisms behind their association have not been studied in depth (30, 39). Dynamic assessment can measure an increase in sensitivity with repeated stimulation (temporal summation), a characteristic associated with central sensitisation. Conditioned pain modulation is a measure of the reduction of pain in response to a standard stimulation at the test site normally experienced in response to painful stimulation at a distant (heterotopic) site.

The extent to which central processing differs between sensory modalities remains incompletely understood, but might explain differences sometimes observed between findings using mechanical or thermal stimuli. Mechanical stimuli might be more relevant than are thermal nociceptive stimuli, given the mechanical nature of arthritis pain. Cutaneous innervations differs from that in deeper structures such as synovium and bone. For example, the skin contains specialised sensory endings, and slow conducting cutaneous sensory C-fibres comprise both peptidergic (containing substance P and calcitonin gene-related peptide) and non-peptidergic populations. By contrast, synovium and bone appear to be devoid of non-peptidergic, unmyelinated sensory nerves (44, 45).

Joints affected by active synovitis are more sensitive to pain, due to peripheral sensitisation induced by local inflammation. This increased sensitivity results in increased nociceptive input in response to a standardised stimulus. However, regions distal or remote from affected joints can also display increased pain sensitivity (46), indicative of pain augmentation by the central nervous system and/or a blunting of normal antinociceptive modulation in people with RA. Pressure pain detection thresholds at the trapezius are increased in response to painful cold stimulation of the hand in people without chronic pain, but this conditioned pain modulation was impaired in people with RA (47, 48). Anxiety or depression (47, 48), or impaired sleep (47) might mediate blunting of this endogenous analgesic pathway. Pressure pain detection thresholds are lowered in people with RA, and even more so when fibromyalgia classification is fulfilled (39). This occurs across the whole body and does not rely upon proximity to a joint (39).

Exercise and RA pain

People with RA often reduce their physical activity levels, due to the mechanical drive to pain during movement and weight bearing, and fear that activity might induce further pain, or flare of inflammatory disease activity. Healthcare professionals have long believed that ongoing activity can main-

tain synovitis, and that rest might facilitate suppression of inflammatory disease activity. Indeed, bedrest might reduce RA disease activity for some people (49, 50), although a RCT from 1971 showed no benefits from bedrest for flares (51). However, bed rest has both medical and social disadvantages, including risk of deep vein thrombosis and physical deconditioning. Many people with chronic medical complaints tolerate and benefit from physical activity (52). Non-arthritic people display reduced pain sensitivity during exercise (53), and in a recent RCT people with RA also demonstrated exercise-induced analgesia (54). Submaximal cycling exercise reduced temporal summation and augmented conditioned pain modulation both in non-arthritic individuals and in those with RA, indicating that analgesic effects of exercise might be mediated through central pain modulation.

Increasing aerobic fitness is also associated with increased pain tolerance in non-arthritic individuals (55). RCTs in people with RA also show important reductions in pain following cardiorespiratory aerobic exercise (56), resistance-based exercise (57) and hand exercises (58), both in established RA and in early RA (59). Aerobic exercise is also beneficial for managing pain in people with fibromyalgia (60), again supporting effects on central pain modulation. Advice for exercise should therefore represent a balance between facilitating suppression of inflammatory disease activity, and discouraging deconditioning and concomitant augmentation of central pain processing. Modern rheumatology practice has moved a long way from acceptance of inevitable disability and pain, to facilitating health benefits and aiming for maintaining fitness, activity and social engagement. Activity should be graded and paced, whilst encouraging optimism and a graded return to normal and healthy activity. Pacing is a common self-management strategy (61) which can retain optimal activity levels (62).

Neuropathic-like pain in RA

Pathology of the peripheral or central nervous systems can directly cause pain (neuropathic pain) in the absence of nociceptive input nor peripheral tissue damage. Pain from peripheral nerve pathology is seen in the radicular pain of sciatica, and characterised by qualities such as radiation, shooting, tingling, burning, sensitivity to warm or cold objects placed on the skin, and allodynia (pain experienced in response to what is normally non-painful stimulus). RA can be associated with peripheral neuropathy, due to compression (*e.g.*, carpal tunnel syndrome), comorbidities (*e.g.,* diabetes mellitus), or, more rarely, vasculitis (mononeuritis multiplex) or drug treatment (*e.g.,* gold, leflunomide).

The painDETECT questionnaire displays acceptable psychometric properties in people with RA (63), good discrimination between neuropathic and mechanicial pain in people with low back pain (64), and enables classification of pain quality as likely, possibly or unlikely to be of neuropathic origin. People with RA also often describe these neuropathic-like symptoms, and painDETECT can yield 5% to 20% fulfilling the criteria of "likely neuropathic pain"; with 56% to 67% fulfilling criteria for "unlikely neuropathic pain" (65-68). However, direct measurements of neuropathic features revealed that 33% of people with RA who reported neuropathic symptoms displayed clinical evidence of neuropathy (69). Another study found that 57% of people with RA showed evidence of neuropathy, described as primarily subclinical and axonal (70), although it is not known whether this was associated with neuropathic-like symptoms. Most people with RA and "likely neuropathic pain" classified by painDETECT might have no demonstrable neuropathology.

Categorisation as "likely neuropathic pain" based only on questionnaires such as painDETECT should be interpreted with care due to the confounding effects of pain severity on the scale. People with fibromyalgia also display high painDETECT scores, although definitive evidence of pathology in the peripheral or central nervous system has been difficult to demonstrate. High painDETECT scores might therefore reflect pain mechanisms shared with neuropathic pain, rather than actual neuropathology. People with RA and high painDETECT scores often also display low vitality, low mood and QST evidence of augmented central pain processing. However, analgesics developed for neuropathic pain (*e.g.,* tricyclic antidepressants, gabapentinoids or selective sympathetic and noradrenaline reuptake inhibitiors; SSNRIs) often act through central pain mechanisms. Definitive evidence of efficacy in people with RA who display neuropathic symptoms awaits results of RCTs, but might lead to a personalised medicine based on underlying pain mechanisms (71).

The role of inflammation in centrally-controlled pain mechanisms

Pain processing in inflammatory arthritis might be augmented by a range of factors that are driven by inflammation itself, interacting with other risk factors for pain; such as genetic background (72), premorbid characteristics (3, 28), comorbidities (73, 74) and psychological status (75). Clinical studies have reported associations between inflammatory disease activity, as measured by DAS28, and pain sensitisation (39, 76). However, associations with DAS28 might overestimate contributions of inflammation to central pain processing because patient-reported components (visual analogue scale for global health and tender joint count) are strongly influenced by pain itself. Pain sensitisation might inflate DAS28 values even in the absence of ongoing synovitis (31, 32, 34, 39).

Sustained nociceptive input can lead to changes in central pain processing, and nociceptive input is increased following local sensitisation of peripheral nerves within the joint. Synovitis generates bioactive lipids, kinins, cytokines (*e.g.,* TNF-α, IL-1 and IL-6), neuropeptides (*e.g.,* calcitonin gene-related peptide (CGRP)) (77-79) and neurotrophins (*e.g.,* nerve growth factor (NGF) (80), each of which can sensitise peripheral nerves. Immune cells within the CNS directly contribute to developing central sensitisation through the generation of cytokines such as IL-1 (81, 82). Furthermore, RA

is associated with systemic features of inflammation. Circulating cytokines might gain access to the CNS, particularly given that the blood brain barrier might be compromised in chronic inflammation (83). A causative relationship between synovitis and augmented central pain processing is further suggested by research in rodent models. Inflammatory arthritis in rats is associated with central sensitisation, with behavioural, electrophysiological and histological evidence of altered spinal and supraspinal pain processing that can begin even before clinical features of arthritis become apparent (81, 84). Spinal exposure to TNF-α, IL-6 and IL-1β leads to allodynia and hyperalgesia (85). TNF-α inhibition might act in part through central actions to reduce pain processing in people with RA, although few adequately controlled studies have been reported to date (86, 87). RA treatment focuses on suppression of synovitis and the immune response. Changes in clinical practice now enable rapid access by patients to immunomodulatory treatments but, unfortunately, suppression of synovitis often does not lead to pain-free remission. The maintenance of pain despite successful remission of synovitis in established RA suggests that, once established, central sensitisation is not reversed by standard RA treatments. Analgesic benefit from DMARDs might depend in part on specific interruption of neuroimmune mechanisms that drive central sensitisation, which would mean that different DMARDs might have different effects on pain, despite similar suppression of synovitis. Cytokine candidates that impact upon central neuronal mechanisms might not be those traditionally developed as targets for treating synovitis itself (36, 37), and there remains potential for new regulators of central pain mechanisms to be uncovered. Preventing the development of central sensitisation during the earlier phases of RA, and identifying mechanisms by which central sensitisation might persist in established disease despite suppression of synovitis, has huge potential to reduce the long term burden of pain in this disease.

Evidence from RCTs

Despite their obvious appeal, analgesic agents are not well trialled in people with RA. Many RCTs are of short duration, leading to a lack of long-term evidence, and adverse events from chronic use are of real concern. Evidence bases for paracetamol (88), NSAIDs (89), opioids (90) and nefopam (91) are positive, but generally weak. Trials of DMARDs show real, but incomplete pain relief, a conclusion which is supported by longer-term registry studies showing persistent pain despite conventional treatment or biologic. However, early targeting of recent onset RA, such as in the BeST RCT of combination therapy, has yielded promising results, with participants approaching the Netherlands population average pain score during their long-term follow up (23). It is tempting to hope early, intensive treatment to a target might prevent or reverse chronification of RA pain, although proof from RCTs is still awaited.

RCTs targeting central mechanisms have shown some success in helping people with established RA to manage their pain. Meta-analyses of cognitive behavioural (CBT) or other psychological therapies (such as mindfulness or acceptance) have reported small effect sizes, with the authors of a recent review suggesting that CBT might be the most efficacious (92). Tricyclic antidepressants have been trialled in people with RA, but systematic reviewers were not able to recommend this treatment over placebo due to the limited evidence and equivocal effects (93, 94). RCTs of cannabinoids are also scarce (95). RCTs have often not included mechanistic outcome measures either to ensure recruitment of people most likely to respond to centrally targeted interventions, or proof of concept that tested interventions have indeed modulated central pain processing. One small RCT that has attempted to address this examined Milnacipran in 43 people with RA who fulfilled the ACR widespread pain criteria. This preliminary study did not meet its primary objective of pain improvement, but an interesting subgroup analysis found that pain relief was greater in people with few or no swollen joints (96). Possibly, inflammation might need to be well-controlled to gain maximum benefit from centrally acting treatments.

Conclusions

RA pain remains a major problem, despite advances in treatments that suppress inflammation. Inflammation and pain are closely integrated, not only through acute peripheral sensitisation in the joint, but also by driving changes in central pain processing. Central pain augmentation appears early during the course of RA, and might be resistant to reversal even after suppression of synovitis. Mechanisms driving central sensitisation might include inflammation, both locally within the joint, and through systemic circulation of cytokines and other neuromodulatory factors. Inflammation- associated pain occurs within the context of each patient's genetic, psychological and comorbid constitution, and holistic and individualised approaches to RA pain remain essential. Simplistic approaches presuming that residual pain in RA represents uncontrolled inflammation could lead to over-treatment with potentially harmful conventional synthetic and biologic DMARDs, whilst displacing more effective pain management strategies. On the other hand, labelling of persistent pain as a psychosocial problem risks undertreatment of subclinical synovitis. Judicious assessment of inflammation and non-inflammatory pain mechanisms should inform analgesic approaches offered for RA pain.

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