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The Biology of Pain - Through the Rheumatology Lens

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Abstract

Chronic pain is a major socio-economic burden globally. The most frequent origin for chronic pain is musculoskeletal. In inflammatory musculoskeletal diseases, such as rheumatoid arthritis (RA), chronic pain is a primary determinant of deleterious quality of life. The pivotal role of peripheral inflammation in the initiation and perpetuation of nociceptive pain is well-established among these patients. However, the persistence of pain, even after the apparent resolution of peripheral inflammation, alludes to the co-existence of different pain states. Recent advances in neurobiological knowledge have highlighted the importance of nociplastic pain mechanisms. In this review we aim to explore the biology of pain with a particular focus on nociplastic pain and RA.

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1. Introduction

Chronic pain is a global health challenge causing disability, reduced quality of life and premature mortality (1). This burden is amplified by the lack of effective treatments. Current analgesics offer approximately 50% relief in less than 33% of patients with chronic pain conditions (2). Musculoskeletal diseases represent a common cause of chronic pain and contribute significantly to its global impact (3). For example, rheumatoid arthritis (RA), an articular inflammatory disease, affects up to 1% of the world population (4). Pain is the hallmark feature of this disorder and is the principal source of patients' poor prognosis and quality of life. Moreover, pain persists despite good control of inflammation with immune modulatory drugs in up to 50% of patients (5). Pain in inflammatory arthritis has multifactorial origins where peripheral inflammatory triggers are entangled with structural damage, psycho-social determinants and central mechanisms of pain (6). Indeed, RA pain management is a growing challenge for rheumatologists, and understanding the underlying pain biology is essential to improve treatments, management and patients' well-being.

Pain, as defined by the International Association for the Study of Pain, is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (7). It is a multidimensional subjective experience generated by biological phenomena deeply interconnected with psychological and social factors (3). Acute pain has an adaptative role in the protection from noxious stimuli and preservation of the organism (8). Chronic pain usually reflects a "maladaptive" response to noxious stimuli which may perpetuate even beyond the resolution of the noxious stimuli. In both chronic and acute pain states, painful sensations can arise spontaneously or evoked by normally non-painful stimuli, allodynia, or it may constitute an excessive and sustained response to noxious stimuli, hyperalgesia. Different mechanisms of pain genesis have been classified (7) in 3 groups: 1) nociceptive pain: the somatosensory system response to a noxious stimuli; 2) neuropathic pain: the consequence of a direct nervous system damage; 3) nociplastic pain: subsequent to dysfunctional pain processing in the nervous system in the absence of peripheral tissue or somatosensory system damage, or nociceptor engagement. Nociplastic pain is a recent concept based on decades of research on conditions such as fibromyalgia and other chronic overlapping pain conditions including irritable bowel syndrome, temporomandibular disorder, and interstitial cystitis/bladder pain syndrome (9).

Plasticity is an intrinsic characteristic of the nervous system. Both peripheral and central sensitisation are expressions of neuroplasticity and are characterised by an increased responsiveness and reduced activation thresholds of nociceptive neurons in the peripheral and the central nervous system (CNS), respectively (7,10). Sensitisation is characteristic of nociplastic pain, however, CNS involvement is especially prominent in nociplastic pain since the associated clinical manifestations are commonly characterised by widespread rather than regional pain, and other typically CNS based symptoms such as fatigue, sleep impairment, memory problems, and heightened responsiveness to sensory stimuli other than pain (i.e. increased sensitivity to light, odours, noise) (9,10). Furthermore, numerous objective signs of central plasticity have been observed in the context of nociplastic pain, including changes in the grey matter volume (likely representing neuroplasticity) and altered functional connectivity of brain regions involved in pain and sensory processing (11).

Different pain mechanisms often occur simultaneously in the same individual, especially nociplastic pain which is frequently co-morbid with nociceptive or neuropathic pain. This is likely present in RA where peripheral inflammation initially stimulates a dominating nociceptive pain state that over time might shift towards a nociplastic pain phenotype. This hypothesis is supported by the persistence of pain despite the optimal control of peripheral inflammation with current advanced immunotherapies (5) which may be alternatively explained by nociplastic pain mechanisms. The diagnostic challenge of characterising these mechanistically distinct pain phenotypes can lead rheumatologists to wrongly escalate immunosuppressive treatments on the assumption that all reported pain must relate to peripheral inflammation (nociceptive) (12).

2. Acute and Chronic pain – from nociceptors to the brain

Peripheral pain pathways

Painful stimulations are perceived at the periphery by nociceptors. Nociceptors are neuronal fibers specialised in the detection of mechanical, chemical (including inflammatory mediators), or thermal noxious stimuli. Their peripheral engagement is relevant to the initiation of both acute and chronic pain. The main nociceptors are the unmyelinated C fibers, and the myelinated A-delta and A-beta fibers (13). The characteristics of the different nociceptors are summarised in Table 1. Peripheral nociceptors innervating joints structures, skin, and different organ tissues, can be also classified as peptidergic and non-peptidergic. While both release the excitatory neurotransmitter glutamate, only the peptidergic fibers additionally express neuropeptides. Neuropeptides include substance P (SP) and calcitonin gene related peptide (CGRP) (13). Neurotrophins, e.g., nerve growth factor (NGF), are expressed by cells resident in the tissues surrounding nociceptors, including fibroblasts and immune cells in the synovium. NGF induce the expression of neuropeptides by nociceptors. In animal models stimulated with intra-articular NGF, the ablation of peptidergic nociceptors prevented mechanical and thermal hyperalgesia, while the ablation of non-peptidergic fibers blocked only thermal hypersensitivity, highlighting the role of peptidergic fibers in joint mechanical hyperalgesia (14).

Interestingly, the repeated activation of C fibers can recruit otherwise “silent” C fibers (homosynaptic enhancement). Thus, the C-fibers can sensitise and lower the threshold of the silent C-fibers, normally not activated by mechanical stimuli, which contribute to the sensory input. Moreover, the increased neurons firing at the level of the spinal cord can also lower the response threshold of the secondary sensory neurons. The central sensitisation originating from the peripheral C-fibers, may also involve the A-beta fibers endings in the spinal cord (heterosynaptic enhancement), contributing to increase sensitisation to low intensity mechanical stimuli, perceived as painful. This electrophysiological phenomenon is known as wind-up, and results in short-term increased pain sensitivity to stimuli with constant intensity. If perpetuated over time, this can induce functional changes and increased expression of neurotransmitter receptors and ion channels which contribute to sustained peripheral pain sensitisation (15). Underpinned by the increased release of neuropeptides and pro-inflammatory cytokines, wind-up phenomena can induce an increased Ca^{2+} influx in excitatory neurons which in turn trigger intracellular pathways leading to an upregulation of glutamate receptors, such as N-methyl-D-aspartate (NMDA). NMDA receptor recruitment, known as long term potentiation (LTP), is an expression of neuronal plasticity (16).

The neural bodies of different nociceptors are located in close proximity in the dorsal root ganglia (DRGs) of spinal nerves. DRGs primary sensory neurons receive actions potentials from the sensory endings and propagate them to the secondary sensory neurons. Secondary sensory neurons reside in the superficial laminae of the spinal cord dorsal horn (SCDH). The branching point from the sensory neural body to the spinal cord may have a filter role, able to slow or stop the signals propagation. At this level, the action potentials may just further propagate to the spinal cord and send a "collateral action potential" to the soma of the sensory neuron. In presence of cells damage, spontaneous ectopic action potential from the sensory neurons contributes to neuropathic pain. The close proximity of nociceptor cells bodies in the DRGs and the surrounding satellite glial cells may also modulate the intensity of pain sensory stimuli to the CNS. Glial cells are sensitive to compression and local inflammation. Lymphocytes and macrophages are also present at this level. Different nociceptive and pro-inflammatory mediators (including neuropeptides, neurotrophic factors and pro-inflammatory cytokines) can directly and indirectly affect neuronal activity. In fact, the sensory inputs from the periphery can be either reduced, stopped, or actively propagated , together modulating sensitisation in chronic pain conditions (17). Thus, DRGs are not passive transmitters of the peripheral sensory information.

In humans, the physiological mechanisms of pain involving nociceptors activity and nociceptive pathways can be experimentally investigated with Quantitative Sensory Testing (QST) (Table 2). QST uses standardised protocols to apply stimulations of different modalities (e.g. mechanical/pressure, thermal, chemical and electrical). The skin is the most commonly stimulated area because it is easily accessible, however other systems can be tested (for example, muscles, visceral organs, or visual and acoustic testing) (18). The different stimuli applied assess different nociceptor functions, for example thermal stimulations evaluate the function and activity of C-fibers and A-delta, while the application of mechanical pressure assess the function of C-fibers. QST can either be static (i.e. what is the threshold or tolerance for increasing or decreasing quantifiable stimulations when applied to a region of the body) or dynamic that investigates facilitating or inhibiting pain processes (as in testing temporal/spatial summation or conditioned pain modulation, described below). When pain thresholds or tolerance are found to be reduced in a single location, this can be indicative of either a peripheral (i.e. acute inflammation, sensitisation) or central (spinal or cortical) anomalies in pain processing. Temporal summation is characterised by an increased painful sensation when a stimulus with uniform intensity is repeated over time at a specific frequency. The physiological explanation of this phenomenon is considered to be linked to the repeated activation of the C fibers, recruitment of NMDA receptors and the consequent wind-up phenomenon. This physiological phenomenon can be increased in chronic pain conditions compared to healthy individuals, and it is thought to reflect expression of pain sensitisation mechanisms. When these QST abnormalities are found in many bodily regions, especially in regions where there is no identifiable injury, this strongly suggests central

processes. Similarly, the concomitant presence of sensitivity to other sensory stimuli is one of the hallmarks of nociplastic pain (19–21). Although QST represents a useful tool to investigate the underlying mechanisms of pain, their limitations include implementation challenges in clinical settings as well as modest performances in predicting pain mechanisms and treatment responses.

Central ascending pain pathways

The ascending pathways originate from projecting neurons in the SCDH. These can be divided into two types: 1) *nociceptive specific neurons*, which receive only afferent C and A-delta fibers and 2) *wide dynamic range neurons*, which integrate both nociceptive and sensory information (22). The main ascending pathways are the spinothalamic, spinoreticular and spinomesencephalic tracts. These decussate in the spinal cord before reaching the lateral, posterior and medial thalamus and several other CNS regions, including the periaqueductal grey matter (PAG), parabrachial area (PB), and reticular formation (RF) (Fig. 2) (23). The nuclei of the lateral thalamus project to the primary and secondary somatosensory cortex (SI and SII). SI is most responsible for pain localization whereas SII codes more so for the intensity of stimuli, according to functional neuroimaging studies. In parallel, the posterior thalamus nuclei project to the posterior insula, a key hub for sensory integration of the cognitive components of pain. Finally, the medial thalamus integrates inputs from the RF, and projects to the anterior cingulate cortex (ACC), where motor reactions are mediated, and to the prefrontal cortex (PFC), where attention and emotional aspects of pain are regulated (24). The PB nucleus relays with the limbic system and is responsible for integrating aversion and affective features of pain (25).

3. Central mechanisms of chronic pain – from brain to periphery

Pain-modulation brain networks

The engagement of nociceptors at the periphery is modulated by a plethora of sensory and non-sensory factors which are integrated at different levels of the nervous system. These ultimately elaborate the subjective perception of pain. The ascending spinal tracts bring the source stimuli to a multitude of "pain processing" areas within the brain which are variably connected to each other. At this level, psychological/affective states, memory/learning, expectations, and attention are integrated, adding complexity to the neurobiological pain signature and reflecting the multi-dimensional and challenging experience of patients with chronic pain.

Recent advances in neuroimaging methods, such as functional MRI (fMRI) and spectroscopy, are now bringing new mechanistic insights to chronic pain. We can now non-invasively investigate morphological, functional, and chemical dimensions of neurobiology. In chronic pain disorders such as fibromyalgia (FM), the prototype of nociplastic pain, several areas of the brain are consistently involved in pain processing, both in terms of connectivity between specific brain areas and grey matter volumes, regardless of underlying diagnosis, or imaging technique. Multiple meta-analyses of neuroimaging studies have evidenced pain related alterations in connectivity and morphology in primary and secondary somatosensory cortices (SI-SII), thalamus, PFC, insular cortex (IC), dorsal Anterior Cingulate Cortex (dACC), and

posterior cingulate gyrus (PCC) (11,26–29). These "pain processing" brain areas can be grouped into two networks according to pain dimensions (Fig. 2). The sensory-discriminative network includes the SI-SII, the posterior IC and the lateral nuclei of thalamus; in contrast, the affective and emotional components of pain are processed within the medial network. This includes the medial thalamic nuclei, anterior IC, dACC, with the addition of the amygdala (involved in emotional learning and reward). The regions forming the medial network are involved in modulating the degree of unpleasantness and the possible coexistence of depressive and anxiety symptoms (30–35). Other brain regions that are involved in processing chronic pain include the limbic areas, physiologically elaborating information associated with stress, emotions and salience (the selection of stimuli deserving attention). The limbic areas include and are linked with the amygdala, medial PFC, and insula; additionally, the hippocampus (role in memory and reward) and the nucleus accumbens within the ventral striatum forming the basal ganglia (processing reward and salience) are part of the limbic areas. These limbic regions are more activated in chronic pain patients with co-morbid psychological issues and in processing chronic pain when compared with acute pain states (36,33).

Brain regions, including the afore mentioned pain-processing areas, are intrinsically organised in functionally associative networks, including nodes and hubs. In fMRI studies, the functional connectivity between different regions of the brain can be investigated with specific techniques, while subjects are in a resting state (not performing any prompted task) or during specific tasks (that usually involve a painful stimulation in chronic pain studies). Altered connectivity between networks during resting state or pain-evoked tasks has been associated with chronic pain states and has predicted transition from acute to chronic pain in different musculoskeletal diseases (34,37–44). Moreover, MR spectroscopy and PET studies have also enhanced our knowledge of chronic pain disorders, allowing the determination of chemical components of interests, such as excitatory or inhibitory neurotransmitters, in brain regions of interest. For example, in people with FM spectroscopy studies an imbalance towards excitatory (i.e. glutamate) rather than inhibitory (GABA) neurotransmitters in the posterior insula has been evidenced and so highlighting the importance of molecular changes in critical pain-processing area (45–47). However, in these studies, the relationship between neurotransmitter imbalance and pain sensitivity, was also noted in healthy controls - suggesting that this phenomenon is not exclusive to chronic pain states.

Descending pain modulation

The genesis of chronic pain is not limited to pro-nociceptive pathways. Defective anti-nociceptive networks, such as descending inhibitory systems, may also have a pathogenetic role (48). An imbalance between facilitating and analgesic descending signals has a relevant role in patients with chronic pain conditions (49). Conditioned pain modulation (CPM - in the past referred to as diffuse noxious inhibitory control or DNIC) is a QST test that attempts to measure the magnitude of the descending inhibitory control of pain by applying a brief (usually less than 30 seconds in duration) and painful stimulus that should engender this descending activity, and then re-assessing the pain threshold in a different body area concomitant with the first stimulus (50). Reduced CPM has been associated with an increased risk of developing chronic pain and is demonstrated to be dysfunctional in patients with FM compared to healthy controls (51,52). Although the neurobiology underlying CPM is not completely understood, several centres in the brain are known to modulate the nociceptive input using descending modulatory pathways (Fig. 2). For example, the PAG and the

interconnected rostral ventromedial medulla (RVM) can directly inhibit the secondary sensory neurons, via serotonergic (5-HT) and opioidergic pathways. The PAG relay the integrated signals from SCDH and pain-processing brain regions to the RVM, before transmitting inhibitory signals to the spinal cord (53). PAG altered functional connectivity and reduced grey matter volume has been recently associated with increased pain facilitation in FM, compared to healthy subjects (54). The basal inhibitory activity of the RVM serotoninergic neurons is mediated via GABAergic fibers within the SCDH (55). However, RVM neurons have the ability to reduce the constitutive inhibition and enhance excitatory activity after integration of peripheral nociceptive and PAG signalling (53). The serotoninergic neurons in the RVM, located in the nucleus raphe magnus, can exert direct facilitator or suppressive effects according to their binding of either excitatory or inhibitory 5-HT receptors (56). Moreover, signals from PAG and RVM stimulate the expression of endogenous opioids within the spinal cord. The endogenous opioids, including beta-endorphins, enkephalins and dynorphins, act directly at the level of the SCDH in coordination with serotoninergic and noradrenergic descending modulation systems. Thus, opioids potentiate the inhibitory activity of the RVM (57). In fibromyalgia, general deficits in endogenous opioid tone have been noted in pain-processing regions of the brain, and these deficiencies were found to be associated with weaker activity in pain-inhibition pathways (58,59).

The noradrenergic neurons of the locus coeruleus (LC), located in the brainstem, represent another major descending control mechanism. LC integrates information from SCDH, PAG and brain areas involved in processing emotions and stress, including insula, amygdala and hypothalamus and so is also likely to influence these dimensions in the context of pain (60). LC has a dual effect on SCDH. Noradrenaline inhibits afferent fibers and projecting neurons directly and indirectly, via the activation of spinal GABAergic interneurons. Nonetheless, NA descending modulation can also increase the activity of nociceptive inputs within the SCDH.

4. Inflammation and pain persistence – role of inflammation in the pain genesis and perpetuation in rheumatoid arthritis

Clinical symptoms of RA are characterised by a recurrent or persistent articular and systemic inflammation, with raised circulating inflammatory markers. Individuals with RA invariably experience acute pain, i.e., during inflammatory flares and at early stages of the disease, and are highly vulnerable to evolving chronic pain over time. Both local and systemic inflammation may alter pain perception and processing. Peripheral inflammation and consequent tissue damage are responsible for the nociceptive component of pain in RA (61). Articular inflammation is characterised by the release of several pro-inflammatory cytokines and chemokines which are essential in the pathogenesis of RA leading to local and systemic inflammation and consequent tissue damage. Erosive joint damage is not strongly associated with reported pain in early and established RA cohorts (62). Moreover, the role of neuropathic pain is likely limited since true peripheral nerve injury has only been proven in a small proportion of people with RA (61). Indeed, the inhibition of pro-inflammatory cytokines is currently a key treatment strategy in RA.

Trials of agents which antagonise JAK-STAT, IL-6 and TNF evidence a large effect on reported pain (63–65). A metanalysis study showed that anti-TNF blockers and tocilizumab (anti-IL-6) in combination with methotrexate were similarly effective in pain reduction when compared to placebo (changes from baseline 32.53, CI 13.46-52.09, and 30.71, CI 15.14-

46.97, respectively) and methotrexate alone (17.85, CI 13.02-23.08, and 15.97, CI 6.26-26.34, respectively) at 24 weeks (63). JAK inhibitors appear to have a greater effect on pain than other classes. For example, the RA-BEAM study compared the JAK inhibitor baricitinib with adalimumab, controlled with a placebo arm, in patients who failed to respond to methotrexate and naïve to biologics. Intriguingly, the reported pain (measured on a NRS 0-100 mm scale), was significantly lower in the baricitinib group compared to adalimumab, as early as week 2 of treatment and to week 12 (-31.5 least-squares mean (LMS) vs -26.4 LMS), but also sustained at week 24 (-33.6 vs -28.8 LMS) and at week 54 (-36.1 vs -30.3 LMS, not reached statistically significant difference) (64). In the study SELECT-COMPARE, the selective JAK1 inhibitor upadacitinib showed greater LMS changes from baseline compared to adalimumab, at 12 and 48 weeks (-31.76 vs -25.31 and -36.68 vs -32.07, respectively) (66). Upadacitinib also demonstrated higher pain reduction at 12 weeks (-35.3 vs -30.0 LSM) and 24 weeks (-41.5 vs -37.7 LSM), when compared to the T cell inhibitor abatacept (67). The reduction on pain but also on other domain associated with central sensitisation, including fatigue, after treatment with pro-inflammatory cytokines inhibitors suggest these may have a direct effect on nociplastic pathways. In fact, a post-hoc analysis demonstrated that the apparent analgesic effect was not entirely explained by markers of peripheral inflammation.

The immune system interacts with the nervous system at different levels: from joint nociceptors to the brain. Articular inflammation represents a direct noxious stimulus which leads to joint tissue damage and activation of a neuroinflammatory loop which perpetuates nociceptive output. At the periphery, nociceptive fibers and DRGs can sense inflammation directly via receptors for pro-inflammatory cytokines relevant in arthritis pathogenesis, e.g. interleukin-1β (IL-1β), TNF-alpha, IL-6, and IL-17. Articular nociceptors respond to the inflammatory insult by upregulating their responsiveness and expressing neuropeptides, including CGRP, and SP (68). Moreover, in inflamed synovium, endothelial cells and fibroblasts further contribute to the release of NGF which enhances the expression of neuropeptides by the peptidergic fibers, subsequently maintaining the neuroinflammatory loop (14). Neuropeptides are responsible for neurogenic inflammation by directly activating immune cells and increasing local blood flow (69). The synergistic action of neuropeptides and pro-inflammatory cytokines further upregulate nociceptor responsiveness and their expression (70). Moreover, immune cells, e.g. macrophages and T-cells, can migrate and release mediators directly into the DRGs. At this level, the glial cells, comprising non-neuronal cells resident within the nervous system, further contribute to pain enhancement. In more details, glial cells are specialised resident macrophages which express cytokines, such as IL-6, TNF-alpha and IL-1β, but also release excitatory neurotransmitters, neurotropic factors (i.e. NGF) and other pro-inflammatory mediators (ATP, NO, and prostaglandins) (70–72). Therefore, glial cell activation and pro-inflammatory mediator expression significantly contributes to the local neuroimmune crosstalk (71,72).
The neuro-inflammatory loop between immune cells and nociceptors, facilitated at the nociceptors cells bodies by satellite glial cells at the level of the DRGs, ultimately increasing sensory neuron activity, resulting in regional thermal and mechanical hyperalgesia characteristic of acute inflammatory states. When perpetuated and unbalanced, neuronal activation can promote nociplastic changes responsible for the peripheral sensitisation and a potential disconnect from the initial inflammatory triggers. For example, in RA, a novel pathway involving CXCL1 and IL-8 has been associated with the production of anti-citrullinated protein antibodies which appears to mediate pain perception independently to the level of peripheral inflammation (73).

Systemic inflammation may influence the CNS via alternative mechanisms. Pro-inflammatory cytokines can directly reach the CNS through the passive or saturable active passage of the brain-blood barrier, but also via central afferent nerves (1). Moreover, circulating cytokines can activate microglia and astrocytes at the level of circumventricular organs (74), which maintain direct access to inflammatory mediators in circulation. Activation of these same cells in the brain, further contributes to the local production of pro-inflammatory mediators, including prostaglandins. TNF and IL-1β. The presence of pro-inflammatory cytokines and mediators can contribute to central sensitisation due to their effect on neuronal transmission characterised by increased excitatory and reduced inhibitory activity (75). This was demonstrated by the pro-inflammatory stimulation, with lipopolysaccharide, of rodent models which induced the development of hyperalgesia (76). In addition, other centrally mediated symptoms are observed including fatigue, sleep, cognitive and mood disturbances (77). These behaviours aim to protect the organism during acute damage and facilitate recovery in the short-term, however, when prolonged, chronic states can evolve, including, possible, nociplastic pain.

Patients with RA have a high risk of developing nociplastic pain, which often endures, even following the resolution of peripheral inflammation (61,78). Clinically, this is evidenced by the high prevalence of co-morbid FM among patients with RA, diagnosed in up to a third of patients across the rheumatological spectrum (6). One also needs to remember that, within any nociceptive pain state, there will be individuals with pre-existing nociplastic pain disorders when they first present with a nociceptive condition. Moreover, neither nociplastic pain nor FM are discrete constructs. Even in patients who do not meet the ACR FM survey criteria, a certain degree of central sensitisation can still be present (79). In a neuroimaging study in individuals with RA, we have shown that the degree of central sensitisation, measured with the total scores of the ACR FM criteria, had a strong correlation with the increased connectivity between the default mode network (DMN - active during wakeful rest) and the posterior insula. Similar hyperconnectivity has been consistently demonstrated in people with a diagnosis of FM (80). Further, the sensitisation of nociceptive pathways has been investigated by QST (Table 2). In the context of inflammatory arthritis, mechanical QST stimulations are the most commonly used because these are thought to better reflect the modality of stimuli leading to sensitisation. For example, studies by Lee and colleagues in RA have shown that a lowered mechanical threshold (i.e. tenderness) in regions of the body involved by RA (e.g. small joints of hands or wrists) was related to measures of inflammation whereas tenderness in "neutral" regions not involved by RA (e.g. trapezius) was more so related to indices of central sensitisation (81). A study evaluating PPTs in patients with stable RA, showed that reduced PPTs, reflecting sensitisation, were associated with greater reported pain, poorer mental health and higher presence of FM (42). In other RA studies, pain sensitisation, manifest with lower PPTs and higher TS, was also associated with higher disease activity and reported pain. Moreover, dysregulation of CPM was significantly correlated with the tender joint count and potentially associated with sleep disorders (43,82). A recent study from Heisler and collaborators, showed an association between reduced response to DMARDs and altered CPM in 182 patients with active RA. (83). Together these studies confirmed the presence of pain sensitisation in RA and highlighted the potential implications for assessing disease activity and treatment response.

Neuroimaging studies are now helping provide insights into how inflammation may interact with central pain pathways. A recent study was the first to correlate brain functional connectivity and grey matter volumes with inflammation in RA. The left inferior parietal lobule (IPL) and medial PFC and their functional connectivity with DMN, dorsal attention,

salience, and medial visual networks were positively correlated with the level of peripheral inflammation, as measured as ESR (44). Importantly, these 'inflammatory brain hubs' also related to patient-reported measures of nociplastic pain, including widespread pain and fatigue. In the same group of individuals with RA, the presence of FM clinical features and increased level of ESR were positively associated with an increased connectivity of the left IPL with key regions implicated with nociplastic pain (posterior insula and the dorsal ACC) (84). This alludes to a putative role for systemic inflammation in the development of nociplastic pain, at least in the context of systemic inflammatory disease, offering evidence for a 'bottom up' nociplastic dimension provoked by peripheral inflammatory nociceptive processes which sensitise pronociceptive CNS pathways. In fact, variability in how different individuals respond in the CNS to peripheral inflammation due to genetic and environmental factors is likely an underappreciated contributor to overall variability in symptoms (85). In many patients, however, the classical 'top down' nociplastic dimension will likely dominate and explain why almost 50% of patients with RA continue to report clinical important levels of pain despite achieving full remission of their systemic inflammatory disease (5).

5. Conclusions

In chronic inflammatory musculoskeletal diseases, such as RA, a combination of different pain mechanisms may be simultaneously present. Recent advances in pain research point towards an important role of nervous system sensitisation in pain perception among patients with RA.

Local joint pathology driven by inflammatory mechanisms represents a direct nociceptive trigger which accounts for the significant acute pain experienced by patients during phases of active inflammation. However, even when underlying inflammation is clinically controlled, patients with RA continue to experience pain. Superimposed nociplastic pain, which occurs in predisposed individuals and is expressed as peripheral and central sensitisation, may explain pain persistence in patients with RA. Local and systemic inflammation may further contribute to establish nociplastic pain. Neuroimmune interactions at the level of the joint and afferent nociceptive pathways are characterised by complex communications mediated by pro-inflammatory mediators and neuropeptides, which ultimately facilitate the process of sensitisation in this group of patients. Circulating pro-inflammatory cytokines also contribute to sensitise the CNS in RA through multiple mechanisms resulting in conserved behavioural and physiologic changes. Hyperactivity of the peripheral and central nervous systems have been demonstrated in RA by several studies exploiting neuroimaging techniques and QST. Interestingly, the expression of nociplastic pain can explain the reduced response to anti-rheumatic drugs in RA.

Despite these recent advances in pain research, our understanding of the complex biology of pain genesis and persistence is far from complete, particularly in rheumatological conditions, such as RA. Further studies will need to confirm the clinical associations between systemic inflammation and nociplastic pain, and how sensitised nociceptive pathways may affect the clinical evaluation of disease activity and response to treatment. Cutting-edge neuroimaging methodologies in combination with QST are promising tools to better define clinical pain phenotypes in inflammatory arthritis. Unravelling molecular and biological chronic pain mechanisms, not only will aid in the distinction of chronic pain phenotypes, but will also unveil novel interesting therapeutic targets for pain management. Ultimately, a better understanding of pain biology in rheumatological conditions will enable rheumatologists to optimise treatment and improve the quality of life of patients.

Table 1. Peripheral nociceptors

Nociceptor	Kind of stimulation	Intensity stimulation	Transmission of input	Target in SCDH	Perception
C fiber	Polymodal (thermal, Chemical, mechanical)	Low intensity stimuli	Unmyelinated, slow conducting	Lamina II	Dull, pressure, large areas
A-delta fiber	Mechanical, thermal	High intensity stimuli	Myelinated, fast conducting	Lamina I	Sharp pain in well-localised areas
A-beta fiber	Mechanical	Low intensity stimuli	Myelinated, fast conducting	Lamina III-IV	Touch, stretching, mechanical.

Peripheral nociceptors involved in pain processing are activate by different kind of noxious stimuli and have different activation threshold and velocity of transmission of the nociceptive inputs to the SCDH (spinal cord dorsal horn).

Table 2 – Quantitative sensory testing, measures of pain sensitisation in rheumatoid arthritis.

Measures	Modality stimuli	Domain	Testing technique	Evidence in RA
Threshold/Tolerance	Mechanical, thermal, electrical, chemical	Pain facilitation	Intensity of first painful and maximum tolerated stimuli.	Lower pain threshold reflect higher pain, disease activity, and prevalence of FM and

				psychiatric comorbidities (42,43).
Temporal and spatial summation	Thermal, mechanical, electrical	Pain facilitation	Increased pain sensitivity or area of pain, after repeated identical noxious stimuli	TS dysregulation was associated with high disease activity (measured as CDAI) and was able to predict reduced EULAR response to treatment alone and in combination with CPM dysregulation (43,82).
CPM	Mechanical, thermal	Descending analgesic response*	Reduced pain sensitivity, during painful stimulation in a distant area	CPM dysfunction was associated with higher disease activity, sleep disturbances and reduced response to DMARDs (83).

CPM, conditioned pain modulation; WDR, wide dynamic range neurons.
*both lack of inhibition and pain facilitator mechanisms are assessed with CPM testing, a clear distinction between the two different mechanisms is not possible.

Figure 1 link

Figure 1: Peripheral nociceptors, C and A-δ fibers, are responsible for detecting thermal, chemical and mechanical stimuli from peripheral tissues and transduce the input in electric signals which reach the lamina I-II in the spinal cord dorsal horn (SCDH). A-β fibers are mechanoceptors able to detect non-painful stretch of articular structures (e.g. tendons and joint capsule). Repetitive and high-intensity stimulation from the periphery increases the responsiveness of primary and secondary sensory neurons by upregulating excitatory receptors and increasing the connectivity between different sensory fibers in the SCDH. After repetitive or high intensity stimuli A-β fibers transmit nociceptive inputs to the lamina III-V that increase the connection with lamina I-II afferent nociceptors (red). Primary sensory neurons cells body are located in the dorsal root ganglia (DRGs). DRGs are surrounded by glial cells and immune cells (i.e. T cells and macrophages), which release pro-inflammatory cytokines (IL-1-beta, TNF-alpha, IL-6, IL-17) when activated. Peripheral inflammation contributes to pain sensitization activating nociceptors. Cytokines bind their receptors on primary sensory neurons and satellite glial cells inducing the expression of neuropeptides. Neuropeptides enhance the inflammatory response at the periphery and increase the sensitivity to afferent inputs.

Figure 2 link

Figure 2: In the spinal cord projecting neurons (PN) fibers decussate and reach different sensory areas in the CNS. Spinothalamic tract targets the thalamus (TH). From here the nociceptive input is conducted to specific brain areas: the somato-sensory cortex I and II (SI-

II), the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the insula cortex (IC), and the amygdala (Am). There two pain-processing associative networks: 1) the affective-emotional network (in red), including medial TH, PFC, ACC, Am, and anterior IC; 2) sensory-discriminative network (in blue), lateral TH, SI-II and posterior IC. Peripheral nociceptive stimuli reach also the periaqueductal grey matter (PAG), parabrachial area (PB), and reticular formation (RF) in the brainstem. The PAG modulate sensory inputs via the rostral ventromedial medulla (RVM), formed by nucleus raphe magnus (NRM) and RF. Serotoninergic (5-HT), from RVM, and noradrenergic (NA), from locus coeruleus (LC), originate descending fibers. 5-HT and NA induces production and release of excitatory neurotransmitters (Glut) and inhibitory mediators (endogenous opioids) by the spinal interneurons with a dual effect, both excitatory and inhibitory. The balance between excitatory and inhibitory signals to the secondary sensory neurons filter the sensory information reaching the brain.

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