

Tissue Acidosis and Persistent Pain Mechanisms CME/CE

Disclosures

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At a basic science symposium moderated by Timothy Brennan, MD, PhD, participants discussed the role of tissue acidosis and other mediators in the development of persistent pain. Inflammation results from the release of a complex mixture of cytokines and other neuroactive agents at the injury site.^[1] Postoperative pain arising from acute incisional tissue damage exhibits molecular mechanisms similar to inflammation.^[2] At the site of tissue injury, chemically diverse mediators act on specific receptors and on the ion channels of nociceptor terminals to elicit a pain response (Figure). These mediators include adenosine triphosphate (ATP) and protons released from damaged cells, serotonin and prostaglandins released from mast cells, and cytokines and nerve growth factor released from macrophages. When stimulated, the primary afferent fibers themselves contribute to the inflammatory response by releasing substance P and calcitonin gene-related peptide (CGRP). These neuropeptides initiate a neurogenic response within the periphery and act on some inflammatory cells, augmenting the system further.^[3] Some of the ion channels and receptors that transduce nociceptive information are activated or sensitized by protons.

It has long been presumed that tissue pH is reduced at the site of injury, but experimental evidence of this has been slight. In a well-performed study, Dr. Timothy Brennan^[2] quantified tissue pH in an animal model of postoperative incisional pain. He showed that tissue pH fell from an average of 7.2 before the incision to 6.9 following injury and that this reduction was sustained before recovering to control levels 1 week following injury. This change occurred locally, at the site of injury, and paralleled the increase in and subsequent resolution of pain behavior witnessed in the animals. Such tissue pH differences match well with those perceived as painful in humans (pH 7.0 or less)^[4] and those critical to the initiation of cardiac pain (pH 7.1-6.7).

In elegant work presented by Dr Edwin McCleskey,^[5] he showed that the acid-sensing ion channel 3 (ASIC3) acts as an extremely sensitive pH detector within this range. The channel opens at pH 7.0 and displays steep activation, releasing a massive current -- in fact, one of the largest depolarizing currents present in the nervous system. Thus, ASIC3 is likely to be the molecular transducer of cardiac pain.

A further cause of angina is ischemia resulting from poor blood flow caused by blocked arteries. Dr. Brennan^[2] has shown that lactate, a key mediator of ischemic pain,^[6] doubles in concentration in damaged tissue, and Dr McCleskey^[5] demonstrated that lactate can act directly on ASIC3 to further enhance currents. ATP was also shown to modulate ASIC3, although it acted indirectly through another receptor to increase channel sensitivity.

However, ASIC3 is not the only channel in the body able to sense a reduction in tissue pH. Dr. Peter Reeh^[7] detailed other exciting work that examined the central role of the vanilloid receptor, TRPV1 in proton detection. The TRPV1 channel is a sensory receptor for noxious heat.^[8] This receptor is also activated by capsaicin, the pungent ingredient in chili peppers, and is modulated by protons. Dr Peter Reeh^[7] has shown that in mutant mice, which lack this receptor, the behavioral writhing response elicited

by acetic acid injected into the peritoneum is significantly reduced. He went on to show that normally CGRP is released in relatively high quantities by the neurons of the sciatic nerve in response to acid (pH 6.1-5.2), but in the TRPV1 knockout animals this response was completely abolished. Neurons innervating the skin, dura mater, esophagus, and heart also showed no proton-induced CGRP release in the TRPV1^{-/-} animals. TRPV1 is therefore a vital mediator of neurogenic inflammation and proton levels can govern its action.

Understanding the processes induced by tissue acidosis is central to the development of drugs that will treat this component of chronic pain. Selective ASIC3 channel blockers, for instance, could bring side-effect-free treatment for sufferers of angina, which affects 6 million people within the United States alone.

References

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