Acupuncture Analgesia: I. The Scientific Basis

Shu-Ming Wang, MD*
Zeev N. Kain, MD, MBA†‡
Paul White, PhD, MD§

Acupuncture has been used in China and other Asian countries for the past 3000 yr. Recently, this technique has been gaining increased popularity among physicians and patients in the United States. Even though acupuncture-induced analgesia is being used in many pain management programs in the United States, the mechanism of action remains unclear. Studies suggest that acupuncture and related techniques trigger a sequence of events that include the release of neurotransmitters, endogenous opioid-like substances, and activation of $c-fos$ within the central nervous system. Recent developments in central nervous system imaging techniques allow scientists to better evaluate the chain of events that occur after acupuncture-induced stimulation. In this review article we examine current biophysiological and imaging studies that explore the mechanisms of acupuncture analgesia.

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Acupuncture is an important part of health care in Asian culture that can be traced back almost 3000 yr. This ancient Chinese intervention consists of applying pressure, needling, heat, and electrical stimulation to specific acupuncture points to restore patients to good health.¹² The practice of acupuncture in the United States was largely limited to Asian ethnic groups until about 30 yr ago. President Richard Nixon’s visit to China in 1972 was the seminal event opening the door to Chinese medical practices. Since that time, there has been a growing interest in integrating acupuncture into Western medical practice.³ In 1992, Congress established the Office of Alternative Medicine. Based upon the results of well-designed and appropriately controlled clinical trials, the National Institutes of Health (NIH), in November 1997, issued a statement that supported the efficacy of acupuncture for specific conditions, such as pain, nausea, and vomiting.⁴ In 1998, acupuncture became the most popular complementary and alternative medicine modality prescribed by Western physicians.⁵ In 1999 the National Center for Complementary and Alternative Medicine was established within the NIH.

Despite the widespread use of acupuncture for pain management, the mechanism of acupuncture-induced analgesia remains unclear. The objective of this review article is to critically evaluate available peer-reviewed scientific literature, examining the neurophysiologic mechanisms and clinical efficacy of acupuncture analgesia. The aim of this article is not to translate the Eastern theory of acupuncture into a Western conceptual framework, but rather to provide a scientific interpretation of acupuncture analgesia and related forms of acupuncture based on peer-reviewed basic science and clinical research. We will focus on recent developments, including imaging studies, to complement other recent reviews of the biological basis of acupuncture and its electrical equivalent (electroacupuncture; EA).⁶⁷

TRADITIONAL ACUPUNCTURE THEORY

Traditional Chinese acupuncture is a philosophy that focuses more on prevention than treatment of illnesses. The Chinese medical acupuncture philosophy presumes that there are two opposing and complementary forces that coexist in nature: Yin and Yang. These two forces interact to regulate the flow of “vital energy,” known as Qi. When a person is in “good health,” Yin and Yang are in balance, and the flow of Qi is smooth and regular. When Yin and Yang become “unbalanced,” there are disturbances in Qi, which lead to illness and disease. The ancient Chinese believed that Qi flows through a network of channels called meridians, which bring...
Qi from the internal organs to the skin surface. Along these meridians there are acupuncture points that can be stimulated to correct the imbalance and restore the body to normal health.1

MODERN ACUPUNCTURE THEORY

The traditional Chinese perspective is not based on anatomical, physiological, or biochemical evidence, and thus cannot form the basis of a mechanistic understanding of acupuncture. Western theories are primarily based on the presumption that acupuncture induces signals in afferent nerves that modulate spinal signal transmission and pain perception in the brain.

In 1987, Pomeranz proposed that acupuncture stimulation activates A-δ and C afferent fibers in muscle, causing signals to be transmitted to the spinal cord, which then results in a local release of dynorphin and enkephalins. These afferent pathways propagate to the midbrain, triggering a sequence of excitatory and inhibitory mediators in the spinal cord. The resultant release of neurotransmitters, such as serotonin, dopamine, and norepinephrine onto the spinal cord leads to pre and postsynaptic inhibition and suppression of the pain transmission. When these signals reach the hypothalamus and pituitary, they trigger the release of adrenocorticotropic hormones (ACTH) and endorphins. Pomeranz’s theory was confirmed by a large series of experiments by his research laboratory and other investigators.8–17 This conceptual framework for acupuncture-induced analgesia has also been investigated in a series of neurophysiologic and imaging studies over the last three decades.

Neurophysiological Studies

Volunteer Data

One of the first volunteer studies that examined the scientific basis of acupuncture analgesia was published in 1973 by a group of investigators who used a model of acute pain mediated by potassium iontophoresis with gradual increases of electrical current.9 The volunteers were randomized to receive acupuncture at large intestine 4 (LI4) (Fig. 1) and stomach 36 (ST36) (Fig. 2) or IM morphine. The investigators found that both acupuncture and morphine increased the subjects’ pain threshold by an average of 80%–90%. The acupuncture-induced increase in the pain threshold was gradual, with a peak effect at 20–40 min, followed by an exponential decay with a half-life of approximately 16 min, despite continued acupuncture stimulation.9 Impor-tantly, when the researchers injected local anesthetic into these acupuncture points before the stimulation, the acupuncture became ineffective in increasing the pain threshold (Fig. 3). This suggested that an intact sensory nervous system is essential for the transmission of acupuncture signals. The investigators also found that the analgesic effect was the same regardless of which side of the body was stimulated. Finally, a greater cumulative effect was observed when multiple acupuncture points were stimulated simultaneously.

In a follow-up study, Lim et al.10 found that direct stimulation of peripheral nerve sensory fibers increased the pain threshold in a manner similar to that caused by standard acupuncture technique. These findings are remarkably consistent with the findings from a more recent clinical study involving the use of transcutaneous electrical stimulation for minimizing postoperative pain.18

Experimental Data

The difficulty in developing suitable animal models has been one of the major obstacles in the experimental study of the mechanism of acupuncture anesthesia.11 Professor Han and his colleagues at Peking

Figure 1. The locations of acupuncture points: large intestine 4 (LI4) and lung 5 (Lu 5).

Figure 2. The locations of acupuncture points: gallbladder 34 (GB34) and stomach 36 (ST36).
University performed multiple trials using various animal models in search of the ideal experimental model for acupuncture research. The investigators initially used a rabbit model, but later adopted a rat model because rats are commonly used in pain research and are easier to handle.

In 1973, Professor Han and his colleagues applied acupuncture stimulation to a rabbit for 30 min to achieve an analgesic effect. The cerebrospinal fluid (CSF) was then removed and infused into the lateral ventricle of an acupuncture-naive recipient rabbit. This resulted in an increase in the pain threshold in the recipient rabbit. The investigators concluded that acupuncture-induced analgesia was associated with the release of neuromodulatory substances into the CSF. The investigators also noted that there was no increase in analgesic response when saline or CSF from nonacupuncture control was infused into an acupuncture-naive recipient rabbit.

In 1976, Pomeranz and Chiu, using a mouse model, found that administration of the opioid antagonist-naloxone blocked the acupuncture-induced analgesic activity. Similarly, in a human model, Sjølund and Ericksson, as well as Mayer, were able to demonstrate increased levels of endorphins in CSF after EA stimulation, and the reversal of acupuncture analgesia by naloxone. This again suggested the involvement of endorphins in human acupuncture analgesia. Several subsequent studies supported the hypothesis that acupuncture triggers the release of endorphins and other endogenous opioids within the central nervous system (CNS), and this appears to be responsible for the analgesic properties of acupuncture. Recent EA studies also indicate that low-frequency EA induces the release of enkephalin and β-endorphin, whereas high-frequency EA induces the release of dynorphin.

The development of tolerance to EA analgesia was first described in 1979 after the observation that the duration of the acupuncture analgesic effect was not directly correlated to the duration of acupuncture administration. In a follow-up study, this research group described that EA applied to a rat model for a 30-min period increased the pain threshold by 89%. When the EA stimulation was repeated over six consecutive sessions with 30 min between each session, however, the resulting analgesic effect diminished progressively and eventually returned to a baseline level. This tolerance to acupuncture analgesia is thought to be the result of desensitization or “down regulation” of CNS opioid receptors, as well as the release of antiopioids such as cholecystokinin octapeptide. Subsequently, Han et al. were able to reverse acupuncture tolerance by an intraventricular injection of cholecystokinin antiserum in a group of rats which received continuous 6-h EA stimulation.

Guo et al. investigated whether high-frequency EA differs from low-frequency EA in gene expression using c-fos as a marker of activation in various parts of the rat brain. These investigators found that low-frequency EA resulted in much higher c-fos expression in the arcuate nucleus when compared with that after high-frequency stimulation, and when compared with that after simple needle insertion into an acupoint without electrical stimulation in a control group. In situ hybridization studies revealed that low-frequency stimulation increased the expression of messenger RNA for the enkephalin precursor protein, whereas high-frequency stimulation increased the expression of mRNA for the dynorphin precursor protein. Thus, there appear to be differential effects of low versus high-frequency EA stimulation on c-fos expression, as well as on the transcription of mRNA by various opioid genes in the brain. However, c-fos expression can also be caused by nonspecific stimulations (e.g., immobilization or handling of the animal). Furthermore, mRNA levels may not correlate with actual peptide levels. It is important to note that while these studies suggest EA analgesia is at least partly mediated through endogenous opioids, further work is required. For example, it is possible that acupuncture needles simply function as electrodes, and that the endogenous opioid production is a result of electrostimulation with no relationship to acupuncture.

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1Direct communication with Professor Han, January 2007.
Pan et al.31–33 studied whether there is an overlap of central pathways between noxious stimulation and acupuncture stimulation in rats. These investigators found that noxious stimulation (caused by immersing the footpad into 52°C water) and EA (4 Hz) both induced c-fos expression in the anterior lobe of the pituitary gland and in the arcuate nucleus as well as in nearby hypothalamic nuclei. These researchers also found similar c-fos expression in the anterior lobe of the pituitary gland in response to immobilization stress in awake rats. It seems that, although the anterior pituitary cells that respond to stress are activated by both acupuncture and pain stimulation, the mechanism of pituitary cell activation seems distinct from the activation occurring in stress because different hypothalamus nuclei are involved.31 A follow-up study by the same research team was conducted to identify the function of these activated pituitary cells.32 The investigators found that fos-immunoreactive cells activated by noxious stimulation or EA, co-localized with adrenocorticotropic hormone or thyroid-stimulating hormone, and that noxious stimulation and EA were associated with a similar rise in plasma adrenocorticotropic hormone and β-endorphin. At the hypothalamic level, c-fos expression was increased in the mediobasal nuclei (mainly arcuate nucleus and adjacent nuclei) and in the para-ventricular nucleus after EA stimulation, but not after noxious stimulation. These data suggested that both somatosensory noxious input and EA activate the hypothalamic-pituitary-adrenocortical axis analogously to stress, but with a specific activation of the mediobasal hypothalamic nuclei, and no activation of intermediate lobe.

Pan et al.33 confirmed that intact nociceptive primary afferent input is needed to transmit both EA and noxious stimulation signals to the CNS. These investigators found that neither noxious stimulation nor EA stimulation activated the hypothalamic-pituitary-adrenocortical axis or increased plasma ACTH in rats after sensory deafferentation by subcutaneous capsicain injection to eliminate nociceptive primary afferent input. In contrast, immobilization stress caused a decrease in c-fos activation in the hypothalamic pituitary, with no decrease in plasma ACTH.33 Thus, both noxious stimulation (i.e., pain) and EA activated the hypothalamic-pituitary-adrenocortical axis in a similar fashion. Thus, there appears to be a significant overlap in pain and acupuncture central pathways.

Choi et al.34 studied the effects of three frequencies of EA (2, 15, and 120 Hz) on chemically induced inflammation of the rat hindpaw. These investigators found that the edema and mechanical sensitivity of rats’ hindpaws were strongly inhibited by EA through modulating expression of ionotropic glutamate receptors, particularly N-methyl-D-aspartate receptor in the dorsal horn of the spinal cord. Unfortunately, there was no sham-control intervention in this study. Therefore, the phenomena observed may not directly relate to acupuncture alone.

Several conclusions can be made based on the above neurophysiologic studies. First, afferent nociceptive pathways are essential for acupuncture analgesia. Second, acupuncture analgesia is mediated by way of various endogenous neurotransmitters, systemic release of enkephalin and dynorphin, and probably by decreasing the local inflammatory response via N-methyl-D-aspartate receptors. Third, the acupuncture-induced increase in pain threshold is gradual, with a peak effect at 20–40 min, followed by an exponential decay with a half-life of approximately 16 min. Fourth, a prolonged period of acupuncture stimulation results in tolerance that is mediated via release of cholecystokinin octapeptide. Lastly, immunocytochemistry studies indicate that both pain and acupuncture activate the hypothalamic-pituitary-adrenocortical axis.

CNS Imaging Studies

Over the last decade, advanced imaging technologies have been introduced, including positron emission tomography (PET), single-proton emission computer tomography (SPECT), and functional magnetic resonance imaging (fMRI). These powerful imaging technologies have made it possible to noninvasively visualize the anatomic and functional effects of acupuncture stimulation in the human brain.

PET Studies

Using PET imaging, Alavi et al.35 observed that a group of patients who suffered from chronic pain also had asymmetry of the thalamus. This thalamic asymmetry disappeared after acupuncture treatment. One should note, however, that the study did not include a sham-control group. As a result, the PET-related changes do not necessarily indicate a cause-effect relationship.

The “De Qi” sensation is frequently described by patients as soreness, numbness, ache, fullness, or warm sensation that is achieved during manipulation of the acupuncture needles.1,2 This sensation coincides with acupuncturists describing a feeling of the needle being caught as it is twirled (e.g., “the needle is stuck to a magnet”).36 Wang et al.37 suggested that type II afferent fibers are responsible for the sensation of numbness, type III afferent fibers are responsible for fullness (heavy, mild aching), and type IV afferent fibers are responsible for soreness. Hsieh et al.38 used PET images to visualize the effect of De Qi sensation. This study compared acupuncture stimulation at a frequency of 2 Hz that was associated with a De Qi sensation at LI4 (Fig. 1) to the same stimulation at a sham-acupuncture point as control intervention in this study. Therefore, the phenomena observed may not directly relate to acupuncture alone.
a needle at a sham-acupuncture point. The investigators found that only acupuncture stimulation at LI4 with De Qi sensation activated the hypothalamus. Thus, the De Qi at an acupuncture point appears to be the conscious perception of the nociceptive input from the acupuncture stimulation. Biella et al.39 sequentially applied acupuncture and sham acupuncture at bilateral ST36 (Fig. 2) and LI5 (Fig. 1) during a PET scanning sequence and found that acupuncture, but not sham treatment, activated the left anterior cingulum, superior frontal gyrus, bilateral cerebellum, and insula, as well as the right medial and inferior frontal gyri. These are the same areas activated by acute and chronic pain.40–48 This finding suggests a possible mechanism for acupuncture analgesia.

Pariente et al.49 suggested that, in addition to the direct analgesic effect of acupuncture, the anticipation and belief of a patient might also affect the level of therapeutic outcome. Using PET image, these investigators reported that both true and sham acupuncture activated the right dorsolateral prefrontal cortex, anterior cingulated cortex, and midbrain. The investigators suggested that these CNS areas are involved in nonspecific factors such as expectation. The investigators also found, however, that only true acupuncture caused a greater activation in insula ipsilateral to the site of stimulation. Based on the above, one can conclude that the insula region of the brain has a specific role in acupuncture analgesia.

**SPECT Studies**

Newberg et al.50 used radioisotope hexamethylpropyleneamine oxime to image the brain of patients suffering from chronic pain and healthy volunteers without pain. The investigators found significant asymmetric uptake in the thalamic regions of patients with chronic pain, but not in the healthy control group. After 20–25 min of acupuncture stimulation, another hexamethylpropyleneamine oxime was administered to these patients and a repeated SPECT study showed that the original asymmetry reversed or normalized after acupuncture therapy that coincided with the reduction of pain. This finding is analogous to the findings in PET studies reported by Alavi et al.51 and Wu et al.56 reported that both true and sham EA stimulation at a common analgesic acupoint, gallbladder 34 (Fig. 2), activated regions of the amygdala, hippocampus, ventral tegmental area, anterior cingular gyrus, caudate, putamen, temporal lobe, and insula. In a follow-up fMRI study, Hui et al.53 explored the subjective psychophysical perceptions (mainly, the conscious perception of the nociceptive input from the acupuncture stimulation) in relation to the CNS responses. They found that subjects who experienced De Qi deactivated the frontal pole, ventromedial prefrontal cortex, cingulate cortex, hypothalamus, reticular formation, and the cerebellar vermis. Subjects who experienced pain instead of De Qi sensation activated the anterior cingular gyrus, caudate, putamen, and anterior thalamus. When these subjects experienced both De Qi and pain, the CNS responses were mixed with predominance of activation at the frontal pole, anterior, middle, and posterior cingulate (Fig. 4). Based on the above studies, these investigators suggest that acupuncture and pain may share similar central pathways, but CNS activities triggered by these two stimulations are opposite to each other. Support for this hypothesis is provided by an fMRI study that showed that EA stimulation can modify signals generated by experimental cold pain stimulation.54

Of note are the reported discrepancies between the findings of Wu et al. and Hui et al. with respect to the effect of acupuncture on the hypothalamus and nucleus accumbens. There are several possible reasons for the discrepancies between the two studies. First, duration of acupuncture stimulation was different between these studies (1 min vs 2 min). Second, the conscious perceptions of nociceptive input from acupuncture stimulation experienced by study subjects might be different between these studies. Finally, there might be differences in methodology of fMRI image analysis e.g., correction of motion artifact and threshold setting for noise between these two laboratories.

Ulett et al.6 suggested in 1998 that the periaqueductal gray (PAG) region in the brainstem is associated with perception and modulation of noxious stimuli and has an important role in acupuncture analgesia. In an effort to explore these issues using fMRI technology, Liu et al.55 applied acupuncture stimulation to healthy volunteers at LI4 and observed that PAG activity increased with the increasing length of stimulation, with the activated areas ranging from the left ventral to left dorsal lateral to dorsal medial regions. The frequency of activation of PAG after stimulation of the LI4 was calculated by averaging the total number of activations per run (every run consisted four 30-s periods of “acupuncture on”). These investigators also observed that stimulation at a nonacupuncture point resulted in reduction of PAG activity.

**EA Stimulation.** Wu et al.56 reported that both true and sham EA stimulation at a common analgesic acupoint, gallbladder 34 (Fig. 2), activated regions of pain central pathways on fMRI.56 The investigators noted, however, that only true EA stimulation activated the hypothalamus, the primary somatosensory
cortex and the motor cortex, and deactivated the rostral segment of the anterior cingulate cortex. These investigators concluded that the hypothalamus-limbic system was modulated by EA stimulation.

To investigate the direct modulatory effects of EA stimulation in pain responses, Zhang et al.\textsuperscript{54} studied a group of healthy volunteers using fMRI scanning during experimental cold pain with real or sham EA stimulation. Only the subjects who received EA reported a reduction of pain. The brain images obtained by Zhang et al. showed an acupuncture-induced increased activation in the bilateral somatosensory area, medial prefrontal cortices and Brodmann area (BA32), and a decreased activation in the contralateral primary somatosensory areas BA7 and BA24 (anterior cingulated gyrus). With sham stimulation, there was no observed decrease in pain intensity or fMRI image changes. As these areas are frequently involved in pain stimulation, Zhang et al. concluded that EA induces analgesic effects via modulation of both the sensory and emotional aspects of pain processing. This study again demonstrates

**Figure 4.** The influence of subjective sensations on fMRI signal changes on major limbic structures, the secondary somatosensory cortex (SII) and the cerebellum during acupuncture at ST 36. Regions of interest are denoted by yellow arrowheads. (Left) Acupuncture with deqi sensations ($N = 11$). (Middle) Acupuncture with mixed sensations of deqi and sharp pain ($N = 4$). (Right) Sensory control ($N = 5$).

Table 1. The Areas of Brain Affected by Acupuncture Stimulation in Imaging Studies

<table>
<thead>
<tr>
<th>Limbic system</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingular gyrus</td>
<td>39,50–54,56,57</td>
</tr>
<tr>
<td>Amygdala</td>
<td>51,52,54</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>51,52</td>
</tr>
<tr>
<td>Hippocampal gyrus</td>
<td>51,52,57</td>
</tr>
<tr>
<td>Insula</td>
<td>38,49,52,53,56,57</td>
</tr>
<tr>
<td>Periaqueductal gray</td>
<td>38,55</td>
</tr>
<tr>
<td>Thalamus</td>
<td>35,39,50,54,56,57</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>38,39,51,56</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>52–54</td>
</tr>
<tr>
<td>Caudate</td>
<td>52,53</td>
</tr>
<tr>
<td>Neucleus accumbens</td>
<td>39,51–53</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>38,39,52–54,56</td>
</tr>
<tr>
<td>Brain stem</td>
<td></td>
</tr>
<tr>
<td>Substantis nigra</td>
<td>53</td>
</tr>
<tr>
<td>Reticular formation</td>
<td>53</td>
</tr>
<tr>
<td>Pontine nuclei</td>
<td>53</td>
</tr>
<tr>
<td>Dorsal raphe</td>
<td>53</td>
</tr>
<tr>
<td>Somatosensory II</td>
<td>38,50,52–54,57</td>
</tr>
</tbody>
</table>
that the hypothalamus-limbic system plays an important role in acupuncture analgesia.

An fMRI study by Zhang et al.\textsuperscript{57} found that the low-frequency (2 Hz) EA stimulations activated the contralateral primary motor area, supplementary motor area, and ipsilateral superior temporal gyrus, while deactivating the bilateral hippocampus. In contrast, these investigators found that high-frequency (100 Hz) EA stimulations activated the contralateral inferior parietal lobules, ipsilateral anterior cingulate cortex, nucleus accumbens and pons, while deactivating the contralateral amygdala. Therefore, one can conclude that low and high-frequency EA stimulation appear to be mediated by different brain networks. Thus, alternating high/low-frequency EA stimulations may provide the additional analgesia benefit by activating both systems simultaneously.\textsuperscript{24,58–62}

Studies Comparing Different Acupuncture Stimulations. Napadow et al.\textsuperscript{63} compared manual acupuncture, EA at 2 and 100 Hz, and tactile control stimulation at ST36 in a group of healthy volunteers. They reported that low-frequency EA produced more widespread fMRI signal changes than manual acupuncture stimulation. Not surprisingly, both EA and manual acupuncture produced more widespread responses than simple tactile stimulation. These investigators also found that although acupuncture stimulation activated the anterior insula, it deactivated the limbic and paralimbic structures that include the amygdala, anterior hippocampus, cortices of the subgenual and retrocingulate, ventromedial prefrontal cortex, and frontal and temporal lobes.\textsuperscript{63} EA at both high and low frequencies produced a significant signal increase in the anterior middle cingulate cortex; however, only low-frequency EA produced activation at the raphe area. Therefore, fMRI studies support the hypothesis that the limbic system is central to acupuncture-induced analgesia regardless of the specific modalities.

Several conclusions can be made based on the above CNS imaging studies. First, the hypothalamus may play a central role in acupuncture analgesia. Second, the significant overlap between acupuncture and pain CNS pathways suggests that acupuncture stimulation may affect pain signals processed in the CNS. Third, superficial needling and traditional acupuncture needling activate two different central pathways and yet both provide clinical analgesia.\textsuperscript{64–66}

Future studies should focus on their effects in releasing different opioid-like substances as well as differences in the level of pain relief. The majority of neuroimaging studies in acupuncture are merely explorations of acupuncture signal network. The clinical relevance of data obtained from these studies is unclear. Indeed, participants in a recent conference held by the NIH indicated that standardization of performing and reporting acupuncture neuroimaging results and data sharing between laboratories must be improved.\textsuperscript{67}

SUMMARY

Physiological and imaging studies are providing insight into the neurophysiological mechanism of acupuncture analgesia. Recent data suggest that acupuncture triggers a sequence of events involving the release of endogenous opioid-like substances, including enkephalin, β-endorphin, and endomorphin, that modulate pain signals processed along the pathway. Imaging studies demonstrate that the limbic system plays an important role in acupuncture-induced analgesia, as summarized in Table 1 and Figure 5. Future studies will continue to enhance our insight into the mechanism of this ancient analgesic modality.

REFERENCES

58. Hamza MA, White PF, Ahmend HE, Ghoname ES. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. Anesthesiology 1999;91:1232–8