Mast Cells
Source of Inflammation in Complex Regional Pain Syndrome?

During the last century, we have heard numerous hypotheses about the pathophysiology of the clinical conundrum complex regional pain syndrome (CRPS), which has an incidence of 2–5% after limb fractures. We have read about sympathetic disturbances, spinal changes, CRPS personality, and malingering. Although all of these suggestions are supported by at least some evidence, none are able to adequately explain all the disturbances seen in patients with proved CRPS. Research in the last decade has focused systematically on two mechanisms: facilitated posttraumatic inflammation in the first months of CRPS and cortical reorganization mainly later. The inflammation is characterized by skin reddening, warmth, edema, trophic changes such as increased hair or nail growth, and sweating. Major mediators for these “visible” symptoms may be neuropeptides such as calcitonin gene-related peptide or substance P (SP). Inflammatory mediators and cytokines such as tumor necrosis factor α might be more important for the “nonvisible” signs, such as movement-related pain and mechanical pinprick hyperalgesia. Cortical reorganization in CRPS is characterized by motor disturbances (e.g., dystonia), allodynia, nonmotoral sensory loss, and neglect-like symptoms. According to these two hypotheses, the most effective current treatments target inflammation (e.g., steroids) and counteract cortical reorganization (e.g., motor learning).

Although cortical reorganization in response to pain is unique to humans and is thus hard to study in animals, a suitable model of posttraumatic inflammation opens a window into molecular CRPS research. In this issue of Anesthesiology, Li et al. present such a model (rat hind limb fracture and subsequent casting for 4 weeks), which has been developed by that group during the past 10 yr. They have been able to model many of the acute CRPS features in rats: pain, limb warmth, edema, loss of motor function, and osteopenia. They have also been able to substantiate their findings by biochemical analyses. They observe increased signaling by cytokines, such as tumor necrosis factor α, interleukin 1 β, interleukin 6, and tumor necrosis factor in peptidergic nerves. This is even more important because the importance of this neuropeptide has been shown repeatedly: It might be the key for MC degranulation and release of inflammatory mediators, which in turn could up-regulate SP in peptidergic nerves. This is even more important because the number and efficacy of SP receptors (neurokinin 1 receptors) on keratinocytes are found to be increased after trauma, which amplifies SP effects. Thus, a vicious circle could be established (fig. 1) that perpetuates posttraumatic inflammation and leads to CRPS. Disruption of this circle by specific antagonism (e.g., against SP or cytokines) would be a proper target for CRPS treatment. Only MC-derived histamine seems to be of minor importance in the current work.

Thus far, these findings are intriguing and will broaden our understanding of—what? One major problem is that human CRPS is an orphan disease that develops only rarely after fractures, whereas the MC changes occur predictably in the rat fracture model. Could it be that the changes seen in the rat model are related to normal trauma healing but unrelated to CRPS pathophysiology? A second uncertainty is the SP-induced MC degranulation itself. In human skin and nerves, SP is released after acute trauma (less than 10−9 M) but not in rodents. Accordingly, an SP effect on skin MC has been seen only when pharmacologic concentrations (10−5 M or higher) of SP were injected, whereas endogenous SP release from primary afferent fibers is ineffective. Li et al. used a pharmacological concentration of approximately 10−4 M. In addition, SP-induced MC degranulation is independent of neurokinin 1 receptors in human skin.

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Fig. 1. Proposed vicious circle pathway for complex regional pain syndrome based on the results of Li et al.16

One possible way to solve this riddle comes from an investigation of different rat strains. Ogawa et al.25 showed that MC degranulation by SP in physiologic nanomolar doses occurred in only one strain of Wistar rats, whereas other rat strains required pharmacologic doses. No such data exist for the Sprague-Dawley rats used by Li et al.,15 but because they used pharmacologic doses, MC degranulation should occur anyway. If there were a similar genetic variance in humans, this could explain why only a minority experiences CRPS after distal extremity fracture. It clearly would be valuable to be able to identify this minority. The findings of Li et al.15 may guide us by providing a detailed analysis of how MC are involved in trauma-related inflammation. It is now up to CRPS researchers to develop diagnostic or therapeutic tools in humans to verify or refute Li et al.’s hypothesis. If verification could be achieved, another piece of the CRPS puzzle might be found.

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References


