Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome

Geoffrey Littlejohn

Abstract | Although fibromyalgia and complex regional pain syndrome (CRPS) have distinct clinical phenotypes, they do share many other features. Pain, allodynia and dysaesthesia occur in each condition and seem to exist on a similar spectrum. Fibromyalgia and CRPS can both be triggered by specific traumatic events, although fibromyalgia is most commonly associated with psychological trauma and CRPS is most often associated with physical trauma, which is frequently deemed routine or minor by the patient. Fibromyalgia and CRPS also seem to share many pathophysiological mechanisms, among which the most important are those involving central effects. Nonetheless, peripheral effects, such as neurogenic neuroinflammation, are also important contributors to the clinical features of each of these disorders. This Review highlights the differing degrees to which neurogenic neuroinflammation might contribute to the multifactorial pathogenesis of both fibromyalgia and CRPS, and discusses the evidence suggesting that this mechanism is an important link between the two disorders, and could offer novel therapeutic targets.

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Introduction

Fibromyalgia and complex regional pain syndrome (CRPS) share many features. Fibromyalgia was formerly known as fibrositis syndrome, a term that implied a notable contribution of peripheral inflammation to the condition.[1,2] CRPS was also initially considered to have an inflammatory origin.[3,4] However, understanding of fibromyalgia and CRPS has long since moved away from those early concepts, and these two pain syndromes are now considered to be primarily centrally driven.

Changes in several brain regions (including the middle cingulate, posterior insula, dorsolateral prefrontal cortex and parietal lobe) are independently linked to both CRPS and fibromyalgia, and are seen as possible drivers of both conditions.[5] Accordingly, current attention is focused on the role of abnormal neurophysiological processes within the brain and spinal cord in the pathogenesis of fibromyalgia and CRPS.[6] For example, substantial evidence suggests that central sensitization (the mechanism whereby normally non-noxious stimuli, such as gentle touch or movement, can stimulate low-threshold mechanoreceptors and so cause pain[7]) is a driving pathophysiological mechanism in both fibromyalgia and CRPS.[6–8] However, embedded within this abnormal central neurophysiology are a number of important peripheral inflammatory mechanisms, collectively termed neurogenic (as opposed to classic) neuroinflammation. Investigation of the role of neurogenic neuroinflammation in fibromyalgia and CRPS might contribute to improved understanding of the fundamental mechanisms leading to these enigmatic disorders, as well as to the identification of new therapeutic targets. These advances could help to improve the management of affected patients, through reduction of symptoms such as peripheral swelling, dysaesthesia and local pain. Ultimately, however, modulation of the central driving mechanisms will have the most profound effect on all symptoms of fibromyalgia and CRPS, both central and peripheral.

This Review summarizes observations regarding the neurogenic neuroinflammatory mechanisms that contribute to fibromyalgia and CRPS, and places them in the context of what is currently known about the overall pathophysiology of these two disorders. The central nervous system pathways implicated in fibromyalgia and CRPS are not described in detail, as several relevant reviews have already addressed this aspect of the pathophysiology of fibromyalgia and CRPS.[9,10]

Department of Medicine, Monash University, Monash Medical Centre, 246 Clayton Road, Clayton, VIC 3168, Australia.
geoff.littlejohn@monash.edu

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Pathophysiology

Central mechanisms

In patients with fibromyalgia, descending pathways from the forebrain and midbrain modulate the sensitivity of deep second-order cells of the dorsal horn (which project to central pain-related regions) via both opioidergic and 5-hydroxytryptaminergic-noradrenergic pathways.[11] The opioidergic pathways seem to function normally,[12] whereas the function of 5-hydroxytryptaminergic-noradrenergic pathways is attenuated[13] in many patients with fibromyalgia. In turn, these midbrain regulatory pathways seem to be modulated by activity in the anterior cingulate cortex and the insula. Connectivity between the default-mode network and the insula is increased[14] and connectivity of the default-mode network with

Key points

- Fibromyalgia and complex regional pain syndrome (CRPS) have distinct clinical phenotypes but share features such as pain, allodynia and peripheral dysaesthesia
- Factors involving the brain and spinal cord lead to central sensitization, which has a dominant role in both disorders
- Neurogenic inflammation, resulting from the release of proinflammatory neuropeptides from C-fibres, is also prominent in both disorders and contributes to allodynia, tissue swelling and dysaesthesia
- Neurogenic inflammation involves interactions of the innate immune system with the peripheral and central nervous systems of patients with fibromyalgia or CRPS
- Although the pathogenesis of both fibromyalgia and CRPS is dominated by central mechanisms, components of neurogenic neuroinflammation might be useful therapeutic targets in patients with these disorders

other pain-inhibitory regions is decreased.[15] Moreover, glutamate levels are elevated in the cerebrospinal fluid (CSF)[16] and the posterior insula[17] of patients with fibromyalgia. Treatment with pregabalin[18] and memantine[19] causes lowering of glutamate levels in the insula, which correlates with a reduction in pain levels in patients with fibromyalgia. These observations imply that processes originating in the brain are critically important in influencing pain in fibromyalgia. However, along with the central factors involved in the pathophysiology of fibromyalgia, affected patients also show increased activity in the sympathetic nervous system[20] and altered function of the neuroendocrine axis,[6,21] which can independently lead to many further symptoms. Of note, many of the comorbid painful conditions associated with fibromyalgia are regional pain disorders in their own right, such as temporomandibular joint pain, pelvic or menstrual pain, and regional pain in the arm or low back.[22] These conditions can often have severe symptoms.

Although some evidence suggests that dysregulation of the autonomic nervous system is present in patients with CRPS, its contribution to key clinical features of CRPS is today considered far less important than it once was.[23] By contrast, central mechanisms seem to predominate, and not only affect the sensory pathways linked to pain but also result in neuroplastic effects that cause changes in sensory mapping and motor function.[24–26] However, the pathophysiology of CRPS is poorly defined. Although CRPS usually seems to be a highly localized condition, the cause of this localization of the manifestations of CRPS remains unclear. Clinical evidence of extensive regional or widespread allodynia is commonly found in patients with CRPS, and not just involving the symptomatic area (G.L., personal observations). Lowering of the pain threshold in a hemilateral distribution can also occur in patients with CRPS,[27] which might suggest either that the severe pain experienced in involved areas induces dysfunction of the descending noxious inhibitory pathways, resulting in widespread allodynia, or that this abnormality is part of the pathophysiology of CRPS in the first place. The dysfunction of descending inhibitory pathway that occurs in fibromyalgia is, therefore, probably also present in CRPS, although the evidence for its presence in CRPS is more limited than that for fibromyalgia.

Box 1 | Neuroactive substances

- Neuropeptides are just one of several classes of neuroactive substances, which can include steroids, growth factors, eicosanoids and amino-acid transmitters
- Neuropeptides are secreted from neuronal cells; they generally facilitate communication between neighbouring neurons
- Neuropeptides are divided into families of molecules encoded by similar or identical genes; many neuropeptides are expressed as large precursor molecules that undergo post-translational processing to result in several different small proteins
- Over 100 different neuropeptides exist in the mammalian nervous system; their actions include analgesia, reward, food intake, metabolism, reproduction, learning, memory, and social behaviours[139]

Peripheral mechanisms

In healthy individuals, a triple response (reddening of the stimulation site, surrounding erythema, and plasma extravasation resulting in a raised weal) occurs after either mechanical[28] or chemical (for instance application of capsaicin) stimulation of the skin.[29] This response is now termed neurogenic inflammation, and is caused by the release of proinflammatory peptides from the peripheral nerve endings of peptidergic C-fibres, a key neuronal type involved in nociception.[30,31] Exacerbation of these neuroinflammatory mechanisms is important in the early stages of both CRPS and fibromyalgia, and can persist over time to contribute to ongoing key symptoms in each disorder. These mechanisms are discussed in detail below.

After activation by a nociceptive stimulus, C-fibres not only transmit action potentials to the spinal cord from the periphery, but importantly can also transmit antidromically (that is, against the normal direction of propagation) from junction points back to the periphery.[32] A number of neuropeptides (Box 1), particularly substance P, calcitonin gene related peptide (CGRP) and neurokinin A, are released after stimulus–induced antidromic firing of C-fibres initiated either by axonal or dorsal root reflexes (Figure 1). Many other neuropeptides are also released, including adrenomedullin, neurokinin B, vasoactive intestinal peptide, neuropeptide Y and gastrin-releasing peptide. These neuropeptides increase skin blood flow, vascular permeability and egress of polymorphonuclear leukocytes, key features of neurogenic inflammation. CGRP (which acts via CGRP1 receptors) is the main transmitter that causes neurogenic vasodilatation of arterioles, owing to its actions on vascular smooth muscle and endothelial cells.[32] CGRP also increases sweat gland activation and promotes hair growth, features often seen in CRPS.[33] Substance P and neurokinin A act on neurokinin A1 receptors to increase vascular permeability.[32] Substance P and CGRP directly attract and activate cell types involved in both innate (mast cells, keratinocytes, dendritic cells) and adaptive (T lymphocytes) immunity.[32] Mast cells are located adjacent to both sensory neurons and blood vessels, and their activation leads to

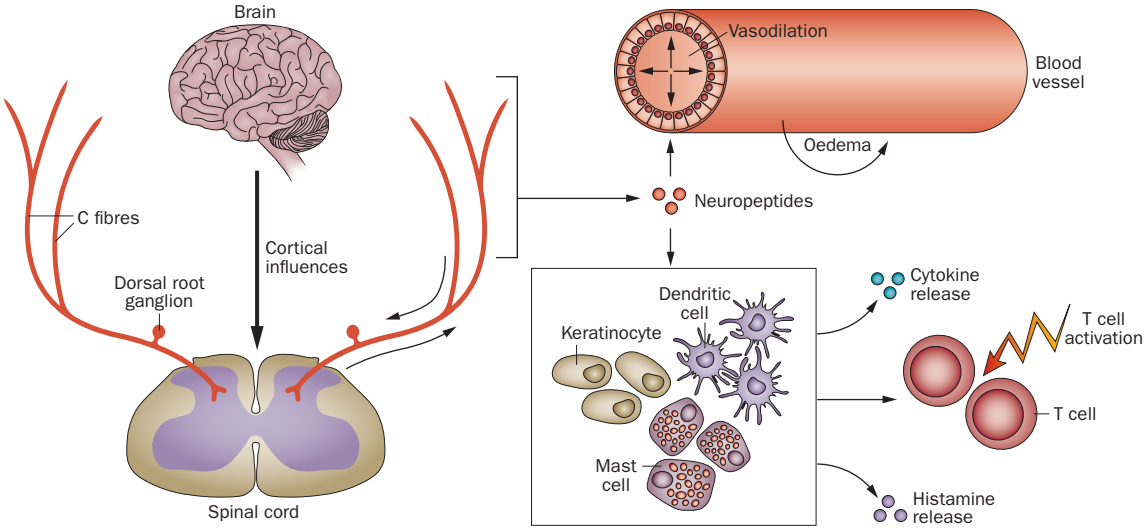

Figure 1 | Central and peripheral effects associated with release of neuropeptides by terminal C-fibres. Left panel: C-fibres transmit nociceptive input to the outer laminae of the spinal cord, where they interact with second-order neurons. These interactions are modulated by influences emanating from the brain and brain stem. Right panel: The C-fibres release neuropeptides, such as substance P, as part of an axonal reflex in peripheral tissues. These neuropeptides act on adjacent blood vessels and cells (including immune-related cells) to cause vasodilatation, oedema resulting from fluid extravasation, and activation of innate and humoral responses.

degranulation and release of several additional neuroactive and vasoactive substances, including bradykinin, histamine, prostaglandins, TNF, vascular endothelial growth factor and 5-hydroxytryptamine. Many of these substances, such as histamine and TNF, in turn sensitize other nearby nociceptive terminals, such as Aδ myelinated fibres, resulting in further amplification of inflammatory changes (comprising vasodilatation, tissue swelling and pain) in the affected site.[33] Other neuropeptides, such as the potent vasoconstrictor endothelin-1 (ET-1)—which is mainly secreted from inflammatory cells and keratinocytes, the predominant cell type in the epidermis—can also contribute to sensitization of primary afferent neurons, although in many cases the precise role of these neuropeptides in neurogenic inflammation remains unclear.

Neurogenic inflammation, therefore, results from the effects of certain neuropeptides on peripheral blood vessels, other sensory neural structures, and regional innate immune cells. Responses of these cells include secretion of cytokines such as TNF that in turn have immune and inflammatory effects both locally and systemically. Cytokines, in contrast to neuropeptides, are released by a variety of cells, including immune cells, and have actions on a variety of other cells. The sympathetic nervous system interacts with this process through upregulation of α-adrenergic receptors in local inflammation, and also through as yet poorly characterized changes in central mechanisms.[34]

Potential triggering events

Peripheral nociceptive input from ischaemia–reperfusion injury is noted to be a trigger of CRPS.[35–37] Although conjectural, perhaps in patients with CRPS an initial trauma to a body part causes an abnormal response in a neural pathway involving this brain–spinal cord–peripheral region, and the subsequent excessive activation of neurogenic neuroinflammation might be attributable to an intrinsic vulnerability of the pain-modulatory pathways. Trauma is also a common trigger of fibromyalgia, but the regional effects are less intense than in CRPS, and the pain and tenderness are more widespread. However, considerable evidence shows that these widespread changes occur on a background of dysfunctional descending nociceptive pathways.[38,39]

The evidence for psychological predisposition to fibromyalgia or CRPS is limited. However, a number of psychological factors modulate fibromyalgia symptoms.[40] Among these, catastrophizing has been linked to increased symptoms and neuroimaging changes.[41] Again, in a similar fashion to fibromyalgia, although no specific personality type or single psychological factor has been clearly identified as a predictor of CRPS,[42] both conditions are associated with high levels of stress, poor coping skills and thinking styles such as catastrophizing. Of note, patients with fibromyalgia or CRPS often report increased exposure to stressful life events.[43–46] Factors that exacerbate stress, such as anxiety, also seem to have a role in the clinical features of CRPS.[47] Abnormal reactivity to stress would act through central mechanisms. In both syndromes, genetic factors are also probably important.[48,49]

Clinical features of fibromyalgia

Clinical features that probably relate to neurogenic inflammation in patients with fibromyalgia include swelling in peripheral tissues, reticular skin discolouration (livedo reticularis), dermatographia, cutaneous dysaesthesia and notable allodynia (Figure 2), which are discussed in detail below.

Cutaneous vascular-related phenomena that might be relevant to neurogenic inflammation include cold-induced vasospasm and Raynaud phenomenon, which

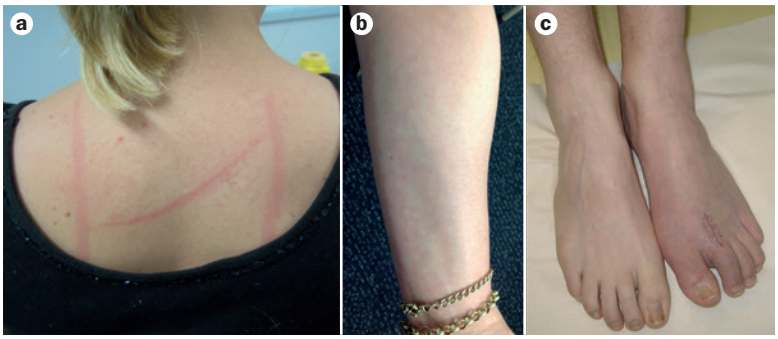

Figure 2 | Clinical features of neurogenic inflammation in fibromyalgia and complex regional pain syndrome. **a** | Dermatographia elicited after gentle stroking of skin in a patient with fibromyalgia. **b** | Reticular skin discolouration in forearm of patient with fibromyalgia. **c** | Redness, swelling and allodynia of the left foot and ankle in a patient who developed complex regional pain syndrome after undergoing surgery for a metatarsal bone fracture.

are seen in ≤40% of patients with fibromyalgia (compared to <5% of healthy controls).[50–53] Reticular skin discolouration and livedo reticularis of varying severity occur in up to 64% of patients with fibromyalgia.[53,54] Many have dermatographia (also termed reactive hyperaemia), characterized by an exaggerated flare in the skin surrounding a mechanical stimulation site.[55] Additionally, patients often report local tissue swelling or fluid retention, which is a consequence of plasma extravasation;[56,57] in one study, 73% of patients with fibromyalgia had self-reported swelling versus 2% of healthy controls ($n = 60$ per group; $P < 0.001$).[58] Although swelling is commonly reported by patients with fibromyalgia, no studies have objectively assessed the prevalence of this clinical feature.

One study compared 50 patients with fibromyalgia (25 with Raynaud phenomenon, livedo reticularis, or both, and 25 without these manifestations) and 25 healthy control individuals. Levels of fibronectin, a marker of endothelial activation, were significantly higher in the patients who had fibromyalgia and Raynaud phenomenon, livedo reticularis, or both, than in the other two groups ($P < 0.0001$ for both comparisons).[53] Endothelial dysfunction in patients with fibromyalgia can also be influenced by sympathetic nervous system dysfunction (discussed below).

Neurogenic flare (that is, mechanically induced or capsaicin-induced reflex vasodilatation) is increased in patients with fibromyalgia compared to unaffected controls, and the extent of allodynia correlates positively with the severity of the skin flare.[59] Skin flare responses in patients with fibromyalgia are also closely correlated with slow-wave sleep deprivation, increased fatigue and a decreased pain threshold, which are all key features of fibromyalgia.[60]

The observed increase in deposition of albumin and IgG at the dermoepidermal junction in patients with fibromyalgia is also probably due to plasma extravasation from blood vessels as part of neurogenic inflammation.[61,62] This notion is supported by studies showing a correlation between the percentage of damaged or degranulated mast cells and the extent of IgG deposition in the dermis and vessel walls.[63,64] Mast cell numbers are increased by severalfold in the skin of patients with fibromyalgia, which is consistent with induction and activation of mast cells by neurogenic processes.[65]

In summary, a number of observations in the literature (albeit derived from small, selective, cross-sectional and comparative studies) present a consistent picture suggesting that neuroinflammatory mechanisms do contribute to specific clinical features of fibromyalgia. Larger, longitudinal studies using improved methods of assessing neurogenic inflammation (such as skin blister fluid analysis) are now required to characterize the components and relative importance of this process in fibromyalgia.

Clinical features of CRPS

Neurogenic inflammation—comprising tissue swelling, vasomotor changes and marked allodynia—also contributes substantially to the clinical features of CRPS.[33] Indeed, these features make CRPS the most readily clinically detected of all chronic pain syndromes. Inflammatory features of CRPS are especially prominent early in the disease course, particularly the first 6 months. By contrast, in fibromyalgia, inflammation-related symptoms tend to fluctuate over long periods of time. Levels of osteoprotegerin (OPG) are also elevated in the early phase of CRPS, indicative of acute effects on bone remodelling.[66] The common and prominent CRPS features of bone marrow oedema and osteopenia are also probably related to neurogenic inflammation, through secretion of neuropeptides such as OPG. Additionally, late clinical features, such as visceral pain, rashes, skin ulceration and fibrosis of palmar aponeuroses and joint capsules might also relate to persistent neurogenic inflammation in CRPS.[44,67,68]

About 80% of patients with CRPS exhibit an increased skin temperature during the first 6 months of the disorder.[69] The accompanying reddish discolouration of the involved region is likely to relate to the vasodilatatory effects of neuropeptides such as CRGP. In the other 20% of patients, the involved regions are cold and have bluish discolouration at disease onset; these effects might be mediated by vasoconstrictive neuropeptides, such as ET-l.[33] Increased sweating occurs in up to 50% of patients with CRPS and increased local hair growth in about 15%, both of which can be caused by neuropeptides such as CRGP.[33]

Reflex vasodilation is greatly increased in both involved and non-involved limbs of CRPS patients; however, protein extravasation is limited to the affected side.[70] Clinical features that probably relate to neurogenic inflammation in patients with CRPS include variable and often considerable tissue swelling, vasomotor changes, trophic changes (that is, of the bone, hair, nails and skin), and notable allodynia of the involved tissues (Figure 1, Table 1).

Factors involved in neuroinflammation

Glial cells

Astrocytes and microglia, collectively termed glia, are implicated in chronic pain.[71] At the level of the spinal

Table 1 | Clinical features of fibromyalgia and CRPS associated with neurogenic neuroinflammation

Study	Feature	Neuropeptide-related mechanism
Chiu *et al.* (2012)[32]	Swelling	Increased vascular permeability
Chiu *et al.* (2012)[32] Birklein & Schmelz (2008)[33]	Vasomotor changes, dermatographia, reticular skin discolouration, skin colour and temperature changes	Vasodilatation* and vasoconstriction‡
Birklein & Schmelz (2008)[38] Herbert & Holzer (2002)[62]	Allodynia	Sensitization of nociceptors
Uceyler *et al.* (2007)[97]	Cutaneous dysaesthesia, numbness, pins and needles sensation	Structural effects on C-fibres
Kramer *et al.* (2014)[66]	Osteopenia (in CRPS)	Abnormal bone remodelling
Birklein & Schmelz (2008)[33]	Increased hair or nail growth (in CRPS)	High local neuropeptide levels

*From Chiu *et al.*[32] ‡From Birklein & Schmelz.[33] Abbreviation: CRPS, complex regional pain syndrome.

cord, activation of peptidergic primary afferent C-fibres leads to the release of various neurotransmitters and neuropeptides, including glutamate, substance P, CGRP, brain-derived neurotrophic factor (BDNF), CX_3CL1 (CX_3 chemokine ligand 1, also known as fractalkine) and ATP.[72] Their receptors are present on nearby resident innate immune cells within the central nervous system, microglia and astrocytes.[72] For instance, expression of Toll-like receptor 4 (TLR4) is upregulated in microglia after activation.[71] Upregulation of TLR4 in turn increases production of nitric oxide, prostaglandins, leukotriene, nerve growth factor (NGF), excitatory amino acids and neurotoxic superoxides.[73,74] In addition, activated microglia and astrocytes release proinflammatory cytokines, such as IL-1, IL-6 and TNF.[71,75] This process is termed neuroinflammation.[72]

The most common triggers of neuroinflammation include infectious micro-organisms, autoimmunity and toxins; the resultant activation of immune cells, vascular cells and neurons is linked in a tightly knit manner.[72] However, augmented neuronal activity itself can trigger neuroinflammation in peripheral tissues.[32] Other triggers include psychological stress, and in this setting the term 'neurogenic' (as opposed to 'classic') neuroinflammation has been proposed.[72] Thus, the nervous system can drive neurogenic neuroinflammation independently of the presence of external noxious triggers. This neurogenically driven cascade of events seems to be associated with many of the clinical features seen in patients with both fibromyalgia and CRPS.

Neuropeptides in fibromyalgia

Substance P levels are markedly elevated in the CSF of patients with fibromyalgia.[76,77] CSF levels of BDNF and NGF are also elevated,[78,79] but studies of other neuropeptides are limited.[80] Substance P and other neuropeptides are widely distributed in the brain, and high levels of these neuropeptides are found in regions that are specific to regulating emotion (hypothalamus, amygdala, and the periaqueductal grey).[81] The cell bodies of C-fibres in dorsal root ganglia also produce neuropeptides.

Psychological factors, such as stress, probably initiate the cascade of events leading to the elevated levels of substance P in C-fibre bodies within dorsal root ganglia. Substance P is fundamental to an evolutionarily conserved, whole-organism stress response.[82] A study of combat veterans with post-traumatic stress disorder showed that their basal levels of substance P in the CSF were elevated, and that subsequent release of substance P was increased by psychological stress.[83] Psychological factors such as stress are the probable initiators of increased production of a variety of neuropeptides in the dorsal horn of the spinal cord, the CSF and in the nerves and tissues. Elevated tissue levels of neuropeptides subsequently contribute to many of the characteristic clinical features of fibromyalgia, as indicated above, and elevated central levels contribute to central sensitization.[7]

The evidence suggests that small-fibre function and structure are impaired in patients with long-standing fibromyalgia compared to healthy controls, and that numbers of nonmyelinated fibres are reduced in the skin of affected patients.[84–87] Electron microscopy shows abnormalities of nonmyelinated fibres and associated Schwann cells,[88] and these changes are also observed in paediatric patients with fibromyalgia.[89] Microneurography shows that the majority of patients with fibromyalgia have structurally abnormal C-fibre nociceptors.[90] The relationship between small-fibre function and C-fibre neurogenic inflammation needs to be clarified, but together these changes might explain the high rates of dysaesthesia and other sensory symptoms in patients with fibromyalgia.[91]

Neuropeptides in CRPS

Increased serum levels of substance P and CGRP occur in CRPS.[92] Plasma extravasation is seen in involved tissues from patients with CRPS on scintigraphy studies using ^{111}In-labelled IgG as a marker of increased vascular permeability.[93] Electrical stimulation of peptidergic C-fibres in clinically involved, but not control (uninvolved) skin, causes substance-P-related plasma protein extravasation.[70]

Epidemiological evidence indicates that disorders involving abnormalities of neuropeptides in their pathophysiology (such as asthma and migraine[94]) are linked to CRPS.[95] Additionally, CRPS is associated with the use of angiotensin-converting enzyme inhibitors, which are involved in the metabolism of neuropeptides.[96] As observed in fibromyalgia, small-fibre changes affecting

both C-fibres and Aδ fibres are present in CRPS[67,97,98] and are associated with a proinflammatory cytokine profile.[97]

Cytokines in fibromyalgia

In addition to secretion of neuropeptides, activated polymodal C-fibres also secrete cytokines.[32] Proinflammatory cytokines can cause sensitization of peripheral neurons through upregulation of responsiveness to nitric oxide and prostaglandin E_2 and might, therefore, contribute to fibromyalgia symptoms. Substance P, glutamate and BDNF can also activate glial cells to release proinflammatory cytokines and a variety of neuropeptides (see above), all of which can exacerbate pain amplification.[71] Nociceptive neurons have close links to the immune system, and many molecules involved in tissue damage recognition pathways are expressed on both immune cells and neurons.[32]

The actions of various cytokines have been postulated to link to particular clinical features of fibromyalgia.[99] Cytokines have effects on the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system and T lymphocytes, which in turn might be associated with fibromyalgia.[100] Studies of cytokine levels in patients with fibromyalgia suggest that levels of the proinflammatory cytokines IL-1, IL-6 and IL-8 are elevated, whereas TNF levels are normal, and levels of the anti-inflammatory cytokines IL-4 and IL-10 are unchanged or reduced.[101–103] However, many of these studies have methodological problems, such as small sample sizes, heterogeneous selection criteria, differing assay techniques, lack of appropriate control groups, and the failure to account for the effects of comorbid conditions (such as obesity) that affect cytokine levels.[101–103] A study that did account for many of these potential confounders, conducted in 707 patients with chronic multisite musculoskeletal pain, provided evidence of an increased innate immune response. Specifically, chronic pain was more strongly associated with lipopolysaccharide–stimulated proinflammatory cytokines (particularly IFN-γ and TNF) than with anti-inflammatory cytokines.[102] This proinflammatory cytokine profile might promote central sensitization.[102]

The source of the increased plasma or serum levels of cytokines in fibromyalgia is unclear. Their presence could reflect peripheral production by activated polymodal C-fibres or neuropeptide stimulation of immune cells in peripheral tissues. Alternatively (or additionally), these cytokines might be derived from activated glial cells in the central nervous system. The finding of elevated levels of IL-8 in the CSF of patients with fibromyalgia supports this idea.[104]

Cytokines in CRPS

Peripheral trauma itself, in the absence of clinical CRPS, causes release of NGF and cytokines that can activate and sensitize nociceptors.[33] Levels of proinflammatory cytokines, such as TNF and IL-6, are increased in suction-induced blister fluids[105–107] and blood[108] from patients with CRPS. Moreover, the expression and levels of anti-inflammatory cytokines such as IL-4 and IL-10 are reduced.[33,109] Patients with CRPS also show elevated CSF levels of certain proinflammatory cytokines (such as IL-1β and IL-6) but not TNF. The quality of the evidence varies in studies of inflammatory markers detected in blood and blister fluid in acute and chronic CRPS.[110] However, in general, CRPS is associated with the presence of a proinflammatory cytokine profile in the blood, blister fluid and CSF. Levels of proinflammatory cytokines are also elevated in the affected limbs of patients with CRPS,[111] and these changes are amplified after transcutaneous electrical stimulation, a feature that is considered to indicate the presence of neurogenic inflammation.[33]

In animal models of CRPS, skin temperature differences, oedema and pain behaviours can be reversed by administration of neurokinin A1 antagonists, neuropeptide-blocking agents,[112] and glucocorticoids.[113] These interventions modulate a number of released cytokines. Further, in humans with early CRPS the cutaneous innate immune system is activated, as shown by exaggerated sensory and sympathetic signalling, activation and proliferation of keratinocytes and mast cells, inflammatory mediator release, and pain.[114] By contrast, in patients with chronic CRPS, keratinocyte proliferation is reduced, resulting in epidermal thinning, and mast cell numbers are normal.[114] Antibodies to β_2 adrenergic and M2 muscarinic receptors on neurons are found in about 35% of patients with CRPS, but the clinical relevance of these findings remains unclear.[115] A working model of neurogenic inflammation in CRPS traditionally starts with injury to peripheral nerves, followed by activation of peripheral neuroimmune mechanisms. However, as is seen in fibromyalgia, it is likely that central mechanisms subsequently come to dominate the pathophysiology of CRPS.[34]

The sympathetic nervous system

The sympathetic nervous system contributes to the clinical features of both fibromyalgia and CRPS.[20,44] Indeed, many previous treatments were based on this association.[116,117] Patients with fibromyalgia show high levels of emotional distress and reduced heart rate variability, indicating ongoing sympathetic hyperactivity. Other studies show that noradrenaline injections exacerbate fibromyalgia-related pain.[118,119] Similar observations have been reported in patients with CRPS; for instance, increased heart rate, reduced heart rate variability, and inability to protect cardiac output during orthostatic stress.[120] Patients with CRPS also show hyperresponsiveness to a vasoconstrictive stimulus (infusion of increasing concentrations of noradrenaline into the dorsal hand vein).[121]

Important interactions between the sympathetic nervous system and the innate immune system occur via dendritic cells, which are modulated by adrenoreceptors.[122] Patients with CRPS show increased levels of α-adrenoreceptors in skin biopsies.[123] Elevated levels of proinflammatory IL-8 but not IL-1β have been found in the CSF of patients with fibromyalgia.[104] These observations are consistent with glial cell activation and might also be related to increased sympathetic activity. However, the exact influence of the sympathetic nervous

Table 2 | Potential strategies for targeting neurogenic neuroinflammation in fibromyalgia and CRPS

Neurophysiological target	Intervention	Comments
Stress system activation	Education, exercise, psychological strategies	Core management approach (modulate central drivers)
Sympathetic nervous system activation	α-Adrenergic blockers*	Decrease sympathetic input
Central (brain) nociceptive pathway modulation	Gabapentinoids, memantine*	Decrease neuropeptide release or glutamate levels, or both
Descending pain-modulation pathways in spinal cord	5-hydroxytryptamine–noradrenaline reuptake inhibitors*	Decrease dorsal horn sensitization
Spinal cord sensitization	*N*-methyl-D-aspartate receptor inhibitors (for example, ketamine)*	Decrease dorsal horn sensitization
Central inflammatory mechanisms	Low-dose naltrexone*	Downregulate activated glial cells
Peripheral (± central) inflammatory mechanisms	Glucocorticoids, intravenous immunoglobulin, cytokine inhibitors*	Modulate neuroinflammatory processes

*Only weak evidence of benefit. Abbreviation: CRPS, complex regional pain syndrome.

system on neuroinflammation in fibromyalgia and CRPS remains unclear.[44]

Therapeutic implications

Neurogenic neuroinflammation clearly comprises a complex set of interacting components with many potentially targetable feedback loops. However, similar to the inflammation occurring in rheumatoid arthritis, the overall process of neurogenic neuroinflammation can probably be downregulated by targeting elements at several levels (Table 2), the most relevant of which are discussed below.

Some evidence suggests that emotional distress and activation of the stress system are present in both fibromyalgia and CRPS.[47,124] The stress response probably drives the peripheral neurogenic process, and can be targeted through education, exercise and psychological strategies.[6] Decreasing sympathetic nervous system inputs through pharmacological interventions, such as propranolol or phenoxybenzamine, might also benefit some patients;[125,126] further strategies to modulate interactions between stress and events upstream of the spinal cord include targeting central (brain and spinal cord) neurotransmitters using drugs such as the gabapentinoids, and modulating descending pain control pathways using drugs such as 5-hydroxytryptamine–noradrenaline reuptake inhibitors.[6] Suppression of neurogenic inflammation does not seem likely to be achieved with NSAIDs. Glucocorticoids have been reported to be beneficial in early CRPS, but the available evidence is of poor quality.[127] Neither glucocorticoids nor NSAIDs are proven to be effective in fibromyalgia.[128]

No clinically available drugs that target neuropeptides are effective in the treatment of either fibromyalgia or CRPS.[129] Biologic drugs that target inflammatory cytokines, such as TNF, have not been proven to be beneficial.[99,127] Intravenous or subcutaneous polyvalent IgG therapy has been proposed for both fibromyalgia and CRPS,[130,131] but convincing evidence of its efficacy from randomized trials is lacking.

A number of drugs target central mechanisms in fibromyalgia and CRPS. Naltrexone is a μ-opioid receptor antagonist that can cross the blood–brain barrier and suppress glial cell activation. At low doses, this agent increases TLR4 levels but does not inhibit other opioid receptors in the central nervous system and, consequently, endogenous antinociceptive pathways involving μ-receptors continue to function. In animal models, low-dose naltrexone can reverse neural pain from chronic constrictive nerve injury.[132] Low-dose naltrexone might reduce symptom severity in patients with fibromyalgia and CRPS,[133] but these results remain to be confirmed. Other attenuators of glial cell activation include ibudilast, which has shown some benefit in treating pain in CRPS,[134] and minocycline, which has shown benefits in animal models that might translate to patients with fibromyalgia.[135] Drugs such as ketamine that target *N*-methyl-D-aspartate receptors (which are present in activated microglia, as well as in dorsal horn transmission neurons) might also downregulate symptoms due to neuroinflammation in patients with fibromyalgia or CRPS, but no adequate trial evidence exists to support this approach.[136,137] Other drugs that target glutamate within the brain and spinal cord, such as memantine, might also downregulate neurogenic inflammation in fibromyalgia and CRPS.[19,138]

Conclusions

Neurogenic neuroinflammation is a key pathophysiological mechanism in both fibromyalgia and CRPS. However, improved knowledge of this process is required to further understand its contribution to the clinical features of these two disorders, and specifically to determine whether neurogenic neuroinflammation is an epiphenomenon or a stress-driven pathophysiological mechanism in its own right. The effect of highly specific targeting of various components of neurogenic neuroinflammation is a current focus of clinical research. This work is expected to lead to improved explanations of the links between central factors—including stress—and peripheral end-organ effects that might be associated with activation of nociceptive pathways, and further contribute to the central sensitization that characterizes both fibromyalgia and CRPS.

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