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Neuroendocrine Interactions in the Immune System

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Abstract

Substantial evidence now exists supporting the bidirectional communication between the neuroendocrine and immune systems. A number of hormonal and neuropeptide mediators have been shown to influence immune development and function in healthy, aged and diseased individuals. Immune cell subsets express receptors for many of these ligands and similarly, receptors for cytokines and growth factors have been identified on cells within the central nervous and endocrine systems. During times of stress or injury, each of these systems come into play and transmits messages to one another. The lines of communication between the immune system and these various neuronal and endocrine organ systems constitute specific axes of interactions, which have been shown to have a profound impact on immune function, disease development and susceptibility to infections and disease. In this Special Issue, experts in neuroendocrine immunology have provided comprehensive reviews on the current advances in this area of research as well as commentary on relevance of the various axes in controlling immunity and disease development.

Keywords

Neuroendocrine; Immunity; Hormones; Neuropeptides; Hypothalamic-Pituitary-Adrenal (HPA); Stress; Thymus; Sympathetic Nervous System

I. Introduction

The cross-talk between the neuroendocrine and immune systems is now well established in that these systems utilize a number of similar ligands and receptors to provide an intra- and inter-system network of communication. It is believed that communication between these systems is essential for maintaining physiological homeostasis and good health [1]. A number of hormones and neuropeptides are known to participate in various aspects of immune development and function in healthy, aged and diseased individuals. Lymphocytes, monocytes and various other immune cell subsets express receptors for many of these ligands including a variety of neurotransmitters and neuropeptides such as corticosteroids, insulin, prolactin, growth hormone (GH), somatostatins, estrogens, testosterone, leptin, ghrelin, opioids, corticosteroids, neuropeptide Y and vasoactive intestinal peptide (VIP). Similarly, receptors for immune-derived cytokines, chemokines and growth factors have also been identified on

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neuronal cells and within endocrine organs under normal physiological conditions and in response to stress and disease. Typically, these regulatory networks form a negative feedback loop by which homeostasis is maintained between the immune and central nervous systems. Disturbances within these systems may lead to immune activation or suppression, depending on the systems being affected and the nature of the stimuli. The hormonal and neuropeptide mediators that provide the link between the endocrine, central nervous and immune systems constitute specific axes of interactions including the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis, hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-growth-hormone axis. Moreover, the autonomic nervous system also communicates with the lymphoid compartment through the release of norepinephrine and acetylcholine from sympathetic and parasympathetic nerves. Also, the administration of exogenous steroidal hormones and opioid-based drugs can influence immune function and susceptibility to infections. Thus, it appears that multidirectional communication networks exist within the body that permit the transmittal of signals between these various systems during times of stress, injury, disease, infection, metabolic alterations and complications of progressive aging and physical decline.

Over the past 20 years, a great deal of scepticism of the relevance of neuroendocrine-immune interactions has been expressed by immunologists and endocrinologists with many of the published findings in this area being described as “phenomenological” or “irrelevant responses” with no true physiological role. It has even been suggested that the expression of hormone and neuropeptide receptors and ligands by immune cells are evolutionary leftovers and that responses to such mediators by immune cells are actually in vitro artifacts. While all of the neuronal-endocrine-immune pathways described would indeed benefit from more detailed mechanistic and clinical studies to further delineate the autocrine and paracrine roles of these mediators in controlling immunity, the current literature in this area is quite impressive and contains many more hypothesis-driven, mechanism-based reports when compared to earlier publications from 10–20 years ago. Today, there is strong support for the existence of these various axes as lines of communication between the CNS and endocrine organs and the immune system. I am pleased to host this ‘Special Issue Series’ on the very exciting and trendy topic of neuroendocrine interactions with the innate and adaptive immune systems and vis-à-vis inflammatory diseases and immune disorders. Experts in specific areas of neuroendocrine immunology were selected to provide both review and commentary on the current advances in the field. This series focuses on the current literature concerning immune interactions with sex hormones, pituitary hormones, metabolic hormones, stress hormones and opioids as well as the products and interactions with the sympathetic nervous system (Figure 1). While more detailed information on these interactions is provided by the reviews, a brief discussion of the various systems examined in this series is detailed below.

II. Sex Hormones

There is extensive evidence for gender-based differences in immune responses leading to differences in a wide array of disorders ranging from susceptibility to autoimmune disorders to immunity against pathogens and mortality following injury. During the reproductive years, females demonstrate more pronounced humoral and cellular immune responses compared to males. Interestingly, females also possess a more developed thymus, greater antibody titers and an enhanced capacity to reject tumors. Progenitors and mature cells of the immune system have been shown to express estrogen receptors (ER) and androgen receptors (AR), suggesting that steroid sex hormones directly influence both the development and function of cells of both the innate and adaptive immune systems. The major effects of estrogen are mediated through two different receptors, ER- α and ER- β , which are expressed in immune cells. Estrogens and testosterone are known to both positively and negatively regulate the various aspects of the immune response either by promoting cell function and repair or complicating inflammation

and morbidity/mortality. In the current series, Dr. Sternberg [2] provides an extensive review of the global role of various neuroendocrine factors, primarily focusing on steroid hormones, in modifying immune activity and host responses against pathogens. She also discusses the relevance and influence of such neuroimmune interactions on the susceptibility and severity of disease development. Further, Dr. Kovacs and colleagues [3] describe the significant differences in the generation of innate and adaptive immune responses between the sexes, with a specific focus on responses to traumatic injuries such as burns and hemorrhage. These gender-based differences in immune development and in the control inflammation post injury appear to be directly due to the presence of estrogen(s). Several possible mechanisms have been proposed by Dr. Kovacs that may facilitate the effects of estrogen(s) on immunity including the direct (promoter-based) and indirect (receptor dimerization to transcription factors) regulation of inflammatory gene expression. Based on this regulation, she also discusses the possible design of sex-specific therapeutics that could be utilized to influence outcome of patients following burns and shock.

Additional information on the impact of estrogens on immunity is provided by Dr. Susan Kovat [4] who describes the specific effects of estrogen on the dendritic cell lineage. Dendritic cells are important antigen-presenting cells responsible for the initiation and maintenance of both innate and adaptive immunity. These cells express estrogen receptors permitting estradiol and other ER ligands the ability to regulate the homeostasis of bone marrow myeloid and lymphoid progenitors of DC. Moreover, estrogens have also been shown to influence dendritic cell differentiation mediated by GM-CSF and Flt3 ligand. Using various experimental models, Dr. Kovacs and colleagues describe the findings that ER agonists and antagonists modulate DC activation and production of inflammatory cytokines. Similar to Dr. Kovacs, Dr. Kovats proposes that these findings may also have implications for the therapeutic treatment of disease and boosting of immune responses as dendritic cells appear to be responsive to estrogen receptor ligands to which an individual is exposed *in vivo*.

Further discussion of the effects of estrogen and estrogen deficiency on immune function and bone loss are discussed by Dr. Pacifici [5]. Menopause is the most frequent cause of bone loss in humans. Estrogen has been shown to play a critical role in the maintenance of skeletal homeostasis and estrogen deficiency appears to mediate bone destruction. It has also been well established that infection, inflammation and autoimmune diseases are associated with systemic and local bone loss. More recent studies have revealed that T cells and cytokines are important regulators of osteoclast and osteoblast formation, life span and activity. Dr. Pacifici reviews the current literature and theories linking immune cells to the etiology of postmenopausal osteoporosis and the bone loss caused by a variety of endocrine conditions. He proposes that a decrease in the ovarian production of sex steroids and an increase in the production of follicle stimulating hormone secondary to estrogen deficiency contribute to postmenopausal bone loss. Dr. Pacifici also discusses evidence supporting that one of the main mechanisms by which estrogen deficiency facilitates bone loss is by inducing the production of osteoclastogenic factors (such as TNF family members) by activated T cells.

A major underlying cause for aging of the immune system is the structural and functional involution of the thymus and the associated decline in naïve T cell output. This loss of *de novo* T cell generation results in a decline in the generation of cellular responses to new antigens and is associated with a peripheral bias towards the expansion of memory T cells against prior viral antigens [6]. Although the precise mechanism(s) responsible for age-associated thymic involution are not clear, studies have revealed an association between thymic loss and sex steroids. Ablation of sex steroids via castration, chemical castration or through the administration of sex steroid antagonists has been shown to result in the rejuvenation of an aging thymus, resulting in a profound increase in thymic mass and cellularity and T cell output. These changes are maintained for quite some time and even temporary sex steroid ablation

may have a significant impact on thymic activity and the circulating T cell repertoire. Dr. Chidgey and coworkers [7] believe that temporary sex steroid ablation may provide a clinically effective means to regenerate the thymus and immune system in immunodeficiency states such as aging or following cytoablative treatments such as chemo- and radiation-therapy and AIDS. Dr. Chidgey also discusses the endocrinology of thymic atrophy and the impact of sex steroids on the immune system as well as the use of gonadectomy to enhance immune reconstitution. She believes that reversing the damage caused by sex steroids forms one of the major, logical strategies to combat immunosuppression associated with aging and in various immunodeficiency disease states.

III. Pituitary Hormones and IGF-I

The pituitary hormone, growth hormone (GH), has been shown to exhibit a number of effects on the cells and organs of the immune function. GH is classically defined as a peptide hormone that is synthesized and secreted primarily by somatotrophic cells in the anterior pituitary. The production of GH is pulsatile, primarily nocturnal, and is controlled by hypothalamic hormones such as GH-releasing hormone (GHRH), hypothalamic GH release-inhibiting factor and somatostatin and by metabolic hormones such as ghrelin and leptin. Circulating levels of GH are highest in the immediate neonatal period, decreasing during childhood but peaking again during puberty. GH secretion falls precipitously during aging. Moreover, GH has been shown to mediate the proliferation of a number of cell types including chondrocytes, fibroblasts, adipocytes, myoblasts and T lymphocytes. Many of these GH effects appear to be mediated or indirectly via the production of insulin-like growth factor-1 (IGF-1). Several in vitro or in vivo studies have suggested that GH could play a role in immune function, inducing the survival and/or the proliferation of lymphoid cells. Thymic atrophy has often been associated with ablation of the pituitary gland and that mice with the dwarf mutation exhibit diminished immune functions [6]. Similarly, hypophysectomized rats or Snell dwarf mice (both defective in the production of GH, prolactin and thyroid hormones) display deficiencies in lymphocyte development and function. These immune deficits were found to be partially corrected upon administration of exogenous GH. Moreover, administration of GH was found to enhance development of the thymus in aged mice and promote the engraftment of murine or human T cells in SCID mice [6,8]. Many of these GH effects were found to be indirectly mediated by IGF-1. GH and IGF-1 were also found to synergize with other cytokines (e.g., GM-CSF) in hematopoiesis. Many of the immune related effects of the pituitary hormones, IGF-1 and GH secretagogues (such as ghrelin) on immune function are reviewed here by Murphy and coworkers [8]. Murphy also discusses the relevance of the JAK-STAT and SOCS proteins in controlling hormone responses and their interplay in regulating cellular activation, cytokine production and signaling and immune function. The relevance of the crosstalk between the cytokine and hormonal signaling pathways in controlling immune function and the potential therapeutic use of hormones in the treatment of transplantation and during states of immunosuppression and aging are discussed.

Typically, the interaction between the immune and endocrine systems is viewed one way, from the perspective that neuropeptides and hormones regulate immune function. However, a great deal of data exists demonstrating that the communication between these systems is bidirectional and that cytokines and growth factors derived from immune cells or produced during states of inflammation and stress can influence the endocrine and CNS functions. Proinflammatory cytokines have been shown to regulate hormonal signaling pathways and are capable of inducing a state of "hormone resistance". Cytokine-induced hormone resistance has significant implications in a number of disorders and disease states ranging from diabetes and other autoimmune diseases to even clinical depression. Several hormonal systems have been shown to be influenced by inflammatory cytokines including insulin, glucocorticoids, GH and IGF-1. In the review by Kelley and his colleagues [9], hormone resistance induced by proinflammatory

cytokines is proposed to serve as a negative regulatory mechanism by which hormone activity is controlled and the utilization of the body's limited resources are regulated. As aging and a number of chronic human diseases are often associated with elevated levels of circulating proinflammatory cytokines, such inflammation may serve to limit the beneficial actions of hormones and other growth factors. Dr. Kelly also reviews the underlying mechanisms by which proinflammatory cytokines interact with the IGF growth factors at both the cellular and behavioural levels with a specific focus on the proinflammatory cytokines, TNF- α and IL-1 β and the hormone, IGF-1. As with many of the ligands that crosstalk with the immune system, it is believed that a more comprehensive understanding of the interactions between these compartments is essential to develop novel and more effective strategies for the treatment of disease and to improve the quality of life.

IV. Metabolic Hormones

The metabolic status of an organism is finely regulated by nutritional status, energy expenditure and hormonal signals. Organs such as the pancreas, liver, stomach and adipose tissue respond to these cues and regulate metabolic homeostasis. A number of hormones participate in regulating these responses including GH, prolactin, IGF-1, insulin, GLP-1 and the orexigenic/anorexigenic hormones, ghrelin and leptin, respectively [10]. Leptin is a non-glycosylated polypeptide produced primarily by adipocytes and released into the systemic circulation during states of positive energy balance. It exerts a multitude of regulatory effects on various organ systems including controlling energy utilization and storage, regulating various endocrine pathways and bone metabolism and controlling thermoregulation. A number of additional studies have also suggested a role for leptin in the generation and maintenance of immune and inflammatory responses. Leptin levels have been shown to increase during infections and both acute and chronic inflammatory processes supporting a role for this hormone-cytokine in the regulating of inflammatory and immune response and in host defence pathways. Leptin has also been shown to play some role in the pathogenesis of several autoimmune disease states including encephalomyelitis, diabetes, inflammatory bowel disease and arthritis [11]. Although the precise role of leptin in these disorders remains unclear, it seems clear leptin is a potent immunomodulatory hormone and cytokine based on its proinflammatory nature, its expression by immune cells and in its ability to regulate innate and adaptive immune responses. The comprehensive review by Dr. Oreste Gualillo and coworkers [11] discusses the most recent advances in leptin biology and immunology and details a role for leptin as both an adipokine and metabolic hormone in relation to inflammation and immunity.

Murphy and his colleagues [8] also discuss the relevance of another metabolic hormone, namely ghrelin, in regulating inflammation and immune function. While leptin is considered a critical sensory anorexigenic mediator that signals to the brain changes in stored energy, ghrelin, the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), is produced primarily from stomach and serves as a potent circulating orexigen controlling energy expenditure, adiposity and GH secretion. More recently, these hormones have been shown to be expressed by immune cells [10]. These hormones, in many ways, serve as counter regulators of each other. For example, an increased leptin in the circulation typically signals the brain that an individual is satiated, while an increase in acylated ghrelin levels informs the CNS that an individual is hungry. A similar manner of crossregulation appears to occur within immune cells as, in contrast to leptin, ghrelin appears to exhibit anti-inflammatory effects within the immune system. GHS-R and ghrelin are expressed by lymphocytes, monocytes and dendritic cells and ligation of GHS-R by ghrelin results in both a specific and potent inhibitory effects on both TCR- and leptin-mediated induction of proinflammatory cytokine expression. Ghrelin administration into various inflammatory and autoimmune disease models also results in a significant inhibition of proinflammatory cytokine expression and an increase in survival. Interestingly, both ghrelin and leptin appear to exert profound effects on thymopoiesis and

thymic output and are capable of partially reversing age-associated thymic involution. Together, these data support the existence of a functional immunoregulatory network involving these metabolic hormones in the regulation of cytokine expression, hematopoiesis, thymopoiesis, cellular activation and survival. These data also support the potential therapeutic use of ghrelin and GHS-R agonists or leptin receptor antagonists in the management of wasting associated with chronic inflammation and cancer and in the restoration of thymic function in immunocompromised individuals.

V. Stress Hormones

Physical and psychological stress can result in neuroendocrine mediators being released from the CNS and endocrine organs that directly impact immune function. The main two neuroendocrine pathways activated in response to stress that control the immune function are the HPA axis, which results in release of glucocorticoids and the sympathetic nervous system which results in release of catecholamines, epinephrine and norepinephrine. In addition, there are several other neuroendocrine factors that are released following stress that also regulate the immune system, including GH, prolactin and nerve growth factor (NGF). Through the action of these stress hormones, significant effects on immune function have been observed including reduced NK cell activity, alterations in peripheral lymphocyte subsets and cell proliferation, diminished antibody production and the reactivation of latent viral infections. It is believed that these stress-associated changes in immune function may also play a role in delayed wound healing, impaired responses to vaccination and development and progression of cancer. Drs. Marketon and Glaser [12] provide an excellent review of the current literature concerning the HPA axis and the various hormones and mediators associated with stress responses and suggest that immune alterations associated with both physical and psychological stress exert a significant impact on the immune system and health.

VI. Sympathetic Nervous System

The efferent nerves of the sympathetic nervous system (SNS) have been shown to innervate both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs, providing a means by which the CNS can influence immune reactivity. Upon stimulation, sympathetic nerves release the neurotransmitter, norepinephrine, into the lymphoid microenvironment, which has been shown to result in both the potentiation and inhibition of immune functions. Additional peptide neurotransmitters that colocalize with norepinephrine, including neuropeptide Y, adenosine triphosphate, opioid peptides, corticotropin-releasing hormone and vasoactive intestinal peptide are also released into the immune milieu upon SNS during times of stress or injury and have been shown to exert potent immunomodulatory effects on immune cells. While the specific role for each of these mediators on immune functions remains to be defined, immune cell subsets do indeed possess specific receptors for these ligands and demonstrate measurable intracellular signaling responses upon ligand-receptor interactions. Dr. Denise Bellinger and colleagues [13] believe that SNS-immune interactions may promote immune activity during disease- or injury-induced responses and that dysregulation of the SNS influences the progression of immune-mediated disease states. In her comprehensive review of the SNS, Dr. Bellinger discusses the patterns of distribution and targets of sympathetic nerves in primary and secondary lymphoid organs across life span and the evidence for neurotransmission with immune cells as the primary targets. She also comments on the functional and clinical significance of aging-induced changes in sympathetic-immune interactions and the consequences of sympathetic dysregulation in the development and progression of immune- and inflammatory disease states including rheumatoid arthritis, microbial infections, injury and cancer. Although Dr. Bellinger primarily focuses on SNS-immune interactions, she also discusses some of the literature on the noradrenergic influences on immunity.

VII. Opioids

Opioids were originally discovered because of their ability to induce analgesia, but further investigation has shown that the opioids regulate the function of cells involved in the immune response. Opioids mediate their effects through three distinct opioid receptor classes designated μ , δ , and κ . These receptors have been shown to be widely expressed throughout the central nervous system as well as on immune cells. Opioid compounds have been shown to modulate immune function and activation, including antibody responses, phagocytosis, natural killer cell activity, cytokine and cytokine receptor expression and thymic development and function. Dr. Thomas Rogers and coworkers [14] have suggested that the regulation of cytokine, chemokine, and cytokine receptor expression is a critical component of the immunomodulatory activity of the opioids and nociceptin, the natural agonist for the orphanin FQ/nociceptin receptor. Moreover, Dr. Rogers also discusses that the activation of the kappa opioid receptor induces a potent anti-inflammatory response through the down-regulation of cytokine, chemokine and chemokine receptor expression, while activation of the mu opioid receptor promotes a proinflammatory response. In addition, another level of regulation appears to be via the capacity of opioids, upon ligating their receptors, cross-regulate chemokine receptor signaling through heterologous desensitization. Dr. Rogers suggests that the broad effects of opioids in the modulation of immune function suggest potential targets for the development of novel therapeutics for the treatment of inflammation and various infectious diseases.

VIII. Conclusions

As described above, the CNS, endocrine and immune systems communicate through multiple anatomical and hormonal-neuropeptide routes. Controlled interactions between these systems are believed to be critical for the maintenance of a homeostatic balance within the body and good health. An imbalance or alterations in these systems in response to disease, stress, injury and/or metabolic alterations can lead to significant changes in immune responsiveness and susceptibility to infections and autoimmune disease states. A greater understanding of the interplay between these systems (such as more detailed studies on the interplay of specific mediators and hormone pathways in immune cells and the role of such interactions in clinically relevant responses) may provide valuable insights into how disruption within one or more of these compartments may influence a host's ability to regulate inflammation, disease development or wound healing. Moreover, a more thorough understanding of these pathways may indeed yield valuable new therapeutics and interventional strategies to control immune and systemic responses to disease, injury and stress.

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Fig. 1.

Neuroendocrine Interactions within the Immune System. As described in the text and within the specific reviews in this series, the crosstalk between the various neuronal and endocrine and immune systems appears to be primarily mediated via the production of and through interactions with soluble immune and neuroendocrine mediators, although there is substantial literature supporting a role for signals provided by the innervations of lymphoid tissues and other organ systems in controlling immune development and inflammation. Several hormonal and neuropeptide systems have been shown to influence immune activation and function including sex hormones (including estrogen, testosterone, GnRH), stress hormones (corticosteroids, ACTH), pituitary hormones (GH, prolactin), metabolic hormones (leptin, ghrelin, IGF-1) and opioids (enkephalins, endorphins and dynorphins) as well as the sympathetic nervous system (SNS). These mediators that provide the link between the endocrine, central nervous and immune systems and constitute specific axes of interactions including the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis, hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-growth-hormone axis. Immune cells, in their resting state or upon activation by specific antigens, cytokines and/or stress/injury, express cell surface receptors for these hormones and peptides permitting responses to ligands. Similarly, cells within the neuronal and endocrine systems can express receptors to various immune-derived cytokines, chemokines and growth factors.

During states of physical (trauma, tissue damage, infection, inflammation, transplantation) or psychological stress, these various organ systems “come to life” and release mediators to facilitate crosstalk with each other controlling cytokine production, immune activation, cytotoxicity, thymopoiesis, hematopoiesis, etc.. Overall, communication between these various systems appears to be multidirectional with specific hormones, peptides, cytokines and growth factors serving as mediators transmitting signals during times of stress, injury, disease, infection, physical decline and states of energy excess and deficit.