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Divergent neuroendocrine responses to localised and systemic inflammation

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Abstract

The sympathetic nervous system (SNS) is part of an integrative network that functions to restore homeostasis following injury and infection. The SNS can provide negative feedback control over inflammation through the secretion of catecholamines from postganglionic sympathetic neurons and adrenal chromaffin cells (ACCs). Central autonomic structures receive information regarding the inflammatory status of the body and reflexively modulate SNS activity. However, inflammation and infection can also directly regulate SNS function by peripheral actions on postganglionic cells. The present review discusses how inflammation activates autonomic reflex pathways and compares the effect of localised and systemic inflammation on ACCs and postganglionic sympathetic neurons. Systemic inflammation significantly enhanced catecholamine secretion through an increase in Ca^{2+} release from the endoplasmic reticulum. In contrast, acute and chronic GI inflammation reduced voltage-gated Ca^{2+} current. Thus it appears that the mechanisms underlying the effects of peripheral and systemic inflammation neuroendocrine function converge on the modulation of intracellular Ca^{2+} signaling.

Introduction

Maintenance of homeostasis in the face of external and internal challenges is a fundamental requirement for life [1]. Homeostasis is achieved by the integrated actions of several systems throughout the body that are often activated or inhibited by deviations from homeostatic set points. Once initiated, the intensity and duration of the homeostatic response is therefore tightly regulated by negative feedback mechanisms. Inflammation is a homeostatic response to injury and infection. Once a potential threat has been detected, the immune system rapidly initiates a localized inflammatory response to eliminate the inciting

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agent and repair damaged tissue. If left unchecked, localized inflammation can progress to overwhelming systemic inflammatory responses or chronic inflammatory disorders, each of which can generate extensive collateral tissue damage. As with all homeostatic responses, inflammation is regulated by negative feedback mechanisms that ensure that the inflammatory response is appropriate for the inciting stimulus and that the response subsides once the homeostatic set point is re-established. Negative feedback is provided by anti-inflammatory mediators that are released by activated immune cells, as well as components of the nervous system, including the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS). The present review will describe how different types of inflammation, exemplified by colitis and sepsis, can differentially affect neurons and neuroendocrine cells of the SNS and discuss the potential consequences of these alterations.

Negative feedback regulation of inflammation by the SNS

The SNS provides important negative feedback regulation of inflammation through the secretion of catecholamines from adrenal chromaffin cells (ACCs) and postganglionic sympathetic neurons [2]. Catecholamines produce predominantly anti-inflammatory effects through the activation of β -adrenergic receptors (ARs) expressed by a variety of immune cell types. β -AR activation enhances anti-inflammatory interleukin (IL)-10 secretion and decreases proinflammatory tumor necrosis factor (TNF)- α production in lipopolysaccharide (LPS)-stimulated macrophages [3–6]. Catecholamines also inhibit macrophage phagocytosis and nitric oxide (NO) production and decrease reactive oxygen species generation in neutrophils [7–11]. In addition, β -AR activation inhibits dendritic cell migration and antigen presentation, and favours the development of Th2 T helper cell-mediated humoral responses over Th1 T helper cell-mediated cellular immunity [12–18]. It is important to mention, however, that catecholamines can also provide proinflammatory effects in certain immune cell populations through the activation of α -ARs [3;19;20].

Recent evidence suggests that catecholamines can also increase the release of acetylcholine from choline acetyltransferase-expressing T cells in the spleen as part of the cholinergic anti-inflammatory pathway [21;22]. Although the SNS has been shown to participate in the cholinergic anti-inflammatory pathway, the mechanism underlying increased norepinephrine release within the spleen remains controversial [21;23]. The SNS also participates in a suite of behavioural responses that help to combat infection. These responses are known as the sickness syndrome and include fever generation, increased sleepiness, hyperalgesia and anorexia, and they reflect the activation of a number of central nervous system (CNS) centres that regulate autonomic output [24;25].

Detection of infection and inflammation by the nervous system

Inflammatory mediators and microbial antigens can modulate SNS output through the regulation of peripheral afferent neurons and central autonomic structures, as well as through direct effects on postganglionic sympathetic neuron and ACC function. Dorsal root ganglion (DRG) afferent neurons participate in spinal and supraspinal sympathetic reflexes [26–28]. During inflammation, DRG afferent neurons detect changes in temperature, stretch and osmolarity, and relay this information to the SNS. DRG neurons can also directly detect

cytokines and other mediators, including damage-associated molecular patterns and microbe-associated molecular patterns that are increased during infection and inflammation [29–33].

Afferent traffic to sympathetic premotor nuclei is also altered during inflammation by baroreceptors and chemoreceptors that detect changes in mean arterial pressure and blood composition, respectively. Systemic inflammation can produce profound hypotension and global tissue hypoxia, both of which can increase SNS activity [34]. Chemoreceptors can also directly detect circulating cytokines and activate central sympathetic reflexes during inflammation [35]. Although initial reports suggested a vital role for the activation of peripheral terminals of vagal afferent neurons in homeostatic to inflammation, some of these studies were confounded by the effects of surgical vagotomy on the ability of animals to mount fever responses due to malnutrition [36–38]. Once malnutrition was controlled for by the provision of liquid diets, it was found that vagotomy had little effect on the febrile response to infection or inflammation [39;40]. However, it is clear that cytokines can directly access the dorsal vagal complex (a circumventricular structure) during inflammation and sensitize vagal afferent varicosities within this region [41;42]. TNF- α increases vagal afferent transmitter release by sensitizing presynaptic calcium-induced calcium release mechanisms. The transduction mechanism responsible for this “calcium amplification effect” is blocked by cannabinoids; compounds with potent anti-inflammatory actions [41–43]. Vagal afferent terminals synapse on neurons of the nucleus of the solitary tract that, in turn, project widely to areas of the brain regulating the activities of both the SNS and HPA axis [44;45]. Circulating cytokines can also cross the blood brain barrier through carrier mediated transport [46;47]. In addition, cytokines can indirectly communicate with central neurons by stimulating the production of prostaglandins by endothelial cells and perivascular macrophages within the cerebral vasculature [48;49]. Prostaglandins subsequently activate central autonomic structures, such as the rostroventrolateral medulla and paraventricular nucleus, to increase sympathetic drive during inflammation [50;51].

Sympathetic ganglia and the adrenal medullae are peripheral structures that do not possess a blood-brain-barrier. Circulating cytokines can readily enter these structures across fenestrated capillaries to directly interact with postganglionic sympathetic neurons and ACCs [52]. Adrenal cortical cells and immune cells residing within the adrenal medulla can also locally release inflammatory mediators [53–55]. Several cytokines have been shown to regulate important ACC and postganglionic sympathetic neuron functions, including Ca^{2+} signaling, catecholamine secretion, gene expression and neuropeptide release [56–61]. Recent studies have provided compelling evidence that non-immune cells can directly detect and respond to invading micro-organisms in the absence of inflammation [32;33;62–65]. In the context of the sympathetic-immune network, LPS has been shown to directly activate DRG and vagal afferent neurons [33;66]. Chronic exposure to LPS also reduces ACC excitability and inhibits neuropeptide Y release through the activation of nuclear factor (NF)- κB [67].

Each of these pathways provides an opportunity for signal integration and enables the sympathetic-immune network to provide dynamic responses to infection and inflammation. The multiple pathways through which the immune system regulates SNS function also

highlight the importance of this reflex in animal survival. A similar complex network exists between the HPA axis and the immune system, and also serves to down-regulate the immune response [68–73]. The remainder of the review will focus on the differential responses of the SNS to gastrointestinal (GI) inflammation and systemic inflammation.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic, debilitating condition characterized by recurrent GI inflammation. The two most common forms of IBD include Crohn's disease and ulcerative colitis [74]. Patients with Crohn's disease exhibit transmural inflammation that commonly occurs within the distal ileum and perianal region, but can affect any part of the GI tract. The inflammatory lesions that occur during Crohn's disease are discontinuous and may result in the development of ulcers, fibrosis, perforations or fistulae. Patients with Crohn's disease commonly exhibit diarrhea, abdominal pain and weight loss [75]. In contrast, ulcerative colitis is characterized by mucosal inflammation that predominantly affects the colon and rectum. Inflammatory lesions in patients with ulcerative colitis exhibit a continuous pattern and can lead to the development of crypt abscesses and mucosal ulcerations. Common clinical manifestations of ulcerative colitis include bloody diarrhea, rectal bleeding and rectal urgency [76].

Although the etiology of IBD remains elusive, it is generally thought that this condition results from an abnormal immune response to the GI microbiota in a genetically susceptible host. The GI immune system must maintain an intricate balance between tolerance of the intestinal normal flora and the development of rapid and effective immune responses against invading micro-organisms. During IBD, GI immune cells appear to become hyper-responsive and stimulate inflammation in the absence of an overt threat. The inflammatory response that occurs during active IBD is characterized by the infiltration of innate and adaptive immune cells into the intestinal wall. These cells then begin to secrete large amounts of proinflammatory cytokines, which further perpetuate the inflammatory response and promote tissue damage (see [77]).

Alterations in SNS function during IBD

Altered SNS function has been observed in IBD patients and animal models of IBD. Patients with active ulcerative colitis exhibit enhanced resting sympathetic activity, as measured by heart rate variability analysis and sympathetic nerve recordings [78;79]. A similar increase in excitability has also been observed in postganglionic sympathetic neurons of the celiac ganglion during the trinitrobenzene sulfonic acid (TNBS) model of acute ileitis in guinea-pigs. TNBS-induced ileitis decreased the threshold for action potential generation, increased the proportion of spontaneously active postganglionic sympathetic neurons and enhanced the number of stimulus-evoked action potentials [80]. Although GI inflammation enhances SNS excitability, patients with ulcerative colitis exhibit reduced GI catecholamine levels compared to healthy controls [81]. In addition, GI inflammation does not affect systemic catecholamine concentrations [78]. Taken together, this would suggest that catecholamine secretion from postganglionic sympathetic neurons and ACCs may be impaired during GI inflammation in the face of enhanced excitability. Indeed, our laboratory [82] and others [83–86] have shown that norepinephrine secretion from postganglionic sympathetic neurons

innervating inflamed and uninflamed regions of the GI tract is impaired during animal models of GI inflammation. Decreased norepinephrine release may result from increased α_2 -AR-mediated autoinhibition [86] or decreased sympathetic innervation of the GI tract [87;88]. Colitis also inhibits N-type voltage-gated Ca^{2+} currents (I_{Ca}) in postganglionic sympathetic neurons. N-type voltage-gated Ca^{2+} channels are the predominant Ca^{2+} channels responsible for norepinephrine release in sympathetic varicosities. Inhibition of I_{Ca} may therefore reduce norepinephrine secretion during colitis [82]. A similar inhibition in I_{Ca} is observed in ACCs during acute and chronic models of colitis and may impair systemic catecholamine release [89].

Sepsis

Sepsis is a severe clinical condition characterized by a dysregulated systemic inflammatory response, known as systemic inflammatory response syndrome (SIRS), to an infection. Sepsis is a progressive disorder that is divided into three stages, including sepsis, severe sepsis and septic shock. Patients with sepsis exhibit SIRS and an infection, without any overt changes in mean arterial pressure or tissue perfusion. During severe sepsis, patients develop hypotension, hypoperfusion or organ dysfunction and often require fluid resuscitation [90]. However, as these patients progress to septic shock, fluid resuscitation becomes insufficient to maintain mean arterial pressure and adequate tissue perfusion. These patients must therefore be treated with vasopressors and positive inotropic agents, such as catecholamines, to prevent vascular collapse [34;90]. The pathological mechanisms responsible for the development and progression of sepsis have been difficult to characterize in human patients. Recent evidence suggests that sepsis is a heterogeneous disease that can result from excessive inflammation, inadequate inflammation, or an appropriate inflammatory response to a severe infection, each of which produces overwhelming tissue damage (see [91]).

Sepsis-induced alterations in SNS function

Sepsis is characterized by a rapid activation of the SNS that is sustained for the duration of the inflammatory response. Patients with sepsis exhibit elevated plasma concentrations of epinephrine and norepinephrine, and systemic catecholamine levels are further increased during septic shock [92–96]. During the endotoxemia model of sepsis, increased circulating levels of epinephrine and norepinephrine have been consistently observed in a variety of animal species [97–100]. Plasma catecholamine levels are also elevated during the cecal ligation and puncture model of sepsis [101;102].

The sepsis-induced increase in circulating epinephrine has been attributed to enhanced epinephrine secretion from ACCs, whereas both postganglionic sympathetic neurons and ACCs contribute to the increased plasma norepinephrine levels that are observed [103–105]. Evidence suggests that increased preganglionic sympathetic neuron stimulation of ACCs and postganglionic sympathetic neurons promotes enhanced catecholamine secretion during sepsis [106–108]. However, endotoxemia is still able to increase catecholamine release in centrally denervated rats receiving a constant level of preganglionic stimulation, albeit to a lesser extent than rats with an intact CNS [108;109]. Similarly, *in vivo* splanchnic nerve stimulation evokes greater epinephrine secretion from ACCs from endotoxemic rats

compared to saline-injected controls [99]. Enhanced catecholamine secretion during sepsis is therefore likely due to a combination of increased preganglionic stimulation and direct alterations in ACC and postganglionic sympathetic neuron function. In support of this possibility, ACCs isolated from endotoxemic mice exhibit an increased number of high-K⁺-evoked exocytotic events and enhanced epinephrine release *in vitro*. These effects are mediated by an increase in Ca²⁺ release from the endoplasmic reticulum. Similar alterations in ACC Ca²⁺ signaling are produced by the cecal ligation and puncture model of sepsis. Furthermore, incubation of ACCs in sera from septic mice enhances intracellular Ca²⁺ signaling, suggesting that circulating factors play an important role in this response [110]. Whether sepsis leads to similar effects on Ca²⁺ handling and transmitter release from postganglionic neurons remains to be determined.

Differential Effects of Systemic and Gastrointestinal Inflammation

Systemic and GI inflammation produce opposite effects on ACC and postganglionic sympathetic neuron Ca²⁺ signaling through two distinct mechanisms: colitis inhibits I_{Ca}, whereas sepsis enhances endoplasmic reticulum Ca²⁺ release. The adrenal medullae and sympathetic ganglia possess fenestrated capillaries that may allow circulating inflammatory mediators to interact with ACCs and postganglionic sympathetic neurons during sepsis and IBD to alter their function. Indeed, sera from septic mice enhance ACC Ca²⁺ signaling [110] and incubation of postganglionic sympathetic neurons in nanomolar concentrations of TNF- α inhibits I_{Ca} similar to colitis [57]. Animal models of sepsis are associated with much larger elevations in circulating cytokine levels than animal models of IBD [111;112]. The differential effects of systemic and GI inflammation on SNS function may therefore be promoted by different concentrations of inflammatory mediators interacting with ACCs and postganglionic sympathetic neurons during each of these conditions. In support of this possibility, micromolar concentrations of PGE₂ have been shown to increase catecholamine secretion from bovine ACCs, whereas nanomolar concentrations of this inflammatory mediator inhibit catecholamine release [113]. Similar concentration-dependent effects may exist for other cytokines associated with sepsis and GI inflammation, and contribute to the dichotomous responses that are observed. The differential effects of GI and systemic inflammation on ACC and postganglionic sympathetic neuron Ca²⁺ signaling may also arise from the different complement of circulating inflammatory mediators that these cells are exposed to during each of these conditions [111;112]. Furthermore, colitis likely promotes the preferential activation of vagal and DRG afferent neurons innervating the GI tract, whereas sepsis produces inflammation in several visceral structures innervated by these neurons. Differences in the activation profiles of vagal and DRG afferent neurons may also have important consequences on ACC and postganglionic sympathetic neuron function during these inflammatory disorders through activity-dependent changes.

Potential consequences of altered SNS function during inflammation

Despite numerous protective mechanisms that exist throughout the body, damaging systemic inflammatory responses and chronic inflammatory conditions can still occur in susceptible individuals. Once initiated, these inflammatory disorders can produce persistent alterations

in the immune system-nervous system network that often have important consequences on disease progression.

Inflammatory Bowel Disease

Catecholamines have been shown to alter the functional properties of several classes of immune cells implicated in the pathogenesis of IBD. Furthermore, stress, which contains a large sympathetic component, can affect disease severity and has been associated with the reactivation of GI inflammation [114–116]. It is therefore likely that the SNS plays an important role during IBD. Indeed, in patients with active ulcerative colitis, the administration of clonidine, an α_2 -AR agonist, reduces clinical symptoms and improves endoscopic damage scores. These effects have been attributed to an α_2 -AR-mediated inhibition of catecholamine release from the SNS [78;117]. The role of the SNS during IBD has also been studied using acute and chronic models of colitis. 6-hydroxydopamine is an isomer of norepinephrine that destroys postganglionic sympathetic varicosities, while leaving adrenal catecholamine levels intact [118–120]. Ablation of postganglionic sympathetic neurons with 6-hydroxydopamine prior to the induction of acute TNBS- or dextran sulfate sodium (DSS)-colitis reduces the severity of colonic inflammation [87;121]. However, when 6-hydroxydopamine is administered during the chronic phase of colitis in IL-10^{-/-} mice or chronic DSS-treated mice, the severity of colonic inflammation is significantly enhanced [87]. These results suggest that during the initial stages of inflammation, norepinephrine release from postganglionic sympathetic neurons exacerbates the inflammatory response, whereas at more chronic time points, norepinephrine release decreases disease severity.

Low concentrations of norepinephrine preferentially activate α -ARs over β -ARs. Acute GI inflammation inhibits norepinephrine secretion from postganglionic sympathetic neurons and enhances α -AR expression within the GI tract [82–86;122]. Norepinephrine released during acute colitis may therefore preferentially activate proinflammatory α -ARs expressed by immune cells and worsen disease severity. In support of this possibility, α_2 -AR antagonists decrease histological severity, reduce MPO activity, and inhibit TNF- α and IL-1 β production during acute TNBS- and DSS-induced colitis [123]. Although the effects of norepinephrine released from postganglionic sympathetic neurons during GI inflammation have been well-characterized, our knowledge of the role of catecholamines secreted by ACCs during colitis is currently limited. Additional studies are therefore required to determine the effects of systemically secreted catecholamines on GI inflammation.

Sepsis

Sepsis increases the firing frequencies of preganglionic sympathetic neurons innervating postganglionic sympathetic neurons and ACCs [106;107]. Sepsis also directly enhances the secretory capacity of ACCs through an increase in ER Ca²⁺ release [110]. A similar increase in Ca²⁺ signaling was observed in postganglionic sympathetic neurons and likely results in enhanced norepinephrine release within peripheral tissues during sepsis (Lukewich & Lomas, unpublished observations). The direct effects of sepsis on ACC and postganglionic

sympathetic neuron function would be expected to amplify the secretory response produced by the increased activity of preganglionic sympathetic neurons.

Catecholamine secretion from ACCs and postganglionic sympathetic neurons provides protective cardiovascular and immunomodulatory effects during sepsis. Inhibition of preganglionic sympathetic neuron activation produces more severe hypotension and increases the mortality rate of endotoxemia [105;109;124]. Similarly, inhibition of ACC catecholamine secretion through adrenalectomy, adrenal demedullation, adrenal denervation or ligation of the adrenal vein increases the severity of hypotension and decreases animal survival during endotoxemia [104;105;108;109;125]. In addition, adrenalectomy increases the mortality rate of the cecal ligation and puncture model of sepsis [126].

Norepinephrine secreted by postganglionic sympathetic neurons is also beneficial during sepsis. Guanethidine treatment, which depletes vesicular norepinephrine in sympathetic varicosities, and ablation of the celiac plexus have both been shown to increase the mortality rate of Gram-negative bacterial sepsis [104;127]. It is important to note, however, that sympathetic nerve ablation with 6-hydroxydopamine decreases the mortality rate associated with endotoxemia in rabbits [128], suggesting that endogenous catecholamine secretion from postganglionic sympathetic neurons may be detrimental under certain experimental conditions.

The consequences of AR activation by endogenously released catecholamines have also been assessed during sepsis using AR receptor antagonists and knockout mice. Patients with septic shock that are homozygous for a β_2 -AR gene polymorphism that accelerates receptor desensitization exhibit a greater degree of organ dysfunction and higher mortality rates than patients without this polymorphism [129]. Similarly, mice that lack β_1 - and β_2 -ARs exhibit higher mortality rates and more severe systemic inflammatory responses during endotoxemia than wild-type mice [130]. Non-selective inhibition of β -ARs also enhances TNF- α production and inhibits IL-10 release during endotoxemia [6;131]. A similar detrimental effect of β -AR inhibition has been observed during the cecal ligation and puncture model of sepsis [132]. However, selective β_1 -AR antagonists reduce the mortality rate of endotoxemia and increase the median survival time during cecal ligation and puncture [133]. Furthermore, β_1 -AR antagonists reduce serum TNF- α and IL-6 levels during endotoxemia [133;134]. Taken together, these studies suggest that while β_1 -ARs promote detrimental proinflammatory effects during sepsis, β -AR activation as a whole is anti-inflammatory and improves sepsis outcomes. It is therefore likely that the positive effects of β_2 -ARs outweigh the negative consequences of β_1 -AR activation during sepsis.

Activation of α_2 -ARs by endogenous catecholamines also modulates sepsis severity. Inhibition of α_2 -ARs has been shown to reduce TNF- α production and increase IL-10 release during endotoxemia [131;135]. Similarly, the selective α_{2A} -AR antagonist, BRL-44408, decreases serum TNF- α and IL-6 levels, and increases animal survival during the cecal ligation and puncture model of sepsis [136;137]. α_2 -AR activation has been shown to increase TNF- α secretion from Kupffer cells of the liver and promote hepatocellular dysfunction during sepsis [136;138]. As a result, α_{2A} -AR antagonists may improve sepsis outcomes by inhibiting cytokine secretion from Kupffer cells and reducing hepatocyte

damage. However, α_2 -ARs are also highly expressed by postganglionic sympathetic varicosities, where they promote autoinhibition of catecholamine release [139]. α_2 -AR antagonists would therefore be expected to increase norepinephrine release from postganglionic sympathetic neurons and activate additional AR subtypes. In support of this possibility, ganglionic blockade and β -AR antagonists prevent the decrease in TNF- α release that is produced by α_2 -AR antagonists during endotoxemia [131].

The endogenous sympathetic response to sepsis is often insufficient to sustain tissue perfusion and many patients progress to severe sepsis or septic shock. During septic shock, patients exhibit severe hypotension that is refractory to fluid resuscitation and are therefore routinely administered exogenous vasopressors and positive inotropic agents to maintain mean arterial pressure at an acceptable level. Catecholamines and selective AR agonists are the mainstay treatment for patients with septic shock [34]. Exogenous catecholamines have been shown to increase mean arterial pressure, elevate cardiac index, enhance global O_2 delivery and improve survival rates in patients with septic shock [140–144]. However, these vasoactive agents are often given as large intravenous bolus doses and are accompanied by various side effects [145;146].

Preganglionic sympathetic neurons are activated during sepsis in an attempt to restore homeostasis. A more effective therapeutic strategy than bolus injections of catecholamines may therefore be to selectively amplify the secretory capacity of ACCs and postganglionic sympathetic neurons, such that a greater amount of catecholamine is released only when the SNS is endogenously activated. This would retain the regulatory mechanisms that normally control SNS function, and allow ACCs and postganglionic sympathetic neurons innervating specific target tissues to be selectively activated when necessary. The observation that sera from endotoxemic and cecal ligation and puncture mice produce similar alterations in ACC function as sepsis *in vivo* suggests that an endogenously released circulating mediator promotes the increased Ca^{2+} signaling that is observed during sepsis. Future studies should therefore be performed to identify this mediator, as it may prove to provide therapeutically valuable effects during sepsis.

Conclusions

Sympathetic neurons and neuroendocrine cells are the motor components of complex integrated neuronal responses to inflammation and infection. Both inflammation and infection can affect the activation of afferent neurons, circumventricular organs, autonomic nuclei within the CNS and postganglionic sympathetic cells. Depending on the location and the type of inflammation or infection, catecholamine release can be inhibited or enhanced independently of any activation of preganglionic input. Thus, the direct effects of peripheral inflammation on the final effector cells of autonomic reflex pathways may be more important than previously thought.

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Highlights

- Infection and inflammation can affect peripheral afferent neurons, integrative autonomic centers in the brain and neuroendocrine cells, including adrenal chromaffin cells (ACCs).
- Catecholamines released from postganglionic sympathetic neurons and ACC can suppress immune system activation.
- Model of localized gastrointestinal inflammation are associated with inhibition of ACCs whereas endotoxemia leads to elevation of catecholamine release from ACCs.
- These differential effects are likely due to direct effects of circulating inflammatory mediators on ACCs.