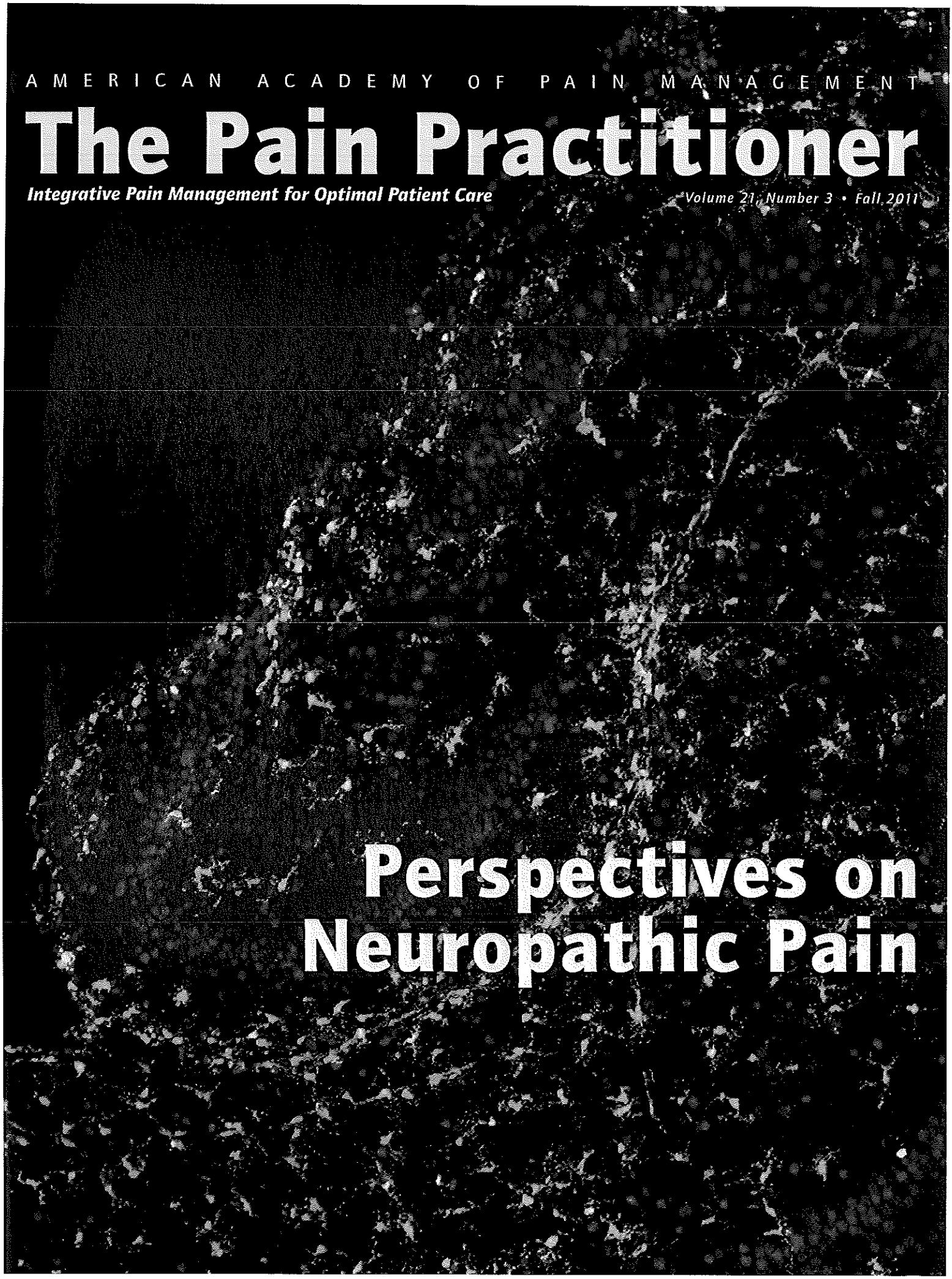
AMERICAN ACADEMY OF PAIN MANAGEMENT

The Pain Practitioner

Integrative Pain Management for Optimal Patient Care

Volume 21, Number 3 • Fall 2011



Perspectives on Neuropathic Pain

Acupuncture Energetics: Clues to an Expanded View of Somatovisceral Homeostasis

By JOSEPH AUDETTE, MA, MD

Based on a presentation at the Academy's 2010 Annual Clinical Meeting.

There are a number of recognized therapeutic effects of acupuncture including hormonal effects via the hypothalamic-pituitary-adrenal axis and the widely appreciated endorphin effect (1-3). However, from a practitioner's point of view, these mechanisms of action are less helpful when considering how to individualize a treatment. Recent advances in the understanding of the neuromodulatory effect of acupuncture and the growing understanding of how our nervous system integrates information from both visceral and somatic afferents provide us with an expanded view of the neuroanatomy of pain. This expanded view provides the basis to scientifically ground our experience as a practitioner within the construct called Acupuncture Energetics and supports the importance of an individualized treatment approach.

An Expanded View of the Pain Modulatory System

In our traditional view of the neuroanatomy of pain, the peripheral nociceptor is a passive structure that lies in wait for tissue injury, and then has the primary role of signaling the Central Nervous System (CNS) via the dorsal horn. The signal then ascends via a second order neuron along the spinothalamic tract to the thalamus and finally reaches the level of perception in the somatosensory cortex. According to this standard view, this strong pain signal then, in essence, wakes up the CNS pain modulatory response and activates the descending pain pathways—from the hypothalamus to the periaqueductal grey region (PAG), the raphe nucleus in the medulla, and finally back down to the dorsal horn where the pain signal can be inhibited.

However, this traditional view underestimates the extent to which the apparatus of the pain neuromodulatory system is in a continually active state, integrating information from the peripheral tissues, the viscera, the CNS, and the immune and hormonal systems to help maintain homeostasis. By expanding our view to include the energetics of acupuncture, we can begin to appreciate the clues to the patient's overall health that subtle palpation of the skin and underlying muscle and fascia can provide. Theoretically, the responsiveness of the surface energetics is so finely tuned that careful palpation can direct us toward pathology that may still be in an emergent state—not fully apparent based on traditional measures of disease used in Western medicine.

State Dependent Effects of Acupuncture

From the point of view of acupuncture energetics, the degree of sensitivity of the superficial somatic structures of the body to palpation or needle stimulation is in a continual dynamic flux. The energetics of an acupuncture point, or the responsiveness to needle stimulation, will change dramatically depending on the underlying health of the organism. To highlight how the pain neuromodulatory system can alter the surface energetics of an acupuncture point in response to pathology, we can look to the phenomenon of the state-dependent effects of acupuncture stimulation. For example, in a study on carpal tunnel syndrome (CTS), we have demonstrated a differential effect on brain activation when comparing CTS patients with healthy controls when stimulating either with a verum acupuncture technique at Large Intestine 4 (Hegu) or with sham acupuncture. When plotting the interaction between stimulation technique (verum versus sham) and level of brain activation in the hypothalamus or the amygdala, we were able to show that the response in the CTS group to verum stimulation at LI4 caused activation of the hypothalamus and deactivation of the amygdala. Sham stimulation had the opposite effect, causing deactivation of the hypothalamus and activation of the amygdala (see Figure 1). In contrast, the healthy control group had the exact opposite activation pattern, ie, deactivation of the hypothalamus

and activation of the amygdala with verum acupuncture. and activation of the hypothalamus and deactivation of the amygdala with sham acupuncture (4).

This dramatically different physiological response to needle stimulation of the same acupuncture point based on the health, or state, of the organism has been demonstrated in other disease models (5). The variability of how an individual with and without a disease process responds to needle stimulation casts doubt on the clinical relevance of findings that are derived from studies on healthy human subjects or animal models. In addition, the state-dependent effect of acupuncture provides important clues about the adaptability of the neuromodulatory system in response to a pathological process. It is these subtle changes in the nervous system and their effects on the somatic tissues that an acupuncturist is trained to detect with surface palpation. To better understand the role of the nervous system in integrating information from throughout the body we must consider the physiological basis of somatovisceral relationships.

Central and Peripheral Sensitization

We know, for example, that in an extremely stress-reactive state, an individual's descending pain modulation system can switch from inhibiting to facilitating the response to a pain signal. This switch has been found to occur at the level of the midbrain, in the region of the raphe nucleus where Field's group found that there are "on" and "off" cells (6). The relative degree of central inhibition or facilitation can also be modulated by changes in hormone status or changes in the immune system (7). In fact, the system can become so facilitated that even in the absence of tissue injury, the nervous system can cause peripheral sensitization via a phenomenon called dorsal root reflexes (DRRs) (9). Thus, in contrast to the normal afferent flow of sensory information from the periphery to the CNS, neuronal activity generated within the CNS can cause signals to travel antidromically, toward the periphery, along the sensory fibers.

Peng et al. demonstrated that stimulation of the PAG can lead to multisegmental activation of the dorsal roots, causing retrograde release of neuropeptides in the periphery and neurogenic inflammation (8). Neurogenic inflammation is inflammation evoked by activities of primary afferent fibers (PAFs), specifically by Aδ and C-fibers, causing the release of the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP). SP and CGRP have been shown to be key agents in the etiology of neurogenic inflammation. It has been demonstrated that SP acts on venules to cause plasma leakage and CGRP acts on arterioles producing vasodilatation (9). In addition, SP and CGRP induce a cascade of chemical activity that leads to elevated levels of histamine, bradykinin, protons, and various cytokines

Figure 1

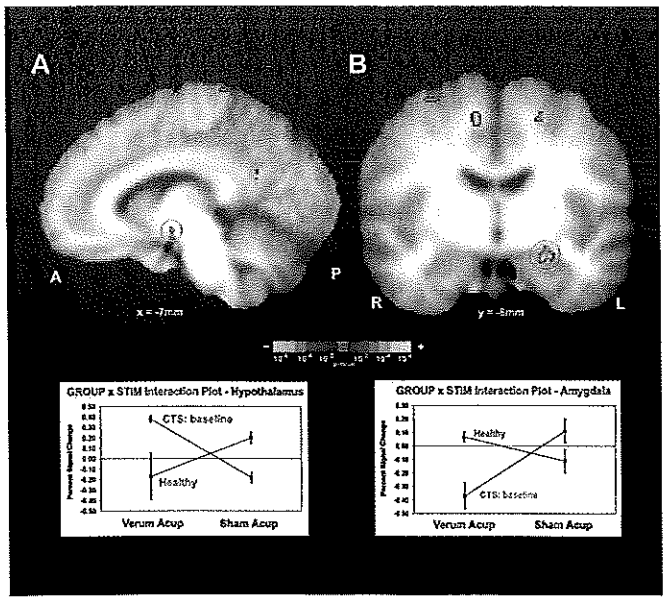
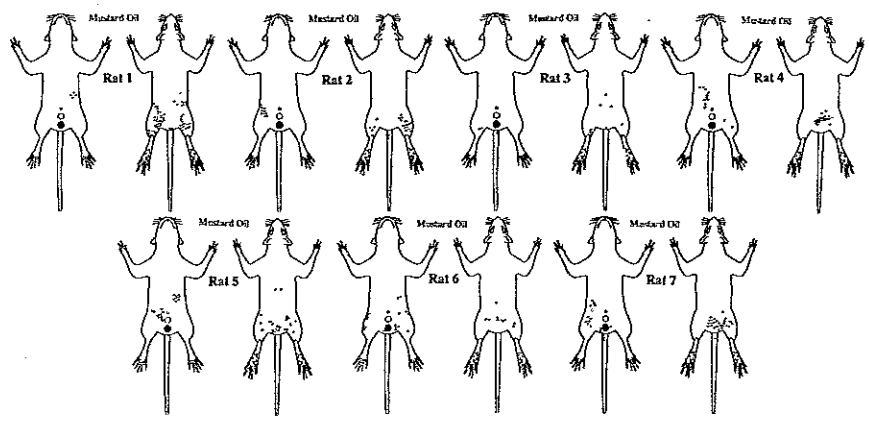


Figure 2



that can induce peripheral sensitization. The role of the PAFs in regulating vasodilitation is critical in healthy organism, as the vasodilatory effects of SP and CGRP can act to balance the effects of the sympathetic nervous system on the peripheral vascular system. As the sympathetic nervous system becomes more active, the smooth muscles contract, causing constriction of arteries (10). Thus, both antidromic vasodilatation via tonic activity of the PAFs and sympathetic vasoconstriction interact with each other to maintain the state of blood perfusion in peripheral somatic tissue. Peng also describes DRRs in response to noxious visceral stimulation with a multisegmental spread, above and below the primary root level of input (11). The presence of DRRs in an animal model of pelvic pain is beautifully demonstrated by Wesselmannn (12). Rats were pretreated with Evans Blue Dye and then mustard oil was applied to the uterine wall, leading to a strong afferent nociceptive barrage to the dorsal horn. The rats then developed punctate areas of dye extravasation in the perilumbar and pelvic region with some rats even developing these punctate areas in the lower limbs (see Figure 2). This demonstrates how visceral disease can lead to antidromic activation of the somatic branch of the PAFs to cause areas of neurogenically induced plasma extravasation in the skin. Much of the integration between visceral and somatic inputs occur in the wide dynamic range neurons in the dorsal horn, where single neurons receive input from viscera, muscle, joint and cutaneous PAFs. Although, in Wesselmann's study the muscles were not biopsied to assess for focal areas of dye extravasation, presumably the root segments influenced by the DRRs would have led to retrograde activation of both muscle and cutaneous PAFs.

Neurogenic Inflammation and an *Active* Point

Another feature of neurogenic inflammation is that the nerve ending becomes sensitized and will respond with an exaggerated response to minimal sensory input. More specifically, when applied to the previously described study of uterine pain, the pattern of extravasated dye reveals distinct areas in the skin where minimal needle stimulation would lead to a strong afferent response, whereas regions of the skin where the dye did not extravasate would presumably have more muted responses. What is interesting is that each rat had a unique pattern of cutaneous trophedema, or dye extravasation. From an acupuncture point of view, the underlying visceral disease (uterine inflammation) led to a unique pattern of active points that became active due to the DRRs. By careful palpation of the surface energetics of the animal, assessing the skin turgor, looking for areas of trophedema and muscular irritability, we can learn about the underlying pathology. This highlights our previous discussion about the state-dependent effect of acupuncture. In a healthy rat, the areas in the leg and pelvis may be inert, and needle stimulation to these points would produce a less profound response or even the equivalent of a sham response on the pain neuromodulatory system. In the rats treated with mustard oil, suddenly a whole array of points activated that are unique to that particular rat. These points can only be discovered with careful palpation that when stimulated, would theoretically have a strong influence on the altered pain neuromodulatory system of the animal. If these rats were hypothetically treated using a typical randomized controlled study design that included a verum or authentic acupuncture treatment based Traditional Chinese Medicine (TCM) theory versus a sham acupuncture protocol, then you would run the risk with the sham protocol of putting a needle directly into a point that has become sensitized and responds strongly to even minimal needle stimulation. Although Wesselmann's study focused on the neurogenic inflammation in the skin, there is evidence that the same process occurs in the muscles of an active point. Shah et al. have done seminal work using a 32-gauge

microdialysis acupuncture needle that is capable of collecting small volumes (~ 0.5 μl), and sub-nanogram levels of solutes <75kDa, from muscle tissue in vivo (13). With this device, the biochemical milieu of an active myofascial trigger point (MTrP) in the trapezius at Gallbladder 21 (Jianjing) can be sampled and compared to subjects with no pain or muscle tightness in the Gallbladder 21 region. The diagnosis of an active MTrP requires careful palpatory examination to determine whether the muscle has certain characteristics of an *active* point, including localized pain in a taut band of muscle associated with excessive muscle irritability as manifest by being able to induce a local twitch response with cross-fiber stimulation of the taut band. The main outcome measures were concentration levels of protons (pH), SP, CGRP, bradykinin, serotonin, norepinephrine, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), all of which were significantly elevated in the subjects with active MTrP when compared to subjects with latent MTrP (no pain at rest, but with a taut band in the trapezius) or healthy controls (no pain at rest and a supple trapezius muscle). If Gallbladder 21 were thought to be a useful point based on TCM theory to treat headaches or liver disease but lacked the palpatory findings or surface energetics of an *active* point, then treatment of this point may be no better than a sham or placebo treatment. Conversely, in examining the surface energetics of a patient with known liver disease, the visceral sensory afferents as well as the somatic afferents from the right diaphragm due to the swollen liver may lead to the activation of Gallbladder 21 through the mechanism of DRRs and neurogenic inflammation. In this situation, minimal needle stimulation would have a profound effect on the CNS and pain neuromodulatory system.

Stimulation of Active Points and Reversal of Disease

The question of whether acupuncture stimulation can reverse the process of central sensitization has been demonstrated in animal models of chronic pain. c-Fos gene expression in the CNS occurs in cells felt to be activated after noxious peripheral stimulation. Fos protein is the nuclear product of the immediate-early gene c-Fos and couples transient intracellular signals to long-term changes in gene expression, which heralds pathological neuroplastic changes in the CNS. EA significantly inhibited spinal cord Fos expression in laminae I–II and V-VI in animal models of chronic pain (14).

The data in animal models suggests that acupuncture strongly activates the descending inhibitory system and can suppress hyperalgesia and spinal Fos expression during peripheral inflammation. There is also evidence to suggest that point specificity is important. For example in a study of inflammatory pain in the hind foot of a rat, Gallbladder 30 produced significant antihyperalgesia, while Triple Warmer 5 (Waiguan) and sham points, an abdominal point, and a point off meridian near GB30 did not (15).

This supports the clinical utility of an Acupuncture Energetic approach, where careful surface palpation is used to find the *active* points and then, by applying needle stimulation, one can provide a sensory conditioning stimulus to reduce central and peripheral sensitization and modulate pain. We have been able to demonstrate this effect in CTS, where peripheral electrical stimulation of digit 3 in subjects with CTS produced an enhanced or exaggerated cortical response on brain imaging. After a course of acupuncture, the brain response to peripheral stimulation of digit 3 approached that seen in healthy normal controls (4).

In summary, with an enhanced view of the neuroanatomy of pain, we can better comprehend the phenomenology of an *active* acupuncture point and the value of careful surface palpation of the body to individualize treatment and discover the underlying state of health the organism. In addition, this model helps us to better understand the hazards of study designs that compare fixed acupuncture points derived from TCM theory as they may be no better than sham treatment points if palpatory techniques are not used to verify the existence of an *active* point. ■

JOSEPH F. AUDETTE, MA, MD, is Chief of the Department of Pain Medicine at Harvard Vanguard Associates and Assistant Professor at Harvard Medical School in Boston, Massachusetts.
Dr. Audette is board certified in physical medicine and rehabilitation and in pain medicine. He also received training at the Tristate School of Traditional Chinese Acupuncture in New York. His research interests include myofascial pain, acupuncture, and chronic pain, and he has lectured nationally on these topics.
Dr. Audette is the Course Director of the Harvard CME course, *Structural Acupuncture for Physicians*.

REFERENCES

1. Organization of endogenous opiate and nonopiate pain control systems. *Science.* 1982 Jun 11;216(4551):1185-92.
2. Takeshige C, Oka K, Mizuno T, Hisamitsu T, Luo CP, Kobori M, et al. The acupuncture point and its connecting central pathway for producing acupuncture analgesia. *Brain Res Bull.* 1993;30(1-2): 53-67.
3. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia.*Pain Physician.* 2011 Mar-Apr;14(2):145-61.
4. Napadow V, Liu J, Li M, Kettner N, Ryan A, Kwong KK, et al. Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. *Hum Brain Mapp.* 2007 Mar;28(3):159-71.
5. Ballegaard S, Muteki T, Harada H, Ueda N, Tsuda H, Tayama F, et al. Modulatory effect of acupuncture on the cardiovascular system: A cross-over study. *AcupunctElectrother Res.* 1993 Apr-Jun;18(2): 103-15.
6. Fields HL, Malick A, Burstein R. Dorsal horn projection targets of ON and OFF cells in the rostral ventromedial medulla. *J Neurophysiol.* 1995 Oct;74(4):1742-59.
7. Watkins LR, Maier SF. Beyond neurons: Evidence that immune and glial cells contribute to pathological pain states. *Physiol Rev.* 2002 Oct;82(4):981-1011.
8. Peng YB, Kenshalo DR, Gracely RH. Periaqueductal gray-evoked dorsal root reflex is frequency dependent. *Brain Res.* 2003 Jun 27;976(2):217-26.
9. Willis WD, Jr. Dorsal root potentials and dorsal root reflexes: A double-edged sword. *Exp Brain Res.* 1999 Feb;124(4):395-421.
10. Magerl W, Koltzenburg M, Schmitz JM, Handwerker HO. Asymmetry and time-course of cutaneous sympathetic reflex responses following sustained excitation of chemosensitivenociceptors in humans. *J AutonNerv Syst.* 1996 Feb 5;57(1-2):63-72.
11. Peng HY, Chen GD, Tung KC, Lai CY, Hsien MC, Chiu CH, et al. Colon mustard oil instillation induced cross-organ reflex sensitization on the pelvic-urethra reflex activity in rats. *Pain.* 2009 Mar;142(1-2):75-88.
12. Wesselmann U, Lai J. Mechanisms of referred visceral pain: Uterine inflammation in the adult virgin rat results in neurogenic plasma extravasation in the skin. *Pain.* 1997 Dec;73(3):309-17.
13. Shah JP, Phillips TM, Danoff JV, Gerber LH. An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. *J Appl Physiol.* 2005 Nov;99(5):1977-84.
14. Lao L, Zhang G, Wei F, Berman BM, Ren K. Electro-acupuncture attenuates behavioral hyperalgesia and selectively reduces spinal fos protein expression in rats with persistent inflammation. *J Pain.* 2001 Apr;2(2):111-7.
15. Lao L, Zhang RX, Zhang G, Wang X, Berman BM, Ren K. A parametric study of electroacupuncture on persistent hyperalgesia and fos protein expression in rats. *Brain Res.* 2004 Sep 10;1020 (1-2):18-29.