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REVIEW

Electroacupuncture therapy in inflammation regulation: current perspectives

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Abstract: Although acupuncture therapy is increasingly used to treat diverse symptoms and disorders in humans, its underlying mechanism is not known well. Only recently have experimental studies begun to provide insights into how acupuncture stimulation generates and relates to pathophysiological responsiveness. Acupuncture intervention is frequently used to control pathologic symptoms in several visceral organs, and a growing number of studies using experimental animal models suggest that acupuncture stimulation may be involved in inducing anti-inflammatory responses. The vagus nerve, a principal parasympathetic nerve connecting neurons in the central nervous system to cardiovascular systems and a majority of visceral organs, is known to modulate neuroimmune communication and anti-inflammatory responses in target organs. Here, we review a broad range of experimental studies demonstrating anti-inflammatory effects of electroacupuncture in pathologic animal models of cardiovascular and visceral organs and also ischemic brains. Then, we provide recent progress on the role of autonomic nerve activity in anti-inflammation mediated by electroacupuncture. We also discuss a perspective on the role of sensory signals generated by acupuncture stimulation, which may induce a neural code unique to acupuncture in the central nervous system.

Keywords: electroacupuncture, anti-inflammation, vagus nerve, animal model, acupuncture mechanism

Introduction

Acupuncture has been used as a traditional medical treatment in East Asia for over 2,000 years,[1] and is becoming a popular therapy worldwide for treating various diseases.[2,3] Acupuncture is a medical intervention in which fine needles are applied to specific parts of the body, called acupuncture points (or acupoints) and penetrated through the muscular or other subcutaneous layers. According to traditional medical theory, acupuncture stimulation facilitates the flow of qi, a life force that is supposedly circulating through the channels called meridians.[4,5] Acupoints are presumed to be pathophysiologically associated with and possibly reflect the status of visceral organs and systemic conditions, and thus the stimulation of specific acupoints may evoke the responsiveness that controls the unbalanced internal milieu and improves body symptoms. Acupuncture stimulation is given right on the acupoint or a nearby affected area ("*ashi* point") for the treatment of local symptoms, such as knee pain or muscle rigidity, whereas distal acupuncture stimulation is applied to treat diseases in the internal organs and systemic abnormalities.

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There are two main types of acupuncture stimulation: manual acupuncture (MA) and electroacupuncture (EA). In MA, an acupuncturist penetrates the skin with a metallic needle and manipulates it by rotating in one or both directions or lifting and thrusting.[6] It is known that during acupuncture practice, acupuncturists experience a special touch sensation perceived as heaviness, tenseness, or terseness, and patients perceive feelings of numbness, heaviness, soreness, and distention around the site of needle stimulation. These are called *deqi* sensations. Clinical data further indicate that patients frequently feel deqi sensations spreading to other parts of the body,[7–9] which is considered a useful criterion to evaluate the therapeutic efficacy of acupuncture.[7,10–12] In EA, a small electric current is applied to pairs of acupuncture needles, and studies have indicated that the therapeutic efficacy of EA can be modulated by varying the frequency, intensity, and duration of electrical stimulation.[6,13] For instance, EA at low and high frequencies of electrical stimulation can activate different types of opioid receptors and different analgesic effects.[14,15] To maximize therapeutic effects, acupuncture is usually practiced first by applying MA to evoke deqi sensation and followed by electrical stimulation for 15–20 minutes.[7]

A growing number of recent reports have indicated that acupuncture may be effective in treating many types of diseases by regulating inflammatory responses. In this review, we highlight important findings that demonstrate how acupuncture stimulation, particularly EA, can improve inflammatory responses in pathological animal models. First, we discuss recent advances in understanding of neuroimmune communication, and then address how it has contributed to establishing experimental approaches to investigate a mechanistic basis of EA. In the last part of the review, we briefly discuss a perspective on the role of a neural code that may transmit sensory information unique to acupuncture in regulating inflammation.

Neuroimmune communication

When an organism is exposed to external pathogens, host-defense response begins with innate immunity, which is critical to induce inflammation as a defense mechanism against pathogenic infections. Pathogen-associated molecular patterns trigger inflammatory reactions in the host via interaction with membranous or cytoplasmic molecules, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), Retinoic acid-inducible gene 1-like receptors (RLRs), and C-type lectin receptors (CLRs), collectively termed "pattern-recognition receptors".[16] Activation of these receptors in target cells induces downstream-signaling pathways, including activation of the MAPK pathway and NFκB transcription factor, and induces the expression of inflammatory cytokines, including TNFα and several types of interleukins and chemokines. Chemokines recruit leukocytes into the inflammation area, and interleukins and IFNγ activate lymphocytes and macrophages.

Cholinergic anti-inflammatory reflex

In the early 2000s, Borovikova et al reported on their seminal work on the regulation of inflammatory responses by vagus nerve activity. They found that the electrical stimulation of the vagus nerve in vivo decreased the production of TNFα in the spleen of lipopolysaccharide (LPS)-injected animals, and treatment with acetylcholine of cultured macrophages attenuated levels of inflammatory cytokines as well.[17] They further demonstrated that the suppression of TNFα production by acetylcholine treatment was mediated by the activation of α_7-nicotinic acetylcholine receptors, which subsequently inhibited NFκB activation while stimulating the STAT3 pathway.[18–20] The vagus nerve is known to account for 70% of the parasympathetic, visceral regulation of internal organs, thus acting as a functional bridge connecting the brain to internal organs. Inflammatory cytokines produced from peripheral organs can activate an afferent part of the vagus nerve, stimulate vagal efferent nerves through the synaptic transmission from the solitary nucleus to the dorsal vagal nucleus in the brain stem, and downregulate the production of inflammatory cytokines, thereby completing the cholinergic anti-inflammatory reflex.[21] Rosas-Ballina et al reported that the vagal efferent nerves are connected to adrenergic postganglionic neurons in the celiac ganglion, which primarily receive splanchnic preganglionic sympathetic inputs from the spinal cord,[22] and further showed that norepinephrine released from celiac ganglion neurons stimulated the secretion of acetylcholine from choline acetyltransferase-expressing T cells in the spleen that binds to nicotinic acetylcholine receptors in macrophages.[23] Similar experimental strategies investigating the effects of vagus nerve activity on the pathologic regulation of several conditions, such as arthritis, obesity, and head trauma, have been considered for clinical application, and the anti-inflammatory reflex is becoming accepted as a concept explaining neuroimmunogenic control of diseases.[24]

Neuroimmunogenic regulation of inflammation further provides insights into studies on how brain activity modulates pathological responsiveness in major internal organs. For

instance, mental activities, such as stress, biofeedback therapy, and meditation, have been reported to be positively related to increased vagus nerve activity.[23] It has also been reported that impaired vagal activity increased the vulnerability of inflammatory bowel disease in an animal model of depression.[25]

It should however be noted that the connectivity between the terminals of autonomic fiber and the target immune cells has not been clearly demonstrated in several organs. While increasing numbers of publications have reported on the role of vagal activity in hepatic hypertension and inflammation based on the concept of cholinergic anti-inflammatory reflex,[17,26,27] hepatic target cells of vagal efferent fibers have not been identified.[28,29] Similarly, autonomic connections to the spleen are unclear and controversial. In this regard, it is worthwhile to note one recent report showing that the electrophysiological and histological identification of serotonin-secreting enterochromaffin cells in the intestine that modulate synaptically connected afferent nerve fibers can fulfill the minimal requirement of brain–gut communication.[30]

Functional intervention of sympathetic activity

While the vagus nerve has been a primary target mediating neuroimmune reaction in many studies, a potential role of sympathetic nerve activity has also been proposed. Martelli et al claimed that neurons from celiac ganglia that are primarily innervated by sympathetic splanchnic nerves were responsible for anti-inflammatory reflexes.[31,32] Adrenergic inputs activated hepatic invariant natural killer T (iNKT) cells and elevated the production of anti-inflammatory cytokines from T-helper 2 cells, rendering the organ more susceptible to infection via immunosuppression.[33] Possible connections of sympathetic nerve activity to immune cells in target organs, such as liver and spleen, for the regulation of inflammatory reactions are depicted in Figure 1.

Experimental studies on EA using pathologic animal models

As a modified version of traditional MA, EA is manipulated at the same acupuncture points as MA, but electric current is additionally applied. Needle rotation, which is performed routinely during MA, can result in mechanical deformation of dermal tissue and may activate special types of mechanosensory receptors (eg, Ruffini corpuscles). Previous studies have suggested that acupuncture-specific responses, such as the production of mechanical torque and induction of specific types of integrin proteins, are related to needle rotation.[34,35] In contrast, electric current, which is applied in EA, would spread to a nearby area and affect the peripheral nerve pulses (ie, action potential) more intensely, which may act as a possible reason to explain a certain level of therapeutic effects caused by sham EA, as reported in human subjects,[36] yet in other studies, sham EA stimulation (EAS) was less effective than a combined manipulation of MA and EA.[37,38]

It has been reported that MA can attenuate inflammatory responses by regulating the production of IL10 in macrophages, hypothalamic expression of IL1β and IL6 mRNA, and serum TNFα production in LPS-injected animals.[39–41] However, edema response by capsaicin injection is reduced by EA, but not by MA.[42] Since the vast majority of studies on the regulation of inflammation have been conducted using EA, here we focus primarily on EA studies unless otherwise indicated.

Anti-inflammatory effects of EA in animal models

A study using animals given radiant heat on the tail identified gene groups (neurotransmitter-related genes vs proinflammatory cytokine-related genes) showing differential regulation of expression in the spinal dorsal horn after

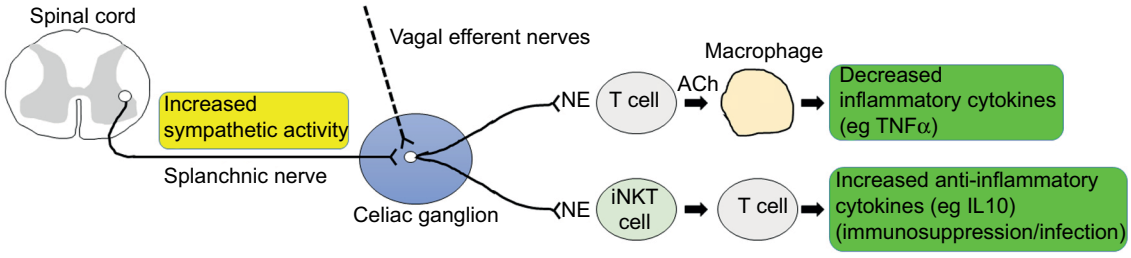

Figure 1 Sympathetic connection to immune cells in target organs.
Notes: Splanchnic nerve activity transmitted to the celiac ganglion may increase the release of norepinephrine (NE) of adrenergic postganglionic neurons. This in turn would activate immune-cell responses in target organs, such as macrophages in the spleen and T_H2 cells in the liver, and these cells regulate the production of pro- and anti-inflammatory cytokines. Vagal input, which has not been clearly identified, may have similar effects on the regulation of inflammation as sympathetic activity.
Abbreviations: T_H, T helper; ACh, acetylcholine; iNKT, invariant natural killer T.

EA,[43] suggesting that EA may be involved in the regulation of inflammation at gene-expression level. In order to investigate the effects of EA on the regulation of inflammation, injury models of complete Freund's adjuvant (CFA)-induced inflammation, collagen-induced inflammation, cerebral ischemia, reperfusion injury, and others have been used. The CFA-inflammatory model is frequently used to investigate inflammation-related pain and is thus useful to investigate pain regulation by EA. EA manipulation efficiently suppresses glial cell-marker proteins and TRPV1 and attenuates pain responses.[44,45] EA also suppresses edema in CFA-inflammation animals by activating corticotropin-releasing hormone-producing neurons in the hypothalamus and increasing levels of adrenocorticotropic hormone.[46] In an animal model of collagen-induced arthritis, EA attenuated inflammatory pain via the mediation of cholinergic and serotonergic receptors and also attenuated the production of inflammatory cytokines, such as IL1β, -6, and -8, TNFα, and NFκB in synovial tissue.[47,48] Moreover, EA was effective in regulating the levels of TNFα, IL1β, IL6, and myeloperoxidase in animal models of ulcerative colitis and zymosan-induced acute arthritis,[13,49,50] increased superoxide dismutase, while reducing death-related proteins, such as caspase 3, and phosphorylation of p38 and JNK in animals with cardiopulmonary bypass-induced lung injury,[6] and suppressed NFκB in a rat-tissue chamber model of inflammation.[51] In an acute alcoholic liver-injury model, EA improved hepatic circulation and adjusted ALT and AST levels.[52] Finally, systemic inflammatory response and survival rate are significantly improved by EA in animals injected with a lethal dose of LPS.[53] Major studies on the regulation of inflammation by EA are summarized in Table 1.

Table 1 Summary of electroacupuncture (EA) studies on the regulation of inflammation in experimental animals

Animal model	Acupoints	Major EA effects	Reference(s)
Intestinal ischemia–reperfusion injury	ST36, ST36 plus stem-cell transplantation	Increased crypt-cell-proliferation index and mucosal mRNA expression of SDF1, CXCR4, EGF, and EGFR Decreased mucosal NFκB, p65 and serum inflammation factor (TNFα, IL6)	97
Spinal cord ischemia–reperfusion injury	GV6, GV9, EX-B2	Decreased TNFα, IL1β, and MMP9 Neuroprotective effects of EA suppressed by autophagic inhibitor (3-methyladenine)	98
TNBS-induced colitis	ST36, ST36 plus VNS	Decreased TNFα, IL1β, IL6, and MPO Increased vagal activity and decreased sympathetic activity	13
	PC3 and PC6	Decreased IL1β and NFκB	99
CPB-induced lung injury	PC6 and LI4	Decreased pp38, pJNK, and caspase 3 Increased SOD activity	6
Thermal injury-induced remote acute lung injury	ST36	Decreased IL1β, IL6, and HMGB1	100
CFA-induced inflammation	ST36–ST37	Decreased TRPV1, pERK, pp38, pJNK, pAkt, pCREB, Nav1.7, and Nav1.8 in DRG and Schwann cells	44, 45
	ST36	Decreased GFAP, IBA1, S100β, RAGE, and TRPV1, in the DRG and spinal cord dorsal horn Blocking opioid and adenosine A_1 receptors reversed the effects of EA	45
	ST36 and GB34	Increased apelin, APJ protein, and mRNA expression in the spinal cord	101
	ST36 and BL60	Decreased mRNA and protein levels of TLR4, MYD88, and NFκB in ankle-bone tissue	102
	GB30	Increased plasma ACTH levels Increased phosphorylation of NR1 in CRH-containing neurons in the PVN	46
Electrical stimulation-induced migraine	GB20 and TE5	Decreased serum CGRP and PGE2 Decreased IL1β and COX2 expression in the trigeminal ganglion Decreased plasma protein extravasation CB1-receptor antagonism reversed the effects of EA	103
Septic brain injury	GV20, ST36	Decreased TNFα, IL6, and MDA Increased SOD and catalase activities in the serum and hippocampus Decreased TLR4, NFκB and IBA1 expression	104
MPTP-induced Parkinson's disease	ST36 and SP6	Increased human placental alkaline phosphatase Decreased microglia activation in the striatum and midbrain	87

(*Continued*)

Table 1 (*Continued*)

Animal model	Acupoints	Major EA effects	Reference(s)
Obesity	CV12 and CV4	Decreased serum TNFα	105
	ST36	Decreased adipose tissue inflammation	106
		Decreased HIFα, hypoxia-related genes (*VEGFA*, *SLC2AL*, and *GPX1*), and inflammation-related genes (*TNFA*, *IL6*, and *MCP1*)	
		Decreased macrophage recruitment and infiltration	
		Decreased NFκB and increased IκBα	
Collagen-induced rheumatoid arthritis	ST36, GB39, BL23	Decreased levels of NFκB (p65), TNFα, IL1β, IL6, and IL8	48
	GB39, ST36	Increased mRNA expression of VPAC1	107
		Elevated $CD4^+FOXP3^+$ T_{reg}-cell frequency and reduced $CD4^+IL17^+$ T_H17-cell frequency	
	ST36	Analgesic effect of EA was mediated by mAChR, $5HT_{1A}$, and $5HT_3$ receptors, but not by $5HT_2$ receptor	47
Ligature-induced periodontitis	LI4, LI11, ST36, ST44	Decreased TRAP-positive multinucleated cells	108
		Decreased expression of IL1β and MMP8 mRNAs	
		Increased expression of IL6 mRNA	
Cerebral ischemia–reperfusion injury	GV20 and ST36	Decreased ACTH and HSP70	2
	GV20 and GV14	Increased rCBF and IL6 expression	109
		Decreased IL1β and JAK2	
	GV20 and GV14	Decreased mRNA level of ChAT, five subtypes of muscarinic receptors and α_7nAChR	92
	GV20 and GV14	Decreased Bax, TNFα, IL6, and IL1β	110
		Decreased excitotoxicity by NMDA	
		Increased antioxidant systems (Bcl2, Nrf2, GCSh, GCSl, Gsh)	
	LI11 and ST36	Decreased microglia activation of IBA1 and ED1 in cortex	78, 111
		Decreased serum TNFα, IL1β, and IL6	
		Decreased cortical p38 MAPK and MyD88	
		Decreased cortical NFκB, TNFα, and IL1β	
	GV20 and ST36	Inhibited neuronal apoptosis, microglial activation of IBA1, and oxidative stress in the hippocampus	79
		Decreased hippocampal and serum IL6 and TNFα levels	
	LI11 and ST36	Decreased TLR4/NFκB signaling and levels of TNFα, IL1β, and IL6	112

Abbreviations: HT, hydroxytryptamine; ACTH, adrenocorticotrophic hormone; APJ, apelin receptor; CFA, complete Freund's adjuvant; CGRP, calcitonin gene-related peptide; CPB, cardiopulmonary bypass; CRH, corticotrophin-releasing hormone; DRG, dorsal root ganglion; Gsh, glutathione; MDA, malondialdehyde; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, *N*-Methyl-d-aspartic acid; PGE2, prostaglandin E_2; PVN, paraventricular nucleus; rCBF, regional cerebral blood flow; TG, trigeminal ganglion; TNBS, 2,4,6-trinitrobenzenesulfonic acid.

EA-related signaling events in the nervous system

While an increasing number of reports strongly indicate that EA can regulate inflammation and associated pathologic symptoms, underlying mechanisms remain largely elusive. Considering that acupuncture and meridian networks encompass the whole body, as does the neural network, it is not surprising that the nervous system has been a primary concern for mechanistic studies on acupuncture. Indeed, a growing number of studies have supported this notion. Cutaneous acupuncture at the *zusanli* acupoint has been reported to elevate levels of focal adenosine and its A_1 receptor for antinociceptive actions[54] and upregulate the expression of purinergic receptors in the dorsal root ganglion,[35,55] suggesting acupuncture-mediated induction of afferent signals. It has been further reported that acupuncture stimulation induced c-Fos expression in neurons in the dorsal vagal complex area, including both nucleus tractus solitarii (NTS) and dorsal motor nucleus, rostral ventromedial medulla, and raphe nucleus, implying that the ascending neuronal signals generated from the cutaneous acupoints relay synaptic inputs into the vagal neural circuits and possibly further up to the cerebral neural circuits.[39,56–58]

Evidence demonstrating the involvement of autonomic nerve activity in acupuncture action largely comes from physiological studies analyzing cardiovascular responses and gastrointestinal (GI) motility in experimental animals and humans. Physiological assessment of GI activity is useful to investigate acupuncture effects on autonomic function, because the regulation of GI disorders is one of the major realms of traditional acupuncture medicine.[59,60] One study reported that the manipulation of EA in dogs improved

gastric emptying and increased vagal activity assessed by spectral analysis of heart-rate variability while suppressing sympathetic activity.[61] Acupuncture effects on regulation of heart-rate variability were similarly demonstrated in a rodent model of inflammatory bowel disease and human subjects.[13,62] Longhurst and Tjen-A-Looi reported that acupuncture stimulation regulated cardiovascular function (blood pressure), whereby neurotransmitter release and neuromodulation in the hypothalamus and several cardiovascular nuclei in the brain stem mediated acupuncture effects.[63]

In addition to nuclei in the vagal complex, EA was reported to induce neuronal activation in the cerebrum. Functional magnetic resonance-imaging studies using human subjects revealed that analgesic effects caused by low-frequency EA (2 Hz) were positively correlated with activation in the contralateral primary motor area, supplementary motor area, and ipsilateral superior temporal gyrus, but negatively correlated in the bilateral hippocampus.[64] However, analgesic effects induced by high-frequency EA (100 Hz) were positively correlated with activation in other areas, such as the contralateral inferior parietal lobule, ipsilateral anterior cingulate cortex, nucleus accumbens, and pons. In another functional magnetic resonance-imaging study, EA activated neurons in the cingulate cortex and modulated the activation pattern of limbic-system networks.[65]

Acupuncture mechanism on anti-inflammation: potential role of vagus nerve activity

Based on the preceding discussion, it is likely that EA generates neuronal signals at the acupuncture point, sends these to the spinal cord and brain, and may trigger autonomic regulation of inflammatory responses in target organs. How would EA-induced sympathetic and parasympathetic nerve activities modulate pathological responsiveness in internal organs? Here, we discuss the role of vagus nerve activity as a principal parasympathetic nerve and then sympathetic nerve activity.

As discussed in the previous section, vagus nerve stimulation (VNS) activates nicotinic acetylcholine receptors in target cells to attenuate inflammatory responses. Here, one intriguing issue is whether the vagus nerve activity induced by EAS is functionally comparable to the VNS. It should be noted that since the VNS acts on both afferent and efferent parts of the nerve, afferent signals transmitted to the brain could indirectly affect inflammatory responses. Likewise, EA signals, if any, would be transmitted directly to the vagal efferent nerves or indirectly by way of brain pathways, and thus the vagal activity caused by EAS and VNS may share some common neural code in acting on a target organ (Figure 2). Previous studies have shown that EA given at several different acupoints activates neurons in the NTS, a brain-stem location receiving somatic nerve activity and afferent vagal inputs, as demonstrated by c-Fos immunostaining and electrophysiological recordings.[57,66,67] EAS-induced neuronal activity in the NTS would send out signals to vagal efferent nerves or ascending neural paths to upper-brain neurons, and combined efferent activity may mediate anti-inflammatory effects (Figure 2). In this respect, one previous study demonstrating the involvement of brain muscarinic receptor-mediated networks in anti-inflammatory regulation of EA in LPS-induced endotoxemia[53] supports the notion that EAS-induced efferent vagal activity may carry the descending brain activity as acupuncture-specific neuronal signals.

Torres-Rosas et al demonstrated that sciatic nerve activation by EA at the zusanli acupoint inhibited the production of major inflammatory cytokines in an animal model of polymicrobial peritonitis, and further showed that vagal activity transmitted to the adrenal gland increased dopamine

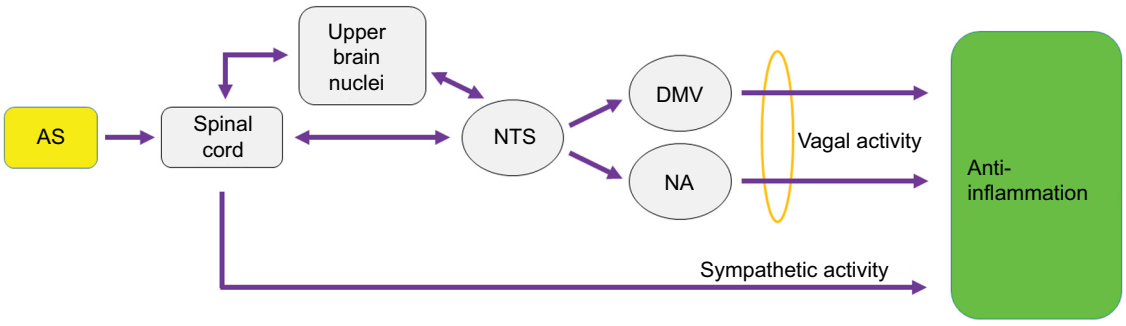

Figure 2 Possible neural pathways that transmit cutaneous ASs ultimately to internal visceral organs and induce anti-inflammatory responses in target organs.
Abbreviations: AS, acupuncture signal; NTS, nucleus tractus solitarius; DMV, dorsal motor nucleus of vagus nerve; NA, nucleus ambiguus.

production and downregulated cytokine production.[68] However, in another study using LPS-induced systemic inflammation animals, EA at the zusanli acupoint activated the vagal pathway connected to the spleen and attenuated the production of TNFα in the spleen.[39] In an animal-sepsis model with a lethal dose of LPS, vagotomy abrogated the effects of EAS (at the *hegu* acupoint) on anti-inflammation and animal survival,[53] suggesting the activation of vagal efferent by EAS. However, EAS (at the zusanli acupoint) activated NTS neurons and improved the pathologic parameters of postoperative ileus, but did not regulate the production of inflammatory cytokines.[66] In ischemia–reperfusion animals, vagotomy or administration of nicotinic receptor antagonist reversed EA inhibition on the release of HMGB1 and myocardial protection.[69] Finally, in a TNBS-induced colitis model, when given together with VNS, EAS effectively decreased the production of inflammatory cytokines and pathogenesis in the colon, but EAS alone did not increase vagal activity above VNS,[13] implying some augmentation effects of EAS on VNS-mediated anti-inflammation. It seems evident that vagal activity is a principal modulating factor for regulation of inflammation by EA; however, further studies are essential to verify vagal modulation of EA in different disease models using various EAS manipulations.

Anti-inflammatory regulation of EA via sympathetic nerve pathway

Possible involvement of sympathetic nerve activity in neuroimmune regulation has been implicated by adrenergic neuronal activity inducing iNKT cells, whose inhibition attenuated immunosuppression and bacterial infection (Figure 1).[33] Can a concept of anti-inflammatory regulation via the suppression of sympathetic activity be applied to acupuncture-mediated anti-inflammation? Previous reports have suggested that in a physiological state, EA may either increase or decrease sympathetic nerve activity in several organ systems. For instance, EAS improves rectal motility by inhibiting sympathetic nerve activity, but suppresses gastric motility by increasing sympathetic activity.[70,71] EA increases cellular uptake of glucose by increasing sympathetic nerve activity.[72] It has further been reported that EA was involved in cardiovascular baroreceptor reflex by modulating hypothalamic inputs to rostroventrolateral medulla, an area relaying signals to preganglionic sympathetic neurons in the spinal cord.[73] In relation to inflammatory responses under a pathological state, EA attenuates inflammatory reaction by activating postganglionic sympathetic nerve activity in carrageenan- and zymosan-induced animal models.[74,75] However, in LPS-induced endotoxemia animals, EA inhibits peripheral sympathetic activity and increases vagal activity to regulate systemic inflammatory responses.[53] This suggests that (possibly reflecting differential experimental systems) either increased or decreased sympathetic nerve activities are involved in mediating anti-inflammatory effects of EA.

Martelli et al claimed that instead of vagus nerve activity, sympathetic activity, which is evoked by electrical stimulation of splanchnic nerve connected to celiac ganglia, might be responsible for regulating anti-inflammatory response in the spleen.[31,32] Therefore, it is tempting to explore the possibility that anti-inflammation by EAS is modulated by splanchnic nerve activity transmitted to celiac ganglia. Immune cells, such as iNKT cells, and a subpopulation of $CD4^+$ T cells are known to receive adrenergic inputs from sympathetic nerve terminals and mediate immunosuppression and inflammation (Figure 1).[23,33] Therefore, one experimental approach to explore the mechanistic basis of the regulation of sympathetic nerve activity by EA would be to investigate whether EAS activates preganglionic neurons in the spinal cord and subsequent celiac ganglia neurons, and analyze the activation of immune cells in pathologic target organs, such as spleen and liver, in association with sympathetic nerve connectivity.

Regulation of ischemic brain injury by EA

EA has been widely used for the treatment of stroke and cerebral ischemia.[76] To understand the biological basis for its efficacy, rodent models of cerebral ischemia–reperfusion and middle cerebral artery occlusion are used widely. Histological and behavioral examinations demonstrated that EA manipulation protected neural tissue from injury and improved motor impairment and cognitive function.[77–81] Studies at cellular and molecular levels showed that EAS regulated the expression of apoptosis-related genes, such as *BCL2* and *BAX*,[77,82] inhibited the production of HMGB1 production,[83,84] known to induce inflammation by activating TLR4 and RAGE,[85] and downregulated mRNA and protein levels of MMP2, Aqp4, and Aqp9.[86,87] EAS also activates several signaling molecules and related pathways, including stimulation of STAT3[88] and PI3K,[89] and upregulates levels of glutamate receptor GluR2 for neuroprotection.[90] Finally, EA affects the activation of microglial cells and astrocytes and the production of astroglial lactate transporter (MCT1), implying that EA may exert its protective function by acting on glial cells and neurons in the central nervous system.[78,80,81,91]

Despite numerous reports on pathologic responses by EA, mechanistic studies underlying acupuncture efficacy on

cerebral ischemia have been limited. Chavez et al described[76] on a mechanistic basis a list of possible beneficial effectors of acupuncture (both EA and MA) in brain areas after ischemic stroke. In an experimental stroke model, EAS has been shown to attenuate cerebral ischemia by activating α_7-nicotinic acetylcholine receptors in penumbra and also vagal motor neurons.[92] However, it is unclear how EA-modulated vagal activity is linked to cholinergic nerve activity in ischemic cerebral tissue and leads to pathological responsiveness in target tissue. Further studies demonstrating the protective effects of EAS on brain and spinal tissue from ischemic damage are critical to gain insights into the mechanistic basis of anti-inflammatory mechanisms of EA.

Perspectives: neural coding of acupuncture signals

All sensory information in humans and animals is received by specific receptors, and the nerve signals generated are transmitted to and perceived by the brain. Modality, location, intensity, and duration are basic features of sensory stimulation at the periphery, and act as basic elements to transduce unique signals to sensory neurons in the brain.[93] Here, the initial stimulation requires the process of neural coding so that the sensory signals can be interpreted through brain circuitry.[94]

Would cutaneous acupuncture stimulation generate its own specific neural responses? Neuroimaging studies on acupuncture indicate the possible existence of neural correlates of acupuncture.[95] Receptive fields of sensory neurons, important to determine perception sensitivity to a stimulus, are affected by receptor density at the stimulation area. We have recently found that α_6/β_1 integrin receptors are highly expressed at the zusanli acupoint after acupuncture stimulation.[35] Since integrin activity plays an important role in mediating intercellular signaling,[96] it will be interesting to explore the distribution and activation of specific types of integrin receptors responding after stimulation at other acupoints. Moreover, it will be of great importance to investigate whether EA manipulation at the acupoint can generate a unique sensory modality, eg, deqi is interpreted as a special sensation distinct from typical somatosensation, which is shared between acupuncturist and patient. EAS induces afferent signals, and may directly affect visceral autonomic nerve activity. Alternatively, it is transmitted to the cerebrum and generates brain acupuncture signals (Figure 2). We speculate that acupuncture stimulation may trigger the responsiveness of sensory receptors and generate neural activity in its own specific way, which may be encoded in the cerebral cortex and autonomic neuronal center and exert its effects on regulating inflammation. Future investigations to explore whether acupuncture-specific vagal activity exists and acts on cells in target organs will be of great importance to gain insights into the mechanistic basis of acupuncture.

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Disclosure

The authors report no conflicts of interests in this work.

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