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REVIEW

# Neural pathways involved in infection-induced inflammation: recent insights and clinical implications

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## Abstract

Although the immune and nervous systems have long been considered independent biological systems, they turn out to mingle and interact extensively. The present review summarizes recent insights into the neural pathways activated by and involved in infection-induced inflammation and discusses potential clinical applications. The simplest activation concerns a reflex action within C-fibers leading to neurogenic inflammation. Low concentrations of pro-inflammatory cytokines or bacterial fragments may also act on these afferent nerve fibers to signal the central nervous system and bring about early fever, hyperalgesia and sickness behavior. In the brain, the preoptic area and the paraventricular hypothalamus are part of a neuronal network mediating sympathetic activation underlying fever while brainstem circuits play a role in the reduction of food intake after systemic exposure to bacterial fragments. A vagally-mediated anti-inflammatory reflex mechanism has been proposed and, in turn, questioned because the major immune organs driving inflammation, such as the spleen, are not innervated by vagal efferent fibers. On the contrary, sympathetic nerves do innervate these organs and modulate immune cell responses, production of inflammatory mediators and bacterial dissemination. Noradrenaline, which is both released by these fibers and often administered during sepsis, along with adrenaline, may exert pro-inflammatory actions through the stimulation of β1 adrenergic receptors, as antagonists of this receptor have been shown to exert anti-inflammatory effects in experimental sepsis.

**Keywords** Autonomic nervous system · Catecholamines · Immune organs · Sepsis · Vagus nerve

## Introduction

Although the immune and nervous systems have long been considered independent, these systems actually mingle and interact extensively. It has long been implicit that inflammation implies activation of neural pathways, because heat and pain, as symptoms of local inflammation, correspond to sensory modalities. Research during the twentieth century has shown that swelling and redness, as the two other symptoms of local inflammation, depend on the peripheral release of neuropeptides by sensory neurons. Inflammation as a response to infection can become systemic, and is called sepsis when fever, tachycardia and hyperventilation accompany altered white blood cell counts. Furthermore, altered mental status is (again) part of the diagnostic criteria of sepsis [1] and likely related to "sickness behavior", characterized by reduced sleepiness, reduced activity, food intake and social interactions, and considered to be adaptive to fighting bacterial infection [2]. As mental status, body temperature and heart and respiratory rates depend on or are controlled by different parts of the nervous system, this implies that inflammatory signals can modulate neural pathways. Finally, recent evidence indicates that autonomic nerve fibers may dampen systemic inflammation. The present review proposes to summarize recent insights into the neural pathways activated by and involved in infection-induced inflammation and to discuss potential clinical applications.

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## Peripheral C-fibers signal inflammation to the brain mediate inflammatory reflexes

According to Cajal's neuronal doctrine, the prototypical flow of electric current in sensory neurons is from dendrites in the peripheral tissues to axons establishing contacts in the spinal cord, and in motor neurons from dendrites in the spinal cord to axons ending on peripheral muscles groups or endocrine glands. Although we do not intend to take position in the scientific debate on whether or not some sensory fibers should be called autonomic nervous system afferents [3, 4], we would like to point out that the activation of poorly or unmyelinated C-fibers with cell bodies in the dorsal root (spinal afferents) or nodose (vagal afferents) ganglia often elicits autonomic nervous system responses as part of reflex arcs.

Visceral C-fiber afferents, like cutaneous C-fiber afferents, contain the peptides substance P and calcitonin gene-related peptide (CGRP) that, in case of activation, can be released in the dorsal horn of the spinal cord. Interestingly, these fibers, often considered nociceptors because of their capacity to detect and transmit potentially damaging stimuli, can also release these same peptides from their peripheral endings in a reflex-like manner and contribute to inflammation by promoting local plasma leakage [5], but in a way that is contrary to the neuronal doctrine. Hence, and although often overlooked, neurogenic inflammation concerns a reflex within a single neuron and not a reflex arc consisting of several neurons establishing serial contacts.

Although neurogenic inflammation as a reflex, and therefore autonomic action, has been most widely studied in the skin, it probably occurs in all tissues that are innervated by unmyelinated C-fibers. Since the gut epithelium is also exposed to the external world and contains numerous bacteria, it may be highly prone to injury-related infection-induced inflammation. Indeed, in the gastrointestinal tract, spinal afferents determine to a large extent gut inflammatory processes [6]. Moreover, recent evidence indicates that visceral sensory neurons can detect specific bacterial metabolites and molecules and may play a role in host defense against *Salmonella typhimurium*, *Citrobacter rodentium* and enterotoxigenic *Escherichia coli* [7, 8].

One of the local defense mechanisms against digestive pathogens is diarrhea through fluid secretion by intestinal epithelial cells. Interestingly, intestinal fluid secretion in response to the presence of bacterial toxins involves afferent C-fibers, as it can be inhibited by capsaicin administration [9, 10]. Since transection of the vagus nerve, which contains both sensory and motor fibers, also attenuates this response [9], it likely involves vagal rather than spinal sensory C-fibers. In addition to the neurogenic reflex mechanisms of vagal C-fibers, the sensory and motor fibers in the vagus nerves can be serially activated with a relay in the caudal brainstem and mediate vago-vagal reflexes involved in gastrointestinal motility [11]. Since the delayed gastric emptying in response to intraperitoneal administration of Gram-negative bacterial lipopolysaccharide (LPS) or endotoxin can be prevented by local application of the C-fiber toxin capsaicin on the vagus nerve or blockade of CGRP, but not by adrenergic receptors [12], gastroparesis in response to infection may involve either intrafiber neurogenic inflammation or vagovagal reflex mechanisms.

Since two of the classical symptoms of local inflammation, heat and pain, correspond to sensory modalities, spinal C-fibers also seem to transmit signals to the central nervous system during inflammation. Indeed, intraperitoneal injection of *E. Coli* cell wall LPS increases the levels of substance P and CGRP in the spinal cord [13]. Furthermore, selective chemical lesions of C-fiber afferents with capsaicin can attenuate the first phase of the fever response in response to systemic administration of LPS in adult rodents [14].

Local inflammation is also characterized by hyperalgesia, an increased sensibility to nociceptive or potentially damaging stimuli. Application of the pro-inflammatory cytokine interleukin-1beta (IL-1β), which is produced in response to LPS, under the skin of a rat paw increases the sensitivity to mechanical and heat stimuli and augments electric activity of sensory nerve fibers involved in nociception [15, 16]. Interestingly, ganglia of spinal sensory nerves express not only IL-1 receptors [17] but also toll-like receptors recognizing bacterial fragments [18, 19]. Taken together, these findings suggest that low doses of IL-1β or bacterial fragments may act on sensory nerve fibers to signal the central nervous system and give rise to early fever and hyperalgesia.

## The role of the vagus nerve in inflammation-to-brain signaling and anti-inflammatory reflexes

In accordance with the hypothesis that sensory nerves are involved in signaling inflammation to the brain to bring about non-specific disease symptoms, subdiaphragmatic vagotomy has been shown to attenuate the reduction in social exploration and food-motivated behavior, conditioned taste aversion, increased sleep and hyperalgesia 2 h after intraperitoneal administration of IL-1β or bacterial LPS [20–25]. Reversible inactivation of the brainstem dorsal vagal complex, containing the central terminals of vagal sensory fibers, by local anesthesia or blockade of brainstem glutamateric metabotropic neurotransmission, also restores social exploration and food intake after LPS administration [26, 27]. However, even though febrile responses to systemic

administration of low doses of IL-1β or LPS were attenuated by subdiaphragmatic vagotomy, fevers after higher doses were not [28–35]. Soon after the first vagotomy studies, intravenous IL-1β administration was found to increase afferent discharge activity of branches of the vagus nerve [36, 37]. Subsequently, vagal paraganglia and the nodose ganglion were observed to bind IL-1ra and to express the signaling IL-1 receptor [38]. Interestingly, ganglia of the vagal nerves also express TLRs [39]. Taken together, these findings suggest that low doses of IL-1β or bacterial fragments may act on sensory nerve fibers to signal the central nervous system to give rise to early fever, hyperalgesia and sickness behavior.

Interestingly, intraportal administration of IL-1β not only results in an increase in hepatic vagal afferent activity, but also induces reflex activation of vagal efferent fibers thought to innervate the thymus (but see below), an effect that can be blocked by hepatic vagatomy [40]. Some 5 years after the initial studies reported that subdiaphragmatic vagotomy attenuates the behavioral and, to a lesser extent, the febrile responses to peripheral administration of bacterial LPS or pro-inflammatory cytokines, it was shown that electrical stimulation of the peripheral vagus nerve inhibits hepatic synthesis and circulating concentrations of tumor necrosis factor alpha (TNFα) and prevents the development of shock in response to high doses of LPS in rats [41]. These effects of electrical stimulation of the vagus nerve were mediated by acetylcholine action on nicotinic receptors [42]. As electrical stimulation of the vagus nerve has long been known to enhance the release of acetylcholine in the spleen [43, 44], and the effect of vagal stimulation on LPS-induced and polymicrobial sepsis-associated TNFα synthesis was even more important in the spleen, and splenectomy sufficient to abolish it [45], subsequent studies focused on elucidating the acetylcholine-dependent mechanisms downstream of vagal stimulation. Although the results of such studies were interpreted within the framework of an anti-inflammatory reflex involving the vagus nerve, these interpretations included contacts between vagal fibers and sympathetic fibers innervating the spleen and acetylcholine production by spleen lymphocytes [46–49].

However, this hypothesis of a vagally-mediated anti-inflammatory reflex has been questioned because the evidence (1) in favor of direct transmission of inflammatory signals from vagal afferent to efferent neurons in the caudal brainstem, which, in turn, downregulates peripheral inflammation is lacking, (2) major immune organs driving inflammation, such as the spleen, are neither directly nor indirectly innervated by vagal fibers, and (3) acetylcholine also seems to be a signaling molecule between immune cells [50]. Martelli and colleagues have also emphasized that acetylcholine-synthesizing T-lymphocytes constitute a non-neural link and that the localization of alpha-7 subunit-containing nicotinic receptors involved in the anti-inflammatory effects of vagal stimulation is still uncertain [50]. Finally, they make the point that the afferent arm of a postulated vagal anti-inflammatory reflex has not been elucidated and that efferent pathways are not necessarily activated during systemic inflammation provoked by administration of high dose of bacterial LPS [50]. Instead, Martelli et al. have shown that transection of the greater splanchnic sympathetic nerves increases TNFα synthesis in response to lower doses of intravenously administered LPS, whereas vagotomy had no effect [51]. Nevertheless, vagotomy has been shown to increase pro-inflammatory cytokine production and mortality in a mouse model of polymicrobial sepsis [52, 53]. Moreover, some recent pilot work indicates that vagal stimulation reduces symptoms and inflammation in patients suffering from rheumatoid arthritis and Crohn's disease [54, 55].

In addition, it is important to point out that the evidence for direct innervation of immune organs and/or cells by the vagal terminal is scarce. Indeed, the immunohistochemical detection of the vesicular acetylcholine transporter, as a marker of cholinergic fibers, only results in very little, and foremost perivascular, labeling in lymphoid organs [56]. This approach thus confirmed earlier work reporting a lack of cholinergic innervation of the spleen parenchyma, but seemed to confirm previous studies showing numerous cholinergic fibers in the thymus using acetylcholinesterase staining [57, 58]. However, as the latter labeling in the thymus is not affected by vagotomy, it does not seem to be of vagal origin [59].

Interestingly, earlier work had shown the presence of acetylcholinesterase in spleen lymphoid and reticular cells [58]. The use of genetically-modified constructs in which fluorescent reporter genes are expressed behind the promotor of choline-acetyltransferase has recently allowed the confirmation of both sparse perivascular cholinergic innervation and the presence of choline-acetyltransferase T- and B-lymphocytes in the spleen [60]. However, in the intestinal lamina propria of the gastrointestinal tract, numerous choline-acetyltransferase-positive fibers, almost exclusively from enteric neurons, often approached macrophages and lymphocytes of the lamina propria, but also lymphocytes of Peyer's patches [60]. Moreover, vagal efferent fibers, identified after injection of an anterograde tracer into the dorsal motor nucleus of the vagus nerve, have been found to end around enteric neurons, which, in turn, were situated in the proximity of intestinal macrophages [61]. Hence, the available anatomical evidence indicates that vagal efferent terminals can indirectly influence immune cells in the intestine but not in the spleen or thymus.

So, although the role of afferent vagal fibers in the signaling of peripheral bacterial infection-induced inflammation to the brain to bring about early fever and sickness behavior

is now clearly established, that of efferent vagal fibers in downregulating inflammation remains to be further clarified.

## The sympathetic nervous system and bacterial infection-induced inflammation

It is of note to point out that IL-1β not only augments discharge rate of the vagus nerves but also increases activity of the splenic nerve, which is part of the sympathetic nervous system [62]. Moreover, intravenous injection of LPS also increases splenic nerve electrical activity [51, 63]. Finally, the intraportal administration of IL-1β beta that results in an increase in hepatic vagal afferent activity also induces reflex-like activation of the splenic nerve, and this effect that can be blocked by hepatic vagatomy [36].

Contrary to the sparse proof for the direct 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 the spleen, bone marrow and lymph nodes (reviewed by Madden et al. [64] and Nance and Sanders [59]). Noradrenaline release by these fibers may modulate immune response as lymphocytes and macrophages, as well as other cells of the immune system, express functional adrenoreceptors [64]. Interestingly, peritoneal *Pseudomonas aeruginosa* infection increases noradrenaline turnover rate in bone marrow [65], where its action can modulate hematopoiesis of bone marrow cells through α1-adrenergic receptors [66].

The thymus is the primary organ where T-lymphocytes differentiate and mature, but also contains an important population of macrophages, in proximity to which many noradrenergic fibers can be found [57]. The available literature suggests that β2-adrenergic receptors are present on cells mainly in the subcapsular/subtrabecular cortex and the corticomedullary junction, but extremely rarely in the medulla [67, 68]. Beta-adrenergic receptor expression is very limited on immature thymocytes, but increases as thymocytes mature [69, 70], while macrophages in the subcapsular cortex and cortico-medullary junction express β2-adrenergic receptors [67]. Numerous experimental and clinical studies support the idea that catecholamines play a role in thymus activity and lymphocyte output [71–75]. Sustained β-adrenergic receptor blockade with propranolol was found to increase both thymocyte proliferation and apoptosis, and to disturb thymocyte differentiation, without altering the relative proportion of circulating CD4+ and CD8+ lymphocytes [75, 76].

Although the exact role of the spleen does still not seem to be fully understood, it can be thought of both as storage for blood (red pulp) and as a large lymph node (white pulp). The spleen white pulp receives a rich catecholaminergic innervation with fibers contacting lymphocytes and macrophages [60, 65, 77–79]. Although the cytoarchitecture of the spleen is not altered by chemical sympathectomy, the expansion of follicles and the formation of the germinal centers after antigen exposure are suppressed [79], indicating that specific immune responses may be modulated by sympathetic nervous fibers.

Lymph nodes are also innervated by the sympathetic nervous system with noradrenergic fibers entering medullary, paracortical and cortical regions, where they supply T cell-, but not B cell-, rich regions and establish contacts with reticular plasma cells as well as lymphocytes [80–83]. Sympathectomy reduces in vitro proliferation of lymph node cells to concanavalin A but increases that of lymph node B cells after LPS [83]. Interestingly, catecholamine treatment of lymphocytes in vitro promotes subsequent homing to the spleen and lymph nodes [84], whereas cells from animals that underwent chemical sympathectomy display decreased migration to lymph nodes [83].

If the thymus, spleen and, more generally, lymph nodes are considered immune organs "par excellence", it is important to keep in mind that the epithelia of the respiratory, urogenital and gastrointestinal tracts first encounter antigens and pathogens present in the environment and food. These tissues contain so-called mucosal-associated lymphoid tissues, which, in the case of the gut, are well known to receive noradrenergic innervation. Indeed, in the appendix and Peyer's patches, noradrenergic fibers ramify among lymphocytes, while in the small intestine they can be found in close proximity to intraepithelial lymphocytes, lamina propria macrophages and a diffuse population of mucosal B cells [78, 85–87].

Although macrophages are obviously present in the thymus, spleen, lymph nodes and the mucosal-associated lymphoid tissues, they can be found in virtually all tissues. Normal macrophages express α2- and β2-adrenergic receptors, but the latter do not seem to be involved in phagocytic activity [88–94]. Noradrenaline-synthesizing fibers end close to macrophages in immune organs (see above), but macrophages of other tissues may also be subject to the effects of adrenaline. Indeed, adrenaline released by the adrenal occurs through activation of the sympathetic nervous systems and can thus be considered a mediator of the activation of neural pathways. Interestingly, endogenous plasma noradrenaline is positively correlated with circulating adrenaline, biomarkers of endothelial activation and damage, and mortality in septic patients [95, 96]. Circulating noradrenaline has also been shown to increase, and to be, in large part, gut-derived in sepsis induced by cecal ligature and puncture (CLP) [97], a model that induces polymicrobial sepsis and mimics the different hemodynamic phases of clinical sepsis better than LPS administration [98].

When blood cells from healthy human volunteers are stimulated in vitro with bacterial LPS after having previously been exposed to adrenaline, their production of pro-inflammatory cytokines is much lower than without pre-exposure [99, 100]. Importantly, this anti-inflammatory effect of adrenaline is attenuated in LPS-stimulated blood withdrawn from patients with prolonged severe shock or septic shock, except for IL-1β [100]. It is interesting to note that the decreased in vitro production of the pro-inflammatory cytokine TNFα by splenic macrophages, which were isolated 3 days after induction of bacterial sepsis by CLP in animals as compared to sham surgery in rodents, is exacerbated by the application of adrenaline to cultures [101]. This effect of adrenaline can be reversed by prior in vivo administration of a β2, but not a β1, antagonist, indicating that it is mediated by β2 receptors [101].

Interestingly, electrical stimulation of splenic sympathetic nerve fibers in a perfused rat spleen system inhibits LPS-induced TNFα secretion via beta-adrenoceptors [102]. However, this in vitro anti-inflammatory has been questioned based on the findings that intraportal noradrenaline concentrations during sepsis are around 20 nM and that such concentrations selectively activate α2 adrenoreceptors and increase TNFα and IL-1β production by Kuppfer cells [103]. However, many studies have used supraphysiological noradrenaline concentrations (around $10^{-4}$ M) or systemic injections of noradrenaline activating β2-adreneoreceptors to study immunomodulation. Indeed, β2-adrenergic receptor agonists have been shown to reduce circulating pro-inflammatory cytokine concentrations and liver dysfunction after intravenous LPS administration [51, 104]. So, in vivo, during sepsis, endogenous noradrenaline seems to have a pro-inflammatory effect.

Transection of the greater splanchnic sympathetic nerves enhances TNFα responses to LPS [51]. However, even though chemical sympathectomy increases splenocyte and peritoneal TNFα, peritoneal phagocytosis and influx of monocytes, as well as reduces bacterial dissemination of Gram-negative *Pseudomonas aeruginosa* or *E. coli*, it attenuates splenocyte and peritoneal macrophage secretion of the anti-inflammatory cytokine IL-4 and lymphocyte infiltration and augments the dissemination of Gram-positive *Staphylococcus aureus* [105]. It is thus possible that adrenergic drugs that are used to counteract hypotension in severe sepsis and septic shock may have beneficial or detrimental effects on the clearance of infectious micro-organisms depending on the bacteria concerned and the timing of the treatment.

Targeting α2 and β2 receptors may provide opportunities to lower bacterial burden and inflammatory responses in sepsis even if, to date, no beneficial anti-inflammatory effects of α2- and β2-specific drugs have been found in clinical practice [106, 107]. In addition to the factors that influence the outcome of adrenergic intervention strategies on bacterial dissemination and inflammation in animals, inflammatory responses in patients are known to be highly variable. It may therefore be necessary to test β2 agonists in selected patients during the early pro-inflammatory phase of sepsis, as has been suggested for other anti-inflammatory treatments [108].

In experimental studies, β1 receptor antagonists have been shown to exert anti-inflammatory effects [109]. These findings are of interest since the selective β1 receptor blocker, esmolol, has beneficial effects on microcirculation and oxygen myocardial consumption during clinical severe sepsis and septic shock [110, 111]. Interestingly, after CLP-induced sepsis in rat, esmolol not only has similar beneficial effects on cardiac and vascular function [112] but also reduces pro-inflammatory and increases anti-inflammatory cytokine production, lowers bacterial burden, and improves gut barrier function and survival [113, 114].

So, even though it is clear that the sympathetic nervous system can influence infection-induced immune responses, adrenergic drugs may have beneficial or detrimental effects depending on the active molecules, the bacteria concerned and the timing of treatment. For example, β2 and β1 antagonists seem to have opposite effects on inflammation. And in spite of the promising anti-inflammatory effects of the β1 antagonist esmolol in an animal sepsis model, they need to be confirmed in septic patients.

## Central nervous system pathways activated during systemic inflammation

Considering that the sepsis symptoms, fever, tachycardia, and hypotension, as well as the anti-inflammatory pathways, involve the autonomic nervous system, it is important to identify the nervous circuits that regulate autonomic activity in thermogenic brown fat, heart, bone marrow, and spleen. Injection of an attenuated neurotropic herpes virus in an organ can reveal the neuronal network relevant to its function, as it first infects neurons of nervous ganglia, then invades preganglionic neurons innervating the first-order neurons, and finally infects neurons in the brain that send projections to the preganglionic neurons. It can thus be used as a retrograde neuronal tracer that migrates opposite to the direction of action potentials in neurons. Indeed, an attenuated form of the neurotropic pseudorabies herpes virus, injected into the thermogenic brown adipose tissue or heart of rodents, infects the thoracic sympathetic ganglia, preganglionic sympathetic neurons of the spinal cord, ventrolateral, ventromedial and caudal dorsomedian medulla, raphe nucleus and locus coeruleus. After longer infection times, the paraventricular, dorsomedial and lateral hypothalamus, ventral bed nucleus of the stria terminalis, central amygdala and preoptic area in the forebrain contain viral particles [115–117]. Interestingly, the organization of central nervous

structures providing input to the spleen and bone marrow through the sympathetic nervous system overlaps in large part with the pattern of central nervous innervation of brown adipose and cardiac tissues [118, 119]. These fore- and hindbrain structures thus have the potential to influence body temperature, heart rate and immune cell activation and traffic via the sympathetic nervous system.

To elucidate whether and how these central nervous networks play a role in sepsis symptoms and inflammatory responses, one can study the activation of or intervene with the action of their components. Induction of the immediate–early gene c-Fos has been widely used as a cellular activation marker and can be combined with the detection of non-viral tracer molecules. Injection of a non-viral retrograde neuronal tracer into the thoracic spinal sympathetic intermediolateral cell column followed by peripheral bacterial LPS injection leads to neurons containing c-Fos and the tracer in the paraventricular hypothalamus and the rostral ventrolateral medulla [120]. In turn, injection of a similar tracer into the paraventricular hypothalamus and subsequent peripheral administration of bacterial LPS results in c-Fos-expressing and tracer-containing neurons in the preoptic area, the bed nucleus of the stria terminalis and the medullar nucleus of the solitary tract [121]. Among these forebrain structures, lesion and inactivation studies have shown that the preoptic area and paraventricular hypothalamus are necessary for bacterial LPS-induced fever [122–124]. Overall, these findings indicate that the preoptic area and the paraventricular hypothalamus are part of a neuronal network mediating sympathetic activation underlying fever during sepsis. Central nervous circuits involving preoptic nuclei probably also play a role in sepsis-associated hypotension, as inactivation of the anterior preoptic hypothalamic area attenuates early LPS-induced hypotension [125]. More recently, it has been shown that systemic LPS-induced early hypotension also depends on the activation of the ventrolateral periaquaductal gray matter [126].

As (1) vago-vagal reflexes play an important role in gastric motility, (2) activated vagal afferents release glutamate in the nucleus of the solitary tract of the brainstem, and (3) glutamatergic projections from the nucleus of the solitary tract to the parabrachial nuclei reduce food intake [127], it was of interest to determine whether brainstem glutamate receptors play a role in the reduction in food intake during LPS-induced inflammation, and, if so, whether receptors are present on the neuronal network innervating the stomach. Indeed, brainstem metabotropic glutamate receptor antagonism was found to attenuate hypophagia and to increase food intake during the first 6 h after peripheral LPS to a greater extent than in a vehicle-treated animal [27]. In parallel, intra-fourth ventricle administration of this metabotropic glutamate receptor antagonist also reduced c-Fos expression in the nucleus of the solitary tract and lateral parabrachial nuclei [27]. However, metabotropic receptors were not abundantly expressed by brainstem circuits innervating the stomach [27]. These findings suggest that brainstem glutamatergic circuits are part of the neuronal substrates that rapidly reduce food intake under inflammatory conditions, but not via autonomic nervous system output to the stomach.

Given that central nervous system circuits are part of the neuronal networks innervating the spleen and bone marrow (see above), it is of interest to determine whether they are involved in the anti-inflammatory effects of the autonomic nervous system. Intracerebroventricular administration of the anti-inflammatory drug CNI-1493 inhibits peripheral LPS-induced TNFα production in a vagus-dependent manner through central, but not peripheral, muscarinic type 1 receptors [48]. Interestingly, the lateral preoptic area and lateral hypothalamus contain acetylcholinergic neurons and are part of the central nervous circuits innervating the spleen [118]. Acetylcholinergic neurons in the lateral preoptic area and lateral hypothalamus may therefore play a role in inhibiting splenic pro-inflammatory cytokine production during sepsis via the vagus and splenic nerves.

Taken together, these findings indicate that the central nervous networks innervating the brown adipose tissue, heart and immune organs are now well established in rodents, and that the nervous pathways mediating sepsis symptoms, such as fever, tachycardia and hypotension, are progressively being elucidated.

## Does heart-rate variability reflect autonomic nervous system activity during infection-induced inflammation?

It is clear that the autonomic nervous system can modulate inflammatory responses to infection. At the same time, intervention studies consisting of transection of autonomic nerves or administration of drugs that affect catecholaminergic or cholinergic signaling have shown that the effects of such interventions depend on bacteria and receptor subtypes as well as timing. One of the factors that may explain why timing is an important factor in the effects of intervention studies is the endogenous activation and tone of the autonomic nervous system. For this and other reasons, it is worthwhile trying to establish a measure that could inform scientists and clinicians on the tone of the autonomic nervous system in a minimally invasive way.

In the heart, the input of sympathetic and parasympathetic nerves almost continuously change the period of heart beats (HP), which is defined as the interval between two consecutive R peaks on the ECG. The global measures of this heart rate variability (HRV), such as the contribution of HP fluctuations to total heart rate variability, can be studied with power spectral analysis. Such measures have proven

extremely useful to assess cardiac physiology and pathology, even though the exact contribution of the sympathetic nervous tone to HRV parameters remains a topic of debate [51, 128–131]. More recently, HRV measures have also been proposed to be relevant for the study of autonomic nervous system modulation of inflammatory responses [48]. However, it is becoming more and more clear that the sympathetic and parasympathetic branches of the autonomic nervous system do not show homogenous activity across peripheral organs, and that many organ-specific responses exist [132–134]. Hence, the very premise that HRV would provide useful information on the autonomic tone of organs relevant to infection-induced inflammatory responses seems questionable. Furthermore, contrary to the heart, many immune organs are actually not innervated by sympathetic and parasympathetic nerve fibers, but solely by the former (see above).

## Conclusion

Various neural pathways are activated during, and involved in, different host responses to bacterial infection, and knowledge in this area continues to increase. One of the first and local responses to bacterial infection is the release of vasoactive peptides by spinal afferent C-fibers and the ensuing neurogenic inflammation. In case an infection becomes systemic, for example by escaping from mesenteric lymph nodes or liver Kupffer cells, vagal afferent C-fibers may be activated, either by the detection of bacterial fragments in the portal vein or locally produced pro-inflammatory cytokines, and signal the central nervous system via the caudal brainstem to give rise to sickness behavior (reduction in activity, social and non-social exploration and food intake) and early fever. Although it is clear that vagal afferent C-fibers can exert neurogenic inflammatory reflex actions, like those underlying some forms of diarrhea, the exact role of efferent parasympathethetic vagal fibers in the proposed vagal anti-inflammatory reflex remains to be elucidated, as these fibers do not seem to directly innervate the major immune organs. Notwithstanding these observations, recent work indicates that vagal stimulation reduces symptoms and inflammation in patients suffering from rheumatoid arthritis and Crohn's disease.

On the contrary, sympathetic nerves innervate the thymus, spleen, bone marrow, and lymph nodes and modulate immune responses. Interestingly, sympathectomy has different effects on bacterial dissemination, innate immune cell responses and inflammatory mediators depending on the kind of bacteria that infect the host. During septic systemic inflammation, noradrenaline turnover increases in immune organs where it can act on α and β receptors present on macrophages. In addition, adrenaline release by the adrenalin into the blood also increases during sepsis, 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. Noradrenaline, which is both released and often administered during sepsis, 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. Nevertheless, the promising anti-inflammatory effects of the β1 antagonist esmolol need to be confirmed in clinical trials on septic patients.

## Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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