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Review

Divergent neuroendocrine responses to localized 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 localized 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.

1. 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 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.

2. 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

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favors the development of Th2T helper cell-mediated humoral responses over Th1T 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 behavioral 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) centers that regulate autonomic output [24,25].

3. 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.

4. 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 Ref. [77]).