Review

Neuroendocrine-Immune Interactions and Starvation in Mucosal Immunity and Mucosal Inflammation

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Mutual communication among the immune, neuroendocrine and metabolic systems is essential for the maintenance of gastrointestinal mucosal function. A unique barrier system by the mucosal immune system handles a myriad of infectious and food antigens, while the neuroendocrine system interplays with the immune system in the intestinal mucosa. The close relation between these two systems is associated with the pronounced effects of stress and metabolic changes.

Key words: mucosal immune system, neuroendocrine system, neuropeptide, starvation, hypothalamic-pituitary-adrenal axis

I. Introduction

The intestinal mucosa is exposed to a myriad of infectious and food antigens, and a unique barrier system by the mucosal immune system handles them on the mucosal surface [23, 34]. This system is modulated by a complex series of neuroendocrine interrelations [21, 29], and there is a great deal of evidence for the neuroendocrine influence on various aspects of the immuno-inflammatory response of the gastrointestinal mucosa [22, 29]. In healthy individuals, nutrients cross the interface from the external environment of the gut lumen into the intestinal mucosa, while the invasion of potentially injurious antigens or the tissue injury by these antigens must be prevented efficiently and completely [20, 34, 40].

The immune system can interplay with the neuroendocrine system, and the mutual expression of receptors and mutual usage of mediators that were originally derived from these two dissimilar systems play an important role in the homeostasis of various gastrointestinal functions [19]. The interplay between immune and neuroendocrine systems is most commonly associated with the pronounced effects of stress on immunity, and also with the metabolic changes in these two systems [12].

The abrogation of such a complex mucosal defense mechanism by the immune system may alter mucosal immunologic and structural homeostases in the gastrointestinal tract, and may be involved in the pathogenesis of chronic active gastritis and inflammatory bowel disease (IBD) [6, 14, 23, 29]. Inflammatory mediators, such as inflammatory cytokines, act either directly or indirectly to increase the production of hormones in the hypothalamus-pituitary-adrenal axes [37, 41], and stress responses may modulate the immuno-neuroendocrine interaction [12]. Leptin, an adipose hormone, regulates body weight at the hypothalamic level and also engages in the immuno-inflammatory and neuroendocrine pathways, leading to the maintenance of homeostasis of these two different physiologic pathways [9, 11].

This review outlines the interaction between the neuroendocrine and immuno-inflammatory systems and the interplay with stress or starvation. Furthermore, we discuss their roles in the pathogenesis and disease process of gastrointestinal inflammatory disorders.
II. Neural Intervention in Mucosal Inflammation

It has been well documented that the nervous system interplays with the immune system and addresses the mutual expression of receptors and mutual usage of mediators that are originally derived from these two dissimilar systems [19]. The close approximation between nerve fibers and lymphoid sites, particularly in mucosal sites of the gut, suggests that elements from the immune and nervous systems are shared [10, 21].

The majority of neurons in the intestinal mucosa contain neuropeptides, including vasoactive intestinal peptide (VIP), substance P (SP), and somatostatin (SOM), which are also found in the central nervous system [14, 17, 22, 29], and these receptors have been identified on mononuclear cells and polymorphonuclear leukocytes [29, 31]. Furthermore, leukocytes are shown to synthesize these neuropeptides [26, 19], which can affect lymphoid function and conversely, cytokines, products of immune cells, can modulate neural function [13, 16, 27]. These neural mediators and cytokines have been shown to concentrate in the mucosal-associated lymphoid tissue, MALT in the gut. These findings lead us to speculate that the neuro-immune network is functionally bidirectional, and suggest that these nerve-derived factors play an important role in inflammation and immunity.

The concept of “neurogenic inflammation”, that the nervous system may be involved with immunity and inflammation, has been discussed extensively in the context of polyarthritis and inflammation of the eye, skin and respiratory tract [29]. The putative role of neuropeptides in inflammatory reaction in the gastrointestinal mucosa is now receiving more attention. Of all known neuropeptides present in the gut, SP has been particularly implicated as a prime candidate in the neurogenic inflammation to affect inflammatory responses including macrophage and neutrophil activation and vascular permeability [27, 29, 30], which are often found in inflammatory disorders in the gut and stomach.

The SP-containing nerve fibers are a major component of the enteric nervous system. In Peyer’s patches SP-containing nerve fibers are present in the T cell zone and associated with macrophages, and in the lamina propria IgA plasma cells are found in densely innervated areas, suggesting that these cells may be more likely to be influenced by neuropeptides [10, 39]. That is, SP induces expression of endothelial cell adhesion molecules, and the migration and adherence of monocytes and lymphocytes to the endothelium of venules [36]. Monocytes are induced by SP to release lysosomal enzymes and to stimulate macrophage phagocytosis [2], and recruitment of various subsets of lymphocytes into the mucosal lymphoid tissue could modulate the mucosal inflammatory processes and regulate the mucosal immune response. Cells derived from Peyer’s patches are enhanced by SP when IL-6 is used as co-stimulator with SP [28, 29]. Neuropeptides, particularly SP, may also influence inflammation through induction of proinflammatory cytokines, such as IL-1, IL-2, IL-6 and TNF-α [16], and at the same time cytokines induce neuropeptide expression; for example, IL-1 induces SP production.

VIP is found to coexist in similar enteric neurons of the myenteric plexus, submucosal plexus and the network of nerve fibers in the lamina propria (Fig. 1), and VIP-containing nerve fibers are also found in lymphoid tissue including Peyer’s patches [6, 8, 14, 21, 22]. VIP has several inhibitory effects on immunocompetent cells. For example, VIP inhibits IL-2 and IFN-γ production by lymphocytes and T-cell mitogen-induced proliferation [24]. Interestingly, IgA production by concanavalin A-stimulated cells derived from mesenteric lymph nodes is increased, and production by cells from Peyer’s patches is much more potently increased [38], suggesting that VIP can stimulate B-cell differentiation and may be involved in IgA switching.

Although the effects of SOM on T-cell proliferation

![Fig. 1. The close approximation between VIP-containing nerve fibers (violet) and blood vessels (blown) or colonic gland. The network of VIP-containing nerve fiber is present in the lamina propria rich in IgA plasma cells and T-cells.](image-url)
and immunoglobulin synthesis appear to be complex, a variety of inhibitory actions of SOM are observed in the immune system [38], and the mucosal submucosal concentration of SOM is significantly decreased in Crohn’s disease and ulcerative colitis as shown in the VIP effect [18, 38]. In contrast, SP levels are significantly increased in left-sided ulcerative colitis [18]. From the opposite action of SP on immune cell functions of SOM, it is safe to assume that SOM is an anti-inflammatory neuropeptide. SOM is also known for its ability to inhibit the release of a variety of hormones including growth hormone, insulin and VIP [32].

III. Hypothalamic-Pituitary-Adrenal Axis and Cytokines

In recent years, our understanding of the interactions between the hypothalamic-pituitary-adrenal (HPA) axis and immune-mediated inflammatory reactions has expanded [37, 41]. The neuroendocrine and immune systems communicate bidirectionally, and this bidirectional communication plays an essential role in modulating the adequate response of the HPA axis to the stimulatory influence of interleukins and stress-related mediators [12, 37, 42]. The major cytokines such as IL-1, IL-2, IL-6, TNF-α and IFN-γ are potent activators of the HPA axis, and are known to affect development and cell proliferation of pituitary gland and the release of anterior pituitary hormones by an action on the hypothalamus and/or the pituitary gland [12, 33]. The hypothalamus seems to be an important site of IL-1 on the HPA axis, thereby inducing corticotropin-releasing factor (CRF) secretion, followed by adrenocorticotrophic hormone (ACTH) and glucocorticoid secretion (Fig. 2) [37, 41].

IL-1 and glucocorticoid hormones represent two key mediators involved in the modulation of the neuroendocrine-immune responses to stress [5]. In the immune system, glucocorticoids have an overall inhibitory effect on many immune system functions [12]. They induce decrease in lymphoid cell growth, antibody synthesis, cellular cytotoxicity and inflammatory reactions; that is, glucocorticoids exert a negative control over the recreation of peptides from the immune system such as IL-1 and other inflammatory cytokines as well as from the HPA axis [25]. The stimulation of the HPA axis by IL-1 and IL-6 is recognized as a critical component of the inflammatory responses [12, 37, 42]. It is generally accepted that the stress-related mediators depress the immune responses, but all immune parameters may not work in the same way.

In addition, cells of the immune system including those in the intestinal mucosa are recognized as a source of neuroendocrine peptides including CRF, ACTH and VIP [35]. The regulation of these peptides production in immune cells is remarkably like that observed in neuroendocrine cells [35]. Although immune cells produce considerably less hormones than pituitary cells, this difference is more than compensated for by the greater number of cells in the immune system than the pituitary gland. They are endogenous regulators of immune system as well as conveyors of information from immune system to the neuroendocrine system, representing a sensory function for the immune system wherein immune cells recognize stimuli which are not recognized by the neuroendocrine system.

IV. Starvation and Leptin in the Regulation of Immune System

Leptin is a pleiotropic molecule that regulates food intake as well as metabolic and endocrine functions at the hypothalamic level [7]. Leptin is primarily produced by adipose tissue, with its circulating levels directly correlated with adipose tissue mass [43], and its production acutely increased by inflammatory stimuli [9]. Leptin also plays a regulatory role in immunity, inflammation, hematopoiesis and cytokine production, and the activation of macrophages [9, 11]. In addition, leptin and its receptor share structural
similarities with members of the long-chain cytokines including IL-6, suggesting that leptin should be classified as a cytokine [4]. The long leptin receptor isoform is observed both in the basolateral plasma membrane and in the brush border of human enterocytes [2] in addition to T-cells [9], suggesting that leptin may play a physiological role in the regulation of nutrient absorption, and also participate in the mucosal defense mechanism.

As a major role of leptin in the modulation of T-cell responses, leptin increase IL-2 and INF-γ production while decreasing IL-4 level, indicating that leptin may play an important role in the regulation of T helper (Th) 1/Th2 balance [15]. In both leptin-deficient (ob/ob) mice and starved mice, several T lymphocyte-related immune alterations, including reduced numbers of T lymphocytes and macrophages, were suppressed responsively to T cell-activating stimuli. Starvation and malnutrition, which are characterized by low leptin levels, are also associated with alterations of the immune response leading to diminished immunity and increased susceptibility to infection [9, 11]. Although leptin was initially discovered as a regulator of food intake and energy expenditure, it has been recognized that the immune system is one of the targets of leptin activity (Fig. 3).

Studies of leptin’s involvement in starvation also focused on the metabolic and neuroendocrine effects of diminished leptin which causes obesity and fat storage in the liver, suppression of reproductive, thyroid and growth axes, and activation of hypothalamus-pituitary-adrenal axis [1]. Leptin engages a neuroendocrine pathway which leads to obesity avoidance through reduction in food intake and increase energy expenditure [1]. The decrease in leptin following starvation brings about neuroendocrine changes that favor survival during starvation (Fig. 3).

V. Summary

Starvation and obesity, two conditions characterized by low leptin levels, are associated with alteration of immune and neuroendocrine responses, which also bring about leptin changes which favor survival during starvation or obesity avoidance. Interplay between the immune and neuroendocrine systems has been well recognized, and is commonly associated with the pronounced effects of stress on immunity. Hormones in the hypothalamic-pituitary-adrenal (HPA) axis and cytokines are used as common languages for communication within and between these two systems. Interestingly, both leptin and its receptor share structural and functional similarity with IL-6 family of cytokines. Thus, mutual communications among the immune, neuroendocrine and metabolic systems are essential for the maintenance of gastrointestinal mucosal function (Fig. 4).
VI. References


