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REVIEW

Therapeutically Fine-Tuning Autonomic Nervous System to Treat Sepsis: A New Perspective on the Immunomodulatory Effects of Acupuncture

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Abstract: Recent studies have highlighted the immunomodulatory effects of acupuncture on sepsis and proposed novel non-pharmacological or bioelectronic approaches to managing inflammatory illnesses. Establishing rules for selectively activating sympathetic or vagal nerve-mediated anti-inflammatory pathways using acupuncture has valuable clinical applications. Over the years, studies have revealed the segmental modulatory role of acupuncture in regulating visceral function by targeting the autonomic nervous system (ANS). In this review, we aim to summarize recent findings on acupuncture in treating sepsis, focusing on the underlying ANS mechanism, as well as the rules of acupoint specificity, intensity, frequency, and other parameters utilized in these studies. Mechanistically, the immunomodulatory properties of the sympathetic nervous system have been highlighted. Furthermore, we explore the immunotherapeutic benefits of acupuncture in treating sepsis. A better understanding of the immunoregulatory mechanism of sympathetic nervous system may offer novel approaches for the development of therapeutics to treat or prevent a variety of inflammatory diseases.

Keywords: inflammation, peripheral nerve stimulation, sympathetic nervous system, sympathoadrenal axis, macrophage, bioelectronic medicine

Introduction

Sepsis is a life-threatening visceral dysfunction due to a dysregulated host response to infection.[1] It is often observed in patients with severe trauma, septic shock, or major surgical procedures. Sepsis results in many complications, including cardiomyopathy, coagulopathy, septic shock, and multi-organ failure.[2] Research data have shown that approximately 30 million patients are affected annually, with a high mortality rate of 25–40%.[3–5] Antibiotics are generally used as first-line treatment for sepsis due to foreign invasion. However, continuous or excessive use of antibiotics disturbs microbiota hemostasis and leads to immune dysregulation,[6] resulting in organ failure.

Recently, non-pharmacological or bioelectronic approaches, such as acupuncture and peripheral nerve stimulation, have been beneficial in treating sepsis and other inflammatory diseases, suggesting novel and promising therapeutic strategies.[7–13] Regarding the fewer side effects and tolerance of bioelectronic approaches, the National Institute of Health (NIH) launched the Stimulating Peripheral Activity to Relieve Conditions program in 2016, aimed at refining and developing bioelectronic medicine, particularly peripheral nerve stimulation, for clinical applications. Acupuncture has been the most representative treatment method globally. Notably, over 77 diseases can be treated using acupuncture.[14] According to the NIH, over 15 million Americans have been treated using acupuncture,[15,16] and approximately 41% of these patients were treated for inflammation-related conditions.[17] The World Health Organization currently recommends using acupuncture to treat 16 inflammation-related diseases.[17] Notably, recent studies have highlighted that acupuncture mitigates the inflammatory conditions associated with sepsis through the somatotopic and intensity-dependent triggering

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of the autonomic nervous system (ANS).[18–20] However, the acupoint specificity and the optimal stimulation parameters are required to be further determined. This review will focus on how acupuncture modulates the ANS and discuss current evidence on its immunomodulatory effects on sepsis, aiming to advance the understanding and practice of acupuncture in treating sepsis and other inflammatory conditions, and also highlighting the unexplored areas.

Pathogenesis of Sepsis

Inflammation is a crucial defense mechanism in the body. Moderate inflammation has beneficial effects, including restricting the spread of pathogenic microorganisms and facilitating the removal and repair of necrotic tissue.[21] As a systemic inflammatory response condition,[22,23] sepsis has been recently defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection in 2016.[1] Typically, sepsis is diagnosed when two systemic inflammatory response syndromes (SIRS) and one organ dysfunction manifest within 6 h.[24] Sepsis can be initiated by a broad spectrum of microorganisms. In about two-thirds of intensive care unit (ICU) patients with sepsis, a specific microorganism can be identified. The lungs and abdomen are the most common sites of infection in these cases. Notably, our understanding of the host response trajectory during sepsis is limited primarily because studies predominantly focus on immune dysfunction upon ICU admission, resulting in gaps in our understanding of pre-admission and post-admission characteristics, as well as temporal patterns of the host response.

When the body detects infection or tissue injury caused by invading pathogens like lipopolysaccharide, it triggers the innate immune response by recognizing pathogen-associated molecular patterns (PAMPs) through specific pattern-recognition receptors (PRRs). This recognition activates macrophages and other myeloid cells, leading to the release of various cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β, thus exacerbating the inflammatory condition. Simultaneously, the activated host response during sepsis is further disrupted by the release of damage-associated molecular patterns (DAMPs). PRRs interact with a range of PAMPs and DAMPs, contributing to sustained immune activation and organ dysfunction.[25] The escalating levels of cytokines traverse the blood-brain barrier, recruiting and activating glial cells, leukocytes, and other immune cells to release further cytokines. This process culminates in what is termed a "pro-inflammatory cytokine storm" within the central nervous system. Consequently, it induces brain dysfunction, characterized by confusion, delirium, shock, and multiple organ system dysfunction (MOSD).[26] Meanwhile, the anti-inflammatory process are initiated to counteract these severe inflammatory challenges by releasing glucocorticoids,[27] IL-10, IL-4, and IL-13.[28,29] However, in sepsis, an excessive anti-inflammatory response is a double-edged sword that can inadvertently harm normal tissue cells while attempting to combat the pathogen. This prolonged and persistent immune suppression can potentially lead to secondary infections.[30] This over-activated immune reaction in response to pro- and anti-inflammatory challenges significantly disrupts the immune system and leads to mortality.

Antibiotics serve as the primary treatment for sepsis and other systemic inflammatory conditions. However, despite their effectiveness in treating sepsis, the emergence of antibiotic resistance, particularly in the context of the COVID-19 pandemic, has garnered global attention. The annual report from the Center for Disease Control reveals that approximately 2.8 million antimicrobial-resistant infections occur annually in the United States, resulting in over 35,000 deaths (https://www.cdc.gov/drugresistance/biggest-threats.html). In addition, post-sepsis syndrome sequelae especially persistent immune dysfunction led to recurrent infection, and sepsis, and raises a huge challenge for patient life.[31] Therefore, it is imperative to study and develop non-pharmacological or non-invasive approaches to restore immune homeostasis against various infections and inflammatory challenges.

Inflammation Reflex and Anti-Inflammatory Route in Sepsis

Research on the inflammatory reflex has revealed a functional interaction between the parasympathetic (vagal nerve) and sympathetic nervous systems, which fine-tunes the regulation of the innate immune response. In this reflex, the inflammatory signal conveyed by sensory neurons of the vagal nerve is integrated into the brain, triggering a descending anti-inflammatory pathway to counteract inflammatory challenges.[32] The primary anti-inflammatory pathways comprise the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), and parasympathetic nervous system (PNS) pathways (Figure 1).[8,33] Increasing evidence suggests that the nervous system, especially the autonomic system, represents a novel and promising therapeutic target to treat sepsis and various inflammatory conditions.

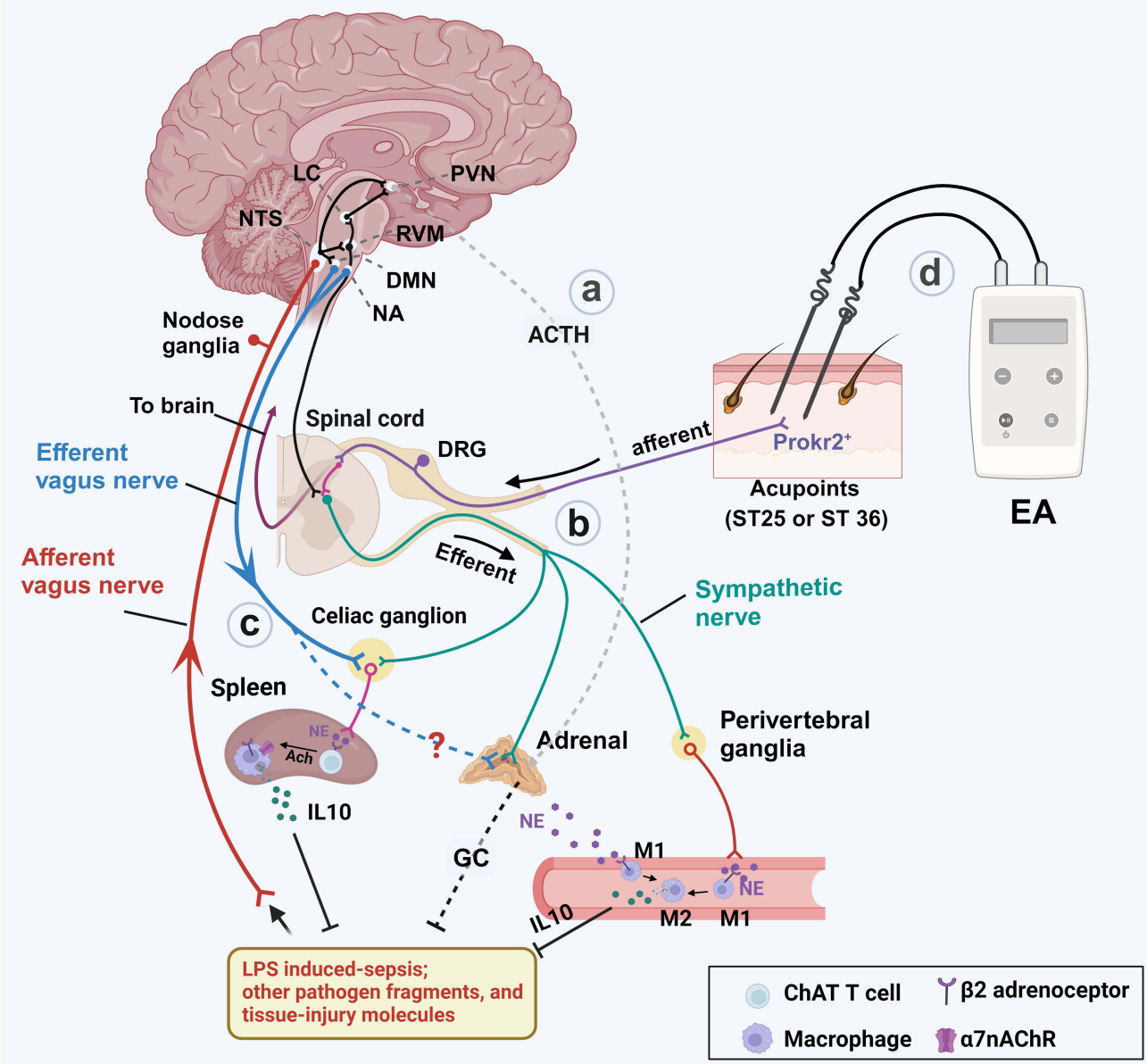

Figure 1 Inflammation reflex route and EA-induced anti-inflammatory action. Sepsis and other pathogen fragments stimulate the afferent activity of the vagal nerve, which then transmits the inflammatory information to the nucleus tractus solitarius (NTS). The NTS can directly or indirectly transmit it to the paraventricular nucleus (PVN) through the rostral ventromedial medulla (RVM). Subsequently, the PVN activates the hypothalamic-pituitary-adrenal (HPA) axis against inflammation (**a**). Simultaneously, the reciprocal connection between the NTS and the dorsal motor nucleus (DMN) leads to the activation of the efferent activity of the vagal nerve in the DMN. This activation then triggers the vagal-spleen/adrenal pathway. Furthermore, upon receiving signal inputs, the RVM descends and activates the preganglionic sympathetic neurons (**b**). This activation not only initiates the systemic sympathetic-adrenal axis but also stimulates the local sympathetic anti-inflammatory process by releasing norepinephrine (NE). Notably, both the vagal nerve efferent and sympathetic nerve propagate to the celiac ganglia. In the celiac ganglia, they activate the postganglionic spleen sympathetic nerve, which releases NE to activate the classic cholinergic anti-inflammatory pathway (CAIP) (**c**). Acupuncture can activate the anti-inflammatory pathway in a somatotopic and intensity-dependent manner (**d**). High-intensity Electroacupuncture (EA) at the homotopic acupoint (ST25) produces an anti-inflammatory effect by triggering the sympathetic-adrenal axis, while low-intensity EA at ST36 exerts the anti-inflammatory effect on sepsis by activating the vagal-spleen or vagal-adrenal pathway.

Abbreviations: NTS, the nucleus tractus solitarius; DMN, the vagal dorsal motor nucleus; RVM, rostral ventrolateral medulla; LC, the locus coeruleus; PVN, the paraventricular nucleus; NA, nucleus ambiguous; ACTH, adrenocorticotropic hormone; NE, norepinephrine; GC, Glucocorticoids; Ach, acetylcholine; DRG, dorsal root ganglion; α7nAChRs, α7-nicotinic acetylcholine receptors; IL10, interleukin 10.

HPA Axis and Sepsis

The HPA axis represents a neuroendocrine pathway characterized by neural communication between the hypothalamic paraventricular nucleus (PVN) and the pituitary gland.[27,34] This neuroendocrine pathway initiates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, thereby inducing the release of anti-inflammatory glucocorticoids, namely cortisol in humans and corticosterone in mice, from the adrenal cortex.[35]

Glucocorticoids denote steroid hormones that exhibit binding affinity to the glucocorticoid receptor (GR), a receptor present within immune cells and various other cell populations throughout the body.[36] HPA activation and subsequent adrenocortical glucocorticoid production during sepsis are important regulatory processes to maintain homeostasis.[27] Currently, administration of systemic corticosteroid therapy has shown encouraging outcomes in mitigating the cytokine storm and reducing the severity of coronavirus disease 2019 (COVID-19) in individuals afflicted with severe acute respiratory syndrome.[37,38] However, the controversy surrounding glucocorticoid dose, treatment duration, and central (secondary) adrenal insufficiency has attracted attention.[34,39–42] In clinics, low-dose glucocorticoids effectively alleviate early septic symptoms and complications, particularly shock, whereas short-term high-dose glucocorticoids increase mortality.[43] In addition, traditional steroids (adrenocorticotropic hormones) and targeted therapeutic agents against specific cytokines (the IL-6 blocker cetuximab and the IL-6R blocker tocilizumab) show limited efficacy.[44]

SNS-Mediated Immunoregulation in Sepsis

SNS (sympathetic nervous system) comprises two types of neurons: preganglionic and postganglionic sympathetic neurons.[45] The SNS mediatted local and systemic sympathetic pathways involving humoral or neuroimmune mechanisms (Figure 1b).[8] The local sympathetic pathway primarily involves the postganglionic nerve endings that mediate local inflammatory reactions, while the systemic sympathetic pathway refers to the sympathetic-adrenal medulla axis.[46] Typically, NE is the primary neurotransmitter, released by postganglionic sympathetic terminals, and functions by binding to metabotropic, G-protein-coupled adrenergic α and β receptors (β-ARs and α-ARs), which are further subdivided and broadly expressed on immune cells. Also, other bioagents such as such as adenosine triphosphate and neuropeptide Y (NPY) can be released by postganglionic sympathetic terminals as well.[45] The regulation of sympathetic neuronal activity is orchestrated by the brain, notably the locus coeruleus and the rostral ventrolateral medulla, which interact with spinal cord preganglionic neurons. Plus, given that preganglionic sympathetic fibers originating from the greater splanchnic nerves directly synapse with and stimulate chromaffin cells of the adrenal medulla, the adrenal medulla can be analogous to the sympathetic postganglionic terminals. Activating the sympathoadrenal axis leads chromaffin cells to release epinephrine, NE, and, to a lesser extent, dopamine into the circulation, which then impacts the systemic immune reaction throughout the body by targeting ARs signaling.[10]

SNS plays a multifaceted and diffuse role in sepsis and other inflammatory conditions by impacting immune cell phenotype and proliferation. Current opinion suggests that the pro- or anti-inflammatory action mediated by the SNS is concentration-dependent (Figure 2). For instance, lower concentrations (10^{-8}-10^{-9} M) are inclined to bind macrophage α-adrenoceptors, which then activate the NF-κB pathway and convert MΦ macrophage to M1 phenotype, releasing TNF-α and exacerbating inflammation. Conversely, higher concentrations of NE (10^{-5}-10^{-6} M) tend to bind macrophage β2 adrenoceptors, which inhibit the NF-κB activation and convert MΦ macrophage to M2 phenotype, releasing IL-10 against inflammation.[47–49] IL-10-exerted inhibitory effect on sepsis-related TNF-α production is strikingly impaired after applying β-blockade such as metoprolol and propranolol.[50] Furthermore, NE plays a role in modulating the functions of T cells, B cells, and NK cells.[51] Notably, recent animal studies reported that the sympathetic nervous system orchestrates inflammation resolution and regenerative programs by modulating repulsive guidance molecule A (RGM-A), thereby resolving the inflammation in a murine peritonitis model.[52] RGM-A not only can be synergic with NE to impact macrophage converting to M2 by suppressing NF-κB signaling and activating RICTOR and PI3K/AKT pathway but also inhibiting the monocyte recruitment.[52,53] Additionally, NE released by postganglionic sympathetic ending could promote the proliferation of bone marrow hematopoietic stem cells (HSCs) and swiftly skew HSCs toward anti-inflammatory myeloid cells (Figure 2).[54] This evidence suggests potential targets of adrenoceptors in macrophages for clinical application.

Even though endotoxin released from bacterial cell walls causes sympathetic activation and increased circulating NE,[55] a systematic review demonstrated that NE has a superior beneficial effect on in-hospital and 28-day mortality in septic shock patients.[56] Early use of NE (<6 hours) has been proposed as a key approach in enhancing septic shock and leading to better outcomes.[57–60] Current clinical opinion about the beneficial role of NE in sepsis mainly attributes its effects to its vasopressor action, which improves the circulatory failure caused by impaired autonomic control of the heart and vessels.[57] However, the immunomodulatory role of NE following early application is less understood.[51] NE can

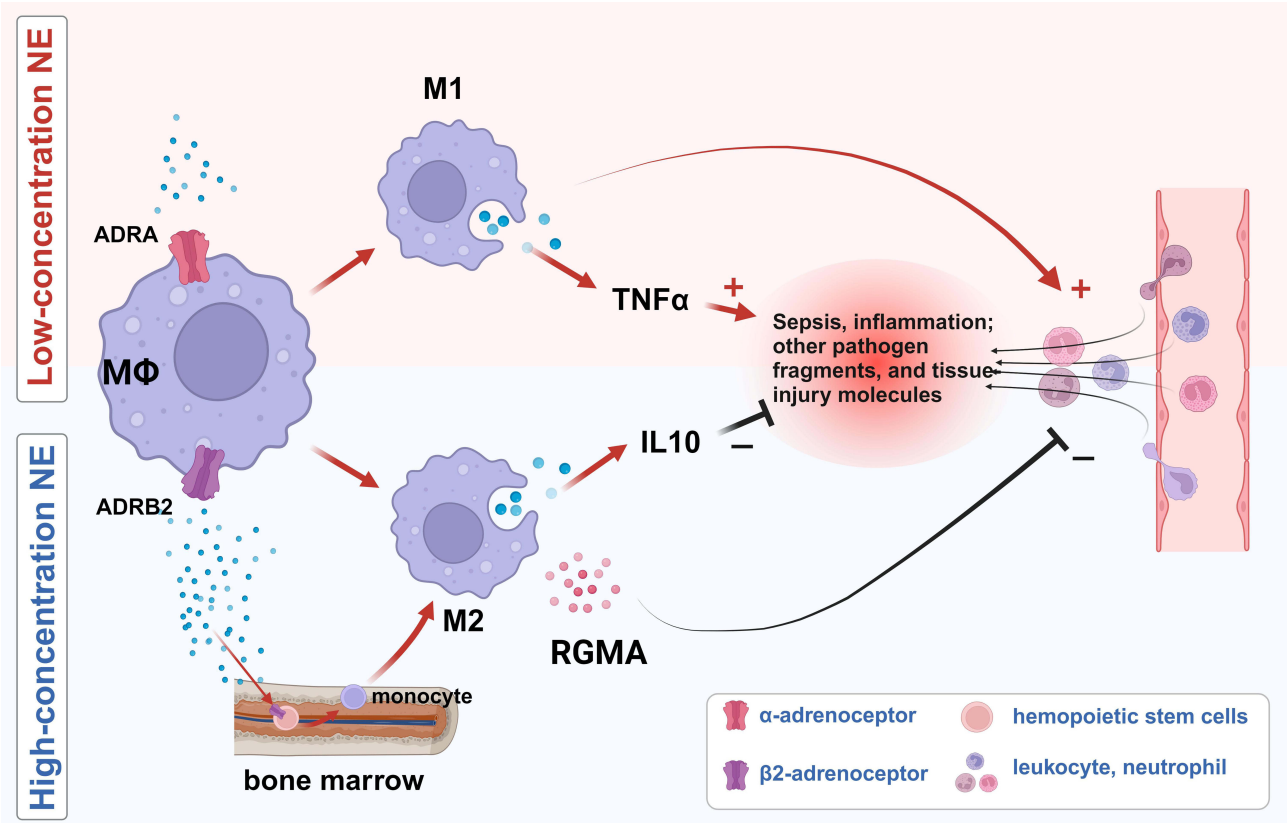

Figure 2 NE modulates macrophage phenotype by targeting ADRB2 signaling in a concentration-dependent manner. Lower concentrations prefer to bind macrophage α-adrenoceptors, which then activate the NF-κB pathway and convert MΦ macrophage to M1 phenotype, releasing TNF-α to recruit leukocyte and adaptive immune cells, exacerbating inflammation. In contrast, higher concentrations of NE tend to bind to macrophage β2 adrenoceptors, which inhibit the NF-κB activation and convert MΦ macrophage to M2 phenotype, releasing IL-10 against inflammation. Furthermore, NE leads macrophages to release repulsive guidance molecule A (RGM-A), which is not only synergic with NE to impact macrophage converting to M2 but also inhibits leukocyte recruitment.

decrease proinflammatory cytokines and increase anti-inflammatory IL10 production not only in mice of LPS-induced sepsis model but also in LPS-challenged primary human leukocytes,[58] suggesting the beneficial immunomodulatory role of NE in combating sepsis-related infection, shock, and mortality, even though the mechanism remains elusive. Therefore, further investigation is warranted to investigate the precise immunomodulatory mechanism of how NE interacts with the immune cells to exert an anti-inflammatory effect.[51] Besides, the sympathetic sprouting following tissue injury and visceral dysfunction has been reported recently, which strengthens the interaction of local sympathetic terminals with peripheral sensory terminals and immune cells by releasing NE and ATP.[59] Its role in the inflammation process and visceral homeostatic regulation is worthy of consideration.[60–62]

PNS-Mediated Immunoregulation in Sepsis

PNS (parasympathetic nervous system) is primarily associated with the vagal nerve, the 10th cranial nerve, which carries 75% of the parasympathetic fibers. The rest of the parasympathetic fibers include the oculomotor nerve (III) for eye function; the facial nerve (VII) for the lacrimal gland, salivary glands, and nasal mucous membranes; and the glossopharyngeal nerve (IX) for the parotid gland. Preganglionic neurons of the PNS originate from the brainstem nuclei and sacral spinal cord, specifically S2–S4. The vagal nerve has been extensively studied among the peripheral nerves involved in immune-brain crosstalk. Its afferent fibers, originating from cell bodies in the nodose ganglia, include visceral and thoracic afferents projecting to the nucleus of the tractus solitarius (NTS) and the area postrema (AP) in the medulla, collectively known as the vagal complex. Vagal nerve is a mixed nerve that not only transmits motor signals (efferent, 20–30%) to its innervated organs, but also conveys sensory information (afferent, 70–80%) from peripheral organs to NTS through releasing acetylcholine, which acts on metabotropic G-protein-coupled muscarinic receptors

located on postganglionic cholinergic neurons,[63] as well as other cells including smooth muscle cells, glandular cells, and cardiac myocytes in the innervated organs.

Numbers of preclinical and clinical studies have explored the role of the vagal nerve in inflammation reflex.[64,65] Studies have shown that the administration of lipopolysaccharide (LPS), cytokines (such as IL-1β and TNF-α), or pathogens like *Campylobacter jejuni* stimulates vagal afferent signaling in rodents, as indicated by increased expression of the neuronal activation marker c-fos in the NTS.[66–68] In recent decades, there has been significant emphasis on the anti-inflammatory effect of the vagal nerve, particularly in the context of sepsis.[69] The efferent component of the vagal nerve transmits signals to the splenic nerve through the celiac-superior mesenteric ganglion complex,[70,71] leading to the release of NE into the spleen. NE release stimulates choline acetyltransferase (ChAT) T-cells in the spleen to secrete acetylcholine, which recruits macrophages via binding to α7 nicotinic acetylcholine receptors (α7 nAChR).[72] This process suppresses the release of pro-inflammatory cytokines such as TNF-α through the nuclear factor kappa beta (NF-κB) pathway without affecting anti-inflammatory cytokines (Figure 1c).[69,73] Thus, the activation of the splenic nerve has been proposed as the main mechanism underlying vagal nerve-mediated anti-inflammatory effect. Vagal nerve stimulation significantly reduces TNF-α levels in LPS-challenged human macrophages and in an LPS-induced sepsis model.[69,74,75]

ANS-Mediated Immunomodulation in Sepsis

Accumulating evidence highlighting the benefits of the ANS in alleviating sepsis and other inflammation conditions. However, some concerns need to be further addressed. Firstly, the neuroanatomical link between the vagal nervous system and the spleen remains controversial. The functionality of vagal nerve stimulation-induced anti-inflammatory effect depends on the integrity of the splenic nerves.[75] Extant evidence shows that the efferent component of the vagal nerves conveys signals to the splenic nerve through the celiac-superior mesenteric ganglion complex.[70,71] Intriguingly, one recent study using retrograde trans-monosynaptic tracing demonstrated that the vagal nerve not only innervates the sympathetic celiac ganglion but also directly innervates the spleen.[76] What's the significance of this evolution that the celiac ganglion, different from other sympathetic ganglions, is innervated by the vagal nerve worthy of consideration. However, vagal nerve stimulation did not induce the firing of the splanchnic nerve raised more concerns about the functional connection.[77] Mughrabi et al investigated the effect of electrostimulation (ES) of the vagal, splanchnic, and splenic nerves on real-time NE release within the spleen using fast-scan cyclic voltammetry.[78] Their findings indicated that ES of the splenic nerve plays a more pronounced role in modulating NE release. Furthermore, the observed real-time changes in NE signaling in the spleen during the vagal nerve and splanchnic stimulation were minor compared with the direct stimulation of the splenic nerve.

A recent study suggests that the spleen, the crucial part of the cholinergic anti-inflammatory pathway (CAIP), is exclusively innervated and predominantly controlled by the SNS.[79–83] Neuroanatomically, two primary splenic sympathetic nerves traverse the splenic artery and subsequently diverge into multiple sympathetic nerves constituting the splenic neurovascular bundle. These nerves then penetrate the splenic parenchyma. Splenic sympathetic innervation is predominantly concentrated around the vascular structures, with a lesser presence of discrete nerves in the white pulp, primarily within the periarteriolar lymphoid sheaths and red pulp. In these regions, sympathetic fibers interact closely with T-cells and macrophages.[84] The cell bodies of these postganglionic sympathetic fibers are predominantly located in the suprarenal (splanchnic) and celiac ganglia. Cao et al investigated the neuromodulatory pathway from the suprarenal-celiac-superior mesenteric ganglion complex to the spleen using neural tracer technology.[85] They observed that LPS directly activated the suprarenal-cavitary ganglion and upregulated the expression level of NPY. This suppresses TNF release from macrophages by binding to NPY1R, suggesting a sympathetic mechanism for spleen-mediated CAIP. Moreover, ablation of the splenic sympathetic nerve impairs prostaglandin E2-induced anti-inflammatory action in response to LPS challenge.[86] Therefore, further investigations are required to determine how sympathetic or parasympathetic coordinately orchestrates to trigger the spleen-mediated anti-inflammatory process. In addition, other results regarding the frequency of vagal nerve stimulation demonstrated that low-frequency stimulation activates two anti-inflammatory pathways, the CAIP and HPA axis, and may also recruit the sympathetic anti-inflammatory pathway.[87,88] Finally, how to navigate NE to binding adrenoceptor of T cell rather than macrophage in spleen is also complex and

confusing,[89,90] due to macrophage highly expressed adrenoceptors as well. Triggering macrophage β2-AR signaling has been reported as a potential target to combat sepsis and resolve inflammation.

Acupuncture Ameliorates Sepsis by Modulating ANS

Acupuncture has been practiced for years and serves millions of people globally. Current opinion on the fundamentals of acupuncture therapy is attributed to its role in driving autonomic function through the somatic-autonomic reflex.[91,92] Our team explored the pattern of acupoint upon acupuncture intervention in modulating visceral sympathetic and vagal function,[93–95] termed the "homotopic-acupoint" and "heterotopic-acupoint" (Figure 3). Specifically, acupoints that activate sympathetic nerve activity in the viscera are in the same dermatome as the viscera and are termed homotopic acupoints. Conversely, acupoints that activate the vagal nerve are located primarily in the extremities relative to the remote segments of the viscera and are referred to as heterotopic acupoints. Combining homotopic and heterotopic acupoints forms a homeostatic regulatory mechanism crucial for acupuncture and other somatic or stimulatory treatments.[96–100] Therefore, the neuromodulatory pattern of acupuncture in modulating the visceral sympathetic or parasympathetic routes is beneficial for studying various somatic stimulation therapies.

Emerging evidence shows that acupuncture-induced therapeutic effects by activating or inhibiting the ANS have been observed in various pathological context.[101] Current interests mainly focus on sympathetic-derived NE and its role in enhancing inflammation following activation. Based on these neuromodulatory principles, researchers have explored the autonomic mechanisms of acupuncture and its beneficial effects on sepsis. Preclinical and clinical studies have demonstrated that acupuncture is essential in mitigating cytokines and enhancing IL-10, a cluster of differentiation $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, and dopamine levels in experimental sepsis models and septic patients.[18,48,102] Nevertheless, the controversy regarding acupoint specificity and stimulation parameters poses challenges to the clinical application of

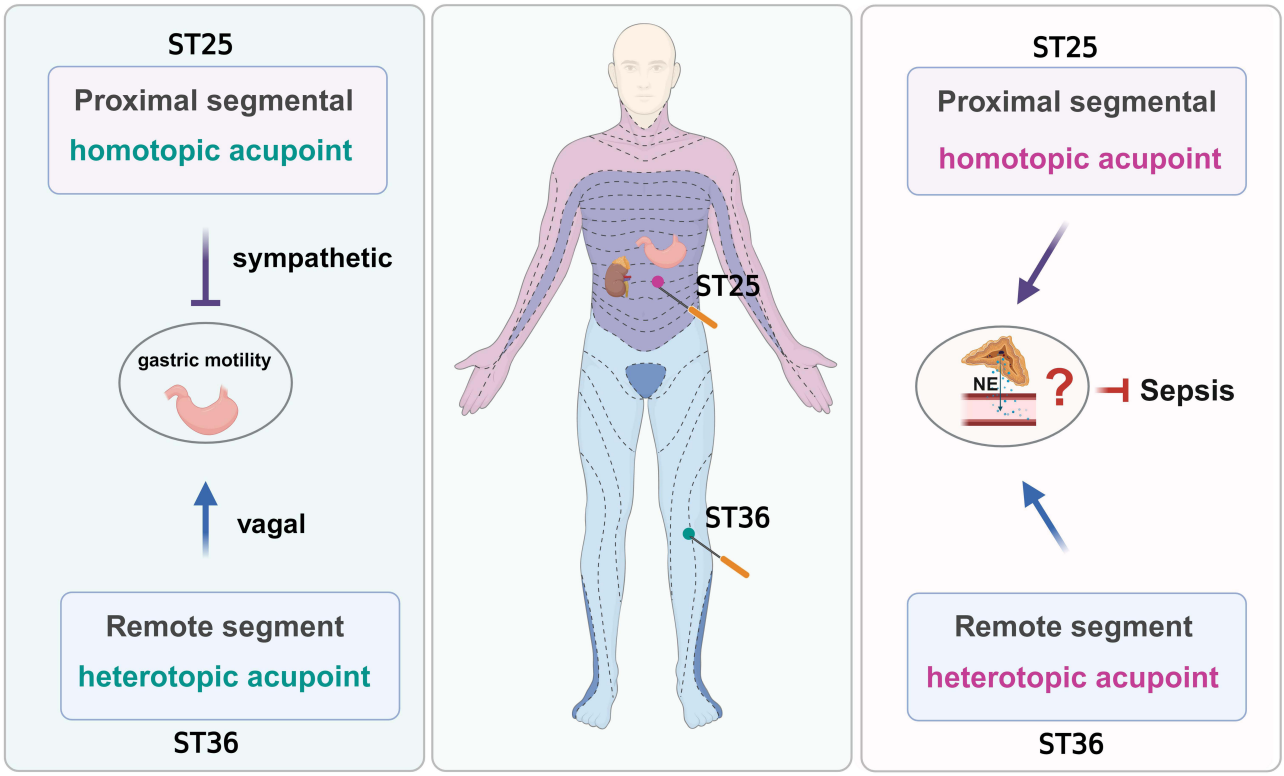

Figure 3 Neuromodulatory pattern of acupuncture in modulating stomach and adrenal gland function. The stomach receives sympathetic innervation from the T6 to T10 spinal segments, while the adrenal gland is innervated by the T9-T10 spinal segments. Acupuncture at the ST 25 acupoint, which shares innervation with both the gastric and adrenal glands from the T9 spinal segment, can activate the sympathetic pathway. This activation suppresses gastric motility and promotes the release of norepinephrine (NE) from the adrenal medulla. Conversely, stimulating the ST36 acupoint, innervated by the L4 spinal cord, a distant segment from the gastric and adrenal glands, promotes gastric motility and adrenal medulla release via the vagal pathway.

acupuncture. The acupoints, stimulation parameters, and corresponding mechanisms summarized in a recent study are listed in Table 1.

Acupuncture Activates Sympathetic Pathways for Anti-Sepsis Immunotherapy

Limited evidence has explored the sympathetic mechanism of acupuncture-mediated anti-inflammatory action during sepsis. Liu et al observed that the timing of intervention is crucial for determining whether acupuncture-driven sympathetic signaling has a pro- or anti-inflammatory role in sepsis. Specifically, pretreatment of mice with high-intensity 3 mA electroacupuncture stimulation (ES) at homotopic acupoints (Tianshu, ST25) alleviates LPS-induced sepsis by activating peripheral NPY^{+} sympathetic neurons, while applying the same ES treatment after LPS modeling exacerbated systemic inflammation.[19] However, our team has recently reported inconsistent results. Using the same stimulation parameters, we observed that the post-sepsis modeling application of ES treatment yielded an anti-inflammatory effect in rats of LPS-induced sepsis model.[114] Whether this discrepancy is linked to the heterogeneity of the sepsis models requires further investigation. High-frequency electroacupuncture at ST 36 activates the preganglionic innervation of the adrenal medulla, leading to the systemic release of catecholamines. In contrast, low-frequency electroacupuncture activates specific postganglionic innervation of sympathetic nerves, inducing the local release of neurogenic NE.[117]

Acupuncture Activates Parasympathetic Pathways for Anti-Sepsis Immunotherapy

Existing evidence extensively addresses the acupuncture-induced anti-inflammatory effects on sepsis through the parasympathetic pathway, categorized into two types based on the targeted areas. The first is the traditional approach involving acupuncture at limb acupoints. The second, increasingly popular style in recent years, is auricular acupuncture, noted for its safety and high efficacy. The beneficial effects of auricular acupuncture are primarily attributed to the auricular branch of the vagal nerve, which projects to the nucleus of the solitary tract and facilitates acupuncture signaling. Nevertheless, the beneficial effects of both types of acupuncture are attributed to the efferent vagal nerve-mediated anti-inflammatory pathway.

Zhu et al conducted an initial comparative study investigating the effects of auricular and cervical branch vagal nerve stimulation and transcutaneous electrical acupoint stimulation at ST36 in a rat model of LPS-induced sepsis.[105] Notably, all stimulation intensities were capped at a maximum of 1 mA, a low level expected to activate a vagal nerve reflex. The study demonstrated that stimulation at the auricular, ST36, or direct vagal nerve significantly decreased pro-inflammatory cytokine levels (TNF-α, IL6, IL1β), attributed to the α7nAChR-mediated CAIP. Hong and Qi reported similar results.[118,119] However, the distinct mechanisms underlying the effects of auricular and transcutaneous acupuncture have not yet been thoroughly addressed. Luis Ulloa et al observed that dopamine released by the vagal-adrenal medulla axis mediated the anti-inflammatory effect induced by electroacupuncture at ST36 in LPS-induced sepsis, emphasizing the crucial role of the adrenal medulla in acupuncture-mediated effects.[18]

Furthermore, Liu made significant efforts to close this gap and demonstrated that the prokr2-positive nociceptor in ST36 is responsible for delivering acupuncture signals, subsequently activating the dorsal motor nucleus of the vagal-adrenal gland pathway and inducing catecholamine secretion against LPS-induced systemic inflammation.[19,20] The current evidence has outlined a primary neuromodulatory loop for acupuncture at ST36 involving the vagal-adrenal pathway, indicating a promising role for acupuncture-driven vagal-adrenal pathways in alleviating inflammatory conditions. Additional studies should validate the current findings across diverse species and optimize the stimulating parameters to confirm this beneficial role. In addition, transcriptional studies should be considered to reveal cellular mechanisms and identify novel targets for controlling inflammation.

Future Perspective

Growing evidence has emphasized the crucial role of the SNS and vagal nerves in controlling inflammation conditions, such as sepsis, rheumatoid arthritis, autoimmune disease, chemotherapy-induced gastrointestinal toxicity, etc.[120–122] Sympathoadrenal medulla-mediated systematic anti-inflammatory axis is a promising mechanism against sepsis and other systematic inflammation. Despite NE released by sympathetic terminals or adrenal medulla

Table 1 Stimulation Parameters and Associated Mechanisms in Acupuncture for Sepsis: A Comprehensive Overview (2009–2023)

Refs.	Species	Sepsis Model	Acupoints	Intensity	Frequency and Time	Acupuncture Pretreatment or Post-Treatment	Autonomic Nerve
Hu S, 2009[103]	Rat	CLP	ST36	2 mA	2 Hz-100 Hz 30 min	Post-treatment	Vagal nerve
Shi X, 2010[104]	Rat	CLP	ST36	2 mA	2 Hz/100 Hz 1 h	Post-treatment	Vagal nerve
ZhaoYX, 2011[105]	Rat	LPS	Auricular concha, ST36	1 mA	10 Hz 20 min	Post-treatment	Auricular concha and vagal nerve
SongJG, 2012[106]	Rat	LPS	LI4 PC6	4 mA	2–100 Hz 45 min	Pretreatment and post-treatment	Vagal nerve
Villegas, 2014[107]	Rat	CLP	ST36	2 mA	30 Hz	Post-treatment	Vagal nerve
Torres, 2014[18]	Mice	LPS	ST36	40mA	2–15 Hz 30 min	Post-treatment	Vagal nerve
Zhang L, 2018[108]	Rat	CLP	ST36	2.0 mA	2–100 HZ, 1h	Post-treatment	Vagal nerve
Han Y G, 2018[109]	Mice	LPS	GV20	4 mA	2 Hz/100 Hz	Pretreatment and post-treatment	Vagal nerve
HARPIN D, 2020[110]	Rat	Escherichia coli	ST36	1 mA	2 Hz 30 min	Pretreatment	Vagal nerve
Xie D P, 2020[111]	Rat	CLP	ST36 LI11 ST25	2 V	3 Hz,15 min	Post-treatment	Sympathetic nerve, Vagal nerve
Liu S, 2020[19]	Mice	LPS	ST36 ST25	3 mA 0.5 mA	Waviness width 50 ms, 10 Hz	Pretreatment and post-treatment	Vagal nerve, Sympathetic nerve
Wu Y R, 2021[112]	Rat	LPS	BL32	Up to the intensity which could induce movement of the lower limb	30 Hz	Pretreatment and post-treatment	The cervical vagal nerve, Nervi erigentes
Yoon-Young Go, 2022[113]	Mice	LPS	Auricular concha	200 uA	15 Hz,10 min 25 Hz,5 min	Pretreatment and post-treatment	Auricular vagal nerve
Zhang, 2022[114]	Rat	LPS	ST25	3 mA	15 Hz, 20 min	Post-treatment	Adrenal sympathetic nerve
Zhang, 2022[115]	Mice	LPS	ST36	0.5 mA	4/20 Hz	Post-treatment	Cervical vagal nerve,
Zhang, 2023[116]	Mice	LPS	ST36	Intensity 5	10 Hz, 15 min	Pretreatment	Undetermined

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mediates either sympathetic or vagal nerve-induced anti-inflammatory effect by triggering β2 ADR signaling or synergic with RGM-A to regulate immune cell function,[51,123] it has been proposed as the potential therapeutic target for sepsis treatment. Hence, how to selectively fine-tune sympathoadrenal medulla axis using somatic stimulation is worthwhile to explore.[12,44] Decades of research have broadly outlined the neuromodulatory effects of acupuncture and other somatic ES on triggering autonomic nervous reflexes.[121,124] A significant challenge lies in advancing clinical translation and optimizing stimulation parameters to engage the autonomic pathway effectively. This challenge extends beyond acupuncture and encompasses the entire field of bioelectronic medicine. Based on the aforementioned neuromodulatory pattern of somatic stimulation in modulating sympathetic activity, we assume that there should be a region, such as proximal dermatome to adrenal,[114] capable of eliciting firing in the splenic or adrenal sympathetic nerves directly through the somatosympathetic reflex pathway. Conducting more studies that systematically examine the frequency, intensity, and timing of effective acupoint modulation of the ANS under physiological and pathological conditions across different species is important to overcome this challenge. With technological advances, more potent stimulation parameters have been generated and tested in the field of bioelectronic strategies. For instance, kilohertz-frequency stimulation is a promising modality, demonstrating advantages across various stimulation techniques.[125] However, in-depth investigations are required to fully comprehend the excitatory or inhibitory role and mechanism of kilohertz-frequency acupuncture stimulation in modulating the ANS and neuroimmune modulation.

In addition, the contradiction in the direct connection between the vagal nerve and the adrenal gland raises concerns about which branch, sympathetic or parasympathetic, predominantly innervates or drives adrenal function to mitigate inflammation. Further neuroanatomical and neuroimmune studies should examine the evidence and mechanisms of sympathetic or vagal-adrenal pathways in inflammation. This pursuit is essential for advancing our understanding of and potentially discovering new therapeutic targets for inflammatory disorders.

Furthermore, it is crucial to acknowledge and address the controversial results of acupuncture studies because they can, in part, be attributed to the observed heterogeneity across these studies. The diversity in methodologies, species, and outcome measures among acupuncture studies should be noted. Plus, further validation is required to enhance the reliability and robustness of our findings. Finally, advancements in next-generation sequencing have facilitated the exploration of cellular chatting or interactions at single- and multi-tissue/organ levels, enhancing our understanding of transcriptional profiles in immune organs such as the spleen and adrenal glands in the context of sepsis.. The potential for identifying novel targets to manage inflammation through acupuncture therapy in light of these unexplored areas deserves careful consideration.

Summary

The nervous system is crucial in maintaining immune homeostasis. Non-pharmacological interventions, especially acupuncture, have gained attention for their potential to mitigate sepsis and other inflammation by modulating the ANS. However, precise modulation of the sympathetic and vagal nerve pathways to alleviate sepsis requires further investigation. We highlighted the potential efficacy of acupuncture in controlling sepsis by targeting the sympathetic pathway through a comprehensive review that includes the pathophysiology of inflammation and sepsis and an exploration of the current understanding of the roles of sympathetic and vagal nerves in inflammation control. Furthermore, optimizing current stimulation parameters and elucidating transcriptional changes in immune organs and cells during sepsis following acupuncture presents challenges and opportunities.

Moreover, sepsis, cancer, multiple sclerosis, and other autoimmune diseases exhibit several shared pathophysiological features stemming from the inability of the host immune system to cope with the initial insult.[126,127] This suggests that understanding acupuncture's modulatory mechanisms, patterns, and other biomedical approaches could advance the clinical translation of acupuncture-related bioelectronic medicine strategies in inflammatory and immune disease treatment. In conclusion, this review provides valuable insights into the current landscape and future directions of acupuncture-mediated anti-inflammatory action in treating sepsis.

Data Sharing Statement

No data was used for the research described in the article.

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Disclosure

All authors disclose no competing interests in this work.

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