

## **Evidence for immune system involvement in reflex sympathetic dystrophy**

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The authors review 6 case histories of RSD in which they performed biopsies, which were processed for immunohistochemistry staining (immunostained) for inflammation and neuropeptides. They note:

"Reflex sympathetic dystrophy (RSD) and causalgia are conditions characterized by a seemingly exaggerated response to tissue trauma, associated with severe and often intractable pain."

"The International Association for the Study of Pain has recently revised the taxonomy to 'complex regional pain syndrome.'"

"Current theory on pathophysiology favours the sensitization of the central nervous system following peripheral injury. Peripheral sensitization of nociceptors is known to occur following tissue injury due to chemicals released at the injury site. They may then be activated by low intensity stimuli. This in turn produces alterations in sensitivity of neurons in the dorsal horn. Thus, central sensitization is thought to be triggered by primary afferent discharge from the site of injury and may be maintained by increased excitability, decreased inhibition in the spinal cord along with structural reorganization."

Immunostaining found elevated Langerhans cells in all biopsies at sites of injury. These greatly increase the production of nerve growth factor (NGF) by skin and nerve derived fibroblasts.

"NGF can produce hyperalgesia very similar to that accompanying inflammatory tissue injury but with no visible signs of skin inflammation. NGF is retrogradely transported to the neuronal cell body where it can lead to an alteration in phenotype, with consequent large increases in the production of certain neuropeptides such as SP (substance P) and CGRP (calcitonin gene-related peptide). When transported peripherally, SP and CGRP have important roles in oedema formation and inflammation, and when transported centrally can cause excitation, possibly by increasing the excitability of N-methyl-D-aspartate (NMDA) receptors."

"It is of interest that increases in Langerhans cell numbers have been noted in painful hypertrophic scarring, together with elevated levels of SP and CGRP, suggesting similarities in the pathophysiology of painful scarring and RSD."

The authors note a relationship to the development of post-surgical scar hyperpathia and the development of causalgia.

"The possibility that the immune system may play a role in pathological pain states has been reviewed. Evidence for interactions between the neuroendocrine and immune systems is overwhelming."

In 1945 it was demonstrated that the bone marrow is innervated by sympathetic nerve fibres. **[Very Important]**

Since 1987, all lymphoid organs are known to be innervated by autonomic nerve fibres, and sympathetic nerve stimulation causes release of immune cells from the marrow into the general circulation.

"The neuroendocrine and immune systems share common hormones and receptors and the immune system is regarded by some as a diffuse sensory organ, while cells of the immune system have been referred to as 'mobile synapses', mediating in the flow of information to and from the brain via afferent and efferent limbs of the neuroendocrine system."

The hypothalamus plays a key role in regulating interactions between the neuroendocrine and immune systems. Immune responses generate electrical activity in the hypothalamus. It has been demonstrated that nociceptors send fibres directly to the hypothalamus, and the hypothalamus is activated by peripheral noxious stimuli. Fibres from this spinothalamic tract arise from all levels of the spinal cord and send fibres to both sides of the hypothalamus.

"Interactions between the neuroendocrine and immune systems should be considered when planning research into pathological pain states."

#### COMMENTS FROM DAN MURPHY

This is a great article from an unusual source. It has a lot, and supports our classroom model very well:

- \*Trauma
- \*Activation of fibroblasts
- \*Release of nerve growth factor, resulting in receptive field enlargement and supersensitivity
- \*This causes structural reorganization of cord synapses (synaptogenesis/neuroplasticity)
- \*And reduced descending pain inhibition
- \*Which involves the hypothalamus, and therefore also the response of the immune system.