

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),¹ which has an incidence of 2–5% after limb fractures.² We have read about sympathetic disturbances,³ sympathonociceptive coupling,⁴ spinal changes,⁵ CRPS personality,⁶ and malingering.⁷ 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 CRPS⁸ and cortical reorganization mainly later.⁹ The inflammation is characterized by skin reddening, warmth, edema, trophic changes such as increased hair or nail growth,¹⁰ and sweating.¹¹ Major mediators for these “visible” symptoms may be neuropeptides such as calcitonin gene-related peptide or substance P (SP).¹² 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.⁹ Cortical reorganization in CRPS is characterized by motor disturbances (*e.g.*, dystonia), allodynia, nondermatomal sensory loss, and neglect-like symptoms.¹⁰ According to these two hypotheses, the most effective current treatments target inflammation (*e.g.*, steroids¹³) and counteract cortical reorganization (*e.g.*, motor learning¹⁴).

Although cortical reorganization in response to pain seems 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.*¹⁵ 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.¹⁶ 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 (IL1 β), and interleukin 6, in the tissue; increased neuropeptide content (SP and calcitonin gene-related peptide) of the peripheral nerves; and IL1 β -dependent upregulation of nerve growth factor in the affected skin. This group has also demonstrated specific effects of targeted antagonism for most of these mol-

ecules. The current work centers on the role of mast cells (MC) in this rat model.¹⁵ This focus may have been triggered by a recent finding in human CRPS, in which analysis of interstitial fluid from skin suction blisters showed that MC tryptase is up-regulated in the affected epidermis.¹⁷ In addition, involvement of skin MC can be suspected because they constitute a major part of the skin immune system and are an important source of histamine, cytokines, prostaglandins, and last but not least, proteases that are all able to sensitize nociceptors. MC numbers and degranulation rate are increased after fracture and casting. They get into closer contact with peptidergic nerve fibers, and MC depletion reduces nociceptive sensitization and hyperalgesia behavior. The effect of MC on the visible inflammatory signs seems of minor importance. However, the most fascinating part of this story concerns the role of SP. Not only in the rat fracture model of the group of Li *et al.*,^{15,18} but also in human CRPS,¹⁹ 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.²⁰ 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,¹⁹ 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,²¹ 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 concentration is far lower (less than 10^{-10} M) than in rodents.²² 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.²³ 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.²⁴

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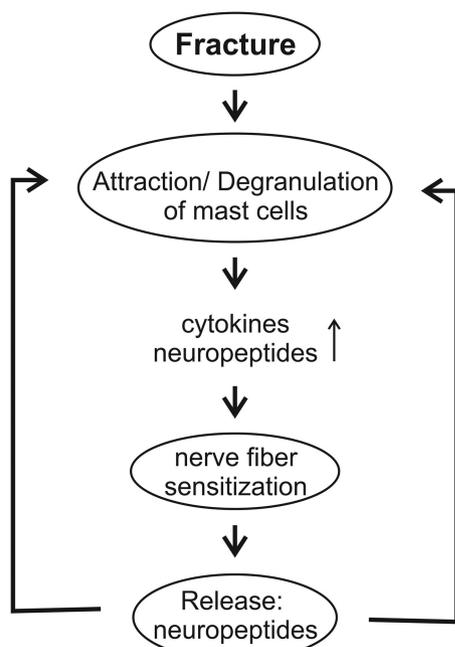


Fig. 1. Proposed vicious circle pathway for complex regional pain syndrome based on the results of Li *et al.*¹⁵

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 substrain 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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