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REVIEW ARTICLE

Complex regional pain syndrome: a focus on the autonomic nervous system

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Abstract

Purpose Although autonomic features are part of the diagnostic criteria for complex regional pain syndrome (CRPS), the role of the autonomic nervous system in CRPS pathophysiology has been downplayed in recent years. The purpose of this review is to redress this imbalance.

Methods We focus in this review on the contribution of the autonomic nervous system to CRPS pathophysiology. In particular, we discuss regional sympathetic and systemic autonomic disturbances in CRPS and the mechanisms which may underlie them, and consider links between these mechanisms, immune disturbances and pain.

Results The focused literature research revealed that immune reactions, alterations in receptor populations (e.g., upregulation of adrenoceptors and reduced cutaneous nerve fiber density) and central changes in autonomic drive seem to contribute to regional and systemic disturbances in sympathetic activity and to sympathetically maintained pain in CRPS.

Conclusions We conclude that alterations in the sympathetic nervous system contribute to CRPS pathology. Understanding these alterations may be an important step towards providing appropriate treatments for CRPS.

Keywords Complex regional pain syndrome · Sympathetic nervous system · Central disturbances in autonomic activity · Immune system

Complex regional pain syndrome: an introduction

Complex regional pain syndrome (CRPS) is a painful distally generalized condition of an extremity that is a source of great psychological distress for the person affected. The syndrome may develop after peripheral nerve injury (CRPS type II) or after tissue injury to a limb such as a fracture, contusion or sprain combined with immobilization (CRPS type I) [13]. It is characterized by changes in skin temperature in the affected limb [47], and by local sweating abnormalities, edema and changes in hair and nail growth [11, 58]. The skin may appear glossy, and muscle weakness develops [11]. In the later stages, the limb typically becomes cold [14], and tremor and dystonia may develop [11].

After many years of research, we have made significant progress in understanding CRPS pathophysiology. We still do not know why only a minority of trauma patients develop CRPS, but the first step in CRPS pathophysiology might be posttraumatic immune activation, which is most obvious in primarily "warm" CRPS cases during the acute phase [27]. Careful clinical observation reveals signs of inflammation such as redness, swelling, hyperthermia, pain and trophic changes such as hypertrophic scarring. Keratinocytes proliferate and produce proinflammatory cytokines as part of the innate immune response [9]. Cytokines themselves activate connective tissue cells, which leads to the contractures [6], high-turnover osteoporosis and bone loss associated with CRPS [129]. Cytokines further induce sensitization of peripheral nociceptors and second-order neurons in the

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spinal cord with subsequent mechanical hyperalgesia, and they facilitate release of neuropeptides from primary nociceptive afferents [91]. Neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP) are released from the cytokine-sensitized nociceptors and induce a phenomenon known as neurogenic inflammation, which could be responsible for reddening, warmth and edema in acute CRPS [128]. Another peptide, endothelin 1, contributes to cold, bluish skin [57]. Throughout the course of CRPS, most of these signs normalize, which demonstrates a change in pathophysiology [75].

The second important mechanism of CRPS pathophysiology is detrimental plasticity in the central nervous system, which develops as a consequence of ongoing, probably inflammation-related posttraumatic pain and the associated peripheral and central sensitization. For instance, shrinkage of the representation area of the CRPS limb in the contralateral primary somatosensory cortex is seen [81]. Inflammatory pain after trauma increases during movement or weight bearing and can be avoided by limb nonuse. Although speculative, it seems plausible that longer-lasting nociceptive input to the spinal cord and brain in combination with inhibition of the motor output to the limb could lead to changes in sensorimotor integration in the brain. Sustained pain intensity and hyperalgesia in the CRPS limb are associated with the degree of cortical reorganization, and when pain is reduced, cortical reorganization normalizes [82], suggesting that pain and peripheral sensitization drive these changes. If pain disappears shortly after the trauma, this central reorganization would not develop, and we would not diagnose CRPS but normal trauma healing. Thus, central neuroplasticity, i.e. maladaptive "learned nonuse" [93], is especially—but not exclusively—important for CRPS beyond the acute phase. Pain avoidance results in a pathological movement pattern (e.g., while walking), which again increases the pain through nonphysiological muscle and joint load. Other consequences of chronic limb pain and cortical reorganization in CRPS might be the impairment of somatosensory perception [21, 98] or a body midline shift towards the healthy side, and perception of the CRPS extremity as being distorted [87]. Mechanical allodynia is another consequence of central changes in somatosensory processing in the spinal cord or the brain [50, 80]. Pain intensity, hyperalgesia and tactile impairment are all associated with the extent of cortical reorganization [82]. Conversely, graded sensorimotor retuning results not only in normalization of tactile discrimination and cortical maps but also in decreased pain [92]. Thus, cortical reorganization could reflect or perhaps even contribute to tactile impairment and pain in CRPS.

Autonomic features are encapsulated in the diagnostic criteria for CRPS. Nevertheless, despite a long history of human research, the role of the sympathetic nervous system in CRPS pathophysiology has been downplayed in recent years. This is particularly perplexing, as the recent detection of agonistic serum autoantibodies against adrenergic and cholinergic receptors renders an autonomic-immune system interaction very likely [45, 72]. To attempt to redress this imbalance, we focus in this review on the contribution of the sympathetic nervous system to CRPS pathophysiology. The role of inflammation and central neuroplasticity in CRPS pathophysiology was recently reviewed by our group [7, 8]. While the focus has usually been on local changes in blood flow and sweating driven by postganglionic sympathetic nerve fibers in the CRPS limb, it is likely that systemic and/or central disturbances in autonomic function also play a role in CRPS. Below we consider mechanisms that might mediate local and systemic sympathetic disturbances in CRPS, and discuss links between these mechanisms, immune disturbances and pain. An overview of the links between the mechanisms can be seen in Fig. 1.

Local sympathetic disturbances

The affected limb may alternate between warmth and cold over the course of the day [105, 111]. This phenomenon cannot be fully explained by local inflammation as, in this case, the limb should invariably be warm. Sweating often is increased in the affected limb [29]. This appears to involve local neurogenic inflammation [106], particularly in the early stages, and a disturbance in central thermoregulation [10].

Using whole-body warming and cooling, which modulates activity in postganglionic sympathetic nerve fibers that supply dermal blood vessels and sweat glands, three distinct patterns of temperature abnormalities were identified [124, 126]. In acute CRPS type I patients with a mean pain duration of 4 months, the affected limb was persistently warmer and skin perfusion higher than in the contralateral limb; this could be due to inflammation but might also reflect a loss of vasoconstrictor reflexes to cold in the affected limb [125, 126]. In patients with intermediate CRPS type I (mean duration of 15 months), the affected limb either was warmer than the contralateral limb when the body was warmed and colder than the contralateral limb when the body was cooled, or vice versa. In patients with a longer disease duration (mean of 28 months), temperature and perfusion were persistently lower in the affected than the contralateral limb during body warming and cooling. Similarly, in a recent international multisite study of 152 patients with CRPS, median CRPS duration was shorter, and symptoms of inflammation were more prevalent in the warm than cold CRPS subtype [14]. In addition, clinical symptoms of inflammation declined during a 3-month follow-up period, suggesting that if inflammatory mechanisms contribute directly to increases in limb temperature, they do so for a limited period after injury.

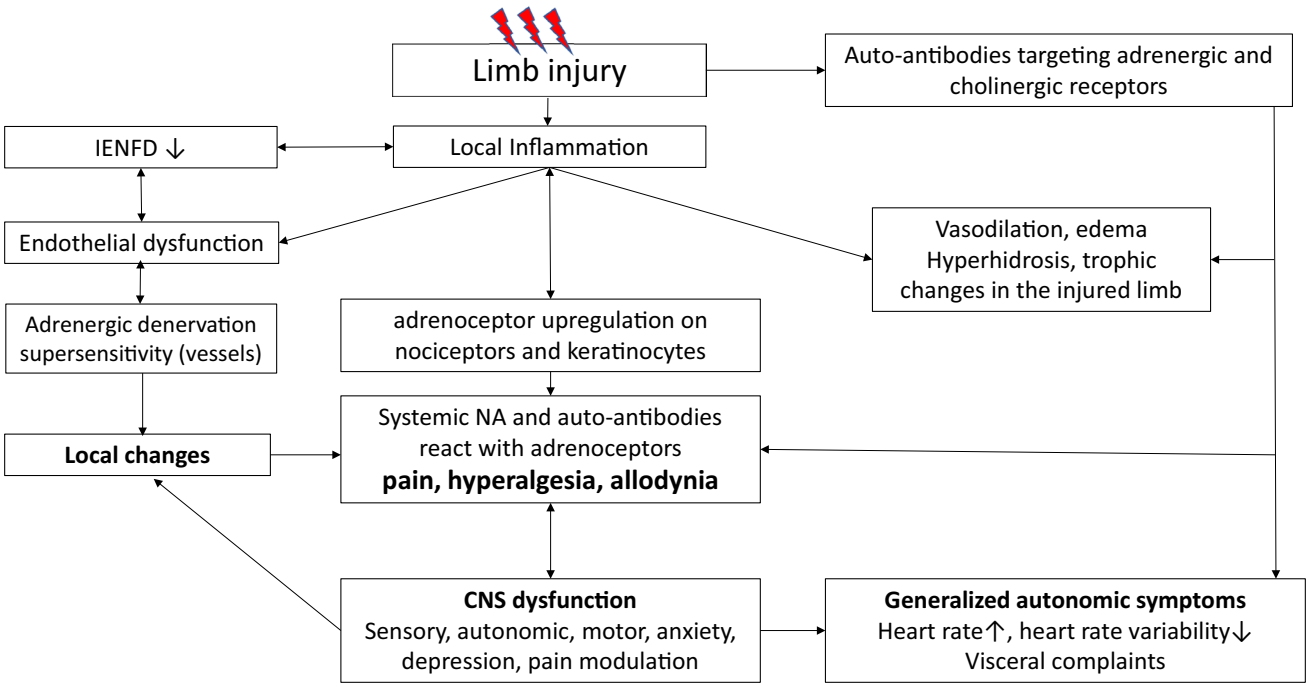

Fig. 1 The contribution of the autonomic nervous system to CRPS. The trauma is the trigger. Local inflammation not only causes visible inflammatory symptoms but also upregulates α_1-adrenoceptors on keratinocytes and nociceptors, resulting in pain and hyperalgesia because nociceptors become responsive to locally or systemically released noradrenaline (NA) during sympathetic nervous system (SNS) activity. Keratinocyte activation by NA reinforces inflammation. Simultaneously, autoantibodies which were either prevalent before or developed in response to the trauma activate these upregulated adrenoceptors and bind to neurons at the injury site and to distant autonomic organs. This further enhances the pain and causes unusual autonomic symptoms. Chronic pain triggers disturbances in CNS (brain) regions which control not only autonomic functions but also sensory perception and motor activity, pain modulation and psychological factors. These CNS changes in particular reinforce pain (e.g., via increased NA in the bloodstream or defective pain modulation) and contribute to generalized autonomic, sensory and motor problems. At the site of the injury (left column), inflammation probably reduces intraepidermal nerve fiber density (IENFD) and causes endothelial dysfunction, which both in turn prolong inflammation. It is also possible that reduced IENFD is present prior to injury. Reduced IENFD is associated with aberrant sympathetic innervation and subsequent increased responsiveness of the adrenoceptors on the blood vessels. This contributes to local perfusion disturbances and probably also to nociceptor activation

One of the difficulties associated with establishing CRPS thermal subtypes is that skin temperature varies substantially with physical activity and depends largely on ambient conditions. Since skin temperature appears to be less responsive to ambient conditions in the affected than the contralateral limb, skin temperature asymmetry (i.e., the affected extremity is warmer or colder than the contralateral extremity) may depend principally on cutaneous vasoconstrictor activity in the contralateral limb [73]. A perfusion index, calculated as the ratio of the pulsatile to nonpulsatile component of a photoplethysmograph signal, appears to be more sensitive than skin temperature in detecting vasomotor abnormalities in CRPS [20]. However, this method also relies on comparisons with the contralateral limb, and the stability of this index across different ambient conditions is yet to be explored.

The shift in limb temperature and perfusion from acute to chronic CRPS suggests that vasomotor disturbances evolve over time. However, not all patients follow this sequence, as the limb remains warm in some patients even after many years, whereas others report decreased skin temperature from the outset [14]. Moreover, clinical findings and risk factors for developing CRPS differ between warm and cold types of similar duration. This indicates that these two different phenotypes are not only a consequence of disease duration but may represent different underlying mechanisms [14, 47]. For example, patients with cold CRPS are more likely to have a history of serious life events and chronic pain disorders, and to develop CRPS-related dystonia. Furthermore, cold CRPS presents with cold-induced pain and sensory loss, whereas patients with warm CRPS are more likely to have mechanical hyperalgesia [47].

Older studies in patients with reflex sympathetic dystrophy (RSD—a diagnostic forerunner of CRPS [112]) indicated that venous levels of the neurotransmitters noradrenaline and neuropeptide Y (probably from tissue spillover) were lower in the affected than the contralateral healthy limb in both the acute-warm and chronic-cold stages [4,

41, 58]. These findings were interpreted to mean that loss of sympathetic vasoconstrictor activity in the affected limb resulted in a warm limb in the acute-warm stage of CRPS. However, in the chronic-cold stage of CRPS, reduced release of neurotransmitters could trigger a secondary increase in responsiveness of vascular α-adrenoceptors [17, 119], resulting in a cold and blue limb. In support of this view, superficial veins in the affected limb are more responsive to adrenergic stimulation than veins in the contralateral limb [2]. This increased responsiveness seems not to invariably involve changes in α_1-adrenoceptor density on blood vessels, as their bilateral expression was similar to that of healthy controls in patients with CRPS type I or II [36, 44, 49]. Augmentation of the responsiveness rather than increased density of adrenoceptors on vascular smooth muscle might be the best explanation [122]. For example, the presence of adrenoceptor supersensitivity, in conjunction with normal (or reduced) levels of cutaneous noradrenaline in chronic CRPS [116], might explain the cold and bluish limb in chronic CRPS.

At first glance, it seems plausible that these sympathetic mechanisms (i.e., denervation supersensitivity of blood vessels) are responsible for a decreased tissue hypo-oxygenation and possible acidosis in the affected limb [71], perhaps in combination with endothelial dysfunction [46, 104]. Sympathetic denervation alone does not affect endothelial function [19], but possibly impacts in conjunction with inflammatory mechanisms as discussed above [30, 78]. That the sympathetic deficit alone cannot explain the sympathetic disturbances in CRPS is illustrated by CRPS mimicked by forced immobilization of a limb in healthy subjects. In particular, skin temperature increased in the immobilized limb; however, limb immobilization did not influence vasoconstrictor responses to mental stress or deep breaths [115].

In addition to investigations of adrenoceptor density in blood vessels, adrenoceptor density has been investigated in sweat glands, nerve bundles and epidermal cells of CRPS-affected skin [49]. Expression of α_1-adrenoceptors on sweat glands was similar in patients with CRPS and healthy controls. However, α_1-adrenoceptor expression was greater on dermal nerve fibers and epidermal cells in CRPS-affected skin compared to healthy controls [49]. Interestingly, in patients with CRPS-I, this was seen in both the CRPS limb and the contralateral limb, whereas it was present in only the CRPS limb in CRPS-II. This might reflect a more systemic response to injury in CRPS-I or a preexisting vulnerability in CRPS-I. Pain intensity was associated with the staining intensity of adrenoceptors in epidermal cells [49]. Epidermal cells such as keratinocytes influence nociception by releasing ligands including proinflammatory mediators that act on sensory nerve fibers [65, 76, 130]. Thus, the heightened expression of adrenoceptors on keratinocytes and nociceptors may augment inflammatory disturbances and pain after limb injury as shown in Fig. 1. However, this will need to be investigated further.

Systemic and/or central autonomic disturbances

Although regional venous noradrenaline levels are lower in the affected than the contralateral limb [43, 59], elsewhere in the circulation catecholamine plasma levels (norepinephrine and epinephrine) appear to be higher in patients with CRPS than in healthy controls [60]. Accordingly, heart rate is increased and heart rate variability reduced in CRPS patients compared with healthy controls [5, 117]. This could be a specific autonomic manifestation of CRPS but might also be linked to pain, anxiety or stress. In any case, high systemic levels of catecholamines may contribute to sympathetic disturbances and pain in the CRPS-affected limb by acting on upregulated α_1-adrenoceptors on nerve bundles and epidermal cells [36], as displayed in Fig. 1. Consistent with this, intradermal injection of the α_1-adrenoceptor agonist phenylephrine evoked prolonged pain and pinprick hyperalgesia in patients with CRPS with greater expression of α_1-adrenoceptors on nerve bundles [44].

Central autonomic dysfunction

Very intriguing are findings which support the view that cortical mechanisms contribute to autonomic disturbances in CRPS. For example, simply thinking about moving the painful limb increased pain and swelling in both CRPS patients and pain controls. In CRPS, this was more so in patients with chronic symptoms, catastrophic thoughts about pain and movement, and autonomic arousal in the initial stages of imagined movement [88]. In patients with cold-type CRPS of one hand, the position of the CRPS hand in relation to the body midline influenced its temperature. Temperature increased and pain decreased in the CRPS hand when it crossed the midline to the healthy body side [87]. Intriguingly, this was found to depend on the perceived rather than the actual position of the hands in relation to the body midline—specifically, when patients wore prism glasses to laterally shift the visual field by 20°, the affected hand warmed up when it was perceived to be on the healthy side of the body midline, whereas the healthy hand cooled down when it was perceived to be on the affected side of the body midline even when the hand had not physically crossed the midline [86]. That is, the cortical representation of the hands in relation to the body midline not only modulated pain but also influenced temperature [87, 113].

To investigate the central component of autonomic symptoms in CRPS, patients with CRPS type I were compared with stroke patients whose sympathetic symptoms

(temperature asymmetry, sweating abnormalities) in the paretic limb originated centrally. Similar patterns of autonomic dysfunction, with decreased temperature and increased thermoregulatory sweating in the affected limb, were found in patients with stroke and chronic CRPS, suggesting that these symptoms can be explained, at least in part, by central nervous system pathology [97]. Accordingly, findings of cortical changes (gray matter atrophy) in brain regions controlling autonomic functions such as the ventromedial frontal cortex and the right anterior portion of the insula in patients with CRPS [50] also suggest a central origin of autonomic dysfunction in CRPS. These cortical changes strengthen with pain duration and intensity. Reduced right anterior insula activity is seen in patients with autonomic failure [25, 26], suggesting that the insula regulates autonomic function. The ventromedial prefrontal cortex projects to the hypothalamus and the brain stem, which link emotional responses with autonomic bodily reactions and pain. Thus, the ventromedial prefrontal cortex may play a role in both pain and widespread autonomic abnormalities in CRPS [50].

Generalized pattern of sympathetic dysfunction

Symptoms such as sweating and changes in temperature and skin color, together with pain, may spread beyond the affected limb to the opposite limb or from an arm to a leg [83]. The prevalence of this is unknown, but may be related to a longer disease duration [121]. Consistent with generalized sympathetic dysfunction, rewarming after a cold challenge was impaired in the non-symptomatic limb of patients with reflex sympathetic dystrophy (a diagnostic forerunner of CRPS) [64]. Similarly, a diminished vasoconstrictor response to an inspiratory gasp and contralateral cooling was found in the affected and to a minor degree in the contralateral hand of posttraumatic CRPS patients [107, 108, 123]. In addition, cooling either the contralateral or affected hand failed to reduce nail-fold skin capillary blood cell velocity or skin blood flow in either hand, unlike in healthy controls [99, 100]. In contrast, vasodilatation to local heating appeared to be unimpaired [55]. Together, these findings suggest bilateral autonomic disturbances in CRPS rather than a disturbance limited to the CRPS-affected limb.

Link between autonomic and immune disturbances in CRPS

In response to the trauma, during the acute stage of CRPS, activation of the innate immune system appears to be associated with proliferation and activation of mast cells and keratinocytes, release of inflammatory mediators (e.g., cytokines, neuropeptides) and exaggerated nociceptive signaling [9]. Antigen-presenting cells, such as dendritic cells, are a major source of proinflammatory cytokines, which are key drivers of the proinflammatory cascade. Under normal conditions, norepinephrine inhibits the production of proinflammatory cytokines, including TNF-α, from these cells by acting on ß-adrenoceptors [56]. However, epidermal dendritic cells also express α_1-adrenoceptors [110], and these receptors additionally become expressed in inflamed lymphoid tissue and on circulating lymphocytes in patients with chronic inflammatory disease [68]. In particular, the expression of the α_{1A}-adrenoceptor subtype is driven by inflammatory mediators such as TNF-α and IL-1β [62]. In turn, exposure to norepinephrine increases the production of the proinflammatory cytokine interleukin-6 (IL-6) in cells that express these α_1-adrenoceptors [62, 101].

Cutaneous nerve fiber density appears to be compromised in CRPS, not only in the affected limb [90] but also in the contralateral unaffected limb [85, 96], perhaps as a predisposing factor prior to injury or as a response to inflammation or endothelial dysfunction (see Fig. 1). Although not addressed in studies of CRPS, the relationship between reduced cutaneous nerve fiber density, skin inflammation and endothelial dysfunction has been convincingly demonstrated in several studies of other conditions [24, 79]. Reduced cutaneous nerve fiber density may compromise chemotactic signaling between nerve fibers and mast cells, as a bilateral reduction in dermal nerve fiber density in CRPS was accompanied by a bilateral reduction in proximity between surviving nerve fibers and dermal mast cells [85]. This could be important, as mast cells are involved not only in innate and acquired immunity but also in all phases of wound healing [31]. Thus, failure of mast cell–nerve fiber communication could prolong inflammation and delay healing. Activation of α-adrenoceptors hinders the production of nerve growth factor [95]. Hence, an upregulation of α-adrenoceptors could inhibit the production of nerve growth factor and neurite outgrowth in CRPS, thereby compromising communication with mast cells [85]. The reduced cutaneous nerve fiber density in CRPS may also be associated with the aberrant sympathetic responses mentioned earlier [2].

The prevalence of agonistic autonomic receptor autoantibodies is high in CRPS [52]. Specific immunoglobulin G serum autoantibodies, which activate β2 adrenoceptors, or M2 muscarinic receptors, were first identified in early CRPS. The antibody effects on live cells were blocked by co-application of synthetic peptides located on these receptors' second extracellular loops [72]. Enzyme-linked immunosorbent assays (ELISAs) coated with these peptides detected CRPS sera with high specificity and sensitivity [7]. Surface binding was confirmed by flow cytometry in most preparations. These autoantibodies belonged to IgG1-3 subclasses, and there was no cross-reactivity between them [63]. More

recently, the effects of serum immunoglobulins derived from patients with long-standing CRPS were examined in adult rodent cardiomyocytes. Findings showed activation of either α_{1A} adrenoceptors or muscarinic receptors. These activating antibodies bound with high affinity [45]. Subsequent flow cytometric and spectrofluorometric analysis suggested the presence of distinct pathways of antibody-induced α_{1A} adrenoceptor activation. Additional approaches for identifying autoantibodies in CRPS include the in vivo passive transfer trauma model and in vitro studies on primary dorsal root ganglion neurons. In small studies, rodents that received injections of CRPS patient IgG, unlike animals that received control IgG injections, developed significantly enhanced mechanical hyperalgesia and swelling only in injured hindpaws [53, 114]. This finding suggests that pathogenic autoantibodies may develop their activity only in the context of injury, consistent with the posttraumatic development of CRPS.

Consistent with the autoantibody hypothesis, visceral autonomic complaints such as voiding dysfunctions or urinary incontinence, diarrhea and constipation have been reported in patients with CRPS type I [18, 23, 120]. Alternatively, this widespread autonomic impairment could involve a redistribution of target receptors (e.g., α_1-adrenoceptors) [32, 44, 49].

Do sympathetic disturbances contribute to pain in CRPS?

Normally, activation of the sympathetic nervous system is not associated with pain [3, 48], and primary afferent Aδ fibers and C fibers are not activated or sensitized by sympathetic activity [48, 67]. However, intradermal injection of the neurotransmitter noradrenaline is painful in a subgroup of patients with CRPS [1, 118]. In a recent international multisite study [44], immunohistochemistry was used to investigate the distribution of α_1-adrenoceptors on nerve fibers and other targets in the affected skin of 90 patients, and in relation to pain and pinprick hyperalgesia evoked by intradermal injection of the α_1-adrenoceptor agonist phenylephrine. Expression of α_1-adrenoceptors in nerve bundles was greater on the affected side in patients with CRPS II than in those with CRPS I, particularly within the distribution of the injured nerve, and was greater during the first 12 months of CRPS than later on. In addition, neuronal expression of α_1-adrenoceptors in the CRPS-affected limb was greater in patients who reported prolonged pain and pinprick hyperalgesia around the phenylephrine injection site than in patients with transient pain after the injection, suggesting that these receptors mediate pain and hyperalgesia in a subgroup of patients, as shown in Fig. 1. Conversely, the α_1-adrenoceptor antagonist prazosin inhibited allodynia and hyperalgesia when applied topically to the affected area in patients with an adrenergic component of pain [33].

Posttraumatic inflammation, as discussed in the introduction, might be a co-contributor to sympathetically maintained pain in CRPS, as the sprouting of sympathetic nerve fibers in dorsal root ganglia [84, 94] or in the upper dermis of the skin [102] may be triggered by inflammatory mediators or growth factors [127] which are released in response to the initial trauma (see Fig. 1). Alternatively, another mechanism might be via prostaglandin production, as noradrenaline stimulates de novo synthesis of prostaglandin E2 and prostaglandin I2 in vitro by sympathetic postganglionic neurons [54]. Further possibilities as to how posttraumatic inflammation impacts on sympathetic function include an influence of inflammatory mediators such as TNFα and IL-1β on α-adrenoceptor populations [61] or on access of agonists to these receptors within nerve fascicles [34, 35]. In addition, noradrenaline could directly activate α_1-adrenoceptors on lesioned or regenerating nociceptive afferents [28, 36, 49], in turn triggering the release of neuropeptides from peptidergic nociceptors [77] and contributing to neuropeptide release and neurogenic inflammation and nociceptor activation [51, 66]. Consistent with this possibility, intradermal injection of the α_1-adrenoceptor agonist phenylephrine evoked prolonged pain and hyperalgesia in patients with elevated expression of neural α_1-adrenoceptors in the CRPS-affected limb [44]. However, the contribution of sympathetic activity to pain in CRPS appears to decline with progression of the disease [103].

Stimuli that activate the sympathetic nervous system, such as mental stress, sensory conflict, acoustic startle or skin cooling, increase pain in the majority of CRPS patients [12, 15, 69, 70]. In contrast, these stimuli reduce heat hyperalgesia in the capsaicin-sensitized skin of healthy volunteers [42]. Cutaneous sympathetic vasoconstrictor outflow increases strongly during whole-body cooling. In a study of patients with CRPS type I [3], the intensity and area of spontaneous pain and mechanical hyperalgesia increased during whole-body cooling in patients in whom pain decreased after sympathetic blockade, but did not change in patients without this therapeutic response. Since the pain reduction after sympathetic blocks was greater than the pain increase after body cooling, the authors concluded that sympathetic–nociceptive coupling is not restricted to the skin but also takes place in the deep somatic tissue. Similarly, conflicting sensory (visual) stimuli, such as the Necker cube, increased pain in conjunction with abnormal autonomic activity (asymmetric vasomotor responses) in CRPS patients [22]. However, electrophysiological investigation of the interaction between 54 nociceptive afferent and sympathetic efferent fibers with microneurography failed to show a direct link in 11 patients with CRPS type II or 13 patients with CRPS type I [16]. Therefore, indirect mechanisms of arousal–pain

interaction (e.g., an increase in muscle tone that activates deep somatic sensitized afferents [103]) must be also considered. Randomized controlled studies on the efficacy of sympathetic blocks which include an appropriate number of CRPS patients are urgently needed to determine the clinical usefulness of sympathetic blocks [89].

Importantly, in some patients, stimuli that increase sympathetic activity result in pain even after effective regional sympathetic blockade [37], implying that a mechanism independent of peripheral sympathetic neuronal activity in the CRPS-affected limb contributes to pain in these patients. Catecholamines circulating in the bloodstream could conceivably activate upregulated α_1-adrenoceptors on nociceptive afferents in the symptomatic limb. Alternatively, arousal responses might disrupt activity in central pain modulation pathways. For example, this might involve diminished activity in bulbospinal pain-inhibitory pathways or enhanced activity in pain-facilitatory pathways, as both of these pain modulation processes appear to be compromised, at least in chronic CRPS [109]. Decreased adaptation to repetitive noxious electrical stimulation was, for instance, reported for both the CRPS limb and the contralateral limb compared to healthy controls, indicating reduced inhibition of nociceptive input. In addition, an increased area of pinprick hyperalgesia appeared in the CRPS limb, consistent with increased facilitation of nociception [109]. Similarly, pressure sensitivity increased or remained stable in the forehead of patients with CRPS during noxious cold water immersion of a limb, whereas pressure sensitivity decreased in the forehead of healthy volunteers [69]. However, the ability to inhibit nociceptive input appeared to be intact in acute CRPS [74].

Hyperalgesia and allodynia in the CRPS-affected limb appear to be associated with hemisensory or upper quadrant deficits [98], indicative of functional disturbances in nociceptive processing in the thalamus. Intriguingly, nociceptive sensitivity to mechanical and thermal stimuli is greater on the symptomatic than the non-symptomatic side of the body in the majority of patients [38, 40, 69]. Furthermore, increases in pain evoked by acoustic startle and forehead cooling are greater when these stimuli are presented on the symptomatic than on the non-symptomatic side of the body [39, 69]. Hence, pain modulation processes may fail on the symptomatic side.

Conclusions

It now seems clear that immune reactions, alterations in receptor populations and/or central changes in autonomic drive contribute to local and systemic disturbances in autonomic activity and to sympathetically maintained pain in CRPS. This complex scenario, highlighted in our review and visualized in Fig. 1, raises several questions for future research. For example, how does sympathetic activity interact with inflammation, and why does the inflammatory response and the sympathetic contribution eventually subside? Is the decrease in sympathetic vasoconstrictor activity in the symptomatic limb a direct response to injury or part of a broader systemic disturbance? What role does nonuse of the injured limb play in producing symptoms? Answering these questions is important, because a clearer understanding of autonomic disturbances in CRPS could lead to new and successful treatment approaches.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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