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REVIEW

Vagus Nerve Regulation of Inflammatory Responses in Sepsis: Mechanistic Insights and Translational Applications

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Abstract: The vagus nerve, often regarded as a "guardian" of physiological homeostasis, plays a pivotal role in regulating cardiovascular, neurological, and immune functions. Notably, it modulates inflammatory responses through the inflammatory reflex, a neural circuit, that involves vagal afferent sensing of peripheral inflammation and efferent regulation via the cholinergic anti-inflammatory pathway. Sepsis is a dysregulated immune disorder triggered by infection, characterized by an initial hyperinflammatory phase. In recent years, increasing attention has been directed toward harnessing vagus nerve–mediated neuromodulation to restore immune balance in sepsis. This review summarizes current insights into the mechanisms of vagus nerve–mediated inflammatory regulation, outlines two major translational strategies, and underscore the therapeutic potential of targeting vagus nerve–mediated neuroimmune pathways in sepsis.

Keywords: vagus nerve, sepsis, cholinergic anti-inflammatory pathway, inflammatory reflex, non-neuronal cholinergic system

Sepsis is a life-threatening syndrome marked by organ dysfunction that arises from a profoundly dysregulated immune response to infection.[1] Although early diagnosis and treatment can improve survival, sepsis continues to endanger the lives of millions each year.[2] Its pathophysiology involves a dynamic imbalance between pro- and anti-inflammatory responses, with the severity of this imbalance serving as a predictor of poor prognosis.[3] In the early phase, sepsis-related mortality is frequently driven by excessive production of inflammatory mediators—manifesting as cytokine storm, hemodynamic instability, and metabolic disruption.[3,4] In contrast, late-phase deaths are typically linked to immune exhaustion, impaired pathogen clearance, and increased susceptibility to secondary infections.[3] Therefore, restoring immune homeostasis by intervening the biphasic immune dysregulation may be an effectively therapeutic strategy for sepsis.

In recent years, the advances in neuroimmunology have profoundly reshaped our understanding of how the nervous system actively participates in immune regulation.[5–9] Rather than acting as a passive responder to inflammation, the nervous system can sense, integrate, and modulate immune activity, a process broadly referred to as neuroimmune modulation. Among the various neural pathways, the vagus nerve has garnered particular attention because of mediating inflammatory reflex. The vagus nerve, a major branch of the parasympathetic nervous system, has emerged as a central mediator of neuroimmune regulation beyond its classical roles in autonomic control.[10,11] Its afferent fibers detect peripheral inflammatory signals, and its efferent fibers modulate immune cell activity, primarily through the cholinergic anti-inflammatory pathway.[11] The advances in neuroimmunology and bioelectronic medicine have expanded our understanding of this reflex arc, highlighting the vagus nerve's potential as a target for therapeutic modulation of systemic inflammation in a range of immune-related diseases.

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Both vagus nerve stimulation (VNS) and pharmacological interventions have been shown to suppress systemic inflammation, alleviate organ injury, and improve survival in preclinical and early clinical studies of sepsis.[12] This review summarizes recent progress in our understanding of vagus nerve–mediated neuroimmune regulation and highlights emerging therapeutic strategies that leverage this pathway. In addition, it outlines current challenges and proposes future directions for translating these mechanistic insights into effective clinical interventions.

The Modulation of Inflammation Mediated by the Vagus Nerve

The concept of the inflammatory reflex was first proposed by Kevin J. Tracey et al in the early 2000s, who demonstrated that vagus nerve stimulation could suppress the release of proinflammatory cytokines, such as TNF-α, in endotoxemia models.[13] This discovery revealed that the nervous system exerts active, reflexive control over immune responses, establishing the inflammatory reflex as a neural circuit that links peripheral inflammation to central regulation. Research on the inflammatory reflex mainly focuses on two aspects: how afferent nerves perceive inflammation and how efferent nerves regulate inflammation.[11,14] Recently, numerous studies have aimed to elucidate the mechanisms that vagus nerve regulate immune responses though mediating the inflammatory reflexes.[15–19] Next, it will outline how the vagus nerve mediates the perception and control of inflammation via its afferent and efferent fibers and summarizes its role in immune regulation.

Anatomical Constituents of the Vagus Nerve in Inflammatory Reflexes

The vagus nerve—named from the Latin vagus, meaning "wandering"—was so designated due to its widespread, ramifying distribution throughout the thoracic and abdominal viscera.[20] Anatomically, the vagus nerve is the tenth cranial nerve (cranial nerve X) and is classified as a mixed nerve, composed of approximately 60–80% afferent fibers and 20–40% efferent fibers. It originates from the medulla oblongata, exits the skull via the jugular foramen, and travels bilaterally through the neck, thorax, and into the abdominal cavity—forming extensive neural networks that innervate key visceral organs involved in cardiovascular, respiratory, gastrointestinal, endocrine, and immune regulation.[20–22] The afferent fibers, primarily of visceral sensory origin, detect a wide range of physiological and pathological stimuli—such as mechanical tension, chemical composition, and inflammatory mediators—from peripheral organs including the lungs, heart, gastrointestinal tract, liver, kidneys, and spleen.[23] These signals are relayed via the nodose and jugular ganglia to the nucleus tractus solitarius (NTS) in the brainstem, initiating central processing.[22] The vagus nerve is now recognized as a core component of the parasympathetic nervous system and a crucial bidirectional conduit between the brain and internal organs.

The efferent fibers arise from the nucleus ambiguus and the dorsal motor nucleus (DMN) of the vagus, and include both parasympathetic cholinergic fibers and non-adrenergic, non-cholinergic (NANC) fibers.[20,24] While acetylcholine is the predominant neurotransmitter, other bioactive molecules such as nitric oxide, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) also contribute to its modulatory function. Functionally, the majority of vagal efferent fibers are classified as parasympathetic nerves.[25] While the sympathetic nervous system is crucial for immune homeostasis, emerging evidences suggest that the parasympathetic nervous system also plays a significant role.[26,27] Crucially, both afferent and efferent vagal branches are anatomically positioned to interface with immune-relevant sites such as the spleen, gastrointestinal mucosa, liver, and lungs—organs rich in resident macrophages, dendritic cells, and lymphoid structures.[7,28,29] This strategic anatomical arrangement may underpin the vagus nerve's ability to facilitate real-time monitoring and modulation of peripheral inflammation.

Inflammatory Signal Sensing by the Vagus Nerve

The concept that the vagus nerve can actively sense peripheral inflammation emerged from early observations in the 1990s, when researchers noted that peripheral immune challenges could rapidly activate brain regions involved in autonomic regulation.[30,31] Studies by Goehler et al and others provided the first experimental evidence supporting this idea.[32] They demonstrated that intraperitoneal injection of lipopolysaccharide (LPS) or interleukin-1β (IL-1β) activates subdiaphragmatic vagal afferents, leading to neural activation in brainstem nuclei such as the nucleus tractus solitarius (NTS) and the locus coeruleus (LC). Surgical vagotomy (VGX) or selective transection of the dorsal vagal trunk

abolished these central responses, including the development of LPS-induced fever, confirming the necessity of an intact vagal sensory pathway for central immune detection.[31] Similarly, Borsody et al showed that peritoneal inflammation–induced brainstem activation is eliminated by severing the vagus nerve, but not by blocking circulation, strengthening the case for direct neural transmission.[33]

Mechanistically, subsequent research revealed that vagal sensory fibers, whose cell bodies reside in the nodose and jugular ganglia, extend peripheral terminals into visceral organs where they encounter inflammatory stimuli.[34,35] These nerve endings express pattern recognition receptors (PRRs) such as TLR4, as well as receptors for proinflammatory cytokines like TNF-α and IL-1β, allowing them to directly detect pathogen-associated molecular patterns (PAMPs) and endogenous danger signals.[36–38] For example, Gautron et al showed that TLR4 is expressed on vagal afferents, and its activation by circulating LPS can trigger action potentials transmitted to the CNS.[34] Additionally, Hosoi et al demonstrated that electrical activity recorded from the vagus nerve increases in response to systemic inflammation, further confirming its role as an inflammation-responsive afferent conduit.[37] Recent research reveals that TRPA1+ vagal afferent sensory neurons detect cytokines in the body, thereby activating specific brainstem regions to improve survival against a lethal dose of LPS.[39] Therefore, the vagus nerve functions as a real-time sensor of peripheral inflammation and constitutes the afferent limb of the inflammatory reflex, enabling the brain to perceive and interpret inflammatory states and initiate appropriate neural responses for maintaining systemic homeostasis.

The Inflammatory Reflex Output Pathways Mediated by the Vagus Nerve

Peripheral inflammatory signals are conveyed to the CNS, which integrates them and transmits anti-inflammatory feedback through three main pathways:[5,19,40–42] the cholinergic anti-inflammatory pathway (CAIP), the sympathetic–adrenal–medullary (SAM) axis, and the hypothalamic–pituitary–adrenal (HPA) axis. Through these interconnected pathways, the nervous system exerts both neural and neuroendocrine control over immune responses.

The CAIP, as the vagus nerve's effector pathway in the inflammatory reflex, has become a focal point of current research. In this pathway, the dorsal motor nucleus of the vagus (DMN) activates vagal efferent fibers that release acetylcholine at peripheral sites.[16] This neurotransmitter primarily targets α7nAChRs on macrophages and other immune cells, leading to the suppression of proinflammatory cytokine release and attenuation of systemic inflammation. Over the past two decades, increasing research has revealed that the vagus nerve's effector pathway comprises at least three distinct subtypes:[5,19,43] a spleen-dependent pathway, a spleen-independent pathway, and an adrenal medulla-dependent pathway. The following section highlights recent advances in CAIP research, particularly its anti-inflammatory signaling and effector mechanisms.

Spleen-Dependent CAIP

Over two decades ago, researchers unexpectedly discovered that electrical stimulation of the vagus nerve induces anti-inflammatory effects.[13,16] Subsequently, α7nAChR was identified as critical mediator of these effects.[44] Tracey et al introduced the concept of the CAIP in the context of the inflammatory reflex.[10] This pathway is characterized by acetylcholine release from vagal efferent fibers in peripheral tissues, which activates α7nAChR-expressing macrophages to suppress inflammation.[10] Vagus nerve stimulation (VNS) fails to suppress systemic inflammation in splenectomized septic mice, suggesting that the spleen is essential for CAIP-mediated anti-inflammatory effects.[45] However, the spleen lacks direct vagal innervation.[46] Therefore, extensive research has been conducted to elucidate how vagal signals reach and influence the spleen. Vagus nerve forms synapses with sympathetic postganglionic neurons in the celiac ganglion, transmitting anti-inflammatory signals to the spleen via the splanchnic nerve.[47–49] Choline acetyltransferase-positive ($ChAT^+$) T cells in the spleen are activated by norepinephrine released from the splenic nerve and subsequently secrete acetylcholine.[19] These findings reveal the non-neuronal source of acetylcholine in the spleen, indicating that CAIP can function despite absence of direct vagal innervation. Rana et al reported that VGX reduced the number of $ChAT^+$ T cells in the spleens of septic mice undergoing cecal ligation and puncture (CLP), thereby exacerbating systemic inflammation.[50] Huston et al also found that VGX worsened both splenic and systemic inflammatory responses in LPS-induced sepsis.[45] Summarizing these findings, Pavlov et al[22] described the classical CAIP pathway: activated vagal efferent fibers release acetylcholine in the celiac ganglion, stimulating splanchnic nerves.[47] Then, it releases

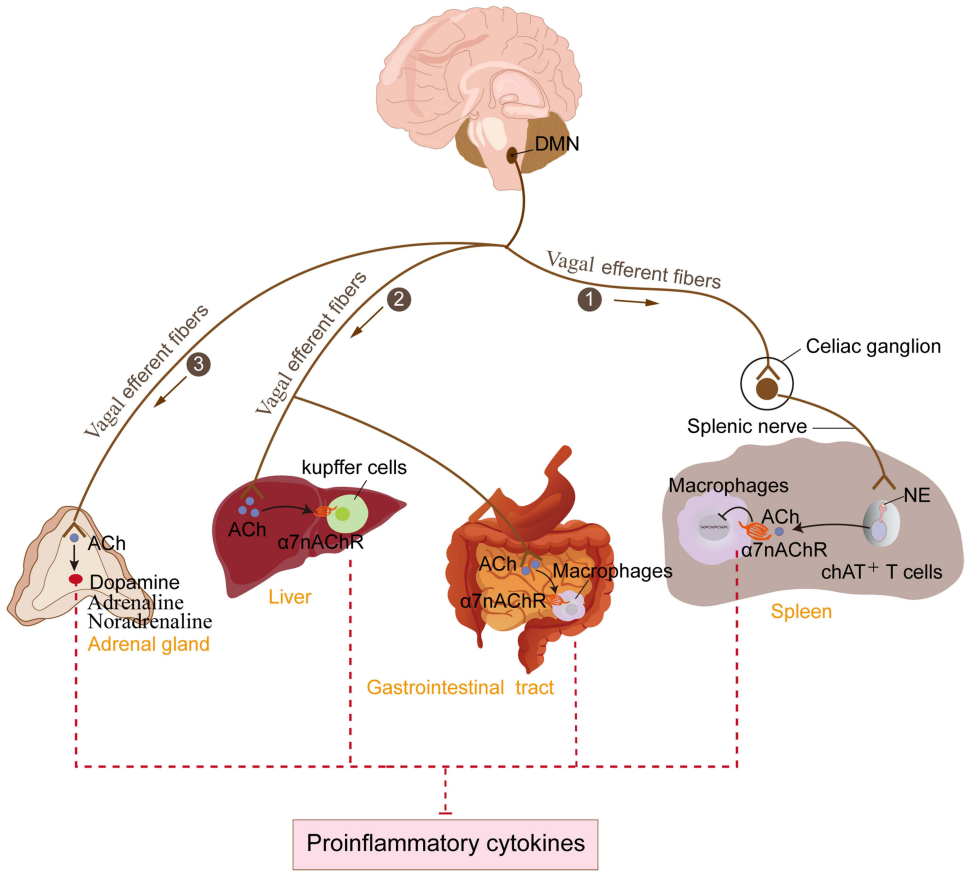

Figure 1 The inflammatory reflex output pathways mediated by the vagus nerve. ① Spleen-dependent CAIP (classical pathway). Vagal efferent fibers release acetylcholine at the celiac ganglion, activating the splenic nerve. Then, norepinephrine released from splenic nerve terminals induces ChAT$^+$ T cells to secrete ACh, which binds to α7nAChRs on macrophages. ② Spleen-independent CAIP. Vagal efferent fibers directly activate α7nAChRs on tissue macrophages by local release of acetylcholine in organs such as the gut and liver. ③ Vagal efferent fibers signaling converts to the adrenal medulla, resulting in catecholamine release. Vagus nerve initiates anti-inflammatory signaling through different pathway, but the results all lead to suppression of pro-inflammatory cytokine production.
Abbreviations: DMN, dorsal motor nucleus of the vagus; VN, vagus nerve; ACh, acetylcholine; NE, norepinephrine; α7nAChR, α7 nicotinic acetylcholine receptor; ChAT$^+$ T cells, choline acetyltransferase-positive T cells; CAIP, cholinergic anti-inflammatory pathway.

norepinephrine in the spleen, activating ChAT$^+$ T cells to secrete acetylcholine, which binds to α7nAChR on macrophages and triggers intracellular anti-inflammatory signaling to suppress cytokine production (Figure 1). This spleen-dependent mechanism remains the most extensively characterized form of CAIP and serves as a prototypical model for understanding neural regulation of inflammation.

Spleen-Independent CAIP

In contrast to the classical spleen-dependent pathway, the spleen-independent subtype of the CAIP describes a distinct mechanism by which vagal efferent fibers directly innervate peripheral organs—such as the gastrointestinal tract, liver, and lungs—and modulate their local immune microenvironments. For example, Matteoli et al showed that the vagus nerve activates cholinergic enteric neurons to release acetylcholine, which directly binds to α7nAChR on intestinal macrophages, thereby inhibiting intestinal inflammation independently of T cells and the spleen.[43] Teratani et al found that vagal efferent fibers form synapses with enteric neurons, promoting acetylcholine release, which modulates antigen-presenting cell activity and suppresses inflammation in inflammatory bowel disease, again, independent of the spleen.[51] Beyond the gut, the spleen-independent CAIP has also been implicated in hepatic inflammation. Nishio et al found that selective hepatic branch vagotomy exacerbated hepatic steatosis and inflammation in murine models of nonalcoholic steatohepatitis (NASH), despite preservation of the vagus–celiac ganglion–spleen circuit.[52] In a fulminant hepatitis model, severing the left cervical vagus nerve significantly elevated TNF-α and IL-6 levels in LPS-stimulated liver tissues,

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with effects mediated by α7nAChR on Kupffer cells.[53] As severing the left vagal trunk does not disrupt the right ventral branch's connection to the celiac ganglion, this further supports that hepatic CAIP functions independently of the spleen.

Collectively, in this pathway, ACh is released directly from parasympathetic nerve terminals at the site of inflammation and binds to α7nAChRs expressed by tissue-resident macrophages and other immune cells, thereby suppressing the local release of proinflammatory cytokines (Figure 1). This direct, non-splenic mechanism bypasses both the spleen and the sympathetic relay seen in the classical CAIP and is characterized by rapid, spatially targeted regulation of inflammation at the site of injury or infection. Therefore, this spleen-independent CAIP represents an important complement to the classical spleen-dependent arc and provides a mechanistic basis for the therapeutic use of vagus nerve modulation in sepsis-related organ damages.

The Vagal-Adrenal Anti-Inflammatory Axis

In addition to vagus nerve's classical anti-inflammatory function via the CAIP, increasing evidence supports a parallel neuroimmune mechanism whereby vagal efferent activity indirectly regulates inflammation through the adrenal medulla. Rafael et al demonstrated electroacupuncture at the sciatic nerve controls systemic inflammation, which is linked to efferent vagus nerve signaling to the adrenal medulla with subsequently increased dopamine production.[40] Increased release of dopamine in this reflex circuitry ultimately leads to suppression of the systemic inflammatory response through D1-receptor-mediated mechanism.[40] Liu et al demonstrated electroacupuncture stimulation at the hindlimb ST36 acupoint drives the vagal–adrenal anti-inflammatory axis in mice with lipopolysaccharide sepsis.[5] It will effectively produce anti-inflammatory effects through activating hindbrain vagal efferent neurons to drive catecholamine release from adrenal glands.[5] This pathway enables the vagus nerve to exert systemic, non-cholinergic control over immune responses by promoting catecholamine release from the adrenal medulla (Figure 1).

Translational Applications Based on Vagus Nerve–Mediated Immunomodulation in Sepsis

Advancements in the understanding of vagus nerve–mediated neuroimmune regulation have increasingly driven translational efforts aimed at targeting these pathways in systemic inflammatory diseases. Two principal therapeutic strategies have emerged from these mechanistic insights. First, VNS—through both invasive and non-invasive modalities—has been employed to electrically activate efferent vagal pathways and suppress inflammation, showing promising effects in both clinical and preclinical models of sepsis and sepsis-related organ injury.[15,28,50,51,54] Second, pharmacological interventions targeting key components of vagal circuits—such as α7nAChRs, acetylcholinesterase (AChE), and catecholamine—also represent a critical direction.[55–57] The following sections summarize recent advances in research on intervention strategies.

Preclinical and Clinical Investigations of the Vagus Nerve Stimulation in Sepsis

VNS—originally developed for the treatment of epilepsy—has emerged as a promising intervention in treating sepsis and sepsis-induced organ damages.[20] VNS is a neuromodulatory technique that delivers electrical impulses to the vagus nerve, either through an implanted device or via non-invasive approaches such as transcutaneous auricular stimulation. Mechanistically, VNS activates efferent vagal pathways that either directly release acetylcholine, which suppresses macrophage cytokine production via α7nAChRs, or indirectly modulate systemic immune responses through engagement of adrenal medulla.

Experimental research over the past two decades has progressively elucidated the therapeutic potential of VNS in sepsis and sepsis-related organ dysfunction—one of the most prototypical and devastating forms of systemic inflammation. The foundational study by Borovikova et al in 2000 first demonstrated that electrical stimulation of the vagus nerve significantly attenuated serum TNF-α levels and improved survival in endotoxemic rats,[13] establishing a mechanistic link between VNS and suppression of macrophage-derived proinflammatory cytokines via the CAIP. Subsequent studies found that VNS in sepsis not only inhibited the production of inflammatory factors by macrophages in splenic tissues but also inhibited the phenotypic switching of splenic neutrophils.[47,58] VNS was found to suppress inflammasome activation and downstream pyroptosis in innate immune cells to reduce inflammatory.[59] In models of septic encephalopathy, VNS

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mitigated neuroinflammation and improved cognitive outcomes, suggesting that vagal modulation extends its protective effects beyond peripheral organs.[60]

Translational efforts have followed, with early-phase clinical studies exploring the feasibility of non-invasive auricular VNS in septic patients. Recent trials have reported that short-term stimulation significantly reduces circulating proinflammatory cytokines such as TNF-α and IL-1β while increasing anti-inflammatory IL-10, paralleling observations from preclinical models.[61] Although improvements in clinical symptoms have been variable, these findings highlight the immunomodulatory potential of VNS in critically ill populations. Notably, a registered pilot randomized controlled trial (ClinicalTrials.gov Identifier: NCT04774705) is currently underway to evaluate the adjunctive use of transcutaneous auricular VNS in ICU patients with sepsis. Studies have demonstrated that cervical VNS significantly reduced multi-organ dysfunction and decreased the need for vasoactive drugs and fluid resuscitation in sepsis.[62] Collectively, these studies suggest that VNS has anti-inflammatory potential in sepsis and warrants further clinical investigation.

Despite promising results, several critical challenges remain. Chief among them is the lack of standardized stimulation protocols—including modality (invasive, non-invasive, or transcutaneous auricular), intensity, frequency, pulse width, and electrode placement—which hampers reproducibility and cross-study comparisons. Moreover, VNS efficacy is influenced by patient-specific factors such as disease type, inflammatory burden, chronicity, and baseline autonomic tone. Safety, tolerability, long-term efficacy, and potential adverse effects also remain incompletely defined. To move the field forward, future studies should implement large-scale, high-quality randomized controlled trials, optimize stimulation parameters, refine patient selection, and deepen mechanistic insights into neuroimmune circuitry. These steps are essential to fully realize VNS as a precision neuromodulatory therapy for inflammatory and immune-mediated diseases.

Pharmacological Interventions Targeting Vagal Neuroimmune Regulation in Sepsis

Compared to device-based neuromodulation, pharmacological interventions offer greater flexibility, broader applicability, and potentially improved patient compliance. Based on the CAIP framework, pharmacological interventions primarily target neurotransmitter receptors, including cholinergic and adrenergic agonists.

α7nAChR Agonists

The α7nAChR, predominantly expressed on macrophages and other innate immune cells, is the principal effector of the CAIP.[44,63] As such, α7nAChR has emerged as a compelling pharmacologic target for modulating systemic inflammation in sepsis and related organ dysfunction. GTS-21 is now the most extensively characterized α7nAChR agonist and serves as a proof-of-concept agent for CAIP-based pharmacological intervention.[64] In multiple preclinical models of endotoxemia and polymicrobial sepsis, GTS-21 administration significantly reduced systemic levels of TNF-α, IL-6, and HMGB1, attenuated histologic injury in key organs such as the lungs, liver, and kidneys, and improved overall survival.[65] Mechanistically, these effects have been linked to both direct suppression of NF-κB signaling in macrophages and attenuation of inflammasome activation. GTS-21 also preserves neutrophil recruitment and bacterial clearance, avoiding the trade-off between inflammation control and immune suppression.[66] Another, nicotine suppresses TNF-α secretion by macrophages in LPS-induced sepsis and mitigates hepatic histopathological injury in *E. coli* sepsis.[67]

Acetylcholinesterase Inhibitors

Acetylcholinesterase (AChE) is a critical enzyme responsible for the rapid hydrolysis of ACh at synaptic junctions, thereby terminating cholinergic neurotransmission. Pharmacologic inhibition of AChE enhances endogenous ACh availability and prolongs its immunomodulatory effects. By stabilizing ACh levels, AChE inhibitors can amplify activation of the CAIP, providing a pharmacological means to engage vagus nerve–mediated immune regulation.

For instance, distigmine administration in CLP-induced sepsis significantly improved survival and decreased circulating levels of inflammatory cytokines.[26] Administration of galantamine in murine models of endotoxemia and cecal ligation and puncture (CLP)-induced sepsis significantly suppressed circulating levels of TNF-α, IL-6, and HMGB1, mitigated histological damage in vital organs such as the lung and liver, and improved overall survival.[68] Cholinesterase inhibitors inhibited hepatic NF-κB expression and reduced neutrophilic myeloperoxidase activity in the lungs, thereby

improving sepsis prognosis.[57] Comparative studies are still lacking, and the relative contributions of central versus peripheral cholinergic enhancement in modulating systemic inflammation continue to be investigated.

Agents Targeting β2-Adrenergic Receptor

The β2-adrenergic receptor (β2AR) functions as a relay node within the CAIP pathway. β2AR agonists activate $ChAT^+$ T cells to secrete acetylcholine, thereby exerting anti-inflammatory effects.[69] Salbutamol has been shown to reduce circulating cytokine levels in LPS-induced sepsis by activating β2AR on T cells and to enhance survival in CLP sepsis.[69] Albuterol also significantly reduces pulmonary inflammation and airway injury in CLP-induced sepsis.[70] Additionally, β2AR is expressed on macrophages and NK cells, and its activation modulates adenylate cyclase and MAPK signaling pathways.[71]

Conclusion and Perspective

It is now well established that the vagus nerve functions as a critical conduit of neuroimmune communication, capable of sensing systemic inflammation and orchestrating anti-inflammatory responses. With the growing understanding of vagus nerve–mediated immunoregulatory mechanisms, vagus nerve stimulation (VNS) and pharmacological modulation of vagal circuits have emerged as promising strategies to mitigate hyperinflammation and protect against organ dysfunction, particularly in the context of sepsis. Looking forward, future research should focus on uncovering the spatiotemporal dynamics and cell-specific regulatory mechanisms underlying vagus nerve–driven immune modulation, along with further elucidation of central neuroimmune circuits to deepen our understanding of vagus-mediated immunoregulation. From a translational perspective, although both neuromodulatory and pharmacological approaches have demonstrated encouraging efficacy in preclinical settings, the clinical application of α7nAChR agonists and AChE inhibitors in sepsis still demands validation through large-scale, high-quality clinical trials. Of particular interest, choline acetyltransferase–positive ($ChAT^+$) T cells, as essential non-neuronal mediators of the cholinergic anti-inflammatory pathway (CAIP), have become a key focus for clinical translation. Accordingly, developing small-molecule compounds or cell-based therapies that promote $ChAT^+$ T cell differentiation or enhance their acetylcholine-synthesizing capacity represents an important and forward-looking direction for future drug discovery and therapeutic innovation.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Guibing Chen: Writing – original draft, Conceptualization, Funding acquisition, Investigation, Project administration. Yang Yan: Writing – original draft, Supervision, Visualization. Shuchang Liu: Writing – review and editing, Conceptualization, Supervision. Yuxin He: Writing – review and editing, Investigation. Tao Ma: Writing – review and editing, Funding acquisition, Project administration. All authors gave final approval of the version to be published; approved on the journal to which this article was submitted; and agree to be accountable to the content of this article.

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Disclosure

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