Editorial

Objectifying CRPS-I

CRPS-I is diagnosed on the basis of the patient's signs and symptoms [4]. Of course, the cardinal symptom is the patient's report of pain and the subjective nature of this report plus our inability to find objective evidence for any cause of the pain has led to many decades of debate and frustration.

But things are changing. The first objective evidence for pain-producing pathology in CRPS-I came from an autopsy study of the affected limb of a patient who elected amputation for the relief of pain [7]. This study revealed peripheral nerve degeneration and abnormalities of muscle consistent with a chronic inflammation. More detailed examination of skin samples from the amputated limbs of two additional CRPS-I patients confirmed the presence of nerve degeneration and evidence of vascular inflammation [1]. Of course, the problem with these autopsy studies is that they examined very severe cases. It was thus a landmark event when Oaklander and her colleagues [6] demonstrated the partial loss of intraepidermal nerve fibers (IENFs; the sensory terminal arbors of the afferents innervating the skin) in skin biopsy punches from 18 CRPS-I patients with typical disease.

Another landmark paper is presented in the current issue. Eisenberg and his colleagues [10] demonstrate very large increases in malondialdehyde, lactic dehydrogenase, and cellular antioxidants (peroxidase, superoxide dismutase, and uric acid) in the serum, and especially in the saliva, of 31 CRPS-I patients with typical disease. Malondialdehyde is produced when the phospholipids of cell membranes are damaged by reactive oxygen species; it is a widely accepted marker for oxidative stress. Lactic dehydrogenase levels are also known to increase in the presence of oxidative stress. The increased levels of endogenous antioxidants almost certainly represent a compensatory response to the oxidative stress. Taken together, these data are unequivocal evidence that oxidative stress is present in CRPS-I patients. These data confirm a large amount of indirect evidence for the presence of oxidative stress in CRPS-I patients and strengthen the rationale for the use of antioxidants and free radical scavengers in the treatment and prevention of CRPS-I.

The results from Eisenberg and his colleagues raise many important questions. For example, do the diagnostic criteria now in use capture all or only some of the patients with markers of oxidative stress? It has been noted that the clinical criteria may fail to identify about 15% of patients who experienced physicians believe to have CRPS-I [4]. Can the status of these patients be clarified by testing their saliva? Is there a correlation between the IENF loss and the magnitude of the increase in inflammatory markers? Are these markers also present in CRPS-II patients? Perhaps the most critical question is whether the markers of oxidative stress tell us anything about the pathogenesis of CRPS-I. Is the presence of these markers related to the cause of CRPS-I or is it a consequence of some other factor? This critical question of cause-or-effect requires an answer to another question: What is causing the oxidative stress?

Markers of oxidative stress are elevated in many diseases, but the strongest association is with inflammation. We have recently proposed that at least some CRPS-I patients have a chronic, deep tissue inflammation due to microvascular pathology caused by an ischemia–reperfusion injury [2]. Our hypothesis comes from the work on an animal model of CRPS-I, chronic postischemic pain (CPIP; [2]), where an ischemia–reperfusion (I-R) injury to the hind paw is produced by placing a tourniquet around the anesthetized animal's ankle for 3 h. Prolonged ischemia leads to the accumulation of oxidases, enzymes that produce free radicals. The return of oxygenated blood upon reperfusion results in the production of a burst of free radicals (superoxide, hydrogen peroxide, hydroxyl radical, perhydroxyl radical, singlet oxygen, and peroxynitrite anion) that causes an I-R injury to the endothelial cells of the microvasculature (i.e., the capillaries, arterioles, and venules). I-R injury to the capillary endothelial cells causes them to swell and extend blebs into the capillary lumen which impede or prevent the passage of red blood cells – the slow-flow/no-reflow phenomenon. I-R injury to post-capillary venules causes them to leak and leads to edema, provided that there is a sufficient flow in the upstream capillary bed. I-R injury also leads to norepinephrine

hypersensitivity in arteries, which is a potential basis for the role of the sympathetic nervous system in CRPS-I. We have evidence for the slow-flow/no-reflow effect in the hind paw muscles of CPIP rats [5] and for the I-R evoked arterial hypersensitivity to norepinephrine [8,9]. Moreover, we have detected elevated levels of malondi-aldehyde in the hind paw muscles [5] and have shown that the animal's pain hypersensitivity is reduced by free radical scavengers and antioxidant therapy [2].

Slow-flow/no-reflow would be expected to lead to a persistent state of hypoperfusion and a consequent persistent inflammatory response in muscle and bone. Such an inflammation would likely be associated with the presence of markers of oxidative stress. Multiple lines of evidence are consistent with the presence of microvascular dysfunction and an inflammatory condition in CRPS-I. Moreover, the presence of a persistent inflammation would be consistent with the reported increase in pro-inflammatory cytokines in CRPS-I patients and the therapeutic effects of cytokine blockers.

Importantly, there is no logical reason why slow-flow/no-reflow should not also affect the microvasculature of peripheral nerves (the vasa nervorum). Distal nerves would be especially vulnerable, simply because they are small and have few capillaries. Inflammation of a nerve yields a neuropathic pain condition (neuritis; [3]). If severe enough, slow-flow/no-reflow in a nerve's vasculature might cause degeneration, suggesting a possible link between the distal nerve injury in CRPS-I patients [1,6,7] and the results of Eisenberg and his colleagues. If these ideas are correct, then CRPS-I might best be thought of as a combination of inflammatory and neuropathic pain mechanisms.

References

[1] Albrecht PJ, Hines S, Eisenberg E, Pud D, Finlay DR, Connolly MK, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. Pain 2006;120:244–66.

[2] Coderre TJ, Xanthos DN, Francis L, Bennett GJ. Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-type I (CRPS-I; reflex sympathetic dystrophy) produced by prolonged hind paw ischemia and reperfusion in the rat. Pain 2004;112:94–105.

[3] Eliav E, Herzberg U, Ruda MA, Bennett GJ. Neuropathic pain from an experimental neuritis of the rat sciatic nerve. Pain 1999;83:169–82.

[4] Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326–31.

[5] Laferrière A, Xanthos DN, Coderre TJ. Short-term exercise increases hind paw muscle lactic acid and allodynia in rats with chronic post-ischemia pain. Poster presentation, IASP 12th World Congress on Pain, Glasgow, UK, August 17–23, 2008.

[6] Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain 2006;120:235–43.

[7] van der Laan L, ter Laak HJ, Gabreels-Festen A, Gabreels F, Goris RJA. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. Neurology 1998;51:20–5.

[8] Xanthos DN, Coderre TJ. Sympathetic vasoconstrictor antagonism and vasodilatation relieve mechanical allodynia in rats with chronic postischemia pain. J Pain 2008;9:423–33.

[9] Xanthos DN, Bennett GJ, Coderre TJ. Norepinephrine-induced nociception and vasoconstrictor hypersensitivity in rats with chronic post-ischemia pain. Pain 2008;137:640–51.

[10] Eisenberg E, Shtahl S, Geller R, Reznick AZ, Sharf O, Ravbinovich M, Erenreich A, Nagler RM. Serum and salivary oxidative analysis in Complex Regional Pain Syndrome. Pain 2008;138:226–32.

Terence J. Coderre
Department of Anesthesia,
McGill University, Montreal, Que., Canada
The Alan Edwards Centre for Research on Pain,
McGill University, Montreal, Que., Canada

Gary J. Bennett
Department of Anesthesia, McGill University,
Montreal, Que., Canada
The Alan Edwards Centre for Research on Pain,
McGill University, Montreal, Que., Canada
Faculty of Dentistry, McGill University,
Montreal, Que., Canada
E-mail address: gary.bennett@mcgill.ca