An Update on the Pathophysiology of Complex Regional Pain Syndrome

Stephen Bruehl, Ph.D.*

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ABSTRACT

Complex regional pain syndrome (CRPS) is a neuropathic pain disorder with significant autonomic features. Few treatments have proven effective, in part, because of a historically poor understanding of the mechanisms underlying the disorder. CRPS research largely conducted during the past decade has substantially increased knowledge regarding its pathophysiologic mechanisms, indicating that they are multifactorial. Both peripheral and central nervous system mechanisms are involved. These include peripheral and central sensitization, inflammation, altered sympathetic and catecholaminergic function, altered somatosensory representation in the brain, genetic factors, and psychophysiologic interactions. Relative contributions of the mechanisms underlying CRPS may differ across patients and even within a patient over time, particularly in the transition from "warm CRPS" (acute) to "cold CRPS" (chronic). Enhanced knowledge regarding the pathophysiology of CRPS increases the possibility of eventually achieving the goal of mechanism-based CRPS diagnosis and treatment.

COMPLEX regional pain syndrome (CRPS) is the current diagnostic label for the syndrome historically referred to as reflex sympathetic dystrophy, causalgia, and a variety of other terms.[1] It is a chronic neuropathic pain disorder distinguished by significant autonomic features and typically develops in an extremity after acute tissue trauma. In addition to classic neuropathic pain characteristics (intense burning pain, hyperalgesia, and allodynia), CRPS is associated with local edema and changes suggestive of autonomic involvement (altered sweating, skin color, and skin temperature in the affected region). Trophic changes to the skin, hair, and nails and altered motor function (loss of strength, decreased active range of motion, and tremor) may also occur. CRPS is subdivided into CRPS-I (reflex sympathetic dystrophy) and CRPS-II (causalgia), reflecting, respectively, the absence or presence of documented nerve injury.[2] Despite this traditional diagnostic distinction, signs and symptoms of the two CRPS subtypes are similar, and there is no evidence that they differ in terms of pathophysiologic mechanisms or treatment responsiveness.

The results of two epidemiologic studies in the general population[3,4] indicate that at least 50,000 new cases of CRPS-I occur annually in the United States alone.[5] It is more common in women and with increasing age.[3,4] Although CRPS can develop virtually after any (even minimal) injury, the most common initiating events are surgery, fractures, crush injuries, and sprains.[6] CRPS patients experience not only intense pain but also significant functional impairments and psychologic distress.[7–11] In clinical settings outside of specialty pain clinics, CRPS may be underrecognized.[12]

CRPS is one of the more challenging chronic pain conditions to treat successfully.[13] There is no definitive medical treatment, and clinical trials have failed to support the efficacy of many commonly used interventions.[14–16] Because of the absence of other effective medical treatments, invasive and expensive palliative interventions are often used, such as spinal cord stimulation and intrathecal drug delivery systems, contributing to the high costs of managing CRPS. Lack of adequate treatments for CRPS has resulted in part from incomplete under-

* Associate Professor, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee.

Address correspondence to Dr. Bruehl: Vanderbilt University Medical Center, 701 Medical Arts Building, 1211 Twenty-First Avenue South, Nashville, Tennessee 37212. stephen.bruehl@vanderbilt.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

standing of its pathophysiologic mechanisms. Indeed, a National Institutes of Health State-of-the-Science Meeting on CRPS concluded that existing research on mechanisms of human CRPS is inadequate and that it has failed to capture adequately the complex nature of the condition observed in clinical patients.[17] Several issues regarding existing animal models of CRPS will first be briefly addressed, followed by more detailed presentation of current research regarding key mechanisms that may contribute to the clinical syndrome of CRPS.

Animal Models of CRPS

Although definitive human studies documenting CRPS pathophysiology are the ultimate goal, well-validated animal models of CRPS could also help to elucidate its pathophysiology and to provide opportunities for evaluating new pharmacologic options for CRPS management. Until relatively recently, animal models of CRPS were restricted to general neuropathic pain models, which at best might parallel CRPS-II (causalgia), that is, CRPS associated with clear evidence of a peripheral nerve injury. These models include the sciatic nerve ligation model[18] and the sciatic nerve resection model,[19] both of which can produce allodynia, hyperalgesia, edema, temperature changes, and trophic changes similar to CRPS-II. Although clearly useful as animal models of neuropathic pain in general, they do not adequately reflect CRPS-I, a syndrome of neuropathic pain associated with edema and autonomic features in the absence of clear nerve injury.

Animal models that may better reflect CRPS-I have been developed in the past several years, an important advance given that CRPS-I is much more common than CRPS-II. Availability of such animal models is important because they allow prospective evaluation of pathophysiologic mechanisms of CRPS-I after experimental injury. Two relatively recent models seem to produce a syndrome resembling CRPS-I with no evidence of nerve injury.[20] These models are the postfracture chronic pain model[21] and the ischemic reperfusion injury model (leading to chronic postischemic pain).[22] Evidence supports the potential utility of both models. For example, using the postischemic pain rat model of CRPS-I, enhanced nociceptive firing is observed in response to the presence of norepinephrine,[20] supporting the concept of sympatho-afferent coupling that has been suggested by several human CRPS studies (detailed in Altered SNS Function). Recent work using this model further suggests that a transcription factor, nuclear factor κB, could play a role in CRPS and may provide an upstream link between increased proinflammatory neuropeptides and increased proinflammatory cytokines in CRPS.[23] This potential mechanism has not yet been investigated in humans, and in this case, the animal model could point toward fruitful avenues of investigation in human CRPS-I patients.

The postfracture rat model of CRPS-I has also shown heuristic value, revealing that proinflammatory neuropeptides and cytokines contribute to allodynia, hyperalgesia, temperature changes, and edema similar to that observed in human CRPS-I.[21,24,25] Despite the research potential of

these animal models of CRPS-I, their validity is not without question. For example, in Wistar rats, neither ischemic reperfusion injury nor sham injury led to significant trophic changes, edema, differences in skin color or temperature, or other signs suggestive of CRPS-I.[26] Additional work is needed to determine the extent to which the various available animal models of CRPS successfully mirror clinical features and mechanisms underlying human CRPS. Moreover, direct comparisons between available animal models of CRPS-I and CRPS-II would be helpful to clarify the validity, advantages, and disadvantages of each. It should be noted that the pathophysiologic mechanisms detailed in the remainder of this review are based on the findings in both animal and human studies, with reliance on the latter where available.

Pathophysiologic Mechanisms of CRPS

Although multiple attempts have been made to reduce CRPS to a single pathophysiologic mechanism (*e.g.*, sympatho-afferent coupling),[27] it has become increasingly accepted that there are multiple mechanisms involved. Only in the past few years, has it been recognized that CRPS is not simply a sympathetically mediated peripheral pain condition but rather is a disease of the central nervous system as well.[28] Evidence for this comes from the fact that CRPS patients display changes in somatosensory systems processing thermal, tactile, and noxious stimuli, that bilateral sympathetic nervous system (SNS) changes are observed even in patients with unilateral CRPS symptoms and that the somatomotor system may also be affected.[28] There is some evidence that subtypes of CRPS may exist, reflecting differing relative contributions of multiple underlying mechanisms.[29] The remainder of this review will summarize the current findings regarding the CRPS mechanisms most widely accepted and documented in the literature (table 1).

Altered Cutaneous Innervation after Injury

It is now believed that even in CRPS-I, some form of initial nerve trauma is an important trigger for the cascade of events leading to CRPS.[30,31] This proposition is supported by the evaluations of skin biopsy samples obtained in patients with CRPS-I, in whom there were no clinical signs of nerve injury.[31,32] In one such study,[31] significantly lower densities of epidermal neurites (up to 29% lower) were observed in CRPS-affected limbs relative to contralateral unaffected limbs, with these changes affecting primarily nociceptive fibers. Similar asymmetry in neurite density was not observed between the affected and unaffected limbs of patients with unilateral non-CRPS pain conditions such as osteoarthritis.[31] Comparable findings were obtained in a separate study. Albrecht *et al.*[32] reported decreased C-fiber and Aδ-fiber density in the affected limbs of CRPS-I patients compared with nonpainful control sites on the same extremity and compared with healthy controls. Abnormal innervation around hair follicles and sweat glands was also observed.[32]

Findings such as those described earlier indicate that CRPS-I, in which there are no clinical signs of peripheral

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Table 1. Summary of Pathophysiologic Mechanisms that May Contribute to CRPS

Mechanism	Supporting Pattern of Findings
Altered cutaneous innervation	Reduced density of C- and Aδ-fibers in CRPS-affected region[31,32]
	Altered innervation of hair follicles and sweat glands in CRPS-affected limb[32]
Central sensitization	Increased windup in CRPS patients[37,38]
Peripheral sensitization	Local hyperalgesia in CRPS-affected *vs.* -unaffected extremity[43]
	Increased mediators of peripheral sensitization (see Inflammatory Factors later)
Altered SNS function	Bilateral reductions in SNS vasoconstrictive function predict CRPS occurrence prospectively[50,51]
	Vasoconstriction to cold challenge is absent in acute CRPS but exaggerated in chronic CRPS[46,55,61]
	Sympatho-afferent coupling[48]
Circulating catecholamines	Lower norepinephrine levels in CRPS-affected *vs.* -unaffected limb[55,62,63]
	Exaggerated catecholamine responsiveness because of receptor up-regulation related to reduced SNS outflow[63,64]
Inflammatory factors	Increased local, systemic, and cerebrospinal fluid levels of proinflammatory cytokines, including TNF-α, interleukin-1β, -2, and -6[72–76]
	Decreased systemic levels of antiinflammatory cytokines (interleukin-10)[74]
	Increased systemic levels of proinflammatory neuropeptides, including CGRP, bradykinin, and substance P[80–82]
	Animal postfracture model of CRPS-I indicates that substance P and TNF-α contribute to key CRPS features[21,24,25]
Brain plasticity	Reduced representation of the CRPS-affected limb in somatosensory cortex[85–89]
	These alterations are associated with greater pain intensity and hyperalgesia, impaired tactile discrimination, and perception of sensations outside of the nerve distribution stimulated[86,88,91]
	Altered somatosensory representations may normalize with successful treatment,[87,89] although other brain changes may persist[90]
Genetic factors	In largest CRPS genetic study to date (n = 150 CRPS patients),[109] previously reported associations were confirmed between CRPS and human leukocyte antigen-related alleles[105–109]
	A TNF-α promoter gene polymorphism is associated with "warm CRPS"[106]
Psychologic factors	Greater preoperative anxiety prospectively predicts acute CRPS symptomatology after total knee arthroplasty[39]
	Emotional arousal has a greater impact on pain intensity in CRPS than in non–CRPS chronic pain, possibly *via* associations with catecholamine release[7,119]

CGRP = calcitonin gene-related peptide; CRPS = complex regional pain syndrome; SNS = sympathetic nervous system; TNF = tumor necrosis factor.

nerve damage, is nonetheless associated with significant loss of C-fibers and Aδ-fibers in the affected area.[31,32] Available human studies cannot determine whether this neurite loss is related causally to the injury initiating CRPS, although results of one animal study support this view. A single needle stick injury (18-gauge needle) to the distal nerves in rats led to reductions in nociceptive neuron density of up to 26%,[33] a reduction similar in magnitude to the findings in human CRPS-I patients.[31,32] This animal study highlights the possibility that the altered distal extremity innervation observed in CRPS-I patients may be a result of the injury triggering CRPS. Whether reduced density of nociceptive neurites in human CRPS-I is an epiphenomenon or rather is directly related to expression of other characteristic CRPS signs and symptoms remains to be proven.

Central Sensitization

Persistent or intense noxious input resulting from tissue damage or nerve injury triggers increased excitability of nociceptive neurons in the spinal cord, a phenomenon termed central sensitization.[34] Central sensitization is mediated by the nociception-induced release of neuropeptides, such as substance P and bradykinin, and the excitatory amino acid glutamate acting at spinal *N*-methyl-D-aspartic acid receptors.[34,35] Central sensitization results in exaggerated responses to nociceptive stimuli (hyperalgesia) and permits normally nonpainful stimuli such as light touch or cold to activate nociceptive pathways (allodynia).[34] An objective measure associated with central sensitization is windup, which is reflected in increased excitability of spinal cord neurons that is evoked by repeated brief mechanical or thermal stimulation occurring at a frequency similar to the natural firing rate of nociceptive fibers.[36] CRPS patients display significantly greater windup to repeated stimuli applied to the affected limb than on the contralateral or other limbs.[37,38]

It is not known whether central sensitization precedes, follows, or cooccurs with development of other CRPS signs and symptoms. Previous prospective work found that greater knee pain intensity before undergoing total knee arthroplasty

predicted who developed CRPS at 6-month follow-up.[39] To the extent that higher clinical pain intensity might be a marker of greater central sensitization,[34] these findings suggest the possibility that increased central sensitization might contribute to later development of CRPS. This possibility remains to be tested directly.

Peripheral Sensitization

Although persistent nociceptive input after tissue injury triggers central sensitization processes in the spinal cord and brain, the initial tissue trauma itself also elicits local peripheral sensitization.[40] After tissue trauma, primary afferent fibers in the injured area release several pronociceptive neuropeptides (e.g., substance P, bradykinin; see Inflammatory Factors for additional information) that increase background firing of nociceptors, increase firing in response to nociceptive stimuli, and decrease the firing threshold for thermal and mechanical stimuli.[40,41] These latter two effects contribute, respectively, to the hyperalgesia and allodynia that are key diagnostic features of CRPS.[42] Local hyperalgesia likely resulting from both peripheral and central sensitization can be seen in findings of significantly reduced acute pain thresholds in the affected extremity of chronic CRPS patients compared with their unaffected extremity.[43] Given that peripheral sensitization is triggered by the initial tissue trauma leading to persistent pain, it is likely that it is present in CRPS patients very early in the development of the condition. However, its role in the development of CRPS has not been tested directly.

Altered SNS Function

Historically, it was assumed that common autonomic features of CRPS, such as a cool, bluish limb, were the result of vasoconstriction reflecting excessive SNS outflow and that the pain in CRPS was sympathetically maintained.[27] The presumed role of excessive SNS outflow in key CRPS characteristics was the traditional rationale for clinical use of selective sympatholytic blocks (e.g., stellate ganglion) for pain and symptom relief in CRPS patients. Possible reasons for links between CRPS pain and SNS activity have been suggested. Animal studies indicate that after nerve trauma, adrenergic receptors are expressed on nociceptive fibers, providing one mechanism by which SNS outflow might directly trigger nociceptive signals.[44,45] Given that even in CRPS-I, some type of nerve trauma seems to be involved in onset of the condition,[30,31] expression of adrenergic receptors on nociceptive fibers might help to explain the impact of SNS outflow on CRPS pain.

Expression of adrenergic receptors on nociceptive fibers after injury may contribute to sympatho-afferent coupling, a phenomenon demonstrated in several human studies. For example, forehead cooling (which elicits systemic SNS vasoconstrictor activation) and intradermal injection of norepinephrine both significantly increase CRPS pain intensity.[46,47] Experimental manipulations of SNS vasoconstrictor function using whole body cooling and warming also support sympatho-afferent coupling.[48] Specifically, in patients with sympathetically maintained CRPS pain, high (relative to low) SNS activity increased spontaneous pain by 22% and increased the spatial extent of dynamic and punctate hyperalgesia by 42 and 27%, respectively.[48] Follow-up work using this same methodology suggests that SNS innervation of deep somatic structures may be more important than cutaneous SNS innervation as a determinant of sympatho-afferent coupling in the acute phase of CRPS.[49] Although using a cross-sectional rather than prospective design, examination of the pattern of results in this latter study as a function of pain duration suggested that the SNS-mediated component of CRPS pain may diminish over time.[49]

Although the findings regarding sympatho-afferent coupling indicate that CRPS pain and other symptoms may in some cases be linked to SNS activity, they do not necessarily imply that excessive SNS outflow is responsible. Indeed, the only prospective human studies on the issue of SNS function in CRPS do not support this common clinical assumption. Schürmann et al.[50] assessed SNS function (peripheral vasoconstrictor responses induced by contralateral limb cooling) in unilateral fracture patients shortly after injury. Development of CRPS 12 weeks later was predicted by early impairments in SNS function (reduced vasoconstrictor response). Impaired SNS function was observed before the onset of CRPS on both the affected and unaffected sides, suggesting systemic alterations in SNS regulation shortly after injury. These findings are confirmed by more recent work examining CRPS incidence after carpal tunnel surgery in patients with previously resolved CRPS.[51] Among asymptomatic former CRPS patients who displayed impaired vasoconstrictive responses to SNS challenge before surgery, 73% had a postsurgical recurrence of CRPS. In contrast, among patients showing normal SNS vasoconstrictive responses before surgery, only 13% developed a recurrence of CRPS. As in the study by Schürmann et al.,[50] SNS impairments in the former group were generally bilateral (82% patients). Cross-sectional studies in patients with acute CRPS further confirm findings of impaired SNS function relative to pain patients without CRPS.[52,53] Reduced SNS function (and the resulting excessive vasodilation) in early acute CRPS would help to account for the observation that acute CRPS is most often associated with a warm, red extremity rather than the cool, bluish presentation often noted in chronic CRPS.[50,54]

Other work indicates that whole body cooling and warming produce symmetrical vasoconstriction and vasodilation in healthy controls and non-CRPS pain patients but elicit dysfunctional SNS thermoregulatory activity in CRPS patients.[55] Vasoconstriction to cold challenge in this study was absent in patients with acute CRPS ("warm CRPS"), but it was exaggerated in patients with chronic CRPS ("cold CRPS").[55] Although controlled studies have failed to find evidence to support Bonica's[56] traditional three sequential stages of CRPS,[29,57] a transition from a warm, red CRPS presentation to a cold, bluish CRPS presentation is common as CRPS moves from the acute to the chronic state.[55] It

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should be noted that vascular abnormalities in CRPS may be impacted by non-SNS mechanisms as well. Studies suggest that chronic CRPS patients exhibit impaired endothelial-dependent vasodilatory function and altered levels of endothelin-1, nitric oxide, and nitric oxide synthase.[32,49,58–60]

Role of Circulating Catecholamines

Changes in the pattern of CRPS signs and symptoms as the condition moves from the acute to the chronic phase may in part reflect a progression in catecholaminergic mechanisms. Despite evidence that chronic CRPS patients often display exaggerated vasoconstriction to cold challenge on the affected side,[46,55,61] they nonetheless exhibit lower norepinephrine levels on the affected side compared with the unaffected side.[55,62,63] These lower norepinephrine levels may imply diminished local SNS outflow. Taken together, these findings suggest that the exaggerated vasoconstrictive responses observed in chronic CRPS patients may occur even in the context of reduced SNS outflow. It is believed that this paradoxical pattern may be a result of receptor up-regulation, that is, the decreased SNS outflow noted earlier in acute CRPS would be expected to lead to compensatory up-regulation of peripheral adrenergic receptors.[63,64] The resulting supersensitivity to circulating catecholamines may then lead to exaggerated sweating and vasoconstriction on exposure to circulating catecholamines (*e.g.*, released in response to life stress or pain itself) and thus the characteristic cool, blue, sweaty extremity typically seen in chronic CRPS patients.[65] Whether vasoconstriction in CRPS is related to direct SNS actions, circulating catecholamines acting at up-regulated receptors, endothelial dysfunction, or reduced nitric oxide levels, this vasoconstriction may contribute to development of trophic changes often associated with CRPS *via* local tissue hypoxia.[66]

Inflammatory Factors

Findings in several small clinical trials indicate that corticosteroids significantly improved symptoms in some patients with acute CRPS, suggesting the possibility that inflammatory mechanisms might contribute to CRPS, at least in the acute phase.[67,68] Recent work supports this hypothesis. Inflammation contributing to CRPS can arise from two sources. Classic inflammatory mechanisms can contribute through actions of immune cells such as lymphocytes and mast cells, which, after tissue trauma, secrete proinflammatory cytokines including interleukin-1β, -2, -6, and tumor necrosis factor (TNF)-α.[40] One effect of such substances is to increase plasma extravasation in tissue, thereby producing localized edema similar to that observed in CRPS.

Neurogenic inflammation may also occur, mediated by release of proinflammatory cytokines and neuropeptides directly from nociceptive fibers in response to various triggers, including nerve injury.[69] Neuropeptide mediators involved in neurogenic inflammation include substance P, calcitonin gene-related peptide (CGRP), and bradykinin (which is also involved in initiating cytokine release[70]). These neuropep-

tides both increase plasma extravasation and produce vasodilation and thus can produce the warm, red, edematous extremity most characteristic of acute CRPS.[30] Substance P and TNF-α activate osteoclasts that could contribute to the patchy osteoporosis frequently noted radiographically in CRPS patients, and CGRP can increase hair growth and increase sweating responses—both features sometimes noted in CRPS patients.[30,71] Proinflammatory cytokines and neuropeptides also produce peripheral sensitization leading to increased nociceptive responsiveness.

A number of studies have specifically examined the associations between CRPS and proinflammatory and antiinflammatory cytokines. Several studies indicate that compared with pain-free controls and non-CRPS pain patients, CRPS patients display significant increases in proinflammatory cytokines (TNF-α, interleukin-1β, -2, and -6) in local blister fluid, circulating plasma, and cerebrospinal fluid.[72–76] CRPS patients also seem to have reduced systemic levels of antiinflammatory cytokines (interleukin-10) compared with controls, which may also contribute to increased inflammation in the condition.[74] Increased TNF-α levels do impact on sensory CRPS symptoms. CRPS-I patients with hyperalgesia had significantly higher plasma levels of soluble TNF-α receptor type I than CRPS patients without hyperalgesia,[73] and neuropathic pain patients with allodynia display higher plasma TNF-α levels than similar patients without allodynia.[77] TNF-α is a key cytokine because not only does it have direct pronociceptive actions but it also induces production of other cytokines involved in inflammation, including interleukin-1β and -6.[78] Interestingly, administration of a TNF-α antibody (infliximab) may produce notable reductions in CRPS symptoms in some patients.[79]

Other work supports an association between CRPS and proinflammatory neuropeptides. Birklein *et al.*[80] reported increased systemic CGRP in CRPS patients compared with healthy controls. CGRP can produce vasodilatation, edema, and increased sweating—all features associated with acute CRPS.[80] Successful treatment of CRPS was associated with reduced CGRP levels and decreased clinical signs of inflammation.[80] Another study also found significantly higher plasma levels of CGRP in CRPS patients compared with pain-free controls and further noted significant increases in plasma bradykinin.[81] Other work indicates that plasma levels of substance P are significantly higher in CRPS patients than in healthy controls.[82] Moreover, intradermal application of substance P on either the affected or unaffected limb in CRPS patients has been shown to induce protein extravasation in that limb, whereas it does not do so in healthy controls.[83] These authors suggested that the capacity to inactivate substance P was impaired in CRPS patients. In summary, inflammatory factors can account for a number of the cardinal features of CRPS, particularly in the acute "warm" phase. Findings in clinical research that edema is less likely with increasing CRPS duration are also consistent with a greater role for inflammatory mechanisms in the acute

phase.[6] To date, no human studies have directly evaluated the role of inflammatory factors in the onset of CRPS.

Brain Plasticity

A recent review of the neuroimaging literature[84] concluded that there is little support for a distinct "pain network" associated with neuropathic pain, nor is there a consistent brain activation pattern associated with allodynia (a key clinical characteristic of CRPS). However, several neuroimaging studies in CRPS patients suggest at least one consistent and specific brain alteration associated with the condition: a reorganization of somatotopic maps. Specifically, there is a reduction in size of the representation of the CRPS-affected limb in the somatosensory cortex compared with the unaffected side.[85–89] Two studies indicate that these alterations return to normal after successful CRPS treatment,[87,89] suggesting that they may reflect brain plasticity occurring as a part of CRPS development rather than reflecting premorbid brain differences. Other brain imaging work, although not addressing somatotopic maps *per se*, stands in contrast. Comparisons of brain activity in children during active CRPS *versus* when their CRPS is clinically resolved suggest that significant differences in brain activation patterns in response to thermal and tactile stimuli (affected compared with unaffected side) may persist even after CRPS symptoms have resolved.[90]

It is not yet known at what point in development of CRPS reorganization of somatotopic maps occurs. However, these brain changes have meaningful clinical effects, which is evident from several findings. The degree of somatotopic reorganization correlates significantly with CRPS pain intensity and degree of hyperalgesia.[86] Moreover, CRPS patients exhibiting such reorganization demonstrate impaired two-point tactile discrimination[88] and impaired ability to localize tactile stimuli, including perceiving sensations outside of the nerve distribution stimulated.[91] This latter finding could help to explain the nondermatomal distribution of pain and sensory symptoms often noted in CRPS patients (*e.g.*, stocking or glove pattern[92]). Previous findings that sensory deficits to touch and pinprick in CRPS patients are often displayed throughout the affected body quadrant or the entire ipsilateral side of the body may be accounted for in part by somatotopic reorganization.[93]

Although the origin of somatotopic reorganization in CRPS is not known, work in other pain conditions indicates that similar reorganization occurs when afferent input from an extremity is substantially reduced or absent (*i.e.*, phantom limb pain[94]). Studies in non-human primates are consistent with this view. Partial loss of sensory inputs as a consequence of peripheral nerve damage[95] or partial spinal cord lesions[96] leads to extensive reorganization of multiple brain areas, including subregions of S1, with expansion of the somatotopic representations of adjacent nondeafferented areas into those cortical areas whose inputs have been lost. This reorganization can lead to blurring of the four distinct somatotopically organized areas of S1 (areas 1, 2, 3a, and 3b). Although the

significance of these latter findings is yet unclear, recent reports of differential activation of these subregions of S1 in response to noxious *versus* nonnoxious levels of the same somatosensory stimulus[97] suggest that these findings might represent the neural correlates of aberrant early processing of nonnoxious sensory stimuli that could have relevance to characteristic signs of CRPS (*e.g.*, allodynia).

Beyond somatotopic reorganization, the limited neuroimaging studies in CRPS have shown evidence suggesting altered activity in sensory (*e.g.*, S1, S2), motor (M1, supplementary motor cortex), and affective (anterior insula and anterior cingulate cortex) brain regions compared with healthy controls or stimulation of the contralateral limb.[73,98,99] Although too few studies in CRPS are available to draw firm conclusions, these brain activations seem similar to the nonspecific changes noted in other neuropathic pain conditions.[84] Other brain imaging work suggests that CRPS patients (compared with pain-free controls) may exhibit gray matter atrophy in the insula, ventromedial prefrontal cortex, and nucleus accumbens and also exhibit altered connectivity between the ventromedial prefrontal cortex and other regions.[100] These latter findings have yet to be replicated, but they do suggest additional areas for exploration in future CRPS imaging studies.

Genetic Factors

Genetic factors have been hypothesized to increase susceptibility to CRPS in some individuals. Studies examining familial CRPS occurrence patterns indirectly support genetic contributions. In the largest study of this type, 31 families with between 2 and 5 affected relatives each were described recently, with these familial CRPS patients having more frequent spontaneous CRPS onset and onset at an earlier age than comparable nonfamilial CRPS cases.[101] Another recent study in a large sample found that among CRPS patients younger than 50 yr (but not older patients), the risk of a sibling also developing the disorder was increased at least threefold.[102] Other indirect evidence for genetic involvement comes from a study indicating associations between childhood onset CRPS and evidence for mitochondrial disease in seven families, with pedigree analysis suggesting probable maternal inheritance.[103] In summary, studies of familial aggregation of CRPS provide support for the possibility that CRPS could be heritable in some cases.

To date, most studies directly evaluating the role of genetic factors in CRPS have been limited by sample sizes too small for making reliable genetic links. One focus of such studies has been on genes of the major histocompatibility complex, which encodes human leukocyte antigen (HLA) molecules; previous work suggests that these genes may contribute to several neurologic disorders.[104] One small genetic study found a significantly higher frequency of certain major histocompatibility complex-related alleles in a group of 26 CRPS patients with dystonia compared with healthy controls.[105] These alleles included D6S1014*134, D6S1014*137, C1_2_5*204, C1_3_2*342, and C1_3_2*354. In addition, D6S1014*140 and C1_3_2*345 alleles

were found to be significantly less common in CRPS patients. Interpretation of these findings is limited by the small number of CRPS patients examined. However, other studies have found similar associations between CRPS susceptibility and specific HLA class II alleles, including HLA-DQ1, HLA-DR6, and HLA-DR13.[106–108]

Recently, the first relatively large genetic CRPS study examined 150 CRPS patients with CRPS-related fixed dystonia of at least one limb and compared the frequencies of 70 HLA alleles with the frequency in more than 2,000 non-CRPS controls.[109] The HLA-B62 and HLA-DQ8 alleles were found to be associated significantly with CRPS even after correcting for multiple comparisons.

Other genetic factors have been examined as well. A TNF-α promoter gene polymorphism at position -308 was investigated for associations with CRPS when compared with a healthy population.[106] The TNF2 allele was significantly more likely to be present in warm CRPS patients than in controls. The functional effect of this allele is production of higher amounts of TNF-α, which could help to contribute to an exaggerated inflammatory response in these CRPS patients.[106] Other inflammation-related work focuses on the fact that angiotensin-converting enzyme helps to degrade pronociceptive neuropeptides such as bradykinin.[110] One small study in CRPS-I patients (n = 14) found a significantly greater likelihood of a deletion/deletion genotype for the insertion/deletion polymorphism at intron 16 of the angiotensin-converting enzyme gene compared with the general population.[111] This finding is intriguing given recent evidence that contemporaneous use of angiotensin-converting enzyme inhibitors at the time of injury significantly increases the risk of developing CRPS in a dose-dependent manner.[23] However, an attempt to replicate the angiotensin-converting enzyme genetic study by other investigators failed to reveal any genetic association between CRPS and this gene polymorphism.[110]

It may be important to consider genes unrelated to inflammation as well. For example, one prospective study has reported that haplotypes reflecting variability in eight polymorphisms in the β_2-adrenergic receptor gene were associated with risk for later development of chronic temporomandibular joint pain.[112] Such β_2-adrenergic receptor polymorphisms play a role in regulation of vascular tone and thus may be relevant to understanding the vasomotor characteristics of CRPS.[113] This possibility remains to be examined.

In summary, there is as yet no consistent and compelling evidence for specific genetic factors playing a role in the development of CRPS. However, the potential importance of genetic factors is suggested by the ability of some to influence inflammatory and other mechanisms that are believed to contribute to CRPS. Large, multisite genetic studies in CRPS patients will be necessary to address these issues definitively.

Psychologic Factors

Historically, the extreme distress exhibited by some CRPS patients, the unusual nature of CRPS symptomatology (*e.g.*, pain in a nondermatomal glove pattern), and its poorly understood pathophysiology led many to assume that CRPS was purely psychogenic. This opinion continues to be espoused by some.[114] Although a pure psychogenic model is clearly not supported by the evidence (*i.e.*, psychogenic factors are not necessary and sufficient to produce objective signs of CRPS), a contribution of functional psychophysiologic links to the development of CRPS is theoretically possible.

Given the other pathophysiologic mechanisms described in this review, any psychologic factor associated with increased catecholamine release could potentially exacerbate vasomotor signs of CRPS (*via* up-regulated adrenergic receptors), directly increase CRPS pain intensity (*via* adrenergic receptors sprouting on nociceptive fibers postinjury), and by exacerbating pain, could indirectly help to maintain the central sensitization associated with CRPS. Psychologic factors such as emotional distress (*e.g.*, anxiety, anger, and depression) can be associated with increased catecholaminergic activity[115–117] and, thus, could in theory interact with the adrenergic pathophysiologic mechanisms believed to contribute to CRPS. Consistent with this hypothesis, results of a diary study indicate that increased depression levels are a predictor of greater subsequent CRPS pain intensity,[118] and other work suggests that the pain-exacerbating effects of emotional distress are significantly greater in CRPS patients than in non–CRPS pain patients.[7,119] Although these studies did not assess circulating catecholamines, other work indicates that greater depression[116] and stress[120] levels in CRPS patients are associated with significantly higher circulating levels of epinephrine and norepinephrine, in line with hypotheses.

More recent work suggests that the interactions between psychologic and immune factors may also be important to consider. For example, laboratory work in healthy individuals has revealed that greater pain-related catastrophic thinking is associated with increased proinflammatory cytokine activity in response to painful stimuli.[121] Moreover, in CRPS patients, psychologic stress has been shown to be associated with alterations in immune function that could impact on inflammatory cytokines hypothesized to contribute to CRPS.[122]

A review of the existing research literature indicates that most studies assessing the role of psychologic factors in CRPS have been limited to case series descriptions or cross-sectional psychologic comparisons between CRPS patients and non–CRPS chronic pain patients.[92] Several studies suggest that CRPS patients may be more emotionally distressed than patients with non–CRPS chronic pain conditions,[7,9,123,124] although similar studies with negative findings have also been reported.[125,126] This leaves open the possibility that the positive findings simply reflect bias because of clinic referral patterns (that is, such differences may occur at specialty pain

clinics that receive large numbers of the most severely affected CRPS patients). Regardless, cross-sectional studies cannot address causation. Prospective studies are required, and to date, few CRPS studies of this type have been published. One prospective study indicated that among 88 consecutive patients assessed shortly after acute distal radius fracture, 14 had significantly increased life stress but did not develop CRPS, and the one patient who did develop CRPS had no apparent psychologic risk factors (no major life stressors and average emotional distress levels).[127] However, other prospective work indicated that higher levels of anxiety before undergoing total knee arthroplasty were associated with significantly greater likelihood of a CRPS diagnosis at 1

month postsurgery, with a similar nonsignificant trend for depression.[39] In summary, although theoretical links and these latter prospective findings suggest that psychologic factors could potentially impact on CRPS development, empirical tests of this hypothesis to date have been inadequate. Additional prospective tests of hypothesized psychologic CRPS mechanisms are required.

A Speculative Model of Interacting Pathophysiologic Mechanisms in CRPS

Although interactions between the mechanisms described in this review have not been subjected to empirical evaluation,
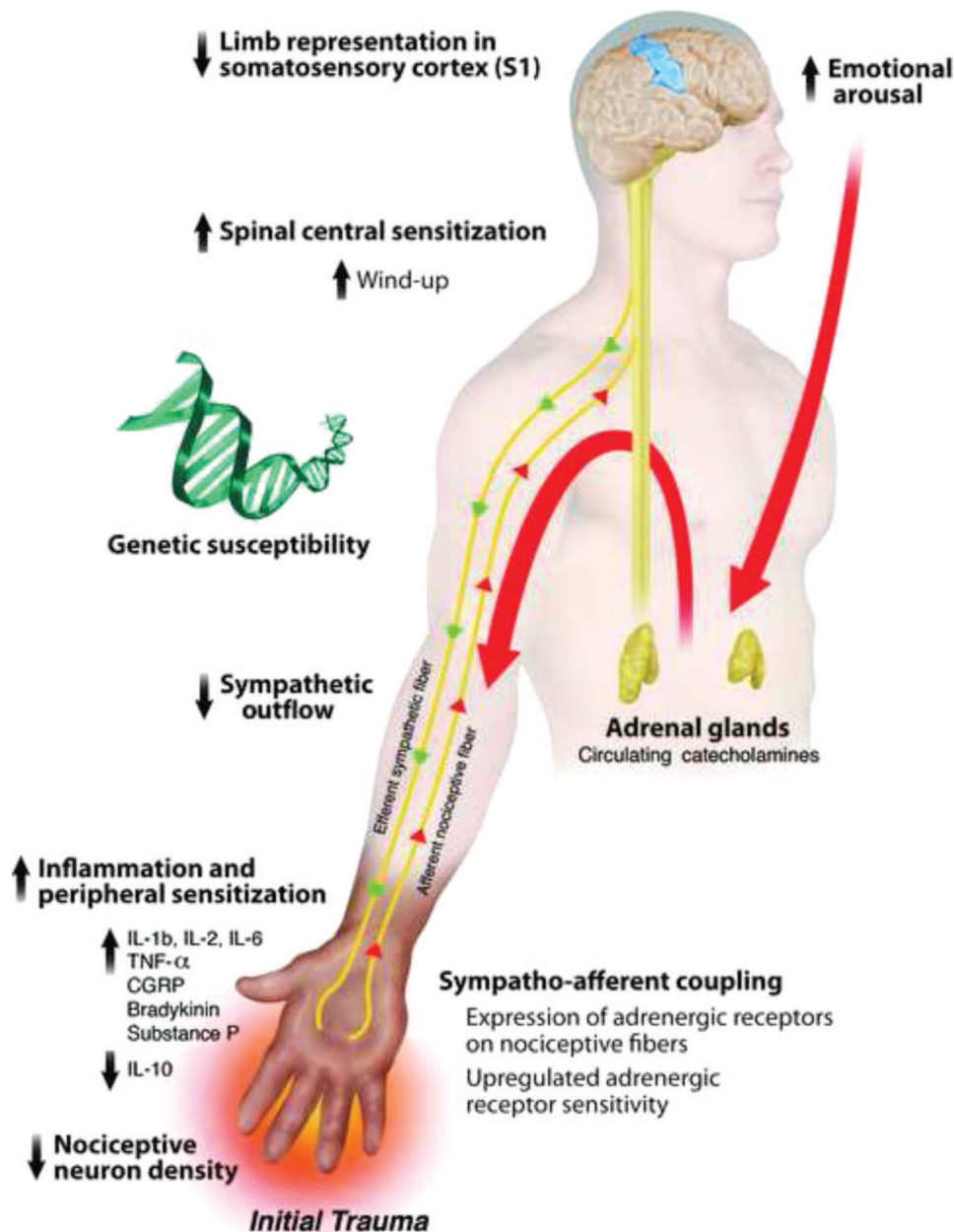

Fig. 1. Speculative model of interacting complex regional pain syndrome mechanisms. CGRP = calcitonin gene-related peptide; IL = interleukin; TNF = tumor necrosis factor.

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there are numerous ways in which such interactions could occur in theory.[1] A speculative model of CRPS pathophysiology based on the available data is summarized in figure 1. Tissue injury to an extremity may result in minimal nerve trauma that elicits local release of proinflammatory cytokines and neuropeptides, producing signs of inflammation and locally increased nociceptive responsiveness (peripheral sensitization). This response may be exaggerated in individuals susceptible to CRPS because of genetic factors. This nerve trauma may also lead to reduced density of nociceptive fibers and altered innervation of sweat glands and hair follicles in the affected area, potentially contributing to altered sweating. After the initiating injury, nociceptive fibers in the area begin to express adrenergic receptors, after which SNS activity and circulating catecholamines (in part related to emotional distress) can directly trigger nociceptive firing. Reduced SNS outflow in the region after the initiating trauma produces signs of vasodilation and impaired thermoregulatory responsiveness. Diminished SNS outflow also contributes to up-regulated sensitivity of local adrenergic receptors, leading to exaggerated vasoconstrictive responsiveness in the affected region in the presence of circulating catecholamines. The resulting reductions in regional blood flow may facilitate regional accumulation of pronociceptive substances (thereby enhancing hyperalgesia) and contribute to local hypoxia and nutritive deficits leading to trophic changes (*e.g.*, skin and nails) associated with CRPS. The ongoing nociceptive input resulting from sympatho-afferent coupling and other mechanisms produces alterations in spinal nociceptive pathways, which further increases nociceptive responsiveness and results in allodynia and hyperalgesia (central sensitization). Altered afferent input from the extremity after the injury contributes to plastic changes in the brain, specifically a reduced somatosensory representation of the affected region in the brain. These changes, in turn, are associated with impaired tactile sensation and nondermatomal sensory symptoms. Although the interacting pathophysiologic model described herein is speculative, it is consistent with known mechanisms. Prospective studies are needed to test these hypothesized mechanisms comprehensively as contributors to CRPS development in human clinical patients after acute tissue trauma.

Conclusions

The pathophysiologic mechanisms of CRPS seem to be multifactorial in nature. They may include peripheral and central sensitization, inflammation, altered sympathetic and catecholaminergic function, reduced representation of the affected limb in the somatosensory cortex, genetic factors, and psychophysiologic interactions. The degree to which individual mechanisms contribute to CRPS may differ from one patient to the other and even within one patient over time. Potential benefits of enhanced understanding of the pathophysiology of CRPS are many. If its pathophysiologic mechanisms were definitively known, these could then be linked to specific signs and symptoms of CRPS, which in turn would become clinical indicators of those mechanisms. A well-defined pathophysiology might also permit identification of diagnostic tests sensitive and specific enough to be clinically useful. Ultimately, the results of a careful clinical examination and diagnostic assessment protocol might have direct implications for understanding mechanisms contributing to CRPS in a given patient and for designing treatment protocols that address the underlying mechanisms in that patient. In addition to facilitating enhanced diagnosis and treatment in established CRPS cases, definitive knowledge of its pathophysiology would also permit better identification of risk factors for developing the condition after tissue trauma. This in turn could potentially lead to interventions to reduce incidence of CRPS after injuries known to be common triggers for CRPS (*e.g.*, fractures[6,50] and total knee arthroplasty[39]). For this type of clinical progress to be achieved, future research will need to examine large samples of CRPS patients using experimental designs that adequately reflect the multifactorial nature of CRPS and using prospective methodology that would facilitate making causal links. Mechanism-based treatment has long been a goal in CRPS management, and further improvements in the understanding of its pathophysiology may eventually permit that goal to be achieved.

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Stephen Bruehl