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# A new hypothesis for the pathophysiology of complex regional pain syndrome

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) has defied a clear unified pathological explanation to date. Not surprisingly, treatments for the condition are limited in number, efficacy and their ability to enact a cure. Whilst many observations have been made of physiological abnormalities, how these explain the condition and who does and doesn't develop CRPS remains unclear. We propose a new overarching hypothesis to explain the condition that invokes four dynamically changing and interacting components of tissue trauma, pathological pain processing, autonomic dysfunction (both peripheral and central) and immune dysfunction, primarily involving excessive and pathological activation of dendritic cells following trauma or atrophy. We outline pathophysiological changes that may initiate a cascade of events involving dendritic cells and the cholinergic anti-inflammatory pathway resulting in the condition, and the changes that maintain the condition into its chronic phase. This hypothesis should provide fertile ground for further investigations and development of new treatments that holistically address the nature of the disorder along its developmental continuum.

## Introduction

The clinical presentation of Complex Regional Pain Syndrome (CRPS) was first clearly and eloquently described by Silas Weir Mitchell in 1872. Many observations have been made on CRPS yet it defies complete understanding. Its variable presentations at onset and its protean presentation over time have made explanation difficult. Progress has been made in codifying the diagnostic criteria [1], which continue to be refined [2–5], however, many of the current hypotheses for explaining the condition are more a description of associated findings for which causality has not clearly been established. No single explanation has adequately explained the condition and this has led to authors even denying its existence [6–8]. The current diagnostic criteria include regional pain that is disproportionate to the initial trauma, skin colour and temperature changes, edema, vasomotor and sudomotor changes, motor dysfunction and trophic changes.

Any model for the condition should ideally explain the following:

1. Typically, only 0.5–2% of injury/trauma patients develop CRPS [9].
2. Some patients with CRPS have no history of trauma [10].
3. CRPS can have protean presentations, with each patient displaying different symptoms and signs such as warm or cold limb, oedema, allodynia, hyperalgesia, abnormal sweating and skin and nail tissue changes [11].
4. CRPS is almost universally restricted to the limb (upper or lower) and, often with chronicity, the symptoms (especially pain) progress proximally up the limb, often to the shoulder/hip but not beyond [12].
5. Whilst appearing to be a neuropathic pain condition, CRPS is mostly unresponsive to standard neuropathic pain treatments [13].
6. Florid dystonia can be a feature of CRPS in a subset of patients and is often treatment unresponsive [14].
7. The peripheral signs of CRPS mostly fade and disappear in the chronic phase of the condition, although the pain mostly remains [15].

The rat tibia fracture model of CRPS developed by Wade Kingery and colleagues has yielded tantalising insights into keratinocyte activation, spinal cord transcriptional changes, autoimmunity development and acute versus chronic changes [16–22], and we believe reframing CRPS into a dynamic multicomponent disease best explains the condition. We present a four-component model of tissue trauma, pathological pain processing, autonomic dysregulation and immune dysfunction to explain the condition and its cardinal features (Fig. 1). These abnormalities interact and reinforce each other to produce the chronic phase of the condition.

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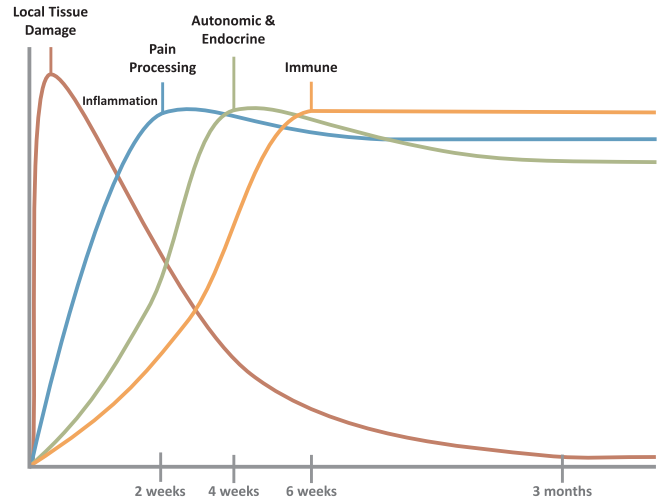


**Fig. 1.** The proposed four component model of CRPS depicted as a time course of homeostatic disturbances: tissue trauma (red line), pathological pain processing (blue line), autonomic dysregulation (green line) and immune dysfunction (orange line). Note: In any individual, these four components can vary in degree in terms of homeostatic disturbance and relative time course of activation.

It is the immune component of our model that has been least clarified to date. We propose that a class of immunosurveillance cells known as dendritic cells are the primary drivers of immune dysfunction [23,24]. Dendritic cells reside predominantly in the skin and subcutaneous tissue. Following antigen-capture, dendritic cells migrate to the draining regional lymph nodes where they present antigen to T-cells and initiate an adaptive immune response [24]. Furthermore, dendritic cell activation and migration into the systemic circulation has effects on both peripheral and central neurogenic signalling [25]. These processes and further downstream effects of dendritic cell activation that may lead to the generation of neuropathic in CRPS are discussed in detail in the second half of this article.

*Components of the model*

The reader should note that what is being presented here is a hypothesis (which is constructed before any applicable research has been done) and not a theory (which is a construct that explains the observable data generated in a series of investigations or experiments). Furthermore, we are not suggesting that each and every factor that is discussed within this article has the ability to activate, exacerbate or maintain the disease in each and every CRPS patient, rather, that these are examples, whether validated by prior investigations in subsets of CRPS patients, or supported by animal models, that would each provide some level of support for one (or more) of the four components in our hypothesis and model. In any individual, these four components can vary in degree in terms of homeostatic disturbance and relative time course of activation.

*Component 1: tissue trauma*

Most cases of CRPS can be linked to some form of trauma. Tissue trauma may include bone fractures, soft tissue injuries, chemical or thermal burns, and may be complicated by factors such as limb immobilisation or disuse [26], tissue hypoxia [27], neurogenic inflammation [28,29], stress [30], and so forth. Tissue trauma brings about a well understood course of inflammation, peripheral nociceptor activation and upregulated neural processing. This is later followed by an anti-inflammatory response that dampens the aforementioned changes and restores the tissue and organism to homeostasis. Under certain circumstances, however, protective mechanisms can become overwhelmed by various compounding, initiating factors, leading to deleterious and profound downstream effects.

Two major activators of immune cells, particularly dendritic cells, involved in the genesis of neuropathic pain include damage associated molecular products (DAMPs), which are endogenous products released after trauma, surgery or sepsis that drive an inflammatory response, such as heme, extracellular hemoglobin, interleukins (i.e. IL-1α, IL-33), heat shock proteins, and high mobility group box protein HMGB1) [31–33], and pathogen associated molecular products (PAMPs), which are exogenous molecules released from infiltrating microorganisms [34–41].

Tissue hypoxia has been identified as a dendritic cell activator [42,43] and has direct relevance to CRPS, with multiple studies indicating impaired tissue oxygenation in the affected limb of CRPS patients [27,44–46]. In addition, sympathetic nervous system hyperactivity and whole-body stress response producing high circulating catecholamine levels have also been implicated in the activation or modulation of dendritic cells [47–50].

The component of tissue trauma directly contributing to CRPS symptoms and signs will wane over time but may be complicated by direct injury to peripheral nerves (in the case of CRPS-II), which will prolong neuropathic pain presentation.

*Component 2: pathological pain processing*

Pain pathogenesis has been well described by Gold and Gebhart [51]. Pathological pain processing is associated with symptoms/signs of allodynia and hyperalgesia and can consist of excessive activation of the peripheral nerve(s), dorsal root ganglion (DRG), dorsal horn of the spinal cord, thalamus, cortex and basal ganglia. Typically, such activity starts peripherally, with activation of more proximal structures occurring over time, however that time course is variable and central nervous system (CNS) changes can occur quickly [52]. Due to the interactions between the autonomic and immune systems with the pain processing system [25,53,54], disturbances in their function can perpetuate abnormal pain processing and produce a state of chronic neuropathic pain [55,56].

Peripheral nerve involvement (i.e. nerve injury, degeneration) can be profound in CRPS [57,58]. An important consequence of nerve involvement is upregulation of microglia in the spinal cord, leading to a state of gliosis, which contributes to central sensitisation and neuropathic pain [59,60]. The first documentation of gliosis in CRPS was in a case report of autopsy findings in the spinal cord of a chronic case of CRPS (Fig. 2) [61].

There is also evidence of neuroinflammation and altered resting functional connectivity of the brain in CRPS [62]. For example, basal ganglia, whilst best known for their role in coordinating motor function, are involved in nociception and CRPS [14,63,64]. An imaging study of the brain of CRPS patients has shown neuroinflammation of basal ganglia, which was attributed to microglial activation, and found a significant correlation between the inflammatory score of the caudate nucleus and pain score as well as the affective dimensions of pain [65]. Basal ganglia outputs to the subthalamic nuclei, thalamus and the spinal cord have also been implicated in CRPS [14]. The dystonia and proprioceptive deficits that are sometimes seen in CRPS have been best explained by dysfunction in the basal ganglia and the basal-thalamic-frontal cortex circuit [66–69]. Additionally, we hypothesise that muscle disuse behaviour, casting or unloading produces both distal peripheral axon degeneration and altered motor cortical maps, with subsequent alteration in basal ganglia output to motor efferents to the spinal cord, and to efferents to the subthalamic nuclei, with subsequent reductions in motor function and “neglect-like” limb behaviour. For a comprehensive review on this subject, we refer the reader to a recent publication by Azqueta-Gavaldon et al. [14].

One common mechanism underlying this aberrant neural activation is the dendritic cell. Activated dendritic cells interact with glial cells on

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