Arthritis & Rheumatology
Vol. 75, No. 5, May 2023, pp 650–660
DOI 10.1002/art.42429

AMERICAN COLLEGE of RHEUMATOLOGY
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REVIEW

The Biology of Pain: Through the Rheumatology Lens

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Chronic pain is a major socioeconomic burden globally. The most frequent origin of 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 patients with musculoskeletal diseases. However, the persistence of pain, even after the apparent resolution of peripheral inflammation, alludes to the coexistence of different pain states. Recent advances in neurobiology have highlighted the importance of nociplastic pain mechanisms. In this review we aimed to explore the biology of pain with a particular focus on nociplastic pain in RA.

Introduction

Chronic pain is a global health challenge frequently leading to disability, reduced quality of life, and premature mortality (1). This burden is amplified by the lack of effective treatments. Current analgesics offer ∼50% relief in fewer 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 effective control of inflammation with immunomodulatory drugs in up to 50% of patients (5). Pain in inflammatory arthritis has multifactorial origins, in which peripheral inflammatory triggers are entangled with structural damage, psychosocial determinants, and central mechanisms of pain (6). Indeed, RA pain management is a growing challenge for rheumatologists, and understanding the underlying biologic mechanisms of pain is essential to improve treatments, disease 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 biologic phenomena deeply interconnected with psychological and social factors (3). Acute pain has an adaptive 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 are evoked by normally nonpainful stimuli, i.e., allodynia, or these sensations may constitute an excessive and sustained response to noxious stimuli, i.e., hyperalgesia. Different mechanisms of pain pathogenesis have been classified into 3 groups (7): 1) nociceptive pain, defined as the somatosensory system response to a noxious stimuli; 2) neuropathic pain, defined as the consequence of direct nervous system damage; and 3) nociplastic pain, defined as a response subsequent to dysfunctional pain processing in the nervous system in the absence of peripheral tissue damage, somatosensory system damage, or nociceptor engagement. Nociplastic pain is a recent concept based on decades of research on conditions such as fibromyalgia (FM) 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 sensitization are expressions of neuroplasticity and are characterized by an increased responsiveness of and reduced activation thresholds of nociceptive neurons in the peripheral nervous system and central nervous system (CNS), respectively (7,10). Sensitization is characteristic of nociplastic pain; however, CNS involvement is especially prominent in

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42429&file=art42429-sup-0001-Disclosureform.pdf.

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Submitted for publication July 19, 2021; accepted in revised form December 20, 2022.

nociplastic pain since the associated clinical manifestations are commonly characterized by widespread rather than regional pain, as well as 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, odors, and 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 comorbid with nociceptive or neuropathic pain. This is likely present in patients with RA, in whom peripheral inflammation initially stimulates a dominating nociceptive pain state that, over time, might shift toward 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 characterizing these mechanistically distinct pain phenotypes can lead rheumatologists to wrongly escalate immunosuppressive treatments on the assumption that all reported pain must be related to peripheral inflammation (i.e., nociceptive pain) (12).

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 specialized in the detection of mechanical stimuli, chemical stimuli (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) (Figure 1). The characteristics of the different nociceptors are summarized in Table 1. Peripheral nociceptors innervating joint structures, skin, and different organ tissues can also be classified as either peptidergic or nonpeptidergic. While both release the excitatory neurotransmitter glutamate, only the peptidergic fibers additionally express neuropeptides. These 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. NGFs induce the expression of neuropeptides by nociceptors. In animal models involving stimulation of joints with intraarticular NGF, the ablation of peptidergic nociceptors prevented mechanical and thermal hyperalgesia, while the ablation of nonpeptidergic 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 sensitize 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 sensitization originating from the peripheral C fibers may also involve the A-beta fiber endings in the spinal cord (heterosynaptic enhancement), contributing to increased sensitization to low-intensity mechanical stimuli, a state that is often reported to be perceived as painful. This electrophysiologic 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 sensitization (15). Underpinned by the increased release of neuropeptides and proinflammatory cytokines, wind-up phenomena can induce an increased Ca^{2+} influx in excitatory neurons, which in turn trigger intracellular pathways leading to an up-regulation of glutamate receptors, such as *N*-methyl-D-aspartate (NMDA). NMDA receptor recruitment, known as long-term potentiation, 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. DRG primary sensory neurons receive action 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 propagation of signals. At this level, the action potentials may further propagate to the spinal cord and send a "collateral action potential" to the soma of the sensory neuron. In the presence of cellular damage, spontaneous ectopic action potential from the sensory neurons contributes to neuropathic pain. The close proximity of nociceptor cell bodies in the DRGs and the surrounding satellite glial cells may also modulate the intensity of pain sensory stimuli applied to the CNS. Glial cells are sensitive to compression and local inflammation. Lymphocytes and macrophages are also present at this level. Different nociceptive and proinflammatory mediators (including neuropeptides, neurotrophic factors, and proinflammatory cytokines) can directly and indirectly affect neuronal activity. In fact, the sensory inputs from the periphery can be either reduced, stopped, or actively propagated, and these actions together modulate sensitization in chronic pain conditions (17). Thus, DRGs are not passive transmitters of the peripheral sensory information.

In humans, the physiologic mechanisms of pain involving nociceptor activity and nociceptive pathways can be experimentally investigated with quantitative sensory testing (QST) (Table 2). QST uses standardized protocols to apply various stimuli via different

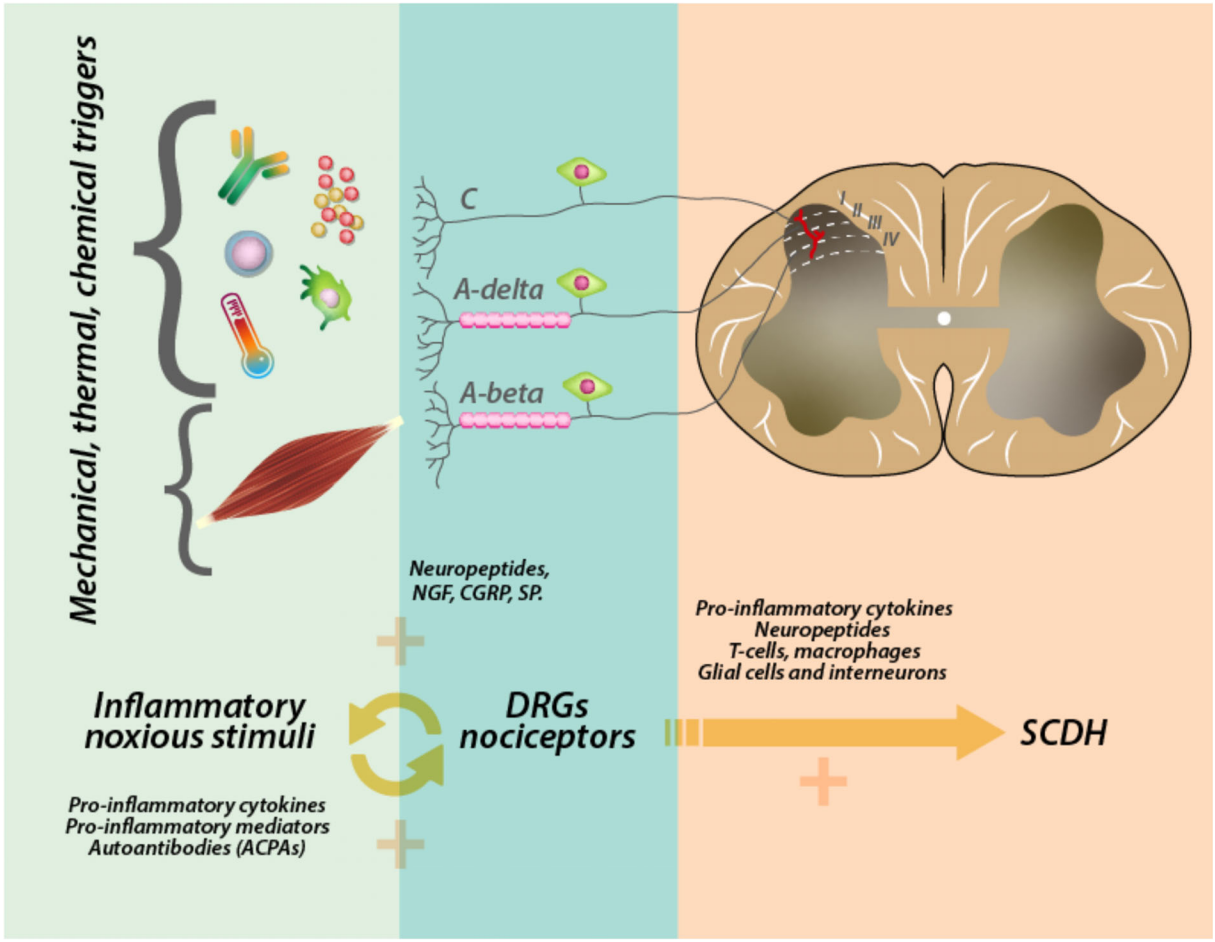

Figure 1. Involvement of peripheral nociceptors in pain processing. C fibers and A-delta fibers are responsible for detecting thermal, chemical, and mechanical stimuli from peripheral tissues and transduce the input in electric signals, which reach laminae I–II in the spinal cord dorsal horn (SCDH). A-beta fibers are mechanoceptors able to detect nonpainful stretches 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 up-regulating excitatory receptors and increasing the connectivity between different sensory fibers in the SCDH. After repetitive or high-intensity stimuli, A-beta fibers transmit nociceptive inputs to laminae III–V, which increases the connection with laminae I and II afferent nociceptors (in red). Primary sensory neuron cell bodies are located in the dorsal root ganglia (DRGs). DRGs are surrounded by glial cells and immune cells (i.e., T cells and macrophages), which, when activated, release proinflammatory cytokines (interleukin-1β [IL-1β], tumor necrosis factor, IL-6, IL-17). Peripheral inflammation contributes to pain sensitization–activating nociceptors. Cytokines bind their receptors on primary sensory neurons and satellite glial cells, thereby inducing the expression of neuropeptides. Neuropeptides enhance the inflammatory response at the periphery and increase the sensitivity to afferent inputs. NGF = nerve growth factor; CGRP = calcitonin gene–related peptide; SP = substance P; ACPAs = anti–citrullinated protein antibodies.

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 are designed to assess different nociceptor functions; for example, thermal stimulations are applied

Table 1. Peripheral nociceptors involved in pain processing*

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

* Peripheral nociceptors involved in pain processing are activated by different kinds of noxious stimuli and have different activation thresholds and velocities of transmission of the nociceptive inputs to the spinal cord dorsal horn (SCDH).

Table 2. Quantitative sensory testing for measurement of pain sensitization in patients with RA*

Measure	Modality of 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 thresholds reflect more severe pain, higher disease activity, and prevalence of FM and psychiatric comorbidities (see refs. 42 and 43).
Temporal and spatial summation	Thermal, mechanical, electrical	Pain facilitation	Increased pain sensitivity or area of pain, after repeated identical noxious stimuli	Dysregulation of temporal and spatial summation was associated with high disease activity (higher CDAI scores) and was predictive of a reduced EULAR response to treatment alone and in combination with CPM dysregulation (see refs. 43 and 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 (see ref. 83).

* RA = rheumatoid arthritis; FM = fibromyalgia; CDAI = Clinical Disease Activity Index; DMARDs = disease-modifying antirheumatic drugs.
† Both lack of inhibition and pain facilitator mechanisms are assessed with conditioned pain modulation (CPM) testing, and therefore a clear distinction between the 2 different mechanisms is not possible.

to evaluate the function and activity of C fibers and A-delta fibers, while the application of mechanical pressure is intended to assess the function of C fibers. QST can be either static (i.e., as a means to determine the threshold or tolerance for increasing or decreasing quantifiable stimulations when applied to a region of the body) or dynamic (i.e., as a means to investigate facilitating or inhibiting pain processes, e.g., testing temporal/spatial summation or conditioned pain modulation [CPM], as described in more detail below).

When pain thresholds or tolerance are found to be reduced in a single location, this can be indicative of either a peripheral anomaly (i.e., acute inflammation, sensitization) or central anomaly (spinal or cortical) in pain processing. Temporal summation is characterized by an increased painful sensation when a stimulus with uniform intensity is repeated over time at a specific frequency. The physiologic 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 physiologic phenomenon can be increased in individuals with chronic pain conditions as compared to healthy individuals, and it is thought to reflect expression of pain sensitization mechanisms. When these QST abnormalities are found in many bodily regions, especially in regions where there is no identifiable injury, this strongly suggests that central processes are contributing to these abnormalities. 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 pain pathways originate from projecting neurons in the SCDH. These neurons can be divided into 2 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) (Figure 2) (23). The nuclei of the lateral thalamus project to the primary and secondary somatosensory cortices (SI and SII, respectively). The SI is most responsible for pain localization, whereas the SII codes more for the intensity of stimuli, according to the findings in 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).

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 nonsensory 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

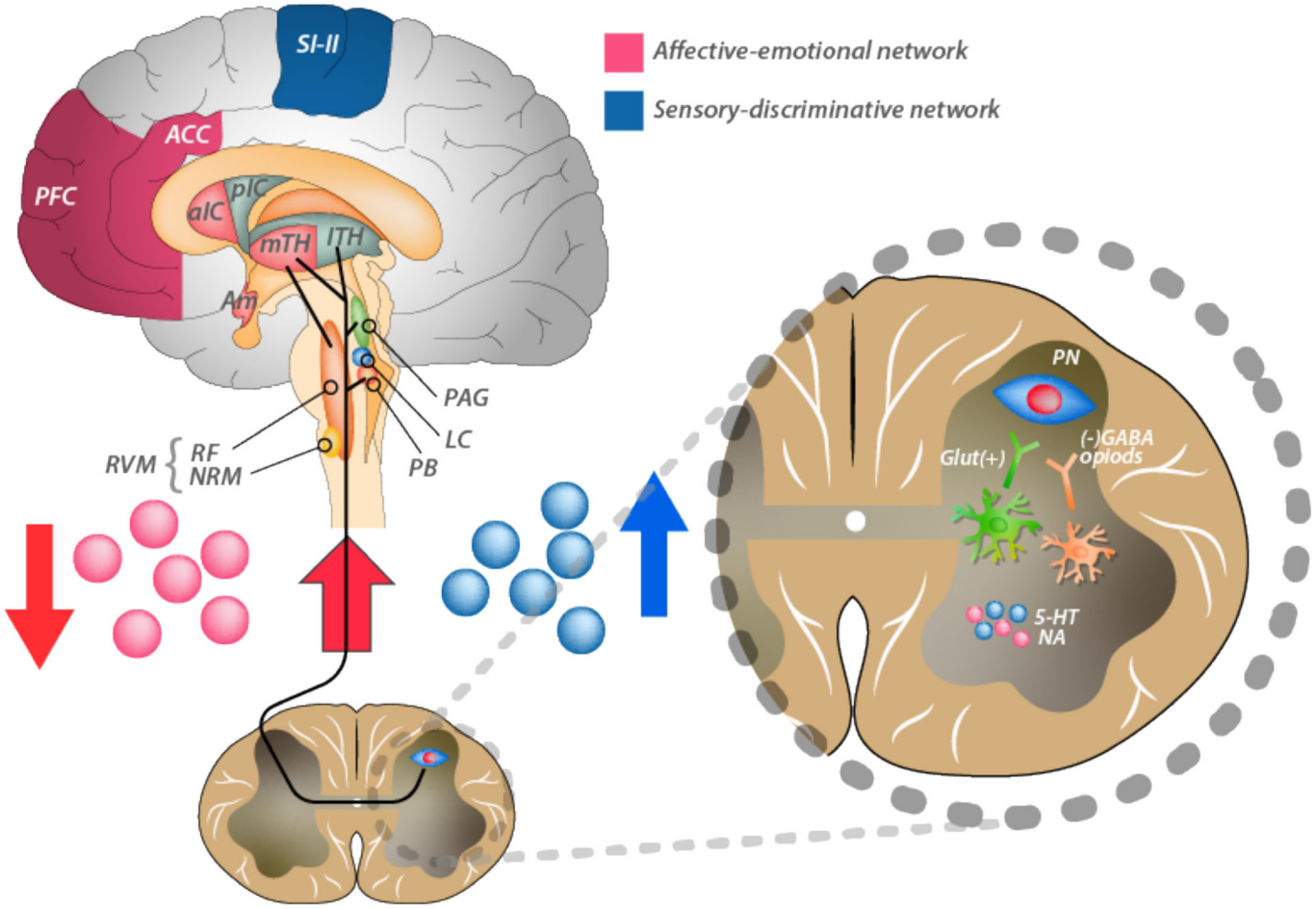

Figure 2. Neurologic pain sensitization pathways. In the spinal cord, projecting neuron (PN) fibers decussate and reach different sensory areas in the central nervous system. The spinothalamic tract targets the thalamus (TH). From here, the nociceptive input is conducted to specific brain areas: the somatosensory cortices I and II (SI–II), the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the insula cortex (IC), and the amygdala (Am). There are 2 pain-processing associative networks: 1) the affective-emotional network (in red), including the medial TH (mTH), PFC, ACC, Am, and anterior IC (aIC); and 2) the sensory-discriminative network (in blue), including the lateral TH (lTH), SI–II, and posterior IC (pIC). Peripheral nociceptive stimuli also reach 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) neurons, from the RVM, and noradrenergic neurons, (NA) from the locus coeruleus (LC), originate descending fibers. The 5-HT and NA neurons induce production and release of excitatory neurotransmitters (glutamate [Glut]) and inhibitory mediators (endogenous opioids) by the spinal interneurons, producing a dual effect, both excitatory and inhibitory. The balance between excitatory and inhibitory signals to the secondary sensory neurons helps filter the sensory information reaching the brain. GABA = γ-aminobutyric acid.

neurobiologic pain signature and reflecting the multidimensional and challenging experience of patients with chronic pain.

Recent advances in neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and spectroscopy, are now bringing new mechanistic insights to chronic pain. We can now non-invasively investigate morphologic, functional, and chemical dimensions of the brain in neurobiology. In chronic pain disorders such as FM, which represents 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 in terms of changes in grey matter volumes, regardless of the underlying diagnosis or imaging technique used. Multiple meta-analyses of neuroimaging studies have presented evidence of pain-related alterations in connectivity and morphology in the primary and secondary somatosensory cortices (SI and SII), the thalamus, the PFC, the insular cortex (IC), the dorsal anterior cingulate cortex (dACC), and the posterior cingulate gyrus (PCC) (11,26–29).

These "pain processing" areas of the brain can be grouped into 2 networks according to pain dimensions (Figure 2). The sensory-discriminative network includes the SI and SII, the posterior IC, and the lateral nuclei of the thalamus. In contrast, the affective and emotional components of pain are processed within the medial network; this includes the medial thalamic nuclei, the anterior IC, and the 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 symptoms of depression and anxiety (30–35). Other brain regions that are involved in processing chronic pain include the limbic areas, which physiologically elaborate 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 patients with chronic pain who have comorbid psychological issues, and also are more active in processing chronic pain than acute pain states (36,33).

Brain regions, including the aforementioned pain-processing areas, are intrinsically organized 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 positron emission tomography studies have also enhanced our knowledge of chronic pain disorders, allowing the determination of chemical components of interest, such as excitatory or inhibitory neurotransmitters, in brain regions of interest. For example, in individuals with FM, spectroscopy studies have revealed an imbalance toward excitatory neurotransmitters (i.e., glutamate) rather than inhibitory neurotransmitters (γ-aminobutyric acid [GABA]) in the posterior insula, thereby highlighting the importance of molecular changes in critical pain-processing areas (45–47). However, in these studies, the relationship between neurotransmitter imbalance and pain sensitivity was also noted in healthy control subjects, suggesting that this phenomenon is not exclusive to chronic pain states.

Descending pain modulation. The pathogenesis of chronic pain is not limited to pronociceptive pathways. Defective antinociceptive 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). 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 <30 seconds in duration) and painful stimulus that should engender this descending activity, followed by reassessment of 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 neurobiologic mechanisms underlying CPM are not completely understood, several centers in the brain are known to modulate the nociceptive input using descending modulatory pathways (Figure 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 relays the integrated signals from the 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 have been recently associated with increased pain facilitation in patients with 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 signaling (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 the 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 patients with FM, 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. The LC integrates information from the SCDH, the PAG, and brain areas involved in processing emotions and stress, including the insula, amygdala, and hypothalamus, and therefore is also likely to influence these dimensions in the context of pain (60). The LC has a dual effect on the SCDH. Noradrenaline inhibits afferent fibers and projecting neurons directly and indirectly, via the activation of spinal GABAergic interneurons. Nonetheless, noradrenergic descending modulation can also increase the activity of nociceptive inputs within the SCDH.

Inflammation and pain persistence—role of inflammation in pain pathogenesis and perpetuation in RA

Clinical symptoms of RA are characterized by a recurrent or persistent articular and systemic inflammation, with raised levels of circulating inflammation 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 characterized by the release of several proinflammatory 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 either early or established RA cohorts (62). Moreover, the role of neuropathic pain is likely limited, since true peripheral nerve injury has been demonstrated in only a small proportion of individuals with RA (61). Indeed, the inhibition of proinflammatory cytokines is currently a key treatment strategy in RA.

Trials of agents that are designed to antagonize JAK/STAT, interleukin-6 (IL-6), and tumor necrosis factor (TNF) have indicated that these treatments have a large effect on reported pain in RA (63–65). A meta-analysis showed that treatment of patients with RA with anti-TNF blockers or tocilizumab (anti–IL-6) in combination with methotrexate (MTX) was similarly effective in achieving pain reduction at 24 weeks, as compared to placebo, when the response was assessed using a 0–100-mm visual analog scale score for pain (mean change from baseline 32.53 [95% confidence interval (95% CI) 13.46–52.09] in the anti-TNF + MTX group versus 17.85 [95% CI 13.02–23.08] in the placebo group; mean change from baseline 30.71 [95% CI 15.14–46.97] in the tocilizumab + MTX group versus 15.97 [95% CI 6.26–26.34] in the placebo group) (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 RA patients who failed to respond to MTX treatment and who had not received treatment with biologic agents. Intriguingly, the reported pain (measured on a 0–100-mm nunerical rating scale) was significantly lower in the baricitinib group compared to the adalimumab group as early as week 2 of treatment and extending up to week 12 (least-squares mean [LSM] change from baseline –31.5 versus –26.4), with the reduction in pain score being sustained at week 24 (LSM change from baseline –33.6 versus –28.8) and at week 54 (LSM change from baseline –36.1 versus –30.3; *P* not significant) (64). In the SELECT-COMPARE study, the selective JAK1 inhibitor upadacitinib showed greater LSM changes from baseline compared to adalimumab at both 12 weeks (LSM change from baseline –31.76 versus –25.31) and 48 weeks (LSM change from baseline –36.68 versus –32.07) (66). Upadacitinib also demonstrated higher pain reduction at 12 weeks (LSM change from baseline –35.3 versus –30.0) and 24 weeks (LSM change from baseline –41.5 versus –37.7 LSM) when compared to the T cell inhibitor abatacept (67). The observed reduction in pain, as well as the reductions in other domains associated with central sensitization, including fatigue, after treatment with proinflammatory cytokine inhibitors suggest that these agents 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, leading to perpetuation of nociceptive output. At the periphery, nociceptive fibers and DRGs can sense inflammation directly via receptors for proinflammatory cytokines relevant in arthritis pathogenesis, e.g., IL-1β, TNF, IL-6, and IL-17. Articular nociceptors respond to the inflammatory signal by up-regulating 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 actions of neuropeptides and proinflammatory cytokines further up-regulate 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. For example, glial cells act as specialized resident macrophages that express cytokines, such as IL-6, TNF, and IL-1β, but also release excitatory neurotransmitters, neurotropic factors (i.e., NGF), and other proinflammatory mediators (ATP, nitric oxide, and prostaglandins) (70–72). Therefore, glial cell activation and proinflammatory mediator expression significantly contribute to the local neuroimmune crosstalk (71,72).

The neuroinflammatory loop between immune cells and nociceptors, facilitated at the nociceptor cell bodies by satellite glial cells at the level of the DRGs, ultimately leads to an increase in sensory neuron activity, resulting in regional thermal and mechanical hyperalgesia, both of which are traits characteristic of acute inflammation states. When perpetuated and unbalanced, neuronal activation can promote nociplastic changes responsible for peripheral sensitization 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 independent of the level of peripheral inflammation (73).

Systemic inflammation may influence the CNS via alternative mechanisms. Proinflammatory 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 proinflammatory mediators, including prostaglandins, TNF, and IL-1β. The presence of proinflammatory cytokines and mediators can contribute to central sensitization via their effect on neuronal transmission, which is characterized by increased excitatory activity and reduced inhibitory activity (75). This was demonstrated in rodent models with the use of lipopolysaccharide as a proinflammatory stimulus, which induced the development of hyperalgesia (76). In addition, other centrally mediated symptoms are observed, including fatigue, sleep, and cognitive and mood disturbances (77). The emergence of these behaviors can be attributed to the need to protect the organism during acute damage and facilitate recovery in the short-term; however, prolonged, chronic pain states may evolve, including, for example, 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 manifested as a high prevalence of comorbid FM among patients with RA, which is diagnosed in up to one-third of patients across the rheumatic disease spectrum (6). One also needs to remember that, within any nociceptive pain state, there will be individuals with preexisting 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 American College of Rheumatology (ACR) survey criteria for FM, a certain degree of central sensitization can still be present (79). In a neuroimaging study in individuals with RA, we have shown that the degree of central sensitization, as measured using the total scores of the ACR FM criteria, had a strong correlation with the increased connectivity between the default mode network (DMN), which is active during wakeful rest, and the posterior insula. Similar hyperconnectivity has been consistently demonstrated in individuals with a diagnosis of FM (80).

Furthermore, the sensitization 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 sensitization. For example, studies by Lee and colleagues in patients with RA have shown that a lowered mechanical threshold (i.e., tenderness) in regions of the body with RA involvement (e.g., the small joints of the hands or wrists) was related to measures of inflammation, whereas tenderness in "neutral" regions without RA involvement (e.g., the trapezius) was more related to indices of central sensitization (81). A study evaluating pressure pain thresholds (PPTs) in patients with stable RA showed that a reduced PPT, reflecting sensitization, was associated with greater severity of reported pain, poorer mental health, and higher frequency of FM (42). In other RA studies, pain sensitization, manifested as lower PPTs and higher temporal summation, was also associated with higher disease activity and more severe 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 colleagues showed an association between reduced response to disease-modifying antirheumatic drugs and altered CPM in 182 patients with active RA (83). Taken together, the findings from these studies confirm the presence of pain sensitization in RA and highlight 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 of central pain pathways, the first to be conducted in RA patients, showed a correlation of 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 the DMN, dorsal attention, salience, and medial visual networks were positively correlated with the level of peripheral inflammation as measured using the erythrocyte sedimentation rate (ESR) (44). Importantly, these "inflammatory brain hubs" were 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 ESRs were positively associated with an increased connectivity of the left IPL, including key regions implicated in 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 that sensitize 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 classic "top down" nociplastic dimension will likely dominate and will continue to be used to explain why ~50% of patients with RA report clinically important levels of pain despite achieving full remission of their systemic inflammatory disease (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 toward an important role of nervous system sensitization in pain perception among patients with RA.

Local joint pathology driven by mechanisms of inflammation 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 sensitization, 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 characterized by complex communications mediated by proinflammatory mediators and neuropeptides, which ultimately facilitate the process of sensitization in this group of patients. Circulating proinflammatory cytokines are also a contributory factor that sensitizes the CNS in RA through multiple mechanisms, resulting in conserved behavioral and physiologic changes. Hyperactivity of the peripheral and central nervous systems in patients with RA has been demonstrated in several studies in which neuroimaging techniques and QST have been utilized. Interestingly, the expression of nociplastic pain can explain the reduced response to antirheumatic drugs in RA.

Despite these recent advances in pain research, our understanding of the complex biology of pain pathogenesis and persistence is far from complete, particularly in rheumatic conditions such as RA. Further studies are needed to confirm the clinical associations between systemic inflammation and nociplastic pain, and how sensitized 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. Unraveling molecular and biologic chronic pain mechanisms not only will aid in the distinction of chronic pain phenotypes, but also will unveil novel interesting therapeutic targets for pain management. Ultimately, a better understanding of pain biology in rheumatic conditions will enable rheumatologists to optimize treatment and improve the quality of life of patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sunzini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sunzini.
Acquisition of data. Sunzini, Schrepf, Clauw, Basu.
Analysis and interpretation of data. Sunzini. Schrepf, Clauw, Basu.

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