New Concepts in Complex Regional Pain Syndrome

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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/effect 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.

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,[1] CRPS exhibits a higher prevalence in female patients, with women affected at least 3 times more than men.[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,[2] 8% after carpal tunnel surgery,[3] and greater than 30% after distal radius fracture.[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.[5] In addition, limb immobilization itself appears to be a risk factor for development of this condition.[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,[8] thus leaving the majority (80%) of patients severely disabled.[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.

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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 mice[17] 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

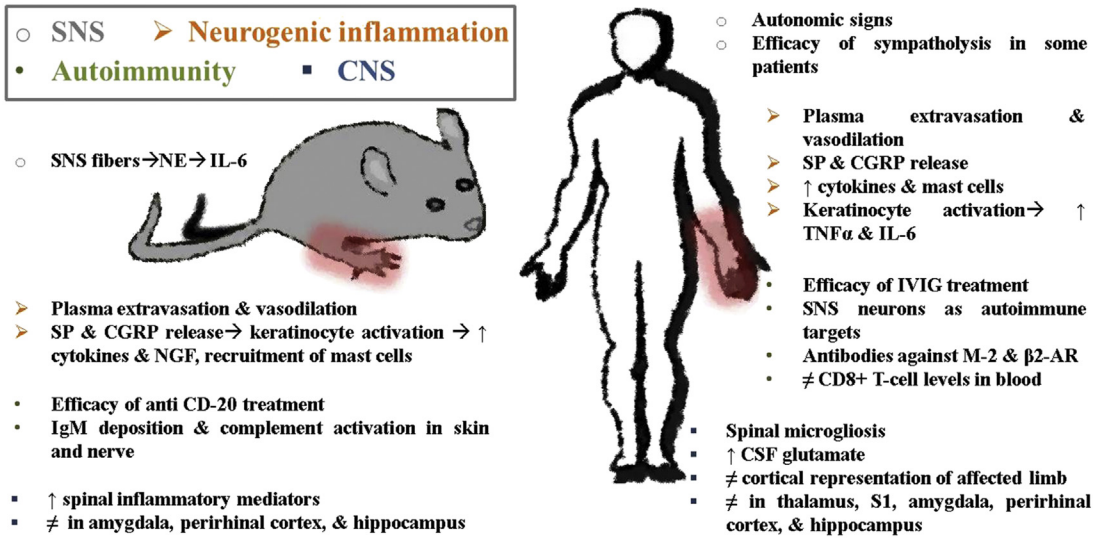

Fig. 1. Summary of some of the basic mechanisms involved in CRPS in preclinical models and patients. CSF, cerebrospinal fluid; M-2, muscarinic acetylcholine receptor 2; NE, norepinephrine; S1, primary somatosensory cortex.