*Deborah J. Culley, M.D., Editor*

# Neural Control of Inflammation

## *Implications for Perioperative and Critical Care*

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## ABSTRACT

Inflammation and immunity are regulated by neural reflexes. Recent basic science research has demonstrated that a neural reflex, termed the inflammatory reflex, modulates systemic and regional inflammation in a multiplicity of clinical conditions encountered in perioperative medicine and critical care. In this review, the authors describe the anatomic and physiologic basis of the inflammatory reflex and review the evidence implicating this pathway in the modulation of sepsis, ventilator-induced lung injury, postoperative cognitive dysfunction, myocardial ischemia–reperfusion injury, and traumatic hemorrhage. The authors conclude with a discussion of how these new insights might spawn novel therapeutic strategies for the treatment of inflammatory diseases in the context of perioperative and critical care medicine. **(Anesthesiology 2016; 124:1174-89)**


NEURAL reflex circuits are the basic organizational units of the nervous system, capable of rapid and precise responses to a myriad of physiologic challenges in both health and disease. In particular, homeostatic autonomic reflexes regulate body temperature, heart rate, blood pressure, and a wide range of other organ functions.[1] Patients in perioperative or critical care are to variable extents unable to maintain homeostasis and fine-tune their internal physiology due to combinations of therapeutic interventions (*e.g.*, surgery and anesthesia) and disease.[1] When homeostatic reflexes fail, clinicians are tasked with replacing neural reflex control with biochemical monitoring and therapeutic interventions to support normal physiology.

Autonomic reflex circuits are composed of a sensory (afferent) arc that report to the central nervous system (CNS) and a motor (efferent) arc that project regulatory signals to target tissues. CNS integration of a multitude of sensory information allows for purposeful and rapid adaptation to changing demands. For example, the baroreflex regulates heart rate and blood pressure to optimize organ perfusion and adjust exchange of oxygen, carbon dioxide, and nutrients according to need[2] (fig. 1A). Detailed understanding of this cardiovascular reflex has enabled clinicians to diagnose and treat hemodynamic instability effectively.

The inflammatory response is crucial for proper antimicrobial defense and healing after an aseptic injury; however, an excessive inflammatory response or failure to resolve the proinflammatory phase may lead to exaggerated tissue injury, circulatory shock, and death.[3,4] The available therapy for treatment of this unbalanced inflammatory reaction remains limited: steroidal and nonsteroidal antiinflammatory drugs, small-molecule compounds, and specific anticytokine drugs in clinical use are not selective to particular tissues and often produce serious undesirable side effects. For example, systemic anti-tumor necrosis factor (TNF) therapy, which has revolutionized the treatment of several chronic inflammatory conditions, may increase the risk of opportunistic bacterial, viral, and fungal infections.[5,6] The need for new, selective treatment options in inflammation is, therefore, pressing.[7]

In this context, the identification of the so-called "inflammatory reflex" provided the first description of a neural circuit capable of providing information in real time to the brain about the body's inflammatory status to allow for rapid neural regulatory responses.[8,9] Yet, the neural reflexes that monitor and

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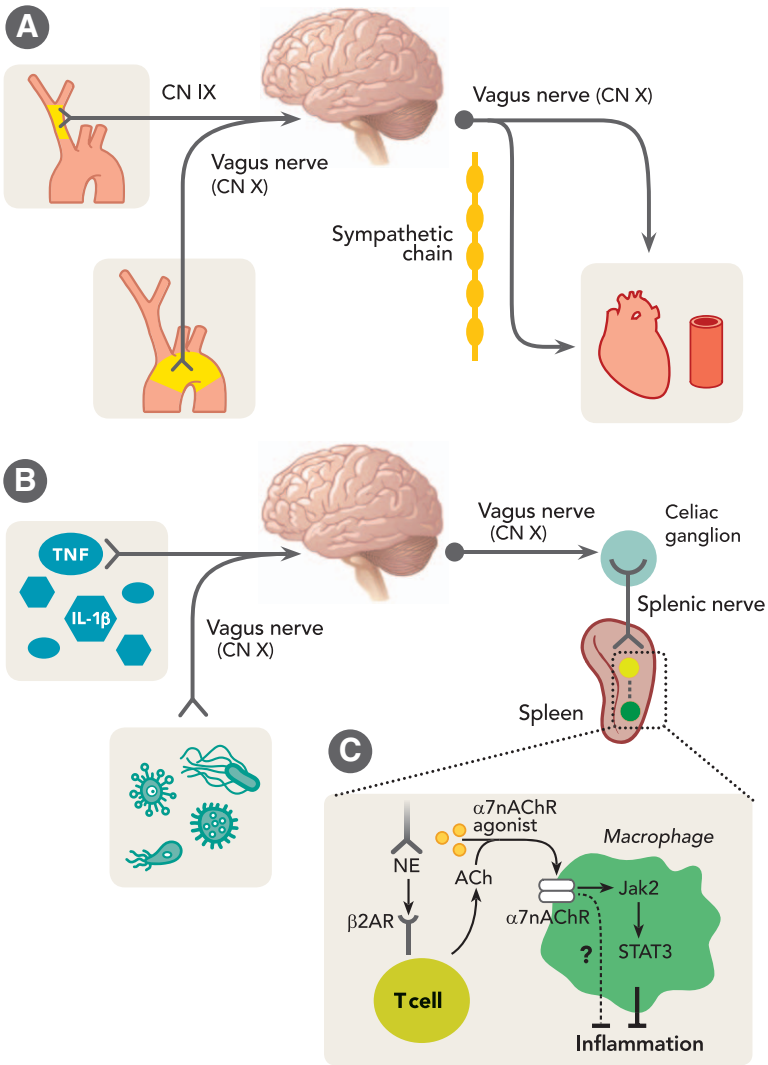


**Fig. 1.** Reflex structure and function. (*A*) The baroreflex is a well-characterized reflex that maintains blood pressure. Like other reflexes, its anatomy consists of a sensory branch coupled with a motor output. The sensory component includes baroreceptors within the aortic arch and carotid sinus, which send information about blood pressure to the central nervous system *via* the glossopharyngeal (CN IX) and vagus nerves (CN X), respectively. Hypertension activates the reflex leading to cholinergic activation and adrenergic inhibition. This manifests as decreased heart rate and peripheral resistance and ultimately decreased blood pressure. Hypotension has the opposite effect and thereby increases blood pressure. (*B*) The inflammatory reflex similarly contains sensory and motor branches. In this case, vagus nerve sensory afferents are activated by the products of inflammatory and infectious stimuli. This information is conveyed to the brainstem. After integration by the central nervous system, the reflex is completed by sending vagus motor signals to the celiac ganglion where the splenic nerve arises. (*C*) The splenic nerve terminates in close proximity to a specialized acetylcholine-producing T cell in the spleen. This T cell behaves similarly to an interneuron: norepinephrine (NE) released by the splenic nerve activates β2 adrenergic receptors (β2ARs) on the T cell, which in turn releases acetylcholine (ACh). The ACh engages the α7 nicotinic acetylcholine receptor (α7nAChR) on splenic macrophages and down-regulates their production of tumor necrosis factor (TNF) resulting in an antiinflammatory effect. The intracellular mechanism for α7nAChR-mediated regulation of cytokine production in immune cells may involve Janus Kinase (Jak) 2 and signal transducer and activator of transcription (STAT) 3 signaling. Pharmacologic α7nAChR agonists (*yellow circles*) that activate the inflammatory reflex are being developed as potential antiinflammatory therapies. CN = cranial nerve; IL-1β = interleukin-1β.

respond to inflammatory stimuli in real time remain oftentimes overlooked. Recent research on how peripheral neural networks both sense and respond to inflammation is providing a possible framework on which to build and implement novel clinical therapies based on the neural control of inflammation.[10]

In this review, we elaborate the anatomic and physiologic basis of the inflammatory reflex as the prototype of inflammation-regulating neural circuits (section "The Inflammatory Reflex") and review the evidence implicating this reflex in modulating clinical conditions (section "Clinical Implications of the Inflammatory Reflex"). We conclude with a discussion of active areas of research into the neuroimmune interface that aim to develop new therapeutics that exploit the nervous system to control dysregulated and

nonresolving inflammation (sections "Cholinergic Anti-inflammatory Pharmacologic Intervention and Bioelectronic Medicine" and "Other Neural Reflexes that Regulate Immunity").

## The Inflammatory Reflex

The vagus nerve ("the wandering nerve") is the longest of the cranial nerves and innervates the majority of the visceral organs including the lungs, liver, and intestine with both sensory and motor fibers. The majority of vagus nerve fibers are sensory, detect a broad spectrum of mechanical and chemical stimuli, and send the information to the brain stem.[11] Notably, these same fibers monitor peripheral inflammatory responses.

The work delineating the interplay between immune mediators and the sensory vagus nerve began with studies by Watkins *et al.,* demonstrating that subdiaphragmatic vagotomies prevent the normal stress and febrile responses elicited by systemic administration of interleukin-1β.[12–14] These physiologic responses were corroborated by direct electrophysiologic recordings from the afferent fibers of the hepatic branch of the vagus nerve in rats, where intraportal injection of interleukin-1β lead to a dose-dependent increase in afferent fiber activity.[15,16] Moreover, bacterial products may also elicit reflex activity mediated by the vagus nerve. Recently, Fairchild *et al.*[17] observed bradydysrhythmias within minutes of administering bacteria or fungi to mice and implicated the vagus nerve by demonstrating simultaneous activation of vagus nuclei in the brain stem. Together, these data suggest that the sensory arm of the vagus nerve can detect immune and inflammatory signals within viscera and convey that information to the brain (fig. 1B). It remains unclear, however, whether the vagus nerve itself is able to directly sense cytokines and bacterial products, if intermediate players are involved, or if both direct and indirect activation pathways are at play. An intriguing possibility is that the afferent fibers of the vagus nerve convey cytokine-specific information to the brain stem, conceivably allowing the CNS to engage differential neurophysiologic responses depending on the immunologic challenge.

In line with this postulate, recent studies of the carotid body suggest that this multimodal sensory organ also serves as a peripheral monitor of inflammation in addition to oxygen, carbon dioxide, and pH, relaying information *via* the carotid sinus nerve and the glossopharyngeal nerve to the brain stem.[18,19] Furthermore, specific sensory nerves have a capacity to directly detect the presence of bacteria to modulate inflammation.[20] Primary sensory neurons in the dorsal root and trigeminal ganglia of the peripheral nervous system express functional toll-like receptors, innate immune receptors that recognize structurally conserved microbial motifs and regulate sensory function including pain and pruritus.[21–24] Interestingly, the selective deletion from nociceptive sensory neurons of myeloid differentiation primary response gene *88*, a downstream signaling molecule in the toll-like receptor activation pathway, results in impaired innate and adaptive immunity.[25] These results suggest that bacterial products could directly modulate neuronal excitability in certain sensory neuron populations.

The efferent arc of the inflammatory reflex (fig. 1, B and C) was first defined by Borovikova *et al.*, who observed that electrical vagus nerve stimulation (VNS) reduced systemic levels of TNF in experimental models of severe systemic inflammation.[26–28] They also found that acetylcholine—the principal neurotransmitter of the vagus nerve—decreased proinflammatory cytokine production in stimulated macrophages.[26] Efferent fibers of the vagus nerve travel to the celiac ganglion where the splenic nerve originates. Splenic nerve axons terminate in close proximity to an acetylcholine-releasing subset of T cells.[29,30] Norepinephrine, the transmitter released by splenic nerve terminals, promotes acetylcholine release from these T cells. This cholinergic signal activates the homomeric neuronal subtype α7 nicotinic acetylcholine receptor (α7nAChR) on immune cells, including macrophages resident within the spleen, and reduces their secretion of TNF.[29,31] The intracellular mechanism for α7nAChR-mediated regulation of cytokine production in immune cells is, however, not entirely clear, but it has been described to involve phosphatidylinositol-4,5-bisphosphate 3-kinase activation, Janus Kinase 2/signal transducer and activator of transcription 3 signaling, and inhibition of the assembly of the nuclear factor κB complex in cells outside the CNS[32–34] (fig. 1C). Furthermore, α7nAChR in mitochondrial membranes may regulate interleukin-1β and high-mobility group box 1 in macrophages by inhibiting inflammasome activation through a mechanism involving mitochondrial DNA release.[35] Further studies of the intracellular mechanisms after α7nAChR activation in immune cells are clearly warranted. The physiologic effects, in cell culture and *in vivo*, are better known.[9] Mice devoid of α7nAChR do not respond to α7 nicotinic acetylcholine (α7nACh) agonists or to electrical VNS with reduced TNF release, and higher levels of systemic TNF were observed in α7nAChR-deficient mice subjected to endotoxemia.[31,36,37] The α7nAChR subunit in immune cells is, therefore, a key component of the cholinergic anti-inflammatory pathway and an essential regulator of inflammation. Disruption of the integrity of the inflammatory reflex conversely inhibits resolution of inflammation.[38] Taken together, these data suggest that the inflammatory reflex tonically balances the production and release of inflammatory mediators and plays an important role in the resolution of inflammation.[39]

## Clinical Implications of the Inflammatory Reflex

Given these important effects of neural signaling on inflammation and immune system activity, it is conceivable that modulation of signals in the inflammatory reflex can be used to regulate inflammation and treat disease. In

fact, the inflammatory reflex has already been implicated as a potential therapeutic target across a variety of clinical conditions of regional and systemic inflammation[26,34,39–59] (fig. 2). In this context, a series of pharmacologic studies in experimental animals have demonstrated a key role for this neuronal pathway in inflammation and, in particular, the essential regulatory role of α7nAChR. Pharmacologic interventions using selective or nonselective α7nAChR agonists improve survival in experimental sepsis, reduce acute neuroinflammation, and result in improved cognitive performance after aseptic surgical injury.[46,60–62] Moreover, there are ongoing trials of the potential benefits from pharmacologic interventions using nicotinic agonists as well as clinical trials evaluating electrical VNS as treatment for chronic inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease (clinicaltrials.gov: NCT01552941, NCT01569503, and NCT02311660).[63] These trials will evaluate the efficacy of α7nAChR agonists or VNS in these chronic conditions; the extensive preclinical and preliminary clinical data suggest promise with this approach.[59,64] Recent research indicates that selective pharmacologic intervention of the α7nAChR or direct electrical stimulation of the cervical vagus nerve may serve as novel treatment strategies in the management of sepsis, ventilator-induced lung injury (VILI), postoperative cognitive dysfunction (POCD), myocardial ischemia–reperfusion injury (IRI), and hemorrhage.

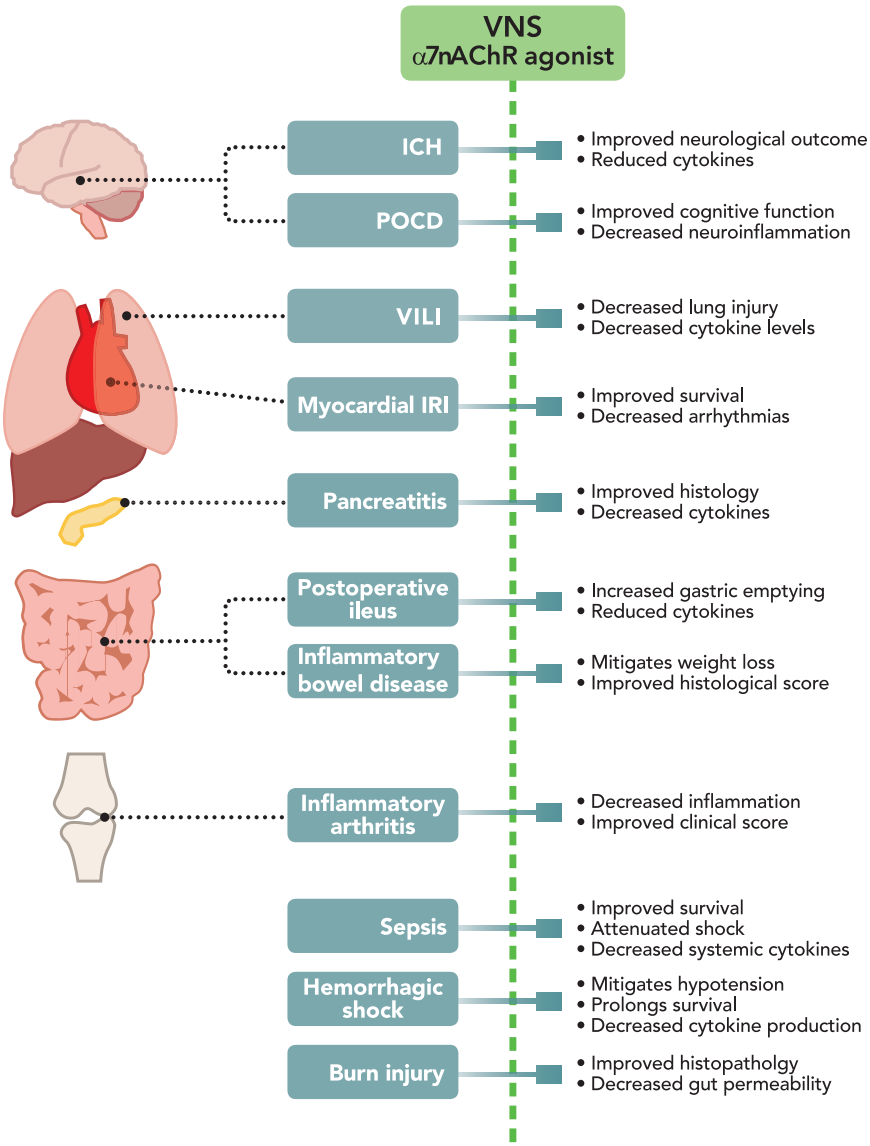


**Fig. 2.** Experimental disease models that respond to pharmacologic or electrical stimulation of the inflammatory reflex. A more detailed discussion of vagus nerve stimulation (VNS) in sepsis, ventilator-induced lung injury (VILI), postoperative cognitive dysfunction myocardial ischemia–reperfusion injury (IRI), and hemorrhage is provided in the main text. ICH = intracranial hemorrhage; POCD = postoperative cognitive dysfunction; α7nAChR = α7 nicotinic acetylcholine receptor.

### Sepsis

Sepsis is a leading cause of worldwide morbidity and mortality and refers to a syndrome of florid systemic inflammatory response as triggered by a microbial infection. Its incidence continues to rise and it has a persistently high mortality.[65] At present, there are no specific therapies available targeting the inflammatory response to infection, and current treatment in sepsis is primarily based on early administration of antibiotics and mechanical removal of damaged tissues, typically combined with aggressive supportive intensive care therapy.[66] The paucity of therapeutic options that directly target the septic inflammatory syndrome partly reflects not only its heterogeneous etiology but also the lack of a more comprehensive understanding of its underlying pathophysiology. A dysregulated inflammatory response and impaired neuroendocrine signaling contribute to disease progression including multiorgan failure with subsequently increased morbidity and mortality.[67]

An association between changes in vagus nerve activity and systemic inflammatory responses has been observed. Analysis of heart rate variability, an indicator of vagus nerve activity, indicates that vagus nerve signals change before severe sepsis[68] and are associated with compromised cardiac function.[69–71] In line with these observations, early changes in heart rate variability recorded at admission in the emergency department have been associated with an increased risk of developing severe sepsis, septic shock, and death,[69,72,73] further implicating a potential role for the vagus nerve in septic patients.

In agreement with these clinical and experimental observations, vagotomy increases mortality in experimental models of sepsis[42,60,74,75] as does genetic ablation of the α7nAChR.[37] Reciprocally, activation of the inflammatory reflex by pharmacologic interventions using selective α7nAChR agonists or direct electrical stimulation of the vagus nerve is protective, yielding not only decreased proinflammatory cytokine burden but also increased survival,[42,60,74] a therapeutic benefit lost in α7nAChR-deficient mice.[37] Sepsis survivors commonly suffer from long-lasting organ dysfunction, including cognitive impairment, which can be reduced by antiinflammatory therapy after recovery from the acute episode in mice.[76] Interestingly, activation of the a7nAChR reduces microglial activation and cytokine release in CNS inflammation.[77,78] Hence, it is conceivable that activation of cholinergic signaling and the inflammatory reflex might be beneficial for mitigating organ dysfunction in sepsis survivors, although this remains to be studied. Notably, in a human trial, nicotine (a nonselective α7nAChR agonist) attenuated the inflammatory response in individuals exposed to intravenous endotoxin.[79] Hence, the α7nAChR is a key component of the inflammatory reflex, serves as a physiologic break on inflammation, and is an attractive pharmacologic target for the development of novel immunomodulatory pharmacologic therapeutics against systemic inflammatory disease and organ injury in acute inflammation due to sepsis and surgical trauma.

### Ventilator-induced Lung Injury

Mechanical ventilation in the perioperative or critical care setting renders patients susceptible to VILI through cycles of stretch and overinflation concomitant to damaging inflammatory responses, so-called biotrauma.[80,81] Multiple strategies to prevent VILI have focused on reducing the amount of mechanical damage to the lung tissue, while optimizing ventilation and gas exchange regimens, yet the clinical burden remains high.[82] Low-tidal volume as part of lung-protective ventilation strategies may still lead to increased release of inflammatory mediators[83,84] with subsequent risk for pulmonary edema and impaired gas exchange. This suggests that even with the development of novel lung-protective techniques, the inflammatory response needs to be addressed to fully abrogate the additional burden of VILI.

Experimental studies suggest that activation of the inflammatory reflex is beneficial in lung injury. For example, in burn-induced or hemorrhagic shock–induced acute lung injury mouse models, VNS reduced neutrophil infiltration into the lung as well as histologic lung injury.[85,86] Similarly, nicotine, choline, or a selective α7nAChR agonist, agents that activate target receptors in the inflammatory reflex, significantly reduce acid-induced lung injury.[87] Surgical vagotomy before the initiation of VILI, in contrast, lead to worsening of pulmonary inflammation and lung function, corroborating that the inflammatory reflex is a modulator of mechanical ventilation-induced biotrauma.[53] In reciprocal experiments, both pharmacologic and electrical stimulation of the efferent vagus nerve was protective in a model of VILI after hemorrhagic shock and resuscitation.[53] Similarly, stimulation of α7nAChR through the systemic administration of a partial agonist reduced TNF release and the alveolar–arterial gradient at clinically appropriate ventilation parameters.[52] In a recent study using a two-hit rodent lung model combining acute lung injury with barotrauma, neither pharmacologic intervention with nicotine nor VNS improved lung function, yet vagotomy lead to a worsening of the pulmonary cytokine response.[88] These results underscore the importance of further mechanistic studies aimed at delineating the involvement of the cholinergic system and the vagus nerve in modulating regional pulmonary and systemic inflammation. VILI offers a unique opportunity for intervention and study as the causative injury is initiated at a well-defined moment of patient care with the prescription of mechanical ventilation.

### Postoperative Cognitive Dysfunction

Surgery and trauma impair cognitive functions and affect a considerable proportion of the surgical population worldwide.[89,90] In surgical care, POCD is one of the most common long-term complications involving memory, learning, and attention capacity, which, when it occurs, impair postoperative rehabilitation and quality of life.[91]

Postoperative cognitive dysfunction develops within the first week after surgery and may remain for several months.

POCD is distinct from acute postoperative delirium, which lasts for hours or days, and from postoperative dementia, which represents a permanent reduction in higher cognitive functions. While reversible, POCD affects up to 30% of middle-aged and elderly patients at 1 week after surgery and 10% of elderly surgical patients at 3 months or even later.[90,92,93] Notably, the incidence of POCD is similar after regional or general anesthesia, indicating that general anesthesia *per se* has minimal direct influence on long-term deficits in cognition after surgery.

The pathophysiology of surgery-induced memory decline remains unclear although preclinical models suggest a role for surgery-induced systemic inflammation leading to activation of immune cells in the CNS with subsequent neuroinflammation[94,95] and neuronal dysfunction.[96] Surgery and tissue damage trigger an innate immune response *via* release of damage-associated molecular patterns such as high-mobility group box 1 and canonical proinflammatory cytokines (TNF, interleukin-1β, interleukin-6). This systemic inflammatory milieu leads to transient endothelial dysfunction and an impairment of the blood–brain barrier (BBB) integrity, which is associated with infiltration of peripheral immune cells into the brain parenchyma and later cognitive dysfunction.[97,98] In this context, activated peripheral macrophages appear to play a pivotal role by orchestrating a systemic release of inflammatory biomarkers combined with short-lasting BBB disintegration, ultimately resulting in macrophage migration into the CNS and distinct hippocampal neuroinflammation with neuronal impairment and ensuing cognitive dysfunction.[46,99] Recent experimental studies have demonstrated that prophylactic administration of α7nAChR agonists before surgery prevents trauma-induced neuroinflammation, BBB disruption, and subsequent cognitive decline by inhibiting TNF release and nuclear factor κB activation in monocyte-derived peripheral macrophages.[46] Efforts to translate these findings into surgical patients by analysis of cerebrospinal fluid have revealed a timely increase in pro- and antiinflammatory molecules after major cardiac and orthopedic surgery,[100–103] suggesting that immune activation in the brain is present within 24 h in surgical patients. These findings demonstrate that therapeutics targeting cholinergic signaling within the inflammatory reflex pathway have the potential to provide a novel prevention and treatment strategy for POCD in humans.

### Myocardial Ischemia–Reperfusion Injury

Ischemic heart disease, common in perioperative and critical care patient populations, is typically treated with reperfusion therapies. A patient presenting emergently with an acute myocardial infarction may undergo reperfusion by thrombolytic therapy or primary percutaneous coronary intervention. Alternatively, stable ischemic heart disease may be treated by coronary artery bypass surgery. Timely intervention limits infarct size, preserves systolic function, and prevents the development of heart failure. Paradoxically, however, the reperfusion process itself independently damages the myocardium, contributing up to 50% of the final infarct size.[104,105] The full extent of the cardiomyocyte death constitutes the IRI.

The pathophysiology of myocardial IRI is complex, involving oxidative stress, cardiomyocyte calcium overload, and mitochondrial dysfunction.[106,107] A robust inflammatory response accompanies an acute myocardial infarction, although the degree to which it is a direct contributor to the development of myocardial injury is unclear.[106] At minimum, the ischemic event and subsequent reperfusion lead to reactive oxygen species production and initiate a local and systemic inflammatory response and the release of proteases, TNF, and other cytokines.[107–109]

Advances directed at improving timely and effective reperfusion along with maintaining the patency of the diseased coronary vessel do not address the full extent of myocardial IRI.[110] To this end, VNS has emerged as a possible therapeutic strategy in the treatment of IRI, with multiple preclinical studies demonstrating that VNS is cardioprotective, improves ventricular function, and decreases arrhythmia in the setting of IRI.[50,111–116] Nevertheless, these animal studies have not been uniformly beneficial. Continuously applied right-sided VNS in a rabbit model of IRI produced increased infarct size, which was suspected to be due to increased sympathetic activation and catecholamine release.[117] Intermittent VNS, in contrast, decreased infarct size in an atropine-dependent fashion.[118] Similar results were observed in a swine IRI model, where left-sided intermittent VNS had a greater cardioprotective effect than a continuous stimulation protocol.[119]

The observed variability likely reflects important differences in the VNS protocols. For example, the decision to stimulate the right or left cervical vagus nerves, intermittently or continuously, may significantly influence the efficacy of the therapy. The right cervical vagus nerve has more efferent cardiac fibers than the left and is thought to have a greater influence on cardiac function.[119] More recently, noninvasive VNS strategies have been tried in IRI. Low-level transcutaneous stimulation of the auricular branch of the vagus nerve in a canine model of cardiac remodeling postmyocardial ischemia produced decreased infarct size and heart remodeling, improved systolic and diastolic function, and decreased systemic C-reactive protein and *N*-terminal probrain-type natriuretic peptide levels.[120]

Mechanistically, VNS during ischemia appears to decrease infarct size through nicotinic receptor activation[112]; however, the specific molecular pathways that are activated remain poorly defined. It has been postulated that VNS can induce a cardioprotective ischemic preconditioning-like state that includes activation of the phosphatidylinositol-4,5-bisphosphate 3-kinase pathway and inhibition of glycogen synthase kinase-3β by phosphorylation.[118,121,122] These signaling pathways ultimately reduce interstitial myoglobin, norepinephrine, and matrix metalloprotease levels important in

tissue remodeling.[123–125] The detailed molecular mechanisms by which these VNS-activated pathways preserve cardiac function remains an active area of research and will likely continue to inform the design of future experimental VNS protocols in IRI management.

### Hemorrhage and Coagulopathy

Coagulopathy and hemorrhage are frequently encountered in high-energy blunt or penetrating trauma and in the critically ill patient populations. Traumatic hemorrhage remains one of the most common causes of preventable death,[126] with a notable morbidity and mortality burden in younger adults. Within the operating room, the ability to maintain hemostasis has benefitted from improvements in surgical approach; however, control of intraoperative bleeding can readily deteriorate in the setting of coagulopathy.

While surgical technique, coagulation factors, and blood products remain central to the management of hemorrhage, clinical best practices continue to evolve. Given the magnitude of this perioperative challenge, the development of so-called neural tourniquet approaches based on animal experiments has been proposed.[127] In particular, recent studies have mapped the effects of VNS and cholinergic agonists in experimental models of bleeding. VNS reduces bleeding time and blood loss in porcine traumatic injury by approximately 50%.[47] Notably, this was not a function of hemodynamic effects resulting from activation of vagus nerve cardiac fibers. In fact, the investigators found that the electrical stimulation as compared to sham controls had increased thrombin-antithrombin complex concentration at the site of injury, suggestive of a *bona fide* biochemical mechanism to the effect.[47] It is tempting to speculate that specific pharmacologic treatment or nerve stimulation strategies that physiologically facilitate coagulation might be used therapeutically pre-, intra-, and postoperatively to reduce blood loss and aid surgical hemostasis. We eagerly await future reports that will provide a greater mechanistic understanding of these observations in animal studies and inform possible novel clinical therapeutic interventions for the treatment of coagulopathies, traumatic injury, and intraoperative hemorrhage.

## Cholinergic Antiinflammatory Pharmacologic Intervention and Bioelectronic Medicine

With the cholinergic inflammatory reflex and the vagus nerve as a prototype, the role of neural control of inflammation is becoming increasingly recognized as a therapeutic target in clinical medicine. The animal studies discussed in the section "Clinical Implications of the Inflammatory Reflex" offer a framework for designing clinical trials that employ pharmacologic or electrical interventions to treat inflammatory conditions through cholinergic pathways.

### Pharmacologic Interventions of the Cholinergic System

Pharmacologically, the neuronal control of inflammation can be modulated by stimulation or inhibition of the cholinergic system using nicotinic α7nAChR agonists or antagonists, respectively. Since the initial demonstration of the role of the α7nACh receptor subtype for the regulation of inflammation, in particular peripheral macrophages,[37] a series of experimental studies on acute inflammation as triggered by either infection or trauma in animals and humans have demonstrated promising effects on outcomes.

Anesthesiologists and critical care physicians have a long-standing familiarity with medications that target the cholinergic system, such as acetylcholinesterase inhibitors for the reversal of nondepolarizing neuromuscular blockade. Yet, the approved agents used routinely in the perioperative setting have not been shown to have clinically significant antiinflammatory effects. Moreover, given the pleiotropic effects of direct and indirect cholinergic agonists, it is unlikely that these agents, used in isolation, will be at the forefront of pharmacologic interventions that target inflammation through the neuroimmune interface. Targeting the α7nAChR specifically will avoid the untoward side effects affecting locomotor activity and autonomic dysfunction that result from stimulation of other nicotinic receptors such as α3nACh, α4nACh, α5nACh, and β2nAChR. To this end, investigators have been developing an array of specific small-molecule modulators of the α7nAChR activity.

GTS-21 (3-[2,4-dimethoxybenzylidene] anabaseine) was one of the first such α7nAChR agonists to be studied for its immune-modulating capacity. GTS-21 was found to suppress proinflammatory cytokine production in human macrophages stimulated by endotoxin[128] as well as improve survival in animal models of sepsis[60] and hemorrhage.[129] To extend these findings toward patient care, a double-blind placebo-controlled pilot human study was conducted in healthy volunteers exposed to intravenous endotoxin.[130] This study did not show any effect of the drug on proinflammatory cytokine serum levels compared with the placebo group; however, high plasma levels of the drug correlated with lower levels of TNF and interleukin-6.[130] The study was largely underpowered and limited by the considerable intersubject variability in cytokine levels and the achieved levels of GTS-21 or its active metabolite. It was further complicated by the incomplete information on the specificity of GTS-21 for human α7nAChR.[131]

The inflammatory reflex can likewise be activated by cholinergic agents that act at the level of the CNS. For example, galantamine, a Federal Drug Agency–approved drug for the treatment of Alzheimer disease, is a centrally acting acetylcholinesterase inhibitor that activates the efferent arm of the inflammatory reflex.[132] In an experimental model of endotoxemia in mice, galantamine decreased TNF levels and improved survival, an effect dependent on α7nAChR. Although galantamine acts centrally, the α7nAChR dependence presumably reflects the importance of this receptor in

completing the antiinflammatory efferent arc at the level of the spleen.[132] Galantamine has been shown to be similarly beneficial in animal models of experimental colitis[133] and obesity-associated inflammation.[134] In the latter study, treatment of obese mice with galantamine decreased circulating levels of proinflammatory cytokines, such as interleukin-6, as well as decreased food intake and body weight while alleviating impaired glucose tolerance.[134] These encouraging preclinical data have since informed the design of a phase 4 clinical trial investigating the efficacy of galantamine in the treatment of patients with metabolic syndrome (clinicaltrials.gov: NCT02283242).

The overall strength of the preclinical findings and accumulating human data maintain the ongoing enthusiasm for pharmacologically targeting antiinflammatory cholinergic pathways. Moving forward, researchers are working toward specific neuronal nicotinic AChR agonists, including for the α7nAChR. To the best of our knowledge, as of yet, no clinical trials of these agents in perioperative or critical care have started but are greatly anticipated.

### Bioelectronic Medicine

Another approach to modulate the inflammatory reflex and the neural control of inflammation is by electrical nerve stimulation. Bioelectronic medicine[63,135,136] is the interdisciplinary field that brings together molecular medicine, neuroscience, engineering, and clinical medicine. The field holds great promise for targeted and specific therapy in the treatment of inflammatory diseases, for example, by modulating signals in neural reflexes (fig. 3). A current objective in the field at large is to develop electrical recording devices that interrogate the neural activity moving through the nerve and translate the neural code into an interpretable physiologic readout. While the field remains in its infancy, the confluence of improved electrical recording hardware, wireless technologies, and data analytics brings our ability to decipher an immunologic code within the realm of possibility. Ultimately, the goal is to develop either implantable or transcutaneous devices capable of recording and interpreting sensory information that inform ensuing modulatory signals in efferent nerves to support homeostasis and treat diseases.

The therapeutic use of electricity has a well-established precedence within the CNS. Deep brain stimulation is approved for treatment of Parkinson disease and depression. It was in fact within the context of illnesses of the CNS that VNS became recognized as a therapeutic modality. First used clinically nearly 30 yr ago, VNS was introduced for the treatment of epilepsy in 1988[137] and eventually approved in both the United States and Canada in 1997. In VNS, a bipolar helical electrode is surgically placed around the cervical vagus nerve, and an implanted stimulator similar to a conventional pacemaker delivers electrical charges that directly activate the vagus nerve. The efficacy of VNS in epilepsy is well defined across adult and pediatric populations with significant reductions in seizure frequency and duration along

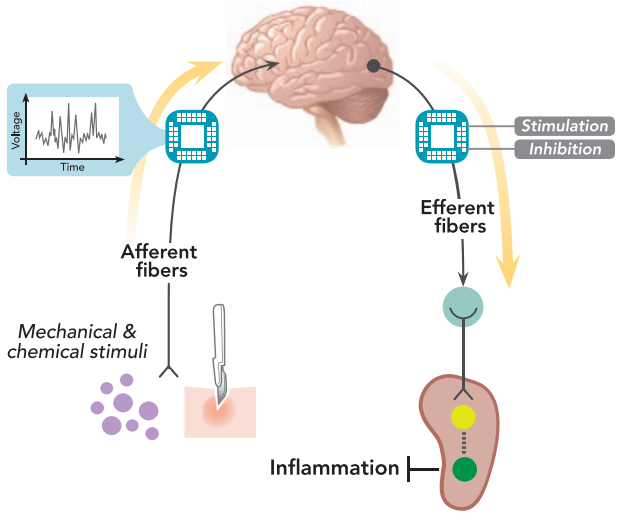


**Fig. 3.** Bioelectronic medicine. Bioelectronic medicine treats disease through the use of electricity to activate or inhibit neural circuits. This therapeutic modality can interface with both the afferent and efferent branches of a neural reflex to modulate the amount of information propagating down the nerve fibers. The long-term objective of this therapeutic approach is to allow clinicians to record the electrical activity in the nerve so as to extract real-time information about patient status. This information can be incorporated into diagnosis and monitoring algorithms as well as inform therapeutic delivery of either electrical or pharmacologic treatment in a patient-specific fashion.

with improved postictal recovery.[138–140] The clinical indication for VNS has expanded to include chronic treatment–resistant depression,[141–144] and VNS is being explored in other diseases involving the CNS, such as migraine and eating disorders.[145,146]

More recently, clinical trials are exploiting the vagus nerve's control of chronic inflammatory responses in the context of autoimmune diseases, including inflammatory bowel disease and rheumatoid arthritis.[64,147] In a pilot, open-label study, eight patients with active rheumatoid arthritis were implanted with a commercially available vagus nerve stimulator and received 6 weeks of daily stimulation. According to preliminary data, the VNS-treated patients showed improved clinical symptoms, with the therapy being well tolerated by study participants.[64,147]

During the implantation procedure, the vagus nerve is stimulated to test device functionality. In less than 0.1% of patients, the test can elicit a bradyarrhythmia or transient asystole, although this adverse event has only been reported at the time of the intraoperative stimulation and resolves when stimulation is stopped.[148] Postoperative surgical site infection and vocal cord paresis are rare, occurring in approximately 3 to 6% and less than 1% of patients, respectively.[148] With use of the vagus nerve stimulator, the reported side effects include hoarseness, throat pain, and coughing and are largely limited to the periods of actual stimulation and commonly alleviate with time.[148–150] Importantly, a 1-min-long

daily electrical stimulation of the vagus nerve is sufficient to alleviate experimental inflammatory disease, with more recent findings indicating that even stimulation times of as little as 500 μs, may be sufficient to significantly reduce an inflammatory response in animal models.[151] Treatment strategies with very low-stimulation duty cycles may allow for innovative, smaller stimulator designs with longer service intervals and fewer side effects in patients with chronic inflammation.

Although extensive experimental data in animal models indicate that VNS is effective for the treatment of acute inflammation, the effect on human acute inflammation has not been evaluated in clinical trials. At present, the only available data come from a few small studies in patients with VNS-treated epilepsy and demonstrate variable changes in serum cytokine levels associated with VNS.[152–155] These data are limited and largely inconclusive given that the patients studied had epilepsy but not inflammatory conditions *per se*. In another small study of 10 patients with treatment-resistant depression, both pro- and antiinflammatory cytokines increased in the 3 months after VNS device implantation.[156]

While medical device technology continues to evolve, VNS has yet to be adapted for temporary, preferably noninvasive, stimulation. Several initiatives are underway, and access to safe and reliable noninvasive methods for specific VNS would significantly facilitate clinical studies of the potential efficacy of VNS in perioperative and intensive care medicine.

## Other Neural Reflexes that Regulate Immunity

In addition to the inflammatory reflex, multiple other peripheral neural circuits that regulate inflammation have been described[157,158] (fig. 4). These include modulation of inflammatory pulmonary airway hyperresponsiveness and nociceptive neuron modulation of infection.

### *Airway Hyperresponsiveness*

The lung contains a dense network of nociceptive neurons that respond to inhaled noxious chemical stimuli *via* transient receptor potential (TRP) channels, including TRP vanilloid 1 (TRPV1) and TRP ankyrin 1. When activated, these nociceptors initiate protective coughing reflexes and mucus secretion.[159] Airway hyperresponsiveness in the setting of chronic inflammation and increased mucus secretion are hallmarks of asthma. These features, including local inflammation, reflect activation of pulmonary airway afferent neural pathways. For example, in allergic and nonallergic mouse models of asthma, genetic ablation or pharmacologic inhibition of TRPV1 and TRP ankyrin 1 channels eliminates airway hyperresponsiveness,[160,161] which appears to be driven primarily by a subset of TRPV1-positive vagus nerve neurons.[162]

Stimulation of pulmonary nociceptors with capsaicin results in increased neuropeptide release and immune cell infiltration, whereas genetic ablation or pharmacologic inhibition of $Na_V1.8$-positive neurons was protective against airway inflammation and hyperresponsiveness in murine models of allergic asthma.[163] Notably, interleukin-5, an important cytokine in eosinophil activation, was shown to directly stimulate nociceptors to release vasoactive intestinal peptide, which in turn activates resident immune cells and promotes the allergic response.[163] These data are consistent with earlier work that demonstrated that allergic asthma is diminished in mice with systemic denervation. In this case, denervation resulted in decreased interleukin-5 release and chemokine production, thereby limiting the number of eosinophils that infiltrated into the tissue.[158,164,165] Accordingly, current work is being directed toward whether pharmacologic inhibitors of pulmonary nociceptive pathways represent a new therapeutic target for asthma and inflammatory pulmonary disease.

### *Infection*

While chemical irritants and sterile inflammatory pathways are modulated by peripheral neural networks, the same appears true for infectious inflammation. The dense network of peripheral nociceptive neurons ensures that invading microorganisms will encounter neural tissue independent of their point of entry. In turn, the peripheral nervous system interfaces with the immune system to modulate the inflammatory response to invading microorganisms. For instance, chemical ablation of sensory neurons in *Mycoplasma* infection increases tissue damage, tracheal thickness, and disease severity.[166] Similarly, genetic deletion of TRPV1 in mice subjected to experimental sepsis impairs bacterial clearance, worsens end-organ damage, and exacerbates a detrimental cytokine production.[167]

Recent work suggests that this relationship stems from direct activation of nociceptive neurons by bacterial toxins so as to initiate a rapid response to infection,[20,168] in part through the production of neuropeptides.[169] Ablation of $Na_V1.8$-positive neurons before *Staphylococcus aureus* inoculation in mice lead to increased leukocyte infiltration to the site of infection and draining lymphadenopathy.[20] In this model, bacterial products, including *N*-formylated peptides and α-hemolysin toxin, directly activate axon–axon reflexes *via* formyl peptide receptors and a disintegrin and metalloprotease 10, respectively, and thereby result in the release of antiinflammatory neuropeptide, such as calcitonin gene–related peptide (CGRP).[20] $Na_V1.8$ neuron ablation prevents CGRP release and thus promotes the inflammatory phenotype. Conversely, administration of exogenous CGRP is protective against otherwise lethal endotoxemia, decreasing pro- and increasing antiinflammatory cytokines.[170]

Further examples of peripheral neural networks that modulate inflammatory processes continue to be described[171–174] and have been reviewed elsewhere.[157,158] It is likely that a large number of additional neural reflex circuits that regulate inflammation and immunity yet remain to be discovered. As our mechanistic understanding of these physiologic processes

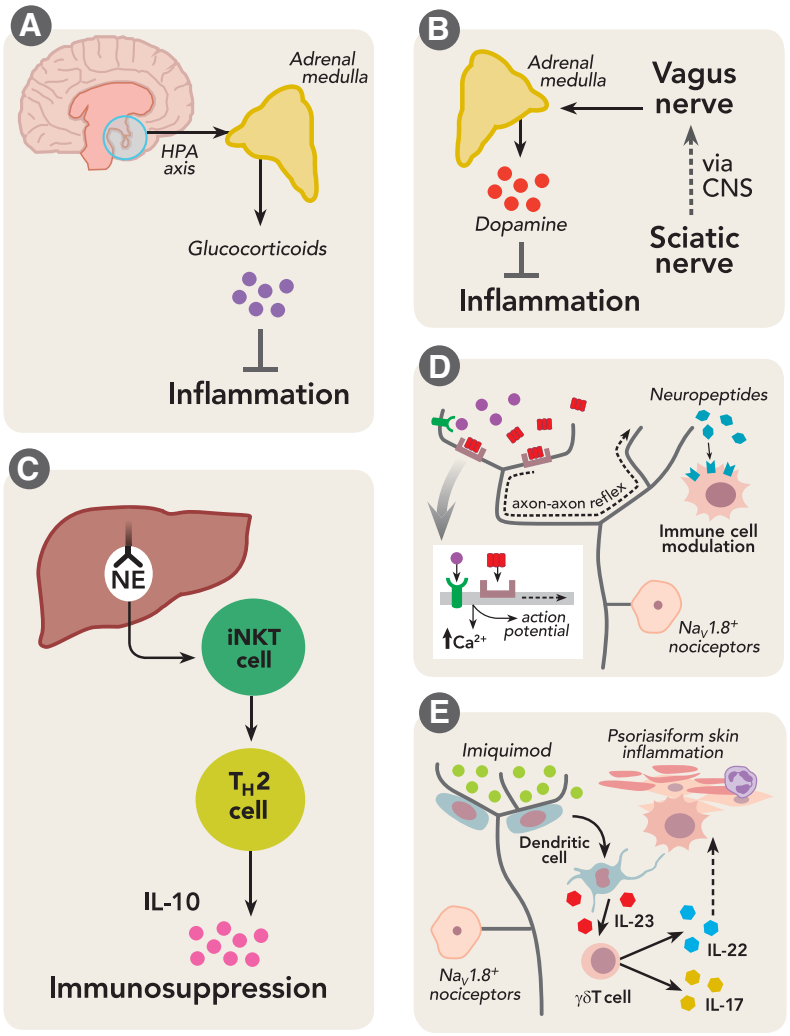


**Fig. 4.** Examples of neural control of inflammatory processes. (*A*) Stimulation of the hypothalamic–pituitary–adrenal (HPA) axis initiates a neuroendocrine sequence resulting in glucocorticoid release and suppression of the inflammatory response. (*B*) Activation of the sciatic nerve by electroacupuncture inhibits cytokine release and improves survival in a mouse model of sepsis. The neural circuit maps from the sensory sciatic nerve to the efferent fibers of the vagus nerve. In this case, the vagus nerve signal results in the release of dopamine from the adrenal medulla. The dopamine engages dopaminergic type 1 receptors to suppress the inflammatory response. (*C*) After stroke, noradrenergic innervation of the liver signal to hepatic invariant natural killer T (iNKT) promotes immunosuppression. Blockade of adrenergic signaling (*e.g.*, β-blockade with propranolol) reduces immunosuppression, protects against infection, and improves survival. (*D*) Infection with the bacterium *Staphylococcus aureus* results in an acute pain response caused by the direct activation of peripheral nociceptors by bacterial products. In addition to transducing a signal toward the central nervous system, receptor stimulation at the nerve terminal generates an antidromic axon–axon reflex that results in the release of neuropeptides that impair the recruitment and activation of locally infiltrating immune cells. (*E*) In an imiquimod-induced model of skin inflammation, a subset of nociceptors that express TRPV1 and $Na_V1.8$ promote local inflammation through the induction of interleukin (IL)-23 production by skin-resident dendritic cells. In turn, the IL-23 activates other immune cells within the skin to secrete the IL-17 and IL-22 that ultimately propel psoriasiform skin inflammation. CNS = central nervous system; NE = norepinephrine; TH2 = T helper cell type 2.

increase, we predict that measuring and modulating activity of specific neural circuits using bioelectronic medicine will eventually become part of patient care in many diseases with an inflammatory component.

## Conclusion and Future Perspectives

The immune system, similar to other organ systems, is regulated by the CNS through neural reflexes, with the inflammatory reflex involving α7nACh-dependent chemical neurotransmission and the vagus nerve being the most highly studied pathway. As inflammation is part of the pathogenesis of a diverse and important set of diseases commonly encountered in perioperative and critical care patients, this neural regulation may allow for new treatment possibilities. Approaching the neural control mechanisms of inflammation by novel pharmacologic and technical principles

provides a new and exciting possibility for prevention and treatment of acute and chronic inflammation.

Future research and clinical trials should focus on introducing pharmacologic interventions applying α7nAChR agonists in clinical practice and work to improve technology for recording nerve activity and delivering specific electrical signals to targeted nerves in order to ultimately mitigate the physiologic trespass of an acute traumatic or chronic inflammatory insult and improve patient health.

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## Competing Interests

The authors declare no competing interests.

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