REVIEW ARTICLE

Current Understandings on Complex Regional Pain Syndrome

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■ **Abstract:** The mechanisms underlying complex regional pain syndrome (CRPS) have been increasingly studied over the past decade. Classically, this painful and disabling disorder was considered to emerge from pathology of the central nervous system. However, the involvement of additional peripheral disease mechanisms is likely, and recently these mechanisms have also attracted scientific attention. The present article provides an overview of the current understandings regarding pathology of the autonomic and somatic nervous system in CRPS, as well as the roles of neurogenic inflammation, hypoxia, and the contribution of psychological factors. Potential connections between the separate disease mechanisms will be discussed. Additionally, currently known risk factors for CRPS will be addressed. Insight into risk factors is of relevance as it facilitates early diagnosis and tailored treatment. Moreover, it may provide clues for further unraveling of the pathogenesis and etiology of CRPS. ■

Key Words: complex regional pain syndromes, CRPS (complex regional pain syndromes), reflex sympathetic dystrophy

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INTRODUCTION

The complex regional pain syndrome (CRPS) is a painful and disabling disorder that can affect one or more extremities. Usually, its onset is precipitated by a physical injury, for example, a fracture, sprain, or surgery.[1,2] The spectrum of symptoms and signs is broad, including pain and sensory dysfunction, characteristics of inflammation, impaired motor function, and trophic disturbances.[3] Differentiated by the presence of a demonstrated nerve lesion, CRPS can be classified into type I and type II, of which type I, without a nerve lesion, is the most common.[4] CRPS can impose great impact on the daily functioning and quality of life of the patient who suffers from it.[5]

Classically, CRPS has been regarded as a disorder of the central nervous system, with sympathetic dysfunction as its major pathogenic mechanism. Recently, the interest shifted toward the contribution of peripheral disease mechanisms, including inflammation and hypoxia. The present article aims to provide an overview of the current understandings on the pathogenic mechanisms that underlie CRPS. Additionally, risk factors and determinants as far as presently known will be summarized.

METHODS

Five disease mechanisms were prespecified as theoretic main contributors to CRPS. The choice of mechanisms was based on discussions with internal and external

CRPS experts, including the investigators within Trauma RElated Neuronal Dysfunction, a Dutch government-funded knowledge consortium that integrates research on CRPS-I (BSIK03016). The prespecified mechanisms included: (1) autonomic (sympathetic) nervous system dysfunction, (2) somatic nervous system dysfunction, (3) inflammation, (4) hypoxia, and (5) psychological factors.

For each mechanism a separate search was conducted in Medline, using the query *Complex Regional Pain Syndromes [MAJR] or sudeck* combined with one of the following queries: for autonomic nervous system dysfunction, *sympathetically maintained pain or adrenerg* or sympathetic nervous system*; for somatic nervous system dysfunction, *sensitization or neuropathic pain or motor*;* for inflammation, *inflammation or cytokine or neuropeptide*; for hypoxia, *hypoxia or ischemia or vascular or microcirculation or free radical;* and for psychological factors, *psychology or psychiatry or behavior*. Case reports and nonresearch articles were excluded. All recovered abstracts (419 in total) were screened manually. Full text articles were studied if the abstract suggested an experimental or observational study design focused on the etiology or pathogenesis of CRPS, a review that discussed one or more of the pathogenic mechanisms, or a clinical trial regarding therapy.

Second, with the purpose to overview known determinants and risk factors, the query *Complex Regional Pain Syndromes [MAJR] or sudeck* was combined with the following terms: *incidence, epidemiology, risk factor, genetics, infection, autoimmunity,* and *comorbidity*. Case reports as well as all other types of research articles were included. Again, abstracts were screened manually, and full text papers were considered if the abstract suggested an association between CRPS and any risk factor.

Only articles written in English or Dutch that were published in the past 10 years (after 1998) were included. The retrieved literature was supplemented with referenced articles from the original yield or with manuscripts that were not indexed in Medline but that were known otherwise by one of the authors.

PATHOGENESIS AND ETIOLOGY

Autonomic Nervous System

Increased sweating, trophic changes, and vasoconstriction-related coldness of the affected limb have long been considered as results of autonomic (sympathetic) hyperactivity. Additionally, in the past, the phenomenon called sympathetically maintained pain (SMP) was considered almost synonymous with CRPS. In SMP, painful sensations are provoked by sympathetic outflow through sympathetic-afferent coupling in which adrenergic receptors are expressed on primary afferent nerve endings.[6,7] The classic treatment of CRPS with sympatholytic blocks was aimed to attenuate the pain and vasoconstriction induced by sympathetic hyperactivity.

However, the role of sympathetic dysfunction in CRPS has currently become somewhat debatable. Sweating and trophic disturbances are not the most predominant features of CRPS[3] and can also be explained as neuropeptide effects[8] (see later). Vasoconstriction does not always reflect sympathetic activity,[9] and alternate mechanisms than sympathetic overstimulation may account for the observed vasotonic impairments.[10,11] SMP may result from pathological failure of spinal inhibitory mechanisms to suppress nociceptive input by normal, instead of increased, sympathetic stimulation.[12] Finally, from a clinical viewpoint, many CRPS patients do not benefit from sympatholytic blocks.[13]

Apart from the actual role of sympathetic dysfunction in CRPS, the mechanism behind it also has become subject to controversy. Increased sympathetic outflow (hyperactivity) is one possibility. Abnormal sensitivity of adrenergic receptors for normal sympathetic outflow is another.[14,15,16] The first mechanism is endorsed by the observation that central sympathetic arousal provokes pain and abnormal vasoconstriction patterns in CRPS.[17,18] Additionally, the sympathetic skin reflexes in CRPS patients are increased.[14] The underlying cause may be sprouting of new sympathetic nerves centrally in the dorsal horn[19] or peripherally in the upper dermis,[20] which can be triggered by inflammatory mediators or nerve injury.[21] On the contrary, adrenergic receptor hypersensitivity is plausible based on the observed increases of pain after intradermal norepinephrine injections in CRPS patients, but not in controls.[22] Moreover, the density of α-adrenoreceptors is enlarged in hyperalgesic skin from CRPS affected limbs,[23] while the sympathetic innervation of sweat glands and vasculature is abnormal.[24] Catecholamine levels in serum derived from the affected side of CRPS patients are usually decreased instead of elevated,[25] which argues in favor of a local hypersensitivity. Temporarily diminished sympathetic stimulation has been suggested as an underlying cause of the adrenergic receptor upregulation and sensitization in CRPS patients.[25,26]

A generally acknowledged view today is that SMP and sympathetic dysregulation can be, but are not, an

obligatory part of CRPS.[27] Sympathetic blocks still remain widely administered for the treatment of CRPS, with beneficial results in a subset of patients.

Somatic Nervous System

Pain and sensory disturbances in CRPS have been attributed to pathology of the sensory somatic nervous system. Histopathological changes in skin innervation have been described, such as a substantial loss of normal C and Aδ fibers, and the presence of fibers with aberrantly branched endings.[24] Compared with controls, a 29% reduction of axonal density was reported in CRPS affected skin.[28] Because of similarities in pain characteristics between CRPS and other neuropathic pain disorders, analogies in the underlying mechanisms of neuroplasticity and sensitization are generally assumed, although they have never been well studied particularly in CRPS patients.

Spinal neuronal sensitization can follow upon continuous nociceptive input or nerve injury, and comprises a state of hyperexcitability and disinhibition, causing a decreased stimulation threshold.[29] Eventually, this can cause a normally nonpainful stimulus to become painful. Animal models have revealed several biochemical processes that underlie spinal sensitization with roles for postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, and the neurokinin-1 (NK-1) receptor.[30] The actual contribution of these mechanisms to human CRPS is difficult to study as it would require investigation of spinal cord neuronal tissue. However, the NMDA-receptor antagonist memantine was effective in relieving pain and motor symptoms in CRPS patients.[31] Antiepileptics, however, that increase neuronal excitation thresholds and are applied generally for neuropathic pains, are only moderately effective in CRPS patients, as was demonstrated in one randomized crossover trial with gabapentin.[32]

In addition to spinal sensitization, supraspinal alterations in CRPS are also present, as suggested by findings of impaired perceptual learning[33] and of a relation between pain severity and impaired tactile discrimination.[34] Brain imaging studies have indicated changes of cerebral blood flow, particularly in the hypothalamus.[35,36] Some CRPS patients experience referred sensations[37,38] or body perception disturbances,[39–41] which are in line with studies that demonstrate altered brain activation patterns[42,43] and sensory mapping.[44,45]

CRPS affects not only afferent sensory systems; efferent motor pathways are also hampered, which leads to clinical signs of a decreased range of motion, involuntary movements, and dystonia.[46,47] Postsynaptic motor reflex inhibition was found impaired in CRPS patients.[48] Moreover, measures of cortical reorganization of motor units correlated with the extent of motor dysfunction.[49,50] Experiments using transcranial stimulation revealed hyperexcitability of both the sensory and motor cortex.[51,52] Based on all these findings, graded motor imagery and mirror therapy have been proposed as beneficial in CRPS treatment as these are considered to reconcile motor output and sensory feedback.[53,54] Beneficial effects of mirror therapy have indeed been observed in relatively small open-label studies.[54–56]

Inflammation

In the early phase, CRPS affected limbs often display the classic "dolor, rubor, calor, tumor" aspects of an inflammatory disorder. Despite the fact that this clinical presentation was appreciated for a long period, it was not until recently that inflammatory mediators actually were demonstrated as involved in CRPS. Classic inflammation is marked by typical immune cells such as lymphocytes, phagocytes, and mast cells, which excrete classic pro-inflammatory cytokines. In fluid derived from artificially produced blisters on CRPS affected extremities, compared to unaffected sides, levels of interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and tryptase were increased.[57,58] Analysis of blister fluid with a multiplex array, testing for 25 different cytokines, revealed an even stronger pro-inflammatory expression profile, with increased markers for activated monocytes and macrophages.[59] A pro-inflammatory cytokine expression profile was also demonstrated in liquor[60,61] (IL-1β and TNFα increased) and occasionally in venous blood[62,63] (messenger ribonucleic acid [mRNA] levels of TNFα and IL-2 increased; levels of soluble TNFα receptor increased; mRNA levels of anti-inflammatory cytokines IL-4, IL-6, and tissue growth factor-β decreased). Additionally, there is enhanced migration of injected radiolabeled autologous leukocytes or nonspecific immunoglobulins toward the CRPS affected location.[64,65] However, systemic parameters of inflammation that are usually applied in clinical settings, including white blood cell count and C-reactive protein, are normal in CRPS patients.[66,67]

Neurogenic inflammation is mediated by neuropeptides, which are excreted by nociceptive C-fibers in response to various triggers and which possess vasoac-

tive and immunologic properties.[8,68,69] The secretory nerve endings of these nociceptives are mainly located in the distal parts of extremities, the typical location for CRPS.[69] However, primary afferent depolarization can also induce neuropeptide release within the dorsal horn, where they can mediate central sensitization. Cardinal mediators in neurogenic inflammation are substance P (SP) and calcitonin gene-related protein (CGRP).[70] In rats, SP application induced or increased CRPS-like symptoms,[71,72] while in humans, CRPS patients' intradermal SP administration provoked abnormal plasma extravasation.[73] Both SP and CGRP have been measured systemically elevated in CRPS patients.[66,70,74] Bradykinin, another peptide involved in inflammation and peripheral nociceptor sensitization,[75,76] was four times higher in venous blood of CRPS patients compared with controls.[74] Neuropeptide Y and perhaps angiotensin converting enzyme (ACE) have been suggested as potential modulators of the neuroinflammatory responses.[77] The involvement of vasoactive intestinal protein has also been suggested but could not be demonstrated.[78] Compared with controls, CRPS patients displayed a facilitated neuroinflammatory response upon electrical C-fiber stimulation, even in the unaffected extremity, as measured by plasma protein extravasation and axon-reflex vasodilation.[79,80]

The important contribution of inflammation to CRPS is underlined by the successful reports from open-label studies on treatment with immunomodulating agents such as infliximab[81,82] and thalidomide.[83] Additionally, one clinical trial showed benefit from treatment with oral corticosteroids.[84]

Hypoxia

The presence of hypoxia in CRPS is endorsed by several observations. In skin, employing micro-lightguide spectrophotometry has revealed decreased capillary oxygenation,[85] and dermal microdialysis has demonstrated increased lactate levels.[86] In muscle, nuclear magnetic resonance spectroscopy revealed signs of acidosis and impaired high-energy phosphate metabolism.[87] CRPS affected limbs display histopathological characteristics consistent with oxidative stress.[88] Hypoxia leads to acidosis and free radical formation, which are well-known triggers for primary afferents to cause severe painful sensations. In CRPS patients, experimentally induced tissue acidosis increased pain.[89] However, blood oxygen was not deprived as was demonstrated with capillary blood gas analysis.[90]

Hypoxia in CRPS has been proposed to be caused by extreme vasoconstriction, either sympathetically thriven (see before) or resulting from a local dysbalance between endothelial factors.[91] In the latter case, nitric oxide (NO) and endothelin (ET-1) are opposite mediators, whereas NO induces vasorelaxation and ET-1 induces vasoconstriction. In CRPS patients, venous ET-1 levels were found equal between the affected and unaffected sides,[10] but in blister fluid, ET-1 levels were increased at the affected side, while NO levels were decreased.[11] As these were findings in chronic CRPS patients, they suggest a role of hypoxia induced by endothelial dysfunction in ongoing CRPS. Consequently, NO donors have been proposed as therapeutic agents.[92]

In addition to sustaining chronic cold CRPS, acute hypoxic injury might also contribute to CRPS induction. In an animal model for CRPS, called the chronic post-ischemia pain model, rats develop CRPS-like symptoms, including swelling, hyperemia, and allodynia, after 3 hours of ischemia caused by tourniquet-binding of the hind limb, followed by rapid reperfusion.[93] In the model, neuropathic pain-like symptoms develop without microscopic-demonstrable nerve damage, similar to CRPS-I in humans. The authors have proposed triggering of afferents and initiation of inflammatory responses by free radicals, which are formed under oxidative stress. Although the model could not be fully reproduced by another research group that used an alternate method for ischemia induction,[94] the involvement of free radicals is likely in view of the positive outcomes of randomized clinical trials in human CRPS wherein scavengers, such as dimethylsufoxide,[95] N-acetylcysteine,[95] and vitamin C,[96] were effective in the early treatment.

Psychological Factors

Psychological factors and behavioral aspects are thought to contribute to chronic pain disorders in general and to CRPS in particular.[97,98] In an extreme view, CRPS has been characterized as "a pseudoneurological disease, i.e. that many features of CRPS are manifestations of somatoform disorders, malingering, and psychiatric pathology."[99] Although "this view is now generally disregarded,"[100] experts do emphasize the need for psychological and behavioral therapy as part of optimal treatment programs for CRPS patients.[101] Still, the actual association between psychological factors and CRPS remains controversial because of the lack of methodological high-quality studies. Most studies do

not include prospectively collected data, have limited patient numbers, and lack a proper control group.[102,103] Few of the studies that addressed psychological factors in the etiology of CRPS have reported increased incidences of stressful life events in close relation to CRPS onset.[104–106] More studies have addressed psychological factors and personality in the *maintenance* (instead of onset) of CRPS, whereby occasionally high prevalences of anxiety, depression, somatization, and hypochondria were observed. However, the majority of studies showed no relation between psychological factors and CRPS,[105–107] not even in particular subgroups.[108]

A psychophysiological mechanism that possibly affects chronic pain in CRPS patients is the mode of anger expression. Anger-out, meaning the tendency to express anger overtly through verbal or physical means, was related with increasing pain in the affected extremity of CRPS patients, but not in controls.[109] Anger-out influences pain intensity in other chronic pain disorders and is assumed to act through reactive muscle activity and by inhibition of endogenous opioid antinociceptive systems activation. Another psychophysiological mechanism in CRPS may be the stress-induced release of catecholamines, which have been observed as systemically elevated in CRPS patients.[110,111] In a vicious circle, emotional distress can sustain the pain, but can also be a consequence of it as well. Affective distress indeed has been demonstrated to be a predictor of pain intensity in CRPS patients.[112]

Extreme fear for pain can lead to disuse of the affected extremity, thereby making a feasible contributor to the disease course of CRPS. Prolonged immobilization can cause a decreased active range of motion, diminished nutritive blood flow, and trophic alterations.[113] Physical therapy with graded activity, conducted at overcoming movement anxiety, is considered of great therapeutic value[114] as it stimulates desensitization for mechanical allodynia and prevents against accumulation of catecholamines, neuropeptides, and inflammatory mediators.[101]

RISK FACTORS AND DETERMINANTS

Demographics

Population-based incidence rates have been investigated in one North American[2] and one European[1] study. The U.S. study reported an incidence rate of 5.5 per 100,000 person-years, while the European study reported 26.2. The striking difference between both studies most likely results from differences in case validation methodology and reflects the importance of uniform diagnostic assessment and nomenclature. However, despite the varying incidence rates, some demographic characteristics were generally similar in both studies. CRPS affected women predominantly with a ratio approximating 3.5. Its onset ranges from childhood through old age, but most cases were seen between their 50s and 70s. It is generally believed that CRPS occurs mainly in Caucasian and Japanese people.[115]

Injury-Related Factors

Wrist fractures are considered the typical initiating trauma for CRPS, but the reported incidences after a wrist fracture vary broadly between 1% and 37%.[116,117] Incidences after other precipitating events vary as well, for example, between 0.7% and 21% after total knee prosthesis surgery,[118,119] and between 1.6% and 48.8% after a stroke.[120,121] The estimated incidence rates appear highly dependent on the applied diagnostic criteria, as well as the time between trauma and assessment of CRPS.[119]

Case reports describe the onset of CRPS after a wide subset of events, including any type of common or iatrogenic injury, cardiovascular events, cancer, infections, and medications.[122] Spontaneous CRPS is rare,[1,122] but does occur. In general, fractures are the most common precipitating events, and the upper extremity is more frequently involved than the lower.[1,118,119] Severity of the physical injury is not related to the risk of CRPS,[97,123,124] although in two studies CRPS patients more often had an intra-articular localization of the fracture.[125,126] Fracture repositions and external fixation are not associated with CRPS occurrence.[123,124] During cast immobilization, increased pressure and early complaints of tightness are predictive factors for the onset of CRPS.[125,127]

Genetics

The risk of CRPS may depend on susceptibility for exaggeration of the underlying disease mechanisms, such as inflammation and sensitization. This idea is supported by the observation of abnormal (neuro) inflammatory responses to triggers in the unaffected limbs of CRPS patients, such as an increased NO release from peripheral monocytes upon stimulation with cytokines[128] and an enhanced axon-reflex vasodilation upon electrical C-fiber stimulation.[79] As these were findings in the unaffected limbs, they suggest that the abnormal responses are innate and do not evolve from the CRPS itself. Hypothesizing that CRPS patients might share a pro-inflammatory genetic profile, polymor-

phisms have been studied of genes that code for potential mediators of inflammation in CRPS, including TNFα (increased in blisters from CRPS patients)[57,60] and ACE (modulator of SP and bradykinin).[129,130] Primarily warm CRPS was associated with a polymorphism in one of the TNFα promoter genes.[131] The ACE I/D polymorphism was increased in a small population of Japanese CRPS patients ($n = 14$),[132] but not in a larger, but still relatively small, European study ($n = 60$).[133] Polymorphisms in the human leukocyte antigen (HLA) system have also been studied, and loci from all three HLA classes have been reportedly associated with CRPS onset,[134,135] treatment resistance,[136] or related dystonia.[137] The associations with the HLA-DR and HLA-DQ polymorphisms were particularly remarkable in view of the similar findings in patients with multiple sclerosis and narcolepsy.[134–136]

Antecedent Infections

As CRPS is suggested to be (partly) the consequence of an exaggerated inflammatory response, an autoimmune approach of CRPS becomes feasible. The many existing case reports of CRPS onset in patients with an autoimmune disease underline this idea.[138–144] Bearing in mind the mechanisms of infection-induced cross-reactivity against autoantigens, some investigators have studied the prevalence of antecedent viral infections in CRPS patients. Two reports revealed increased seroprevalences of Parvo B19 IgG antibodies compared with healthy controls,[145,146] while one report revealed increased levels of IgG antibodies against herpes simplex viruses.[147] Increased immunoreactivity against *Campylobacter Jejuni* was observed in CRPS patients with recent onset.[148] CRPS, after *Lyme borreliosis*, has been described,[149,150] as well as after spirochetal infection.[151] Finally, rubella and hepatitis B vaccination have been noted in case reports to precede CRPS.[152,153] Recently, two studies have demonstrated the presence of autoantibodies against neuronal structures in CRPS patients,[148,154] but their actual contribution is not yet elucidated.

Related Disorders

Mainly, in case reports the co-occurrence of CRPS with other diseases was reported. Patients with bone metabolism disorders, including osteoporosis,[155] osteomalacia,[156] and osteogenesis imperfecta,[157,158] have been suggested as more susceptible for CRPS. However, they are prone for fractures and probably thereby for CRPS. Other case reports describe CRPS in patients suffering from chronic inflammatory disorders, such as rheumatic diseases.[138–144] CRPS as paraneoplastic phenomenon has been suggested twice.[159,160] Additionally, two publications report CRPS in a patient with amyotrophic lateral sclerosis[161,162] and one publication reports CRPS in patients with Ehlers-Danlos syndrome.[163]

A limited number of studies on CRPS-elated disorders have been conducted in relatively small study populations. One retrospective case-control study using questionnaires revealed headaches to be more than twice as common in CRPS patients, even before the actual onset of CRPS.[164] Furthermore, associations between psychiatric disorders and CRPS have been studied, although most of these studies are considered methodologically poor and address the influence on sustaining CRPS rather that the etiological contribution.[103,104] The results are contradictive, but associations between CRPS and depression, anxiety, and somatoform disorders have occasionally been described.[103,104,106,107,165]

DISCUSSION

Several distinct pathogenic mechanisms may contribute to the clinical syndrome that is currently named CRPS. Alternating in time, CRPS has been regarded as a disorder that was mainly based on a neurological, inflammatory, or psychosomatic etiology. In the past decade, significant progress has been made in the understanding of the separate disease mechanisms. Although sometimes speculative, paths for interaction between the different mechanisms can be hypothesized (Figure 1):

1. Hypoxia may trigger inflammatory responses.[93] *(Interaction: hypoxia ↔ inflammation [classic and neurogenic])*
2. Continuous nociceptive input by hypoxia,[89,91] inflammation,[21,62] or sympathetic stimulation[6,17,21,23] may lead to sensitization and alterations in cortical organization of sensory and motor units.[166] *(Interaction: hypoxia, inflammation, and autonomic dysfunction ↔ somatic neuronal dysfunction [sensitization and cortical reorganization])*
3. Neuropeptides (SP) released in the dorsal horn may facilitate sensitization through interaction with NK-1 and NMDA receptors.[8,70,167] *(Interaction: inflammation [neurogenic] ↔ somatic neuronal dysfunction [sensitization])*
4. Sympathetic dysfunction (either central sympathetic hyperactivity or increased peripheral adrenergic receptor hypersensitivity) may cause

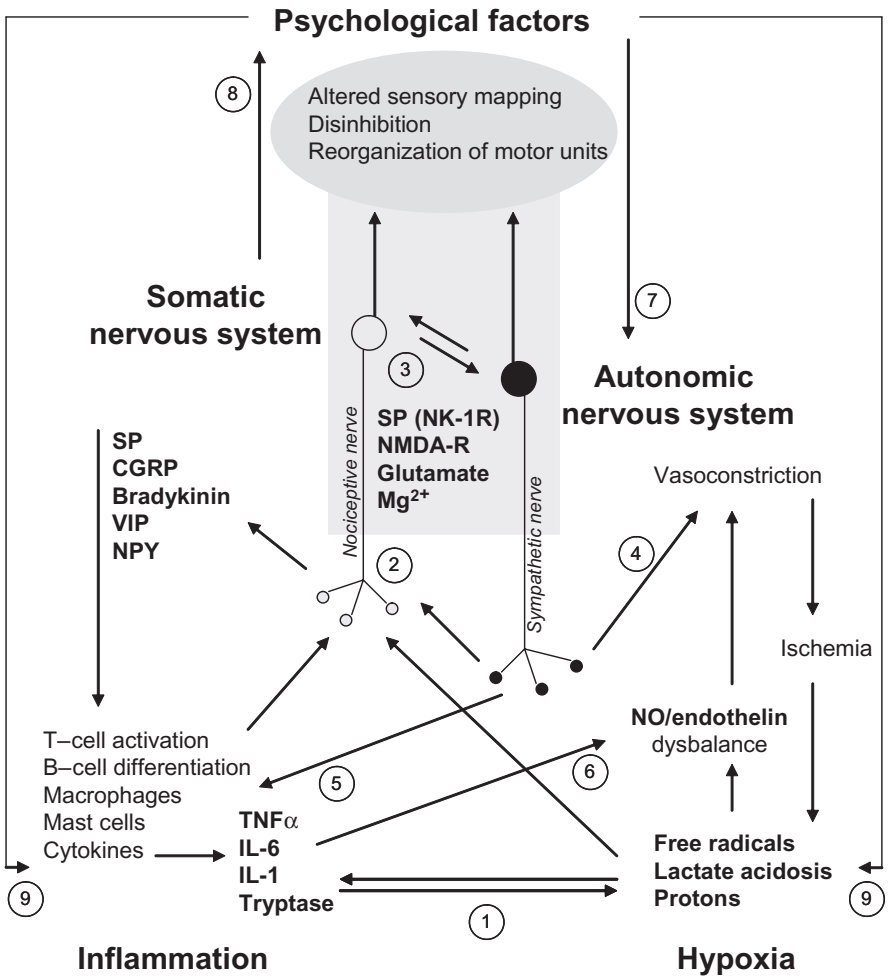

Figure 1. Interaction between the pathogenic mechanisms underlying CRPS. For explanation of the numbers, see the discussion section. CGRP, calcitonin gene-related protein; IL, interleukin; Mg^{2+}, magnesium ions; NK-1R, neurokinin-1 receptor; NMDA-R, N-methyl-D-aspartate receptor; NO, nitric oxide; NPY, neuropeptide Y; SP, substance P; TNFα, tumor necrosis factor α; VIP, vasoactive intestinal pain.

hypoxia because of impaired nutritive blood flow.[8] *(Interaction: autonomic dysfunction ↔ hypoxia)*

5. Adrenergic receptors can be expressed on immune cells, and catecholamines can modulate cellular immunity,[8,111,168] while it also has been speculated that inflammation may change sensitivity or expression of α-adrenergic receptors on nociceptive fibers.[169] *(autonomic dysfunction ↔ inflammation [classic])*
6. Cytokines influence the NO/ET balance.[170] *(Interaction [classic] inflammation ↔ hypoxia)*
7. Psychological distress may influence sympathetic outflow and levels of catecholamines.[16,110,111] *(Interaction: psychopathology ↔ autonomic dysfunction)*
8. Severe chronic pain and disability may cause psychological distress. *(Interaction: somatic neuronal dysfunction [sensitization] ↔ psychopathology)*
9. Fear of movement may result in the accumulation of inflammatory mediators and free radicals, and prevent desensitization.[101] *(Interaction: psychopathology ↔ inflammation and hypoxia and somatic neuronal dysfunction)*

The representation of CRPS as the sum, or even more than the sum, of several involved disease mechanisms makes sensible why CRPS is a disorder with varying clinical presentations and disease severity. However, while separate mechanisms may keep each other ongoing, the origin remains unclear. Are there premorbid alterations in the central nervous system that (genetically) predispose a person for CRPS at the moment of a trauma? Does the disease start with minimal peripheral nerve injury, making CRPS a specific kind of a neuropathic pain syndrome? Are the neuropathic pain symptoms secondary to ischemic injury or an exaggerated immunological response, perhaps subsequent to a viral infection or linked to autoimmunity? Or

is CRPS a somatoform disorder in emotionally unstable patients? Finally, is the initiating or predominant underlying mechanism the same for every patient, or does CRPS consist of many subtypes, all with different etiologies and pathogeneses, but with a clinical presentation that is much similar that they are all gathered under the same painful syndrome?

Apart from these questions addressing etiology, two other clinically relevant issues remain to be clarified. First, which patients develop CRPS? In order to answer this question, determinants and risk factors associated with CRPS need to be assessed. Until today, sound epidemiological studies that compare premorbid characteristics in a large cohort of CRPS patients to a valid control group have been performed scarcely. Of course such studies will encounter many challenges, for example, related to the relative low prevalence of CRPS and its poor diagnostic definition. Nonetheless, such efforts may provide very interesting new information that can lead to new insights in CRPS.

The second relevant issue addresses the lack of effectiveness of most current treatment strategies, despite their interference with plausible underlying disease theories. Considering the complex, multifactor pathogenesis of CRPS, it is understandable that not one single therapeutic modality is sufficient to attenuate all ongoing processes together. Additionally, it is well possible that not all disease mechanisms are equally prominent in each single patient. Finding a common factor that is relevant in all CRPS patients might be a challenging effort, but it would be highly interesting. If a candidate could be identified, it would likely be a general downstream compound in a biochemical pathway. It might not be specific for CRPS, and targeting it would interfere with important physiological processes and provoke unpleasant or even serious side effects. Nonetheless, if such a common factor should be found, then the balance between therapeutic and unwanted effects of targeting this factor needs to be investigated. For severely affected CRPS patients, side effects of therapy may outweigh the pain and disability, safety issues provided.

CONCLUSION

Based on the results from fundamental and clinical studies, it is reasonable to assume that mediators of different disease mechanisms are involved in a complex network of interactions, resulting in the painful and impairing disorder of CRPS. Although ongoing fundamental research is needed to further elucidate the molecular background, from both a clinical and etiological perspective, it is also of high importance to investigate determinants and risk factors for CRPS in epidemiological studies. Increased insight in predisposing factors may facilitate early diagnosis and improve the chance of good outcome, but it may also provide new clues for potential underlying mechanisms. The elucidation of a single biochemical factor common in all potential underlying disease mechanisms would offer a highly interesting target for pharmacotherapy.

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