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Chapter 4

Inflammation and Autonomic Function

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Abstract

Inflammation is generally a temporary and limited condition but may lead to a chronic one if immune and physiological homeostasis are disrupted. The autonomic nervous system has an important role in the short- and, also, long-term regulation of homeostasis and, thus, on inflammation. Autonomic modulation in acute and chronic inflammation has been implicated with a sympathetic interference in the earlier stages of the inflammatory process and the activation of the vagal inflammatory reflex to regulate innate immune responses and cytokine functional effects in longer processes. The present review focuses on the autonomic mechanisms controlling proinflammatory responses, and we will discuss novel therapeutic options linked to autonomic modulation for diseases associated with a chronic inflammatory condition such as sepsis.

Keywords: inflammation, autonomic nervous system, heart rate variability, anti-inflammatory pathway, inflammatory reflex, sepsis

1. Introduction

Inflammation is the physiological response to invading pathogens and tissue damage, such as exposure to extreme heat or cold, ischemia, and trauma [1, 2]. The inflammatory response can be divided into acute or chronic inflammation. An acute inflammatory response is a controlled process, with a short time window of minutes up to a few hours and it is characterized by the abundant presence of a specific type of immune competent cells (neutrophils), responsible for clearing invading pathogens and promote tissue repair, thus restoring homeostasis. However, uncontrolled inflammation, which extends from days up to years, may cause more severe complications. In the latter, if an accumulation of lymphocytes in the inflamed tissue predominates,

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both immune and physiological homeostasis are disrupted, thereby the inflammation can progress to a chronic condition [1, 2]. In its most severe form, it can lead to permanent tissue damage, organ dysfunction, and, ultimately, death [3]. The immune cells residing in tissues, i.e., macrophages, fibroblasts, mast cells, and dendritic cells, as well as circulating leukocytes, including monocytes and neutrophils, recognize pathogen invasion and/or cell damage with intracellular or surface-expressed pattern recognition receptors (PRRs). These receptors detect, either directly or indirectly, pathogen-associated molecular patterns (PAMPs), such as, microbial nucleic acids, lipoproteins, and carbohydrates, often essential for microbe survival, or damage-associated molecular patterns (DAMPs), endogenous molecules normally found in cells, that are released during necrosis contributing to sterile inflammation. Activated PRRs in response to PAMPs and DAMPs, oligomerize and assemble large multisubunit factors, such as, nuclear factor kappa B (NF-kB), activator protein 1 (AP1), cellular transcription factor (CREB), CCAAT-enhancer-binding proteins (c/EBP), and interferon regulatory factors (IRF) transcription factors, which will in turn initiate complex downstream signaling cascades, resulting in the increased expression of key pro- and anti-inflammatory genes [2, 3]. For instance, protease caspase-1, activated by a subset of PRRs, causes maturation of cytokines interleukins IL-1b and IL-18.

Expression of genes encoding enzymes, chemokines, cytokines, adhesion molecules, and regulators of the extracellular matrix promotes the further recruitment and activation of leukocytes to the region, which are crucial for eliminating foreign particles and host debris [2, 3]. Cell adhesion molecules and chemokines facilitate leukocyte extravasation from the circulation to the affected site, the chemokines stimulating G-protein-coupled receptors (GPCRs) [3]. Thus, the immune system plays a crucial and defining role in the overall inflammatory response processes through recruitment of various immune cell types, in addition to the release of pro-inflammatory cytokines into the bloodstream, including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα), which are inhibited by mediators of inflammation resolution, such as anti-inflammatory cytokines, that restore cellular homeostasis and defend the organism from external injuries [2].

The interaction between nervous and immune systems, or the "supersystems" as described by Tada [4], is, in fact, critical in the maintenance and regulation of homeostasis, not only under a daily routine, but also, in adverse environmental conditions caused by injury, infections, and exposure to toxins [5–7]. Indeed, the autonomic nervous system controls the inflammatory processes and immune responses, by finding a balance between pro-inflammatory and anti-inflammatory responses, ensuring an adequate host defense with minimal collateral damage due to overly aggressive responses of the innate immune system [6]. Both parasympathetic and sympathetic efferent nerves have been suggested to affect immune cells and inflammatory responses. The latter interfere in the earlier stages of the inflammatory process, while the parasympathetic nervous system is important to regulate innate immune responses and cytokine functional effects in chronic processes [6, 8, 9].

2. Autonomic nervous system and inflammation

Over the last few years, association between inflammation and common human diseases (e.g., sepsis, obesity, diabetes, rheumatoid arthritis) remains an unsolved mystery of current biology and medicine [10–13]. Inflammation as a response to infection interacts with different

parts of the nervous system. Indeed, recent studies indicate that systemic inflammation can be attenuated by the autonomic nerve fibers [14].

The autonomic nervous system (ANS) includes the sympathetic and parasympathetic nervous system (SNS and PNS, respectively) as its motor systems, and regulates and integrates many human physiological systems and functions, such as the cardiovascular system, the endocrine and exocrine systems, and the digestive system [14, 15]. As reviewed by Kenney and Ganta, to balance the functions of autonomic effector organs, the SNS and PNS work antagonistically, synergistically, or independently [14]. Previous studies have shown that both the SNS and PNS can sense inflammation and influence development and severity of inflammatory processes in animal models [12, 16].

There are many chronic autoimmune diseases in which there is an imbalance of the ANS, for example, rheumatoid arthritis (RA), caused by synovial inflammation, leading to bone erosions, cartilage damage, and ultimately joint deformities and disability [8, 12]. Patients with RA have autonomic modifications, with lower parasympathetic activity and less frequently, alterations in sympathetic function [17]. These alterations are correlated with higher levels of inflammatory markers, such as C-reactive protein (CRP) concentrations and erythrocyte sedimentation rate [17, 18]. Another example is obesity, which consists in the accumulation of abnormal and excessive fat that may interfere with the maintenance of an optimal state of health and is accompanied by an increased morbidity and mortality [19]. This condition is generally associated with other clinical comorbidities including, cardiovascular impairment, atherosclerosis, insulin resistance, and diabetes mellitus [19, 20]. The excess of macronutrients in the adipose tissues stimulates them to release inflammatory mediators (TNFα, Il-6) and reduces production of adiponectin, predisposing to a pro-inflammatory state and oxidative stress [20]. The ANS has a significant role in the integrated short-term regulation of weight, modulating the satiety signal and energy expenditure. The afferent vagal pathways are probably the most important link between the gut and the brain and interact in a complex way with gut hormones. SNS has the physiological function of increasing lipolysis and energy expenditure, through sympathetic innervation in white and brown adipose tissues. However, in obesity, SNS activity is compromised and might trigger alterations in sympathetic regulation of cardiovascular function, thus favoring the development of cardiovascular complications, such as hypertension [21, 22] and organ dysfunction [23, 24].

Another two examples of immune/inflammatory diseases are sepsis and severe burn injury, both characterized by severe global changes to the entire immune system [25]. The immunopathological response to the intense disruptions to the body's homeostatic balance can contribute to the development of systemic inflammatory response syndrome (SIRS), serious metabolic disturbances, and subsequent multiple organ failure and death [25, 26]. During the acute phase, following burn injury, there is an increase in sympathetic activity, which is important for the modulation of energy substrate mobilization, cardiovascular, and hemodynamic compensation and wound repair [27]. Nevertheless, prolonged or excessive sympathetic activity due to the activation of positive feedback mechanism can also be deleterious [27]. Furthermore, the increased susceptibility to infection and other systemic disorders are also accompanied by excessive inflammatory responses that underline the observed cardiac dysfunction, acute respiratory distress syndrome, acute renal failure, increased intestinal permeability resulting in bacterial translocation, hypermetabolism, hypercatabolism, and ultimately, sepsis [28, 29]. Sepsis can, therefore, be

an associated comorbidity of burn injuries, but in its essence is a highly common heterogeneous syndrome in the general population and will be further reviewed in Section 3 [25].

2.1. The role of sympathetic nervous system in the inflammatory processes

The sympathetic nervous system (SNS) is responsible for the "fight-or-flight" response to threatening situations and consists of neural hardwiring emanating from the spinal cord to innervate target organs, including primary and secondary lymphoid organs. About 25% of sympathetic nerve fibers arise from cranial nerves III, VII, and IX and from the second and third sacral spinal nerves [30]. Diverse stimuli (stressors, cytokines, and infection) trigger the SNS and consequent catecholamine release, inducing functional alterations in immune system susceptibility to respond to an invasive infection and other pathologies. As previously mentioned, the SNS interacts in several different manners with the immune system to maintain immune homeostasis under basal conditions, by enhancing host defenses to eliminate pathogens, promoting healing after tissue injury, and restoring homeostasis after pathogen elimination and/or tissue repair. This communication with all immune competent cells occurs directly by stimulated release of its major neurotransmitter, i.e., norepinephrine—NE, and subsequent intercellular signaling via postsynaptic adrenergic receptors (ARs) expressed in closely apposed immunocytes, i.e., T and B lymphocytes, antigen-presenting cells, stromal cells, granulocytes, macrophages, and mast cells [15]. The SNS is highly adaptive, and to appropriately regulate the immune system, it acts through the:

1. Constant up- and down-regulation of diverse target cell functions across time (i.e., expansion, differentiation, apoptosis, and cytokine secretion) and
2. Detection and interaction with the diverse signaling pathways that mediate the above cellular functions [14].

In the initial stages of the inflammatory processes, the body assumes an "inflammatory configuration" with increased systemic SNS and hypothalamic-pituitary-adrenal (HPA) axis activity through the chemoreceptor reflex, the ultimate protective, which can be interpreted as an "energy appeal reaction," resulting in the provision of enough energy-rich fuels, like glucose and free fatty acids, to fulfill the needs of an activated immune system together with the maintenance of appropriate oxygen blood levels. If inflammation evolves to a more severe state, the system changes into a "chronic inflammatory condition," that, according to Pongratz and Straub, is characterized by an increased systemic activity of the SNS, an increased activity of the HPA axis but without immunosuppression (glucocorticoid receptor desensitization and inadequacy), and a local repulsion of SNS fibers from inflamed tissue, including lymphoid organs, to create zones of permitted inflammation [8]. The immune response is more or less uncoupled from central regulation to avoid the anti-inflammatory influence of the brain. All mechanisms ensure an optimal fight against an invading antigen. Nevertheless, if a prolonged or inappropriate activation of either the SNS or immune system persists, the effects are detrimental and can result in the collapse of these two systems, ultimately failing in re-establishing immune system homeostasis within normal physiological ranges [8, 15]. Under such conditions, the immune system and/or SNS can promote pathological and lethal effects, including chronic inflammation, toxic shock, tissue damage, immune deficiency, autoimmunity, and cancer [15], as well as, cachexia, high blood pressure, insulin resistance, leading to increased levels of cardiovascular mortality [8].

Several studies have demonstrated the role of the SNS in inflammation. Martelli et al. showed that in a rat model of intravenous endotoxin, a bilateral section of splenic sympathetic nerves deeply increases inflammatory cytokine release; however, bilateral vagotomy was ineffective, which suggests a splanchnic sympathetic efferent reflex arc of the anti-inflammatory neural pathway [31]. Another clinical phenomenon is immunosuppression after stroke [32]. Indeed, the 6-hydroxydopamine, which blocks a nonselective α-adrenoreceptor and causes pharmacological ablation of the SNS, may also attenuate stroke-induced immunological abnormalities, prevent infections, and improve the survival, and thus SNS activation, instead of the PNS, has a significant role in the immunosuppression response [6, 32–34]. Additionally, in hypertensive patients, the central inhibition of the SNS decreased peripheral TNF serum levels [35]. Moreover, del Rey and colleagues have also found in an animal model of arthritis that during protracted inflammation, there might be a disruption of this communication between the brain and the immune system [36]. There are also several studies indicating that the sympathetic nervous system might be influencing different forms of cancer [37]. In fact, epidemiological studies showed that breast cancer and melanoma improve with the use of beta-blockers, while other studies imply that psychological stress might modulate SNS activity, with a significant impact on inflammation and consequently on the pathogenesis of some cancers [37, 38].

Finally, recent studies show that the SNS plays a significant role in several immune-mediated or immune-related diseases, including sepsis [39], colitis [40], allergic asthma [41], chronic eye inflammation [42], arthritis [8, 36], among others.

2.2. The role of parasympathetic nervous system in the inflammatory processes

The parasympathetic nervous system (PSNS) innervates multiple organ systems, including cardiovascular, respiratory, immune, and endocrine systems [43] and plays a critical role in a diverse array of physiological processes, such as inflammation, immune response, heart rate, gastrointestinal peristalsis, and digestion [13]. About 75% of parasympathetic innervation comes from the tenth cranial nerve, the vagus nerve (VN), that extends throughout the body, and is the largest nerve and main parasympathetic division of the autonomic nervous system [13, 30, 44]. Vagus nerve comprises both sensory afferent neurons, crucial for conducting peripheral immune signals to the brain, which integrate the visceral sensory information and coordinates the autonomic function and visceral activity [13, 33, 34], and motor efferent neurons, which integrate the information that was delivered to the central nervous system and control the peripheral effectors [30, 45]. The vagus nerve not only regulates gut physiology but also mediates cholinergic anti-inflammatory pathway, the inflammatory reflex that controls immune function, and pro-inflammatory responses during infection and injury [35, 45, 46]. The sensory afferent vagus nerve fibers detect peripheral inflammatory mediators, such as cytokines, released by activated macrophages and other immune cells, revealing its pro-inflammatory properties; however, a potent anti-inflammatory effect is exhibited by the efferent branch [46]. The animal models of acute inflammation reveal that the activation of the efferent vagus nerve, probably due to binding of acetylcholine on the alpha-7 subunit-containing nicotinic receptors (α7nAChR), essential for the vagal anti-inflammatory action [47, 48] resulted in reduced systemic production of pro-inflammatory cytokines [46, 49]. This suggests that in the initial phase of inflammation processes, the neuroimmune path eliminates the infectious agent, and in the posterior phase re-establishes the homeostasis [13, 33, 34, 50].

In human studies, the parasympathetic neurotransmitter acetylcholine attenuated proinflammatory cytokine release (e.g., TNFα) in lipopolysaccharide-stimulated macrophage cultures [49], so nicotine was more effective than muscarine in inhibiting TNF release. Human macrophages express α7nAChR subunit, and its knockdown makes macrophages less responsive to nicotine-mediated TNF inhibition [49].

Activating efferent vagus nerve can significantly suppress systemic pro-inflammatory cytokine levels in endotoxemia animal models, as the acetylcholine (Ach) released from the nerve terminals binds to the α7n-AChR expressed on macrophages, to modulate the immune system response [51]. α7nAChR, expressed in the nervous and immune systems, is important for mediating anti-inflammatory signaling by inhibiting NF-κB nuclear translocation and activating the JAK2/STAT3 pathway [48, 49, 51], being also a crucial neural component connecting the parasympathetic vagus nerve with the sympathetic splenic nerve at the mesenteric ganglion [52]. The endotoxemia animal model reveals that peripheral vagal afferents can be activated by responding directly to bacterial lipopolysaccharide (LPS) and cytokines, such as TNFα, interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). IL-1 receptors, expressed on vagal afferents, can be activated by inflammatory stimulation to regulate the immune responses [23, 48]. It has been shown that an excess of proinflammatory cytokine was released in α7nAChR knockout mice, and macrophages from these animals fail to respond to cholinergic agonists [6, 48]. Further, electrical vagus nerve stimulation reduced systemic TNFα concentrations and prevented septic shock in rats [49], and in mice, the vagus nerve stimulation (VNS), as well as splenic nerve electrical stimulation, inhibits lipopolysaccharide (LPS)-induced TNFα release [49, 50, 52, 53]; however, those results were quite surprising because the spleen does not have vagal innervation [53].

Several experiments demonstrated that the sympathetic splenic nerve connects the vagus nerve to the spleen [47, 52]. It is possible that the α7nAchR regulates both the neuronal connection and the macrophage activation. Moreover, the connection between the vagus and splenic nerves has been a matter of constant debate [43]. For example, anatomical and physiological studies have demonstrated no connection between the vagus and splenic nerves [54]. Additionally, denervation of the arterial splenic nerve in mice led to the inhibition of the cholinergic anti-inflammatory pathway [52]. To resolve this inhibition is essential to find a non-neural link in the anti-inflammatory pathway from vagus to spleen. Some authors have proposed an unconventional and theoretical model, where vagus nerve stimulation activates multiple cell types, the choline acetyltransferase positive (CHAT+), epithelial cells, endothelial cells, muscle fibers, and immune cells (such as lymphocytes and macrophages) that are not resident in the spleen, migrating in direction of this organ and subsequently releasing acetylcholine [12, 46, 55]. This electrical nerve stimulation therapy could be applied concomitantly with a pharmacological treatment for a better response. The human studies reveal that the great advantage of this model is the stimulation of ACh/norepinephrine release, reducing interventions with higher doses of anti-inflammatory drugs or even halting their administration [56].

In addition, it has been shown that other organs display a cholinergic control of inflammation, such as gut, kidney, and liver. Despite lung exhibiting vagal innervation, activation of the cholinergic anti-inflammatory pathway is not sufficient to regulate inflammation; however, it is necessary to maintain the homeostasis. In this sense, vagus and/or splenic nerve stimulation appeared as an efficient procedure to minimize inflammation [57]. Furthermore,

in experimental glomerulonephritis, a genetic α7nAChR deletion exacerbates inflammation and fibrosis [6, 54]. Recently, Cedillo et al. showed that increased α7nAChR expression on peripheral blood mononuclear cells was associated with better control of inflammation, disease severity, and clinical outcome in septic patients and prognosis [58].

Concluding, both animal and human studies have suggested that the vagus nerve stimulation has a potential protective regulating systemic inflammation in various pathologies, such as ischemia/reperfusion, sepsis, epilepsy, hemorrhagic shock, migraine, and others [13, 51, 59–61]. However, additional studies are needed to determine the interplay between the vagus and the splenic nerves, and their respective roles in modulating inflammation [6, 12]. According to Martelli et al., several treatments are currently undergoing development, based on the cholinergic anti-inflammatory pathway [46].

3. Autonomic function and sepsis

Sepsis is an important cause of admission in intensive care units (ICU) and remains a major clinical and scientific challenge in modern medicine [53]; this is a huge and expensive medical problem throughout the world, with a mortality rate ranging between 30 and 50% [10, 62]. It is defined as life-threatening acute organ dysfunction, secondary to infection [63], characterized by abnormal body temperature, mental confusion, hypotension, diminished urine output, or thrombocytopenia [53, 63]. Over the past two and a half decades, there has been a tremendous effort to develop standardized diagnostic definitions of sepsis, as described in (**Table 1**). The most prevalent sites of infection, responsible to trigger sepsis in humans, are the lungs, abdominal cavity, urinary tract, and primary infections of the blood stream. After the unsuccessful treatment of sepsis, the patient may develop circulatory, cellular, and metabolic abnormalities, such as, respiratory or renal failure, changes in coagulation, and profound and unresponsive hypotension [53], as well as modifications in cardiovascular, autonomic, neurological, hormonal, metabolic and clotting systems [72, 73]. These marked alterations are characterized by septic shock, the leading causes of death in sepsis [63].

The pathophysiology of sepsis is characterized as a host reaction to infection that involves a balanced inflammatory response, critical to fight the infection, and an unregulated pro- and anti-inflammatory response to induce organ damage in the host [73]. Thereby, the immune response in sepsis results in the increased levels of cytokines, designated hyperinflammatory phase and subsequently evolves to hypoinflammatory phase (immune-suppressive function) [39], the latter being more destructive and aggressive than the initial infection [73]. This imbalance is determined by several factors, such as pathogen virulence, bacterial (i.e., lipoteichoic acid and bacterial lipopolysaccharide—LPS) [74] and patient-related factors (i.e., genetic background, age, and comorbidities) [53], leading the immune system to detect PAMPs (including components of bacterial, fungal, and viral pathogens) and DAMPS (endogenous molecules released from damaged host cells, including ATP, mitochondrial DNA, and high mobility group box 1 or HMGB1) [75]. For transcription of type I interferons and proinflammatory cytokines (i.e., TNF-8, interleukin (IL)-1, and IL-6) initiation, both DAMPs and PAMPs activate innate immune and some epithelial cells through pattern recognition receptors on the

Sepsis definitions	
Previous definitions [64–68]	
Diagnosis	Signs and symptoms
Systemic inflammatory response syndrome (SIRS)	**Two of the following symptoms**: • Body temperature > 38 or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or arterial CO_2 < 32 mmHg • White blood cell count >12.000/mm^3, <4000/mm^3 or > 10% immature forms
Sepsis	SIRS and proven or suspected infection
Severe sepsis	Sepsis in combination with multiple organ dysfunction (MODS).
Septic shock	Sepsis and persistent hypotension (mean arterial pressure [MAP] <65 mmHg) after fluid resuscitation and/or lactate >4 mmol (36 mg/dL)
Revised definitions [63, 69, 70]	
Diagnosis	Signs
Sepsis	• Life-threatening organ dysfunction caused by a dysregulated host response to infection • Suspected or documented infection and an acute increase of >2 sequential (sepsis related) organ failure assessment (SOFA) points (SOFA score [71] is a proxy for organ dysfunction)
Septic shock	• Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality • Sepsis and vasopressor therapy needed to increase MAP ≥65 mmHg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

Table 1. Sepsis: previous and revised definition.

cell surface (toll-like receptors and C-type lectin receptors) or in the cytosol (NOD-like receptors, RIG-I-like receptors) [76, 77]. In the case of bacterial infection, when a microbiological diagnosis is made, about half of the cases show that 60% are caused by Gram-negative and Gram-positive bacterium in the remaining cases [53, 62, 78]. Lipopolysaccharide (LPS) from Gram-negative bacteria (an example of a PAMP) reacts with toll-like receptor 4 (TLR4), causing phagocytic cells to robustly generate a variety of proinflammatory cytokines signaling, leading to systemic inflammatory response syndrome (SIRS) [10].

In sepsis, not only the response of immune cells is highly context dependent to stimuli, but also, the nervous system itself depends on the inflammatory context [10]. Several evidences demonstrate that immune and inflammatory responses are regulated by the autonomic nervous system through PNS and SNS activities [8, 14]. Essentially, to inhibit the inflammatory cytokine production by innate immune cells in the spleen, gut, and other organ, the carotid body chemoreceptors, afferent sensory vagal fibers, and brain areas with a permeable blood barrier respond to local and systemic cytokines, signaling to brainstem nuclei, which in turn send vagal, cholinergic efferents to the periphery [10, 79]. After bacterial infection, one of the

first and local responses is the release of vasoactive peptides by spinal afferent C-fibers and the ensuing neurogenic inflammation. Vagal afferent C-fibers can exert neurogenic inflammatory reflex actions, like those underlying some forms of diarrhea; however, in the proposed vagal anti-inflammatory reflex, the exact role of efferent parasympathetic vagal fibers remains to be elucidated, as these fibers do not seem to directly innervate the major immune organs [79, 80]. The work developed by Tracey and colleagues have shown that, in animal models of sepsis and in another inflammatory conditions (e.g., colitis, hemorrhagic shock, and ischemia-reperfusion injury), neural reflex involving the vagus nerve causes T cells to release acetylcholine and, therefore, interacts with the α7nAch receptor on macrophages to dampen the release of powerful proinflammatory mediators such as TNF-α and HMGB-1 [49, 50, 81]. In an animal model of cecal ligation puncture (CLP), improvements in survival and suppression of the SIRS response of sepsis were described after stimulation of the vagal nerve [81], as does the use of a selective or a universal synthetic agonist for α7nAchR on macrophages [49]. Another recent work indicates that vagal stimulation also reduces symptoms and inflammation in patients suffering from rheumatoid arthritis and Crohn's disease [80].

Contrary to the lack of information on vagal innervation of immune organs and cells, there is longstanding evidence in favor of sympathetic nervous system innervation of primary and secondary immune organs (including, thymus, spleen, bone marrow, and lymph nodes) [82]. Depending on the kind of bacterial infection, there are different effects of SNS on bacterial dissemination, innate immune cell responses, and inflammatory mediators [83]. During septic systemic inflammation, noradrenaline increases in immune organs where it can act on α and β receptors present on macrophages, and adrenaline release into the blood also increases, implying that almost any tissue macrophage could be exposed to adrenaline, which has been shown to modulate pro-inflammatory cytokine secretion by cultured blood cells [81]. Noradrenaline, which is both released and often administered during sepsis [84], may, along with adrenaline, exert pro-inflammatory actions through stimulation of β1 adrenergic receptors, as antagonists of this receptor have been shown to exert anti-inflammatory effects in experimental sepsis [85].

These findings show a specific interest, since, in clinical severe sepsis and septic shock, the selective β1 receptor blocker, esmolol, has shown beneficial effects on microcirculation and myocardial oxygen [84, 85]. Interestingly, in a rat model of CLP, esmolol has similar beneficial effects on vascular and cardiac function [86], and at the same time, it increases anti-inflammatory and reduces pro-inflammatory cytokine production, reduces bacterial component, and improves gut barrier function, ultimately increasing animal survival rates [87]. Although the SNS can influence infection-induced immune responses, depending on the type of bacteria and the timing of treatment, this kind of adrenergic drugs may have beneficial or detrimental effects on the active molecules. Notwithstanding, the promising anti-inflammatory effects of the β1 antagonist esmolol need to be confirmed in clinical trials on septic patients [80].

4. Autonomic modulation and therapeutics in sepsis

Several advancements have been made over time to understand the neuroimmune mechanisms for maintaining and restoring homeostasis during normal and pathophysiologic conditions.

Some studies have already reported that, in adverse conditions, basic reflex mechanisms respond through efferent vagal and sympathetic circuits and that neurotransmitters influence leukocytes with important clinical implications [8, 43, 88]. In this heading, we will review the most relevant therapies associated with autonomic modulation, developed and tested over the last 3 years.

Regarding the importance of sympathetic downstream signaling in anti-inflammation processes, one promising pharmacological approach is the inhibition of phosphodiesterase 4 (PDE4), an enzyme that degrades cAMP [89]. It is reported that, by inhibiting this enzyme, the cAMP increases, and, consequently, shows promising results in several diseases, as psoriatic arthritis, rheumatoid arthritis, Behçet's syndrome [90], and sepsis [91]. Focusing on sepsis studies, inhibitors of PDE4 reduce systemic vascular resistance and improve cardiac contractility and renal function [91]. PDE4 inhibitors also have a potent anti-inflammatory activity effect, by reducing microvascular leakage, all of which could be beneficial in infants with severe sepsis [92]. **Table 2** summarizes the main treatments developed in the last 3 years based on pharmacologic PDE inhibition in sepsis.

It is known that studies in humans have their limitations and confounding variables, such as, differences between groups in age and sex, body mass index, disease severity, smoking, frailty, and physical activity [97]. However, interestingly, clinical responses could be attained through autonomic nervous system modulation, as well as pro- and anti-inflammatory interventions [6, 98]. Several approaches, such as lifestyle interventions, medications, and devices, could be repurposed or further expanded to target inflammation. For example, to lessen systemic inflammation, in metabolic and cardiovascular diseases, it is necessary to develop measures to attenuate sympathetic activity [6, 98, 99]. Similarly, observations in animal models showed that sympathetic inhibition could improve the immunosuppression associated with strokes, and thereby, prevent infectious complications and deaths [6]. At the moment, there are some clinical trials in progress, to evaluate the effects of the cholinergic anti-inflammatory pathway by vagus nerve stimulation in patients with sepsis, severe sepsis, and shock septic, but there are also, at least, five clinical trials that are evaluating the oxytocin in endotoxemia model (https://clinicaltrials.gov/ct2/results?cond=Sepsis&term=esmolol&cntry=&state=&city=&dist).

Taking into account the cholinergic anti-inflammatory pathway, the major discoveries have been associated with: vagus nerve stimulation (VNS) and transvenous vagus nerve stimulation (tVNS) in anti-inflammatory responses, the identification of α7nAChRs in different cell types (macrophages, dendritic cells, and microglial cells) as targets for suppression of inflammation, and the integration of cholinergic T cells into the efferent neuroimmune pathway within the spleen, and also, some pharmacological approaches [98]. Although the vagal neuroimmune pathway is still controversial in specific situations (e.g., sterile or pathogen-induced inflammation), the effect of vagal stimulation could be beneficial to the host by inhibiting exacerbated cytokine production and inappropriate neutrophil entrapment into vital organs [12, 16]. By contrast, the cholinergic anti-inflammatory pathway can inhibit specific innate immune responses that are crucial to eliminate the bacteria (e.g., initial neutrophil migration) and subsequently increase the mortality in sepsis [100, 101]. Nevertheless, while VNS will unlikely replace the standard intensive care therapy, it is quite possible that, in the future, autonomic modulation through VNS would become an adjunct to benefit septic

Pharmacological approach						
	Target	**Study**	**Method**	**Conclusions**	**Perspectives**	**Year**
Dibutyryl-cAMP Rolipram Roflumilast	Inhibition of phosphodiesterase 4B **(PDE4)**	***In vitro:*** macrophage cell line (mouse) Animal (mice)	Cell: LPS (10 ng/ml) Mice: LPS (10 mg/kg)	Upregulates anti-inflammatory cytokine IL-1Ra production in vitro and in vivo	PDE4B-selective inhibitors may retain the anti-inflammatory effects of nonselective PDE4 inhibitors	2017 [93]
Roflumilast	Effects on a CLP-model-induced sepsis	Animal (mice)	CLP	Reduce of bacterial load Inhibition of the IL-6 and TNFα expression Alleviation of liver injury	May be an appropriate treatment of sepsis Needed more studies.	2017 [94]
Rolipram Azithromycin Ethyl pyruvate Metformin	Investigate potential antiendotoxic effects	*In vitro* (cells of horses)	LPS (1 μg/ml)	Rolipram: the most potent inhibitor of cytokine production	Further work is required to investigate the potential use in vivo.	2015 [95]
Rolipram	Impact of the PDE4 inhibition on hepatic integrity	Animal (rat)	LPS (2.5 mg/kg, i.v.)	Improvement of hepatic microcirculation and integrity Protective effect on hepatoma cell line viability	Further studies needed to determine clinical applicability of PD-4-I	2015 [96]

Table 2. Pharmacologic phosphodiesterase (PDEs) inhibition in sepsis disease.

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	Target	Study	Method	Conclusions	Perspectives	Year
Autonomic modulation						
Chemoreflex stimulation and pharmacological intervention	Chemoreflex activation Pharmacological blockade (methylatropine or propranolol)	Animal (rat)	LPS (1.5 mg/kg, i.v.)	Attenuates the use of TNFα, IL-1β, and IL-6 plasma levels Increases the IL-10 plasma levels	Methods to stimulate CSN, which is a promising therapeutic strategy	2017 [102]
Vagal nerve stimulation B(VNS)	Assessed changes in IL-6 and TNFα	Animal (rat)	LPS (0.5 mg/kg, intratracheally)	Attenuates the upregulation of IL-6 and TNFα Viable alternative to antibiotics	Provides a suggestive link between VNS and potential clinical application to treat sepsis in preterm infants	2016 [103]
	Effects on sepsis-associated encephalopathy	Animal (rat)	LPS (i.v.)	Activates anti-inflammatory effect through cholinergic pathway Improves the cerebral function Reduces systemic and cerebral inflammatory reaction	Requires more research	2015 [104]
	Potential role of prostaglandin in cholinergic neuro-regulation	Animal (mice)	LPS (2 mg/kg, i.p.)	VNS decreases the release of pro-inflammatory cytokines both in serum and spleen	Further development of therapeutic directed of inflammatory reflex modulation, and immunosuppression in chronic inflammatory diseases	2015 [105]
Transvenous vagus nerve stimulation (tVNS)	Determine the feasibility and safety, investigated its putative anti-inflammatory effects	Randomized double-blind study	LPS (2 ng/kg, i.v).	tVNS is feasible and safe but does not influence the systemic inflammatory response in vivo	Short-term tVNS does not modulate the innate immune response in humans Require more studies	2015 [106]
	α7 gene expression level in peripheral blood mononuclear cells (PBMC) as marker for CAP	Pilot study	Septic patients within the first 24 hours of diagnosing sepsis	PBMC α7 gene expression level is a clinically relevant marker for CAP activity in sepsis: the higher the α7 expression, the better the inflammation control and the prognosis	The CAP activation in high-risk septic patients has therapeutic potential: this activation could be used as an adjunctive therapy	2015[58]

	Target	Study	Method	Conclusions	Perspectives	Year
Pharmacological intervention						
Esmolol	Effects on reducing apoptosis and inflammation	Animal (rat)	CLP	Reduces apoptosis and inflammatory reaction and protect key organs	Needed clinical trials to confirm the use of esmolol in sepsis treatment	2017 [87]
	Effect on tissue perfusion and the clinical prognosis of patients with severe sepsis	Prospective cohort clinical trial	Continuous infusion of esmolol via central venous catheter	Controlled heart rate reduced the duration of mechanical ventilation No significant effects on circulatory or tissue perfusion	Requires further research.	2016 [84]
	Effects on myocardial and vascular function	Animal (rat)	CLP	Enhances intrinsic cardiac contractility and improves vascular responsiveness to catecholamines	Further investigation needed to determine the effects of β1-blockade on other organ functions and inflammatory patterns in septic shock.	2015 [86]
Oxytocin	Effects on the cardiorespiratory activity	Animal (rat)	LPS (0.1 mg/kg; intraperitoneally)	Potential cardioprotective peptide Diminished tachypnea and restore the cardiorespiratory interactions Provokes a less anticorrelated pattern in HRV Decreased mean heart rate Reduce lethargy and moderated the hyperthermia	These findings confirm the suitability of the electrocardiogram-derived respiration technique to obtain the estimated respiration signal in rodent models	2017 [107] 2016 [108]
Xanomeline	Effect on brain muscarinic acetylcholine receptor (mAChR)-mediated cholinergic signaling	Animal (mice, rat)	LPS (6 mg/kg, i.p) CLP	Suppresses serum and splenic TNF levels Alleviates sickness behavior, and increased survival	Further studies centrally-acting M1 mAChR agonists as experimental therapeutic agents in a broader spectrum of inflammatory conditions	2015 [109]
Other						
ANS indices	Investigate how changes in cardiovascular indices can be a sign of progression of organ failure	Prospective observational cohort study	Follow-up during the first 3 days of ICU stay after development of septic shock	Variability of heart rate significantly increases in septic shock patients presenting improvement of organ function from ICU day 1 to day 3.	Further investigations are required to find specific associations with drug dosage, namely, drugs acting on the sympathetic system, and clinically relevant outcomes	2017 [110]

Table 3. Sepsis: autonomic modulation, therapeutics, and treatments based on the PNS therapy.

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patients [100, 101]. The most relevant treatments and therapies based on parasympathetic nervous system developed over the last 3 years, in animal models and human studies, are shown in **Table 3**.

5. Conclusion

The nervous and immune systems are not fully independent. When the body is inflamed, both systems produce neurotransmitters and cytokines and express receptors that are involved in important physiological functions and in the maintenance of homeostasis. The reactions of the immune competent cells to neurotransmitters are variable, depending on the context of receptor engagement, such as, activation state of the cell, expression pattern of neurotransmitter receptors, microenvironment, cytokine, and distance from the catecholamine source (concentration). It is already well described that autonomic modulation in acute and chronic inflammation has been implicated with a sympathetic interference in the earlier stages of the inflammatory process and the activation of the vagal inflammatory reflex to regulate innate immune responses and cytokine functional effects in longer more chronic processes. The present chapter reviewed the overall autonomic mechanisms controlling inflammatory responses in several conditions such as, burn processes, arthritis rheumatoid, obesity, with a special focus on the inflammatory processes associated with sepsis. Furthermore, the most relevant therapeutic options for the latter, through autonomic modulation, were also reviewed and summarized.

In summary, it is quite clear that sepsis remains a worldwide clinical challenge and therapies' outcomes depend largely on host factors. Henceforth, continuous searching for new and more effective therapies during the initial phases of sepsis is utterly important, in order to reduce the mortality associated with this syndrome (condition).

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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