New Concepts in Complex Regional Pain Syndrome

Maral Tajerian, MSc, PhD\textsuperscript{a,b}, John David Clark, MD, PhD\textsuperscript{a,b,*}

INTRODUCTION

Complex regional pain syndrome (CRPS) is a painful, disabling, and often chronic condition that usually affects a single limb. With an estimated 50,000 new cases annually in the United States alone,\textsuperscript{1} CRPS exhibits a higher prevalence in female patients, with women affected at least 3 times more than men.\textsuperscript{1} The most frequent causes of CRPS involve surgery and trauma, with hand surgery being a particularly relevant factor; for example, the rate of CRPS is 5% to 40% after fasciectomy for Dupuytren contracture,\textsuperscript{2} 8% after carpal tunnel surgery,\textsuperscript{3} and greater than 30% after distal radius fracture.\textsuperscript{4} Interestingly, the likelihood of developing CRPS is not proportional to the extent of injury or surgery, because it can occur after even very minor injuries.\textsuperscript{5} In addition, limb immobilization itself appears to be a risk factor for development of this condition.\textsuperscript{6,7}

Although acute CRPS sometimes improves with early and aggressive physical therapy, CRPS present for a period of 1 year or greater rarely spontaneously resolves,\textsuperscript{8} thus leaving the majority (80%) of patients severely disabled.\textsuperscript{9} The syndrome encompasses a disparate collection of signs and symptoms involving the sensory, motor, and autonomic nervous systems, cognitive deficits, changes in mood, anxiety, bone demineralization, skin growth changes, and vascular dysfunction. Despite the devastating nature of the syndrome, to date, no satisfactory treatments exist for the CRPS patient, mainly due to the heterogeneity of the patient population, the evolving nature of the syndrome, and the overall lack of understanding of its basic underlying mechanisms.

KEYWORDS

- Complex regional pain syndrome
- Preclinical models
- Basic mechanisms
- Neuroinflammation
- Autoimmunity
- CNS plasticity
- Disease progression

KEY POINTS

- Complex regional pain syndrome (CRPS) is initiated by dysfunction of the sympathetic nervous system as well as the release of neuropeptides released from afferent/efferent c-fibers.
- Inflammatory mediators such as cytokines in peripheral tissues such as skin and muscle support CRPS-related pain.
- Autoimmunity may contribute to the manifestations of CRPS, although the immune targets are poorly understood.
- Biochemical and structural changes within the spinal cord and brain may explain the most persistent signs and symptoms of CRPS and may underlie the cognitive and emotional changes that accompany the syndrome.

Funding Sources: N/A (Dr M. Tajerian); supported by National Institutes of Health grant R01NS072143 and Veterans Affairs Merit Review grant I01RX001475 (Dr J.D. Clark).

Conflict of Interest: Nil.

\textsuperscript{a} Anesthesia Service, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA; \textsuperscript{b} Department of Anesthesiology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA

* Corresponding author. Anesthesia Service, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304.

E-mail address: djclark@stanford.edu

Hand Clin 32 (2016) 41–49
http://dx.doi.org/10.1016/j.hcl.2015.08.003
0749-0712/16/$ – see front matter Published by Elsevier Inc.
Multifaceted disorders, including CRPS, are often difficult to explain by a single core mechanism. The current review addresses recent developments in understanding the various mechanisms underlying CRPS using data from preclinical models as well as clinical studies (for a summary, please see Fig. 1). Pursuing these mechanisms will be key to understanding the vulnerability of some surgical and trauma patients to CRPS as well as inspiring mechanism-based treatments that go beyond simple symptom management.

**ANIMAL MODELS OF COMPLEX REGIONAL PAIN SYNDROME**

Animal models reflecting different aspects of CRPS have been invaluable to exploring some of the basic mechanisms of the syndrome. These models include the following:

a. Peripheral nerve injury: One of the earliest described models of CRPS, it relies on induced nerve injury to reproduce some of the clinical symptoms of spontaneous pain, hyperalgesia, and limb edema.10

b. Ischemia/reperfusion injury: Developed in rats over a decade ago,11 this model is based on clinical observations showing ischemic signs in CRPS patients, including decreased levels of hemoglobin oxygenation in skin capillaries,12 increased anaerobic glycolysis,13,14 and decreased skin blood flow.15 This model also has been shown to exhibit altered expression of cerebral proteins.16

c. Limb trauma and immobilization: Characterized in both mice17 and rats,18 this model focuses on the surgery/trauma causes of CRPS and mimics many of the nociceptive and vascular changes observed in humans in the acute and chronic stages of the syndrome.

d. Limb immobilization: Similar to clinical experiments wherein limb immobilization is associated with transient nociceptive hypersensitivity,7 this general model of chronic widespread pain focuses on limb immobilization and potentially tight cast application, as the causative agent of CRPS in rats.19

It is notable that most currently used models rely on physical trauma to the rodent hindpaw, in an effort to mimic injuries shown in CRPS patients, including fractures, strains, tight application of casts, and other traumas. Common to other animal models, none of these models accurately mimics all symptoms experienced by CRPS patients, a notoriously heterogeneous population. Nonetheless, these models reproduce many of the key characteristics of CRPS and allow the study of the molecular details of the disorder as well as the testing of new treatment strategies. The next few paragraphs address some of the recent advances in the understanding of the mechanisms of CRPS in both preclinical models and clinical subjects.

**SYMPATHETIC NERVOUS SYSTEM**

Although the term “reflex sympathetic dystrophy” has been replaced by the less mechanistically presumptive CRPS, there is evidence supporting the...
role of the sympathetic nervous system (SNS) in the development and maintenance of the syndrome. Historically, this role was inferred based on autonomic physical signs and on symptom relief following sympatholysis.\(^{20}\) More recent studies have proposed that sympathetic dysfunction coincides with the onset of the disease but normalizes with time,\(^ {21}\) suggesting a role in the genesis of CRPS rather than its maintenance, although additional studies have revealed significant SNS dysfunction in many chronic CRPS patients.\(^ {22}\) In the rat tibia fracture model of CRPS, it was demonstrated that sympathetic fibers release norepinephrine, which in turn stimulates interleukin (IL)-6 production, supporting the observed CRPS-like changes. More detailed in vitro studies revealed \(\beta-2\) adrenergic receptors (\(\beta-2\)-AR) to be the receptor population mainly responsible for the liberation of IL-6.\(^ {23}\) The upregulation of \(\alpha-1\) adrenergic receptors in skin samples from CRPS patients suggests there is also a role for this receptor population as well.\(^ {24}\) Thus, there are several clinical and molecular clues pointing to the role of SNS in CRPS.

Despite evidence showing the involvement of SNS in the pathophysiology of CRPS, the direct link between SNS activity and nociception remains to be delineated in CRPS patients: for example, in a study examining 24 CRPS patients and using microneurography techniques, no links were found between effenter fiber sympathetic activity and afferent activity in nociceptors innervating the symptomatic areas.\(^ {25}\) These findings might suggest that indirect mechanisms could be responsible for both the activation and the sensitization of nociceptors, not a direct coupling. One such mechanism could be due to a notable symptom of CRPS, vasoconstriction, which could influence nociceptor microenvironment or activate macrophages, which in turn would result in inflammatory mediator release.\(^ {26}\)

Based on the principle that there is some aspect of sympathetically maintained pain in CRPS, it stands to reason that sympatholysis should be efficacious in reversing some of the peripheral sensitization observed in CRPS patients. However, evidence remains mixed for both regional (local block of noradrenaline from sympathetic fibers) and proximal (at the sympathetic ganglion) treatment studies.\(^ {27}\) This lack of efficacy does not necessarily indicate the absence of SNS involvement, but could be due to the heterogeneity of the patient population, whereby only a subset of CRPS sufferers displays sympathetically maintained pain.

### NEUROGENIC INFLAMMATION

There are 2 major components of neurogenic inflammation: plasma extravasation and vasodilation.\(^ {28}\) CRPS is characterized by changes in blood flow, limb temperature, and edema in both humans\(^ {13,29}\) and rodent models.\(^ {11,18}\) Biochemically, neurogenic inflammation is characterized by the release of Substance P (SP) and calcitonin gene-related peptide (CGRP) from afferent neurons.\(^ {28}\) Evidence from both CRPS patients and laboratory animals suggests that, in the early stage of CRPS often known clinically as the warm phase, primary afferent C-fibers and sympathetic neurons function aberrantly, resulting in vascular symptoms, trophic changes, and pain.\(^ {30}\) In the rodent tibial fracture/cast model of CRPS, it has been shown that neuropeptides such as SP and CGRP released from sensory c-fibers lead to pain sensitization by the activation of receptors on keratinocytes and vascular endothelial cells, causing the local production of high levels of cytokines and nerve growth factor (NGF)\(^ {31–34}\) as well as the recruitment of mediator-rich mast cells.\(^ {35}\)

Similar observations showed increased levels of secreted cytokines, including tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and IL-6, in studies conducted in blister suction samples acquired from CRPS patients.\(^ {36–38}\) Likewise, TNF-\(\alpha\) and other pronociceptive cytokines were identified at elevated levels in the skin of CRPS patients\(^ {38,39–40}\) and postsurgical patients with persistent limb pain,\(^ {41}\) as were mast cells, cells capable of releasing a host of nociceptive and vasoactive mediators.\(^ {42}\) Recent studies using skin biopsies from acute and chronic CRPS patients demonstrated that cytokine levels drop and mast cell infiltration resolves as the condition becomes more chronic.\(^ {43}\) Finally, similar to what was seen in the rodent model, keratinocyte activation and proliferation were reported in CRPS skin and shown to be associated with upregulated levels of TNF-\(\alpha\) and IL-6.\(^ {43}\)

These observations of alterations at the molecular level could provide a basis for mechanism-based treatments. For instance, antineuropeptide signaling and anti-mast cell agents might both prove to be of therapeutic value for CRPS, by antagonizing neuropeptide receptors\(^ {44}\) and affecting the division and degranulation of mast cells.\(^ {45}\) Similarly, peripherally restricted biologic anti-TNF-\(\alpha\) agents, such as infliximab, may be effective in reducing pain in CRPS, although this therapy might be most efficacious in acute CRPS when peripheral TNF-\(\alpha\) levels are highest.\(^ {46}\) Despite the availability of such agents, the published evidence remains preliminary. For instance, although a case study in a CRPS patient showed pain amelioration and improvement in the cutaneous dystrophic symptoms after systemic infliximab administration,\(^ {47}\) a double-blind, randomized, placebo-controlled study of the efficacy
infliximab in CRPS was discontinued due to budgetary limitations even though a trend toward drug efficacy was observed.\textsuperscript{48} Clinical trials involving anti-IL-1β and IL-6 are unavailable at this point. Finally, although not a selective immunosuppressant, prednisone used in a short course does seem to have efficacy in speeding the resolution of CRPS.\textsuperscript{49} Modulation of the neurogenic inflammation pathways remains an important area of focus to improve care of the CRPS patient.

**AUTOIMMUNITY**

A collection of observations made over the past decade suggests an autoimmune cause for CRPS, a hypothesis that would help explain the seemingly unrelated nature of the syndrome’s signs and symptoms as well as difficulties in achieving adequate symptom control, remission, or cure using standard therapies. Exploration of CRPS-related autoimmunity began with the opportunity observation of symptom improvement in CRPS patients treated with intravenous immunoglobulin (IVIG) for unrelated conditions. This observation was followed by an exploratory clinical trial\textsuperscript{50} and later a randomized trial of low-dose IVIG showing intermediate duration (3 months) control of long-standing CRPS symptoms in many patients.\textsuperscript{51} These findings were further explored in an animal model, where immunoglobulin G (IgG) from CRPS patients was shown to worsen nociceptive sensitization in laboratory animals undergoing mild tissue trauma.\textsuperscript{52} Similarly, CRPS-like symptoms following fracture/cast immobilization were shown to be less severe in mice treated with anti-CD20 (rituximab) and in mu-MT mice (lacking mature B cells) compared with wild-type (WT) mice that had undergone the same procedure. Furthermore, immunoglobulin M (IgM) deposition and complement activation were observed in the skin and sciatic nerves of WT fracture/cast mice.\textsuperscript{53}

 Clinically, the autoimmune hypothesis was bolstered by 2 additional sets of observations. First, it was demonstrated that a disproportionate number of patients had IgM and IgG profiles consistent with antecedent infections by chlamydia, parvovirus, and campylobacter.\textsuperscript{54,55} Cross-reactivity of infection-related antibodies with self-antigens is thought to explain some cases of autoimmune neuropathy. Second, experiments using immunohistochemical techniques and fluorescence-assisted cell sorting analysis identified SNS neurons as targets for autoantibodies from some CRPS patients with little evidence of such autoimmunity from patients with other types of peripheral neuropathy.\textsuperscript{55,56} Follow-up experiments using in vitro beating cardiomyocyte preparations suggested that most CRPS, but not healthy, patients had autoantibodies binding to and activating the M-2 muscarinic and the β2-AR.\textsuperscript{57} Interestingly, there are other patients without pain who produce anti-β2-AR antibodies, but their symptoms are orthostatic hypotension, suggesting that autoantibody expression alone may not be sufficient to cause CRPS.\textsuperscript{55,56} Importantly, the authors have recently provided evidence suggesting that β2-ARs are critical to CRPS-like changes in the fracture/cast model.\textsuperscript{23} Additional evidence for autoimmune mechanisms in CRPS includes genetic data supporting CRPS associations with specific human leukocyte antigens,\textsuperscript{59–61} studies showing altered CD8+ T-cell levels in peripheral blood, and case reports of Langerhans antigen-presenting cell proliferation in the skin of CRPS patients.\textsuperscript{52}

Approaching CRPS as an autoimmune disease opens entirely new experimental pathways to identifying specific supporting mechanisms and provides opportunities for novel therapeutic development. Further exploration of CRPS-related autoimmunity may help to provide a rational basis for the use of treatments such as IVIG, anti-CD20 (rituximab), or other clinically available immunotherapies. These treatments are disease-modifying rather than being directed toward providing analgesia. Some, like the use of steroids, are suitable for perioperative use, whereas others, such as strong and persistent immune modulators, may be best reserved as second- and third-line agents. Indeed, the adverse consequences of persistent immunosuppression may limit the utility of some of these therapies.

**CENTRAL NERVOUS SYSTEM CHANGES**

Several manifestations of CRPS suggest functional changes within the central nervous system (CNS), including motor changes, autonomic functions, and changes in cortical representation. Motor symptoms have been identified in up to 97% of CRPS patients and include phenomena such as exaggerated tendon reflexes, dystonia, myoclonus, paresis, and tremor; changes thought to rely in large part on CNS dysfunction.\textsuperscript{13} Further evidence of CNS involvement comes from a case report of spinal microgliosis in a cadaveric CRPS subject\textsuperscript{63} and increased levels of glutamate in the cerebrospinal fluid of CRPS patients.\textsuperscript{64} In the fracture model of CRPS, nociceptive sensitization is supported by increased expression of spinal inflammatory mediators (TNF-α, IL-1β, IL-6, chemokine (C-C motif) ligand 2 [CCL2], NGF) that are upregulated by spinal neuropeptides (SP, CGRP) signaling.\textsuperscript{65} The intrathecal administration
of selective receptor antagonists for SP, CGRP, TNF-α, IL-1β, IL-6, CCL2, or NGF ameliorated pain sensitivity in these animals.55

In addition to alterations at the level of the spinal cord, functional, anatomic, and biochemical changes are observed in the brain and are associated with altered behavior in both rodents and humans. In the fracture model of CRPS, signs of anxiety and memory impairment are accompanied by structural and biochemical changes in the amygdala, perirhinal cortex, and hippocampus,66 including changes in dendritic complexity and levels of brain-derived neurotrophic factor and synaptophysin in these regions. In CRPS patients, cortical representation of involved limbs is altered67,68 and is correlated with central pain sensitization.59 Furthermore, clear alterations in cognition, memory, and emotions (anxiety and depression) in CRPS sufferers have been demonstrated,70–75 potentially due to diminished GA-Bergic or N-methyl-D-aspartate–mediated cortical neuroplasticity.76 It is notable that these changes seem to be reversible: for instance, ketamine treatment was associated with improved CRPS symptoms as well as improvements in cognition.77

Finally, neuroimaging studies have identified CRPS-associated changes in several centers including thalamus, S1, and S2 (somatosensory processing), cingulate and amygdala (emotion functioning), hippocampus and perirhinal regions (memory functioning), and other regions as well as the connectivity between these centers.69,78–86 Imaging studies in children demonstrate that some CRPS-related brain structural and functional changes resolve in parallel with symptom resolution, supporting a functional link between these areas and functions, while other areas remain altered, providing a basis for the increased susceptibility to recurrent CRPS known to exist in these patients.67,88

Together, these data emphasize the importance of studying the central correlates of CRPS that could be responsible for the chronification of the symptoms, in addition to inspiring therapeutic interventions that do not necessarily target peripheral mechanisms, but attempt to ameliorate the broader pain experience by targeting its associated cognitive and emotional comorbidities.

ACUTE VERSUS CHRONIC COMPLEX REGIONAL PAIN SYNDROME

Given the changing nature of CRPS over time, it is of great importance to understand the aforementioned mechanisms within the acute and chronic time frames of the syndrome. In CRPS patients, the clinical signs and symptoms seem to be of a dynamic nature, where the impacted limb evolves from an acute warm phase (limb is sensitive, is swollen, and displays an elevated temperature) to a chronic cold phase (resolution of inflamed appearance, but the persistence of pain and disability).13 More generally, the evolution of the syndrome is characterized by the transition from an acute state with prominent peripheral features to a chronic form characterized by persistent pain along with significant cognitive and mood changes.30,89–91

To date, the fracture/cast rodent model of CRPS is the only animal model wherein the acute versus chronic time points were explored using behavioral and molecular tools. This model showed that although mechanical allodynia persists for a long time, it is only at the acute stage that mice exhibit signs of edema and increased hindpaw temperature. These early symptoms are accompanied by the upregulation of various molecules involved in chemokine signaling pathways.92 Furthermore, similar to the clinical population, pain-related cognitive, emotional, and neuroplastic alterations are observed in the chronic stages in the preclinical model.56

In addition to providing a more comprehensive view of disease cause, studying the evolution of CRPS is crucial in determining the choice of treatment. For instance, pinpointing the mechanisms behind the early stages (such as the inflammatory and immunologic aspects) might suggest novel approaches to preventing the occurrence of CRPS as well as halting and reversing the condition at its earliest stages. Conversely, mechanisms unique to the chronic stage (such as central sensitization) might suggest therapies directed toward already-established CRPS. In a recent study conducted in the fracture model of CRPS, chronic ketamine infusions were efficacious when administered in the chronic, but not acute phase of the syndrome,93 suggesting that this centrally directed therapy be used in patients with longer-established CRPS.

SUMMARY

CRPS, once entirely enigmatic, is now appreciated to have a complex and evolving basis. Although mechanisms such as SNS dysfunction and neurogenic inflammation have long been known to regulate the vascular, trophic, and pain-related features of the syndrome, the novel concept of autoimmune involvement is becoming increasingly associated with complex syndromes including CRPS. The recent realization that changes within the CNS may underlie the most chronic sensory features of CRPS as well as the associated
psychological changes also opens the door to the development of new treatments. Taken together, these recent advances in CRPS support the optimistic view that new treatments might be rationally designed based on disease cause and applied to individual patients based on their particular CRPS-related signs and symptoms.  

REFERENCES


