The Neuroimmune Basis of Anti-inflammatory Acupuncture

Ben Kavoussi, MS, and B. Evan Ross, DOM, LAc

This review article presents the evidence that the anti-inflammatory actions of acupuncture are mediated via the reflexive central inhibition of the innate immune system. Both laboratory and clinical evidence have recently shown the existence of a negative feedback loop between the autonomic nervous system and the innate immunity. There is also experimental evidence that the electrical stimulation of the vagus nerve inhibits macrophage activation and the production of TNF, IL-1β, IL-6, IL-18, and other proinflammatory cytokines. It is therefore conceivable that along with hypnosis, meditation, prayer, guided imagery, biofeedback, and the placebo effect, the systemic anti-inflammatory actions of traditional and electro-acupuncture are directly or indirectly mediated by the efferent vagus nerve activation and inflammatory macrophage deactivation. In view of this common physiological mediation, assessing the clinical efficacy of a specific acupuncture regimen using conventional double-blind placebo-controlled trials inherently lacks objectivity due to (1) the uncertainty of ancient rules for needle placement, (2) the diffuse noxious inhibitory control triggered by control-needling at irrelevant points, (3) the possibility of a dose-response relationship between stimulation and effects, and (4) the possibility of inadequate blinding using an inert sham procedure. A more objective assessment of its efficacy could perhaps consist of measuring its effects on the surrogate markers of autonomic tone and inflammation. The use of acupuncture as an adjunct therapy to conventional medical treatment for a number of chronic inflammatory and autoimmune diseases seems plausible and should be validated by confirming its cholinergicity.

Keywords: ***innate immunity; acupuncture; electro-acupuncture; chronic inflammatory disease; cholinergic anti-inflammatory pathway; vagus nerve; acetylcholine; heart rate variability; cytokines; tnf; interleukins***

There are many fields—I shall call them proto-sciences—in which practice does generate testable conclusions but which nevertheless resemble philosophy and the arts rather than the established sciences. . . . In these fields, too, though they satisfy Sir Karl's demarcation criterion, incessant criticism and continual striving for a fresh start are primary forces, and need to be.[1]

—Thomas Kuhn (1922-1996)

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Background

Acupuncture is an ancient healing art that has survived and evolved in the Far East (China) and is currently flourishing in the US and in Europe both as primary and adjunctive therapy for a variety of chronic conditions. It consists of inserting needles at various skin depths into specific points, and stimulating them manually or with a low-voltage electrical current, and heating them with a mugwort incense—according to the tradition—or with a heat lamp—in the modern practice. It might be practiced in conjunction with skin scraping (*gua sha*) or cupping. Laser has recently been used instead of heated needles, but its efficacy remains controversial.[2,3]

Acupuncture is presumed to have its origins in blood ritual, magic tattooing, and body piercing associated with shamanic healing performed during the Neolithic Age (8000-5000 BC) for the purpose of restoring health and safety and protection against demonic infestation and malevolence.[4,5] Sharpened stones and bones discovered in China that have been dated to around 6000 BC and that have been interpreted as acupuncture instruments[6,7] might very well have been used for ritual bloodletting or even for lancing abscesses.[8,9] The shamanic healing hypothesis is further supported by the presence of nonfigurative tattoos on the "Tyrolean Ice Man," a Neolithic native inhabitant of the Oetztal Alps, whose naturally preserved 5200-year-old body displays a set of small cross-shaped tattoos that correspond to current Chinese acupuncture points. Medical imaging shows that the middle-aged man suffered from lumbar arthrosis. The tattoos are located at points traditionally indicated for this condition.[10,11]

The animistic health and safety beliefs of Neolithic shamans have evolved in the Far East into a mechanistic system of therapeutic needling for the adjustment of the vital flow of a putative subtle substance called

BK is at Southern California University of Health Sciences, College of Acupuncture and Oriental Medicine, Whittier, CA. BER is at Cedars-Sinai Medical Center, Department of Medicine, Los Angeles, CA.

Correspondence: Ben Kavoussi, MS, PO Box 72854, Davis, CA, 95617 ; e-mail: kavoussi@ucla.edu.

Qi (pronounced "chee"), that is believed to circulate in a network of 12 primary "channels," also called "tracks," or "meridians," which, like stellar constellations, connect 360 principle points. This art has been practiced in China for thousands of years along with herbal medicine and manipulative therapy (tui-na) and has been conceptualized according to ancient metaphysics, alchemy, astrology, Chinese humoral medicine, numerology, and geomancy (feng shui).[12] Nonetheless, in the 1950s a portion of this vast array of heterogeneous beliefs that were compatible with Marxist dialectical materialism (Yin-Yang theory, etc) was selected and artificially incorporated to create a makeshift medical system to serve the political and public health needs of post-Mao China. It is this makeshift body of knowledge that has been flourishing in the US as "Oriental" or "Traditional Chinese Medicine."[13]

In 1997, the NIH published a Consensus Development Conference Statement summarizing the known actions of acupuncture and acknowledging its efficacy in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain. It also acknowledged its value as an alternative or adjunct treatment for the management of pain and/or inflammation in a variety of conditions such as "addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma."[14] In a large scale study funded by the National Center for Complementary and Alternative Medicine (NCCAM), Berman et al reported the specific benefits of acupuncture for pain relief and functional improvement for knee osteoarthritis. However, there are also many studies that dispute the efficacy of specific acupuncture regimens in pain relief beyond the placebo effect and argue that studies in favor of acupuncture have thus far remained poorly designed and biased.[4,16-18]

Although no single theory has been successful in offering a unified physiological explanation for its effects, many have proposed that the analgesic actions of acupuncture may involve the prevention of pain perception due to a saturation phenomenon that Melzack and Wall have called the "gate control theory."[19,20] An innate mechanism of rebound analgesia after an acute noxious stimulus from the needle, heat, or stimulation, which is called "counter-irritation," "counter-stimulation," or "diffuse noxious inhibitory control" (DNIC), has also been proposed. The acupuncture-induced DNIC is believed to be mediated by the release of endogenous opioid neuropeptides and/or monoaminergic neurotransmitters, mainly because naloxone, a central and peripheral opioid receptor antagonist, is reported to reverse its effects.[3,21-25] DNIC is believed to rely on spino-bulbo-spinal loops that involve the ascending neural pathways in the anterolateral spinal columns, integration in the lower brain stem, and descending influences reaching the dorsal horn neurons via the dorsolateral quadrant of the spinal cord.[26-28] As for the reported anti-inflammatory actions, they have been attributed to an endogenous "counter-inflammation" phenomenon known since the antiquity, in which the effects of a local inflammatory reaction are known to decrease an inflammation at a distant site. Counterinflammation was extensively studied by Fauve et al in the1980s, who showed in mice that it has an effect equivalent or superior to that of glucocorticoids.[29,30]

The Neuroimmune Evidence

An important insight into the physiology of endogenous counterinflammatory mechanisms came from the past 2 decades of research on the pathogenesis of acute inflammation, hypercytokinemia, and fatality associated with severe sepsis and septic shock. Observation and experimentation have shown that the brain and the innate immune system form a bidirectional network via both the neural and humoral pathways, in which the immune system operates as a sensory organ to inform the brain about inflammation and tissue injury, and the brain in return orchestrates a limited and localized inflammatory response.[31-33] This process starts when unmyelinated sensory C fibers found in all major tissues and organs in response to a stimulus release substance P and other proinflammatory tachykinins, induce vasodilation, and increase vascular permeability and leukocyte margination (Figure 1).[34]

According to Matthay and Ware, these peripheral inflammatory events constitute danger signals that are conveyed via a fast transmission pathway involving the afferent vagus nerve to the viscerosensory nucleus tractus solitarius in the brainstem, and also via a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs and diffuse into the brain by volume transmission.[34] The resulting acute stress response from the sympathetic nervous system is mediated directly by the nerve-to-immune-cell interaction, or indirectly by the adrenal neuroendocrine axis. The binding of catecholamine outflow to the β2-adrenergic receptors expressed on immune cells leads to a decrease in proinflammatory (TNF, IL-1β, IL-6, and IL-18) and an increase in anti-inflammatory (IL-10) cytokines, thus controlling the extent of the inflammatory response. The signal is also relayed to the hypothalamus and the dorsal vagal complex to stimulate the release of ACTH, thereby activating the humoral anti-inflammatory pathway (Figure 1).[34]

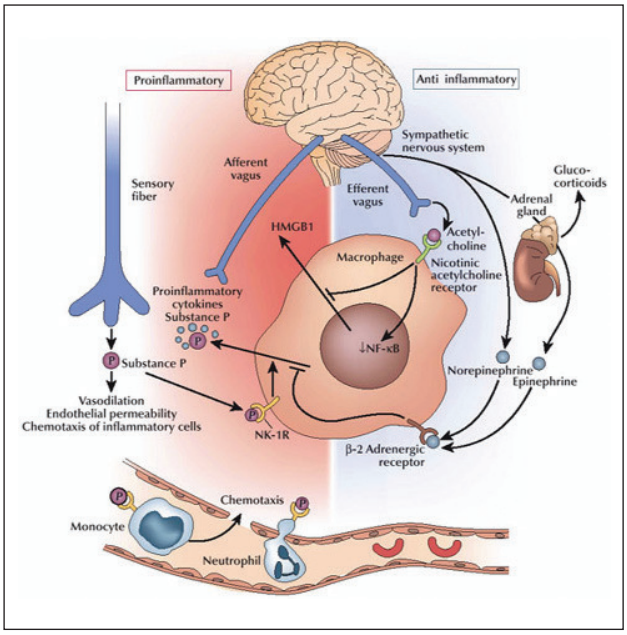

Figure 1 The neural modulation of the innate immune system involves proinflammatory (left) and anti-inflammatory (right) actions. Some of the major pathways are illustrated here. HMGB = high mobility group box; NF-κB = nuclear factor-κB; NK-1R = neurokinin-1 receptor. Image source: Matthay MA, Ware LB.[34] Used by permission of the publisher, Nature Publishing Group. www.nature.com.

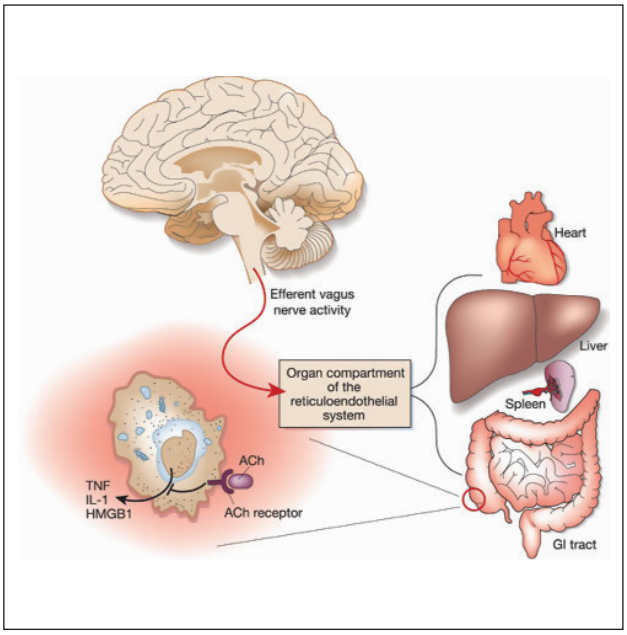

Figure 2. Efferent activity in the vagus nerve leads to acetylcholine (ACh) release in organs of the monocyte-macrophage system, where ACh binds to the α7 nicotinic receptors on tissue macrophages and inhibits the release of proinflammatory cytokines. TNF = tumor necrosis factor; IL-1 = interleukin 1; HMGB = high mobility group box. Source: Tracey KJ (2002).[36] Image used by permission of the publisher, Nature Publishing Group. www.nature.com.

Nonetheless, both laboratory and clinical evidence have shown that it is the parasympathetic nervous system that plays the leading role in the down-regulation of cytokine synthesis and the containment of somatic inflammation. The vagal outflow, which innervates the major organs (including those containing the monocyte- macrophage system, also known as the reticuloendothelial system), has so far been known as the autonomic outflow that keeps the resting heart rate at 60 to 80 bpm and controls the digestive and hormonal activities. Tracey et al found that it also plays a systemic immunoregulatory and homeostatic role called the "cholinergic anti-inflammatory pathway" (Figure 2).[34-37]

They have identified an α7 nicotinic acetylcholine receptor (α7nAChR) expressed on tissue macrophages, to which vagal acetylcholine (ACh) binds in the monocyte-macrophage system to inhibit the synthesis of proinflammatory but not the anti-inflammatory cytokines (Figure 2).[38,39] They have reported that nanomolar concentrations of ACh are sufficient to inhibit the production of proinflammatory cytokines in human macrophage cultures challenged with lipopolysaccharide (LPS). Also, experimental vagotomy in animals is reported to show a significant exacerbation of TNF responses to LPS challenge, causing animals to rapidly succumb to shock.[39]

The parasympathetic origin of the nonspecific anti-inflammatory actions of acupuncture is supported by the observation that the direct electrical stimulation of the efferent vagus nerve in LPS-challenged wild-type mice inhibits the synthesis of TNF in organs rich in cells of the monocyte-macrophage system.[40] Tracey et al also reported that in models of murine acute inflammation and paw swelling, vagus nerve stimulation inhibited the inflammatory response and suppresses the development of swelling.[41-43] Experimental evidence also indicates that the stimulation of the efferent vagus nerve dampens macrophage activation in rodent models of endotoxemia and shock.[35,36] More recently, de Jonge et al used a rat model of postoperative ileus to show that stimulation of the cholinergic anti-inflammatory pathway also attenuates intestinal inflammation and improves gastric motility.[43] The molecular mechanism of this anti-inflammatory effect seems to involve the pathway of the tyrosine kinase Jak2 and the transcription factor STAT3, which is activated via the a7nAChR expressed on gastrointestinal acrophages.[44] In contrast, vagal stimulation is reported to have no effect in knockout

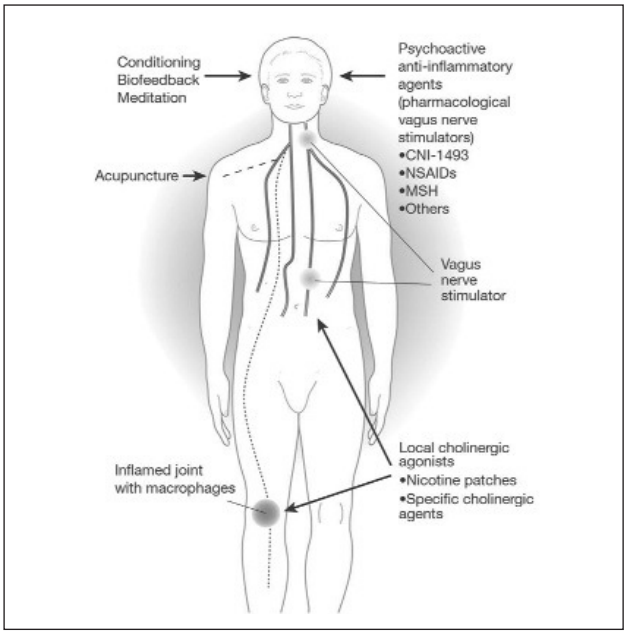

Figure 3. The actions of placebo, hypnosis, meditation, guided imagery, prayer, biofeedback, acupuncture, and other nonpharmaceutical modalities are associated with an increase in the actions of the efferent vagus nerve. Unbroken lines represent known vagus nerve pathways; dotted lines are hypothetical. NSAID = nonsteroidal anti-inflammatory drug; MSH = melanocyte-stimulating hormone; Source: Tracey KJ (2002).[36] Image used by permission of the publisher, Nature Publishing Group. www.nature.com.

mice deficient in macrophage a7nAChR expression, suggesting that it is the binding of vagal ACh to a7nAChR that initiates the down-regulation of innate immunity.[44-46]

The cholinergic anti-inflammatory pathway proposed by Tracey et al could therefore provide a very plausible physiological mechanism for the reported anti-inflammatory actions of acupuncture.[47-49] This pathway would also explain the reported actions of ear acupuncture (auriculotherapy) in treating the symptoms of opiate withdrawal. According to Ulett and Han, the conchea of the ear is the only place on the surface of the body where the vagus nerve could easily be stimulated to produce a "broad parasympathetic effect."[25] The cholinergic anti-inflammatory pathway could also explain the reported antipyretic actions of acupuncture, which are believed to be mediated by the down-regulation of 2 specific cytokines, IL-6 and IL-1β.[50] Moreover, sections of the Stomach and Spleen meridians known to generate parasympathetic stimuli nearly correspond to the known vagus nerve pathways in the supradiaphragmatic and subdiaphragmatic viscera (Figures 3 and 4).[51]

This association would equally explain why, as shown by Teruo Matsumoto in 1974, the stimulation of

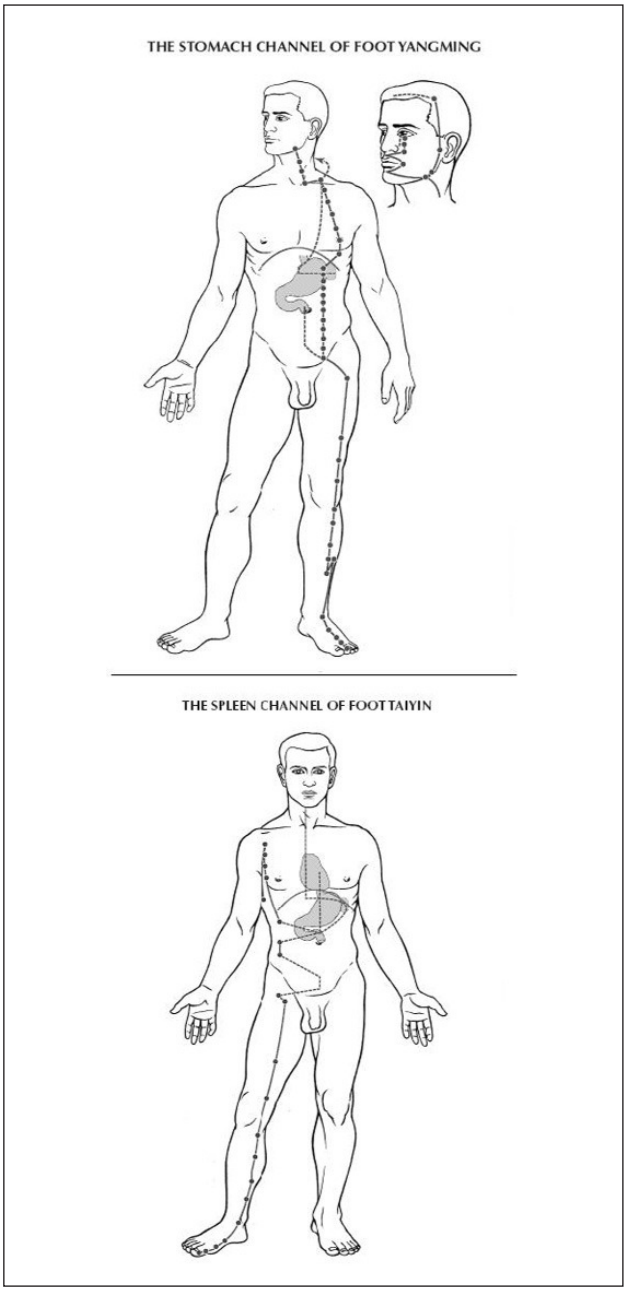

Figure 4. The pathways of the Stomach and Spleen acupuncture channels commonly used in inflammatory conditions nearly correspond to the known and hypothetical vagus nerve pathways. Source: Deadman P et al.[51] Image used by permission of the publisher, JCM Ltd. www.jcm.co.uk.

ST-36, a key point on the Stomach channel (*Zusanli*, 3 inches below the inferior border of the patella and 1 inch lateral to the anterior crest of the tibia), induced peristalsis in postoperative ileus, both in rabbits and in men, and it also reduced the increased peristalsis of the colon after the administration of cholecystokinin 8 (CCK8).[25,52] Noguchi and Hayashi reported in 1996 that the stimulation of ST-36 in anesthetized rats

caused a marked gastric acid enhancement but no response in the rats after vagotomy. They also reported a response amplification after the removal of the spleen, an organ of the monocyte-macrophage system. These results suggested that the stimulation of ST-36 increased gastric acid secretion with somatic nerves as the afferent pathway and branches of the vagus nerve to the stomach as the efferent pathway.[53]

The Epistemological Significance

The systemic inhibition of innate immunity via the parasympathetic outflow as proposed by Tracey et al could ultimately be viewed as the cohesive physiological pathway that would explain the anti-inflammatory actions of an array of nonpharmaceutical modalities, ranging from acupuncture to hypnosis, meditation, prayer, guided imagery, biofeedback, and even the placebo effect (Figure 3).[44] This correlation between acupuncture and placebo directly challenges the objectivity of conventional double-blind placebo-controlled trials for assessing the clinical efficacy of a specific regimen. First, observations by JS Han have indicated that frequencies of stimulation in electroacupuncture are of greater importance than the ancient rules for needle placement.[54,55] Then, Middlekauff et al have confirmed that even needles placed at irrelevant points could have broad physiological effects, "although perhaps to a lesser degree."[56] The control-induced DNIC therefore remains an inherent objectivity issue in acupuncture placebo-controlled trials. Also, the possibility of a dose-response relationship between stimulation and the activation of the cholinergic anti-inflammatory pathway is probable but remains unknown. Finally, the possibility of inadequate blinding using an inert sham procedure also remains an inherent objectivity problem because patients who did not experience a sharp sensation could become aware of their group participation.

This inherent subjectivity is well exemplified in the 2004 double-blind placebo-controlled trials by Berman et al and also by Vas et al to verify the benefits of stimulating specific points for pain relief and functional improvement for knee osteoarthritis. The NCCAM-funded large-scale study by Berman et al involved an intensive acupuncture regimen (23 sessions) for a long period (26 weeks) where 570 patients with a confirmed diagnosis were randomly assigned into (1) a treatment group to receive a tapered acupuncture regimen in 9 relevant points; (2) a first control group to receive 2 needle insertions in irrelevant points on the abdomen, and an inert sham procedure at points utilized in the treatment group; and (3) a second control group to receive educational sessions and learn coping strategies.[15] Although the study was remarkable in many aspects, it has been questioned for several methodological issues, including the potential DNIC effects caused by the insertion of 2 control needles in the abdomen. It was pointed out by RH Baker (personal communication between Berman and Baker, December 24, 2004) that any type of skin irritation and puncture might trigger DNIC effects and that an entirely inert control procedure would have been largely preferable. Moreover, neither Berman et al nor the critics have addressed the possibility of a dose-response relationship between acupuncture stimulation and the activation of the cholinergic anti-inflammatory pathway. Perhaps, if Berman et al had inserted 9 needles instead of 2 in the first control group, especially in the vicinity of the vagus nerve's subdiaphragmatic pathway as they inadvertently did (Figures 3 and 4), they would have obtained results comparable to that of their treatment group. It is also possible that the effects obtained in the treatment group are predominantly due to the electrical stimulation. The smaller European study conducted by Vas et al (88 patients) avoided the possibility of DNIC effects by using an entirely inert sham control, but it also has been questioned for a potential subjectivity in blinding, in that control patients may have become aware of their group assignment.[57]

Inasmuch as assessing the anti-inflammatory actions of a specific acupuncture regimen with conventional placebo-controlled studies inherently lacks objectivity, a paradigm shift to embrace current research methodologies in experimental neuroimmunology is reasonably conceivable. The purpose of a study would then shift to measuring its cholinergicity by determining its effects on the established surrogate markers of autonomic tone, such as the high-frequency spectral component of the instantaneous heart rate variability (HRV).[58,59] Given the reported direct effects of acupuncture on HRV, this approach seems justifiable.[60-63] Perhaps the methodology used by Goldstein et al to measure the HRV and the extent of macrophage activation in patients with rheumatoid arthritis could serve as a model.[64] Their study rationale has been the fact that patients with sepsis, rheumatoid arthritis, lupus, inflammatory bowel disease, and other cytokine-mediated diseases have an impaired parasympathetic tone, which could be observed through an increase in their heart rate and a decrease in their HRV.[65-72] In rheumatoid arthritis, Goldstein et al have also observed an associated macrophage activation, which was determined by measuring the levels of serum cytokines after an in vitro LPS-challenge.[64]

Conclusion

Despite its premodern concepts, the Chinese therapeutic principle of adjusting and harmonizing the internal

elemental/organic environment to achieve stability[73] parallels the modern notion of reestablishing homeostasis by regulating the interactions between the autonomic nervous system, the innate immunity, and several other systems. Ulett and Han have further suggested that certain homeostatic effects of acupuncture and auriculotherapy might be directly explained by the "broad parasympathetic effects" of the vagus nerve.[25] The cholinergic anti-inflammatory pathway provides simple, cohesive, and integrative biomedical evidence for the systemic immunoregulatory actions of acupuncture and auriculotherapy, in view of which, their use as an adjunct therapy to conventional medical treatment for a number of cytokine-mediated diseases is plausible.[40,74]

Recent research also indicates that many cancers arise from sites of infection, chronic irritation, and inflammation, and that inflammation is a critical component of tumor progression. Coussens and Werb report that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival, and migration. In addition, tumor cells have co-opted some of the signaling molecules of the innate immune system, such as selectins, chemokines, and their receptors for invasion, migration, and metastasis.[75] These insights could therefore provide a stimulus for further research in the use of acupuncture in oncology beyond alleviating the nausea and vomiting associated with chemotherapy.

Finally, the evidence presented in this article is predominantly based on laboratory research and must be validated by translational investigation. Only clinical trials that confirm acupuncture's ability to increase the autonomic tone and ACh output while decreasing inflammatory molecules (cytokines, CRP, ESR, etc) could ultimately establish its association with the cholinergic anti-inflammatory pathway and determine its clinical efficacy in treating inflammatory and autoimmune diseases.

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References

1. Kuhn TS. *Criticism and the Growth of Knowledge*. London: Cambridge University Press; 1970 (1965).
2. Brockhaus A, Elger CE. Hypalgesic efficacy of acupuncture on experimental pain in man. Comparison of laser acupuncture and needle acupuncture. *Pain*. 1990;43(2):181-185.
3. Baldry PE. *Acupuncture, Trigger Points and Musculoskeletal Pain*. 2nd ed. New York: Churchill Livingstone; 1994.
4. Ernst E. Acupuncture—a critical analysis. *J Intern Med*. 2006; 259(2):125-137.
5. Ramey D, Buell PD. A true history of acupuncture. *Focus Altern Complement Ther*. 2004;9:269-273.
6. Huang KC. *Acupuncture: The Past and the Present*. New York: Vantage; 1996.
7. Ma KW. The roots and development of Chinese acupuncture: from prehistory to early 20th century. *Acupunct Med*. 1992; 10(Suppl):92-99.
8. Epler D. Bloodletting in early Chinese medicine and its relation to the origin of acupuncture. *Bull Hist Med*. 1980;54: 357-367.
9. Basser S. Acupuncture: a history. *Sci Rev Altern Med*. 1999;3:34-41.
10. Dorfer L, Moser M, Bahr F, et al. A medical report from the Stone Age? *Lancet*. 1999;354:1023-1025.
11. Dorfer L, Moser M, Spindler K, Bahr F, Egarter-Vigl E, Dohr G. 5200-year-old acupuncture in central Europe? *Science*. 1998;282(5387):242-243.
12. Kavoussi B. *Chinese Medicine: A Cognitive and Epistemological Review*. eCAM advance access published on April 11, 2007, DOI 10.1093/ecam/nem005.
13. Ernst E, White A, eds. *Acupuncture: A Scientific Appraisal*. Oxford, UK: Butterworth-Heinemann; 1999.
14. National Institutes of Health. Acupuncture. *NIH Consensus Statement*. 1997;15(5):1-34.
15. Berman BM, Lao L, Langenberg P, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med*. 2004; 141(12):901-910.
16. Ernst E. Acupuncture—a critical analysis. *J Intern Med*. 2006;259(2):125-137.
17. Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: acupuncture for low back pain. *Ann Intern Med*. 2005;142(8):651-663. Review. Erratum in: *Ann Intern Med*. 2005;142(11):950-951.
18. Lee H, Ernst E. Acupuncture for labor pain management: a systematic review. *Am J Obstet Gynecol*. 2004;191(5):1573-1579.
19. Melzack R, Wall PD. On nature of cutaneous sensory mechanisms. *Brain*. 1962;85:331.
20. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:171-179.
21. Pomeranz B, Chiu D. Naloxone blockade of acupuncture analgesia: endorphin implicated. *Life Sci*. 1976;19:1757-1762.
22. Zhou ZF, Du MY, Wu WY, Jiang Y, Han JS. Effect of intracerebral microinjection of naloxone on acupuncture- and morphine-analgesia in the rabbit. *Sci Sin*. 1981;24:1166-1178.
23. Stux G, Hammerschlag R. *Clinical Acupuncture Scientific Basis*. Berlin: Springer-Verlag; 2001.
24. Ulett GA, Han S, Han JS. Electroacupuncture: mechanisms and clinical application. *Biol Psychiatry*. 1998;44(2):129-138.
25. Ulett GA, Han S. *The Biology of Acupuncture*. St Louis, MO: Warren H. Green; 2002.
26. Villanueva L, Le Bars D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. *Biol Res*. 1995;28:113-125.
27. Willer JC, Bouhassira D, Le Bars D. Bases neurophysiologiques du phénomène de contre-irritation: les contrôles inhibiteurs diffus induits par stimulations nociceptives [in French]. *Neurophysiol Clin*. 1999;29(5):379-400. Erratum in: *Neurophysiol Clin*. 1999;29(6):555ff.
28. Tracey I, Dunckley P. Importance of anti- and pro-nociceptive mechanisms in human disease. *Gut*. 2004;53(11):1553-1555.
29. Fauve RM, Fontan E, Hevin MB, Saklani H, Parker F. Remote effects of inflammation on non-specific immunity. *Immunol Lett*. 1987;16(3-4):199-203.

30. Fauve RM. Endogenous counterinflammation and immunostimulation [in French]. *Pathol Biol (Paris)*. 1987;35(2):190-194.
31. Sternberg EM. Neural-immune interactions in health and disease. *J Clin Invest*. 1997;100(11):2641-2647.
32. Blalock JE. The immune system as the sixth sense. *J Intern Med*. 2005;257(2):126-138.
33. Tracey KJ. *Fatal Sequence: The Killer Within*. New York: Dana Press; 2005.
34. Matthay MA, Ware LB. Can nicotine treat sepsis? *Nat Med*. 2004;10(11):1161-1162.
35. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458-462.
36. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420:853-859.
37. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med*. 2003;9(5-8):125-134.
38. Pavlov VA, Tracey KJ. Neural regulators of innate immune responses and inflammation. *Cell Mol Life Sci*. 2004;61(18): 2322-2331.
39. Gallowitsch-Puerta M, Tracey KJ. Immunologic role of the cholinergic anti-inflammatory pathway and the nicotinic acetylcholine alpha 7 receptor. *Ann N Y Acad Sci*. 2005;1062:209-219.
40. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest*. 2007;117(2):289-296.
41. Wang H, Yu M, Ochani M, et al.Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature*. 2003;421:384-8.
42. Wang H, Liao H, Ochani M, et al. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med*. 2004;10:1216-21.
43. de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol*. 2005;6:844-51.
44. Metz CN, Tracey KJ. It takes nerve to dampen inflammation. *Nat Immunol*. 2005;6(8):756-757.
45. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. *Brain Behav Immun*. 2005;19(6):493-499.
46. Czura CJ, Tracey KJ. Autonomic neural regulation of immunity. *J Intern Med*. 2005;257(2):156-166.
47. Libert C. Inflammation: a nervous connection. *Nature*. 2003; 421(6921):328-329.
48. Andersson J. The inflammatory reflex—introduction. *J Intern Med*. 2005;257(2):122-125.
49. Floto RA, Smith KG. The vagus nerve, macrophages, and nicotine. *Lancet*. 2003;361(9363):1069-1070.
50. Son YS, Park HJ, Kwon OB, Jung SC, Shin HC, Lim S. Antipyretic effects of acupuncture on the lipopolysaccharide-induced fever and expression of interleukin-6 and interleukin-1 beta mRNAs in the hypothalamus of rats. *Neurosci Lett*. 2002; 319(1):45-48.
51. Deadman P, Baker K, Al-Khafaji M. *A Manual of Acupuncture*. Oxfordshire, UK: JCM; 1998.
52. Matsumoto T. *Acupuncture for Physicians*. Springfield, IL: Charles C Thomas; 1974.
53. Noguchi E, Hayashi H. Increases in gastric acidity in response to electroacupuncture stimulation of the hindlimb of anesthetized rats. *Jpn J Physiol*. 1996;46(1):53-58.
54. Han JS. *The Neuro-chemical Basis of Pain Control by Acupuncture*. Beijing, China: Hu Bei Technical and Science Press; 1998.
55. Ulett GA. Acupuncture: archaic or biologic? *Am J Public Health*. 2003;93(7):1037; author reply 1037-1038.
56. Middlekauff HR, Yu JL, Hui K. Acupuncture effects on reflex responses to mental stress in humans. *Am J Physiol Regul Integr Comp Physiol*. 2001;280(5):R1462-R1468.
57. Vas J, Mendez C, Perea-Milla E, et al. Acupuncture as a complementary therapy to the pharmacological treatment of osteoarthritis of the knee: randomised controlled trial. *BMJ*. 2004;329(7476):1216. Epub 2004 Oct 19.
58. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996;93:1043-1065.
59. Berntson GG, Lozano DL, Chen YJ. Filter properties of root mean square successive difference (RMSSD) for heart rate. *Psychophysiology*. 2005;42(2):246-252.
60. Shi X, Wang ZP, Liu KX. 1995. Effect of acupuncture on heart rate variability in coronary heart disease patients [Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 15:536-538.
61. Mori H, Nishijo K, Kawamura H, Abo T. Unique immunomodulation by electro-acupuncture in humans possibly via stimulation of the autonomic nervous system. *Neurosci Lett*. 2002; 320:21-24.
62. Chang CH, Huang JL, Ting CT, Chang CS, Chen GH. 2005. Atropine-induced HRV alteration is not amended by electroacupuncture on Zusanli. *Am J Chin Med*. 33:307-314.
63. Hsu CC, Weng CS, Liu TS, Tsai YS, Chang YH. Effects of electrical acupuncture on acupoint BL15 evaluated in terms of heart rate variability, pulse rate variability and skin conductance response. *Am J Chin Med*. 2006;34(1):23-36.
64. Goldstein RS, Gallowitsch-Puerta M, Bruchfeld AN, et al. Proinflammatory cytokine responsiveness and autonomic dysfunction in patients with chronic inflammation. *Acad Emerg Med*. 2006;13(5):43-44.
65. Edmonds ME, Jones TC, Saunders WA, Sturrock RD. Autonomic neuropathy in rheumatoid arthritis. *Br Med J*. 1979;2(6183): 173-175.
66. Toussirot E, Serratrice G, Valentin P. Autonomic nervous system involvement in rheumatoid arthritis. 50 cases. *J Rheumatol*. 1993;20(9):1508-1514.
67. Tan J, Akin S, Beyazova M, Sepici V, Tan E. Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function. *Am J Phys Med Rehabil*. 1993;72(4):196-203.
68. Evrengul H, Dursunoglu D, Cobankara V, et al. Heart rate variability in patients with rheumatoid arthritis. *Rheumatol Int*. 2004;24(4):198-202. Epub 2003 Sep 11.
69. Lindgren S, Stewenius J, Sjolund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. *Scand J Gastroenterol*. 1993;28(7):638-642.
70. Laversuch CJ, Seo H, Modarres H, Collins DA, McKenna W, Bourke BE. Reduction in heart rate variability in patients with systemic lupus erythematosus. *J Rheumatol*. 1997;24(8): 1540-1544.
71. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J*. 2004;25(5):363-370.
72. Ghia JE, Blennerhassett P, Kumar-Ondiveeran H, Verdu EF, Collins SM. The vagus nerve: a tonic inhibitory influence associated with inflammatory bowel disease in a murine model. *Gastroenterology*. 2006;131(4):1122-1130. Epub 2006 Aug 15.
73. Unschuld P. Traditional Chinese medicine: some historical and epistemological reflections. *Soc Sci Med*. 24:1023-1029.
74. Tracey KJ. Fat meets the cholinergic antiinflammatory pathway. *J Exp Med*. 2005;202(8):1017-1021.
75. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860-867.