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Neuroendocrine regulation of inflammation

Caroline J. Padro^a and Virginia M. Sanders^{b,c}

Caroline J. Padro: padro.5@osu.edu; Virginia M. Sanders: Virginia.sanders@osumc.edu

^aThe Biomedical Sciences Graduate Program, The Ohio State University Wexner College of Medicine, Columbus, OH 43210

^bThe Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University Wexner College of Medicine, Columbus, OH 43210

^cThe Institute of Behavioral Medicine Research, The Ohio State University Wexner College of Medicine, Columbus, OH 43210

Abstract

The interaction between the sympathetic nervous system and the immune system has been documented over the last several decades. In this review, the neuroanatomical, cellular, and molecular evidence for neuroimmune regulation in the maintenance of immune homeostasis will be discussed, as well as the potential impact of neuroimmune dysregulation in health and disease.

Keywords

Neuroimmune; adrenergic receptor; beta2-adrenergic receptor; sympathetic nervous system; norepinephrine; stress

1. Introduction

It is well known that organ systems function autonomously. However, the level of cellular activity within a given organ system is regulated by input from sympathetic nerve fibers, which originate from the central nervous system (CNS) and release the sympathetic neurotransmitter norepinephrine (NE). For example, a heartbeat is an autonomous function that is mediated by the contraction of cardiac muscle fibers, but the intensity and rate of the beat is regulated by NE released in close apposition to cardiac muscle fiber cells that express adrenergic receptors (ARs). In this manner, homeostasis is maintained, i.e., contractions will increase in number and intensity when more blood flow is needed to carry oxygen to tissues during times of intense effort. Although such a connection between the sympathetic nervous system (SNS) and various organ systems to maintain homeostasis is undisputed, it is

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To whom correspondence should be addressed: Virginia M. Sanders, Ph.D., The Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University Wexner College of Medicine, 319 IBMR, 460 Medical Center Drive, Columbus, OH 43210 Tel: (614) 685-6749 Fax: (614) 366-2074 Virginia.Sanders@osumc.edu.

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generally thought that the immune system functions autonomously. This review will present and discuss the evidence for an SNS-immune connection and how a disruption of this connection affects immune homeostasis, as well as disease development and progression.

1.1 Early Clinical Support

One of the earliest studies to suggest that a relationship existed between the immune and nervous system was reported in 1919 and showed that psychosocial factors imposed upon Japanese students with pulmonary tuberculosis decreased the phagocytic capacity of cells within the blood [1]. This finding suggested that the high rate of death from tuberculosis in the Japanese young might be related to the depression of the immune system that occurred from “over taxation of the mind” by a school system that dictated severe entrance examinations and had overcrowded learning conditions. Also, the high incidence of industrial workers succumbing to the common cold and pneumonia in the 1920's prompted the design of studies to determine if a relationship existed between a worker's perception of fatigue and their susceptibility to infection. This possibility was first tested with rabbits, in which a state of fatigue increased disease susceptibility to, and mortality from, *Streptococcus pneumoniae* [2]. These findings are considered to be the first documented clinical examples that a connection between the nervous and immune systems exists.

In 1936, Selye introduced the concept of stress [3, 4]. Stress was defined as a biological response to a noxious stimulus, such as heat or cold, that induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and, most likely, the SNS. Selye described the structural changes that occurred during the biological response to stress, including the appearance of lymphoid organ atrophy. By the 1960's, studies by Solomon and Moos showed that a relationship existed between the psychological and immunological profiles of individuals afflicted with the immune-mediated disease rheumatoid arthritis (RA) [5, 6]. These studies introduced the concept that emotions could influence disease and, more importantly, emphasized the need for interdisciplinary approaches to understand the relationship between nervous system activity and immunity. It was later shown in Pavlovian-like experiments that antibody suppression could be conditioned [7, 8], providing the first experimental evidence of a link between the nervous system and immune systems. Also, changes in immunity caused by stress have been reported to influence the susceptibility to, or severity of, clinical immune diseases, such as infections, allergies, and cancer, which may all be related to a stress-induced release of NE and hormones [9-11]. Interestingly, neuromodulation of immunity appears to be evolutionarily conserved and suggests an important benefit of neuroimmune communication for survival [12, 13].

1.2 Basic Research

The clinical associations described above prompted more work to be done at the basic science level to confirm the existence of a neuroimmune interaction. It was necessary for basic scientists to show that 1) NE-containing nerve fibers terminated within the parenchyma of lymphoid tissue; 2) NE was released within lymphoid tissue upon the administration of antigen; 3) Immune cells within lymphoid organs expressed ARs that bind NE, and, after stimulation, mediated the intracellular activation of signaling intermediates;

and 4) The level of immune cell gene expression, cellular activity, and function changed after AR engagement.

Three landmark findings began to address these criteria. First, the study by Ader and Cohen, in which they showed the effect of taste aversion conditioning on a humoral immune response [7], indicated that behavior influenced immunity, and that immunity influenced behavior. These results suggested that a bidirectional relationship between behavior and immunity existed, and that such a relationship would have biological relevance for the treatment of disease [8]. Second, Besedovsky and DelRey showed that the activated immune system released a soluble product that changed the firing rate of neurons in a specific location within the brain, the hypothalamus [14, 15]. The importance of this finding was that the hypothalamus represents the brain region that controls activation of nerve pathways that communicate with the periphery. These pathways include the SNS, which releases the neurotransmitter NE from nerve terminals, and/or the HPA axis, which releases a variety of hormones, such as corticosteroids. Also, they showed that the SNS regulated the magnitude of an antibody response [16, 17]. Thus, an immune-to-brain, as well as a brain-to-immune, circuit was now in place to explain how immunity might affect behavior and vice versa. In this review we will focus on the brain-to-immune communication. For a discussion of the immune-to-brain communication, the reader is referred to the following excellent reviews on this topic [18-21].

Finally, immunohistochemical studies showed that both primary and secondary lymphoid organs [22-24] were innervated with sympathetic nerve fibers that contain NE. There is evidence of sympathetic nerve fibers that penetrate the parenchyma of the spleen, ending in the white pulp near the T cell-rich periarteriolar lymphatic sheath (PALS) [22, 25, 26]. Closer examination using electron microscopy showed that sympathetic nerve terminals were in direct apposition to lymphocytes, forming close synaptic-like contacts [27] that are spaced at 6 nm apart [28], as opposed to either the 20 nm synapse that forms between neurons in the CNS [29] or the 15 nm synapse that forms between an antigen-presenting cell (APC) and a naïve T cell [30, 31]. Thus, these three findings established a structural basis for a mechanism by which communication between the SNS and immune system occurs to provide neural regulation of immune cell activity.

1.3 Sympathetic Innervation and NE Release

As shown in Figure 1, sympathetic neurotransmission from the CNS to the periphery occurs via projections from the hypothalamus [32] to preganglionic sympathetic neurons located within the spinal cord, with axons that pass out of the spinal cord and synapse on postganglionic sympathetic neurons. The postganglionic axons then follow the vasculature to innervate all primary and secondary lymphoid organs [22, 29], where the sympathetic neurotransmitter NE is stored in granules within the nerve terminals. The close proximity of nerve terminals to immune cells responding to antigens not only provides a way for the SNS to directly target immune cells, but also allows for a high concentration of NE to be localized within the microenvironment of antigen-activated immune cells. For NE to have an effect on the immune target cell, a high concentration of NE must be released because NE is either rapidly metabolized and/or taken back up into the nerve terminal. Therefore, if NE is

involved in regulating the level of immune cell activity after antigen exposure, then a high concentration of NE needs to be released within the microenvironment of activated immune cells shortly after antigenic challenge. To address this point, NE turnover and release were measured following antigen administration to immunodeficient mice that received an adoptive transfer of antigen-specific Th2 cell clones and an enriched population of splenic antigen-specific B cells [33]. When the mice were immunized with either a cognate or non-cognate antigen, the level of splenic NE turnover and release increased between 8 and 18 hours following only cognate antigen immunization. Furthermore, microdialysis of splenic tissue revealed that the concentration of NE in a whole spleen after antigen administration increased to approximately 1 mM [34], while capillary electrophoresis of splenic tissue indicated that NE concentration within the direct vicinity of lymphocytes was on the order of 0.3-3.0 mM [35]. The latter findings were particularly important for understanding the data collected from immune cells exposed to NE in culture, where supraphysiological concentrations of NE, i.e., 10^{-6} M, were required to induce functional changes in immune cell function. Thus, a mechanism exists after antigen exposure within lymphoid organs to specifically target the release of a large amount of NE into the microenvironment where not only T cells are in direct apposition to a nerve terminal, but also other immune cells that reside within a close vicinity to the T cell zone.

Interestingly, in addition to sympathetic nerve terminals, NE release is also derived from phagocytes and CD4⁺ CD25⁺ T cells that express the enzymes for NE synthesis and degradation [36, 37]. Immune cell release of NE provides a mechanism to regulate anti-apoptotic and pro-apoptotic gene and protein expression, allowing for autocrine control of immune cell activity [38]. In addition, immune cell-derived neurotrophic factors appear to direct sympathetic nerve fibers to the site of an immune response [39, 40], suggesting a mechanism by which immune cells themselves recruit more help from the nervous system to maintain immune homeostasis.

An additional theory has been proposed by which the vagus nerve operates during infection and inflammation to also maintain immune homeostasis [41, 42]. However, the vagal nerve theory of immune modulation has been modified in response to neuroanatomical evidence [43] and new data showing that both the efferent vagal nerve and T-regulatory (T_{reg}) cells directly regulate SNS activity, which then regulates immunity [44-46]. For the purpose of this review, we will focus entirely on the data that support a role for the SNS in mediating immune homeostasis.

1.4 Adrenergic Receptor Expression

As mentioned above, immune cells are exposed to NE released from sympathetic nerve terminals upon antigenic challenge. This finding led researchers to determine if immune cells expressed the receptor for NE, which can be ARs that are either of the α - or β - subtype, which can be further distinguished pharmacologically and biochemically as α_1 , α_2 and α_3 or β_1 , β_2 and β_3 . It will be important to keep in mind that the level of AR expression varies among the different immune cell types and is regulated by a variety of factors, including the activation state of the cell, cytokines, and neurotransmitters [reviewed extensively in [47]],

and that the timing of receptor expression may play an important role in mediating neuroregulation of immune cells [48].

ARs are seven-transmembrane spanning receptors that associate with heterotrimeric GTP-binding proteins (G-proteins) and are, therefore, known as G-protein coupled receptors (GPCRs) that, when activated, induce an increase in the level of adenylyl cyclase activity and intracellular cAMP [For a comprehensive review of the findings from early studies on AR expression and cAMP-mediated effects in immune cells, refer to [49, 50]. The β_2 AR is able to associate with a stimulatory or inhibitory G-protein, G-protein-coupled receptor kinases (GRKs), or β -arrestins, each of which activates a distinct molecular pathway within an immune cell to differentially regulate its function [51-53]. The predominant association is between the β_2 AR and the stimulatory G-protein, which activates adenylyl cyclase and cAMP. Downstream from cAMP is protein kinase A (PKA), which becomes phosphorylated to activate the well-known transcription factor CREB. In contrast, another minor pathway can be activated downstream from PKA that involves the activation of p38 MAPK, which will be discussed later in this review under the B cell IgE response.

1.4.1 Primary Lymphoid Organs—In the bone marrow (BM), both the β AR and α AR are expressed, with the β AR being expressed predominantly during early stages of BM activation and the α AR during later stages [54, 55]. Stimulation of the β_2 AR suppresses BM cell proliferation and differentiation [56], while stimulation of the α_1 AR expressed on BM stem cells suppresses myelopoiesis, but enhances lymphopoiesis [57, 58]. In addition, NE influences the mobility of precursor cells from the BM into the peripheral blood [59] and neutrophil release [60].

In the thymus, the β_2 AR is expressed on thymocytes, while both the β_1 AR and the β_2 AR are expressed by thymic epithelial cells [61-63]. When exposed to antigen, the β_2 AR number decreases initially from baseline, but is higher at the peak of an immune response [62]. *In vivo* exposure of mice to NE or a β AR agonist decreased murine thymic weight, thymocyte number [64, 65], and mitogen-induced proliferation [66]. Also, *in vitro* exposure to a β AR agonist decreased basal and serum-stimulated proliferation of thymic epithelial cells [63] and induced thymocyte apoptosis [65, 67], via a cAMP-mediated mechanism [67-69]. In contrast, exposure of rat thymic epithelial cells to an α AR agonist increased basal and serum-stimulated IL-6 production, but not IL-1 production [70]. Thus, these findings suggest that the β_2 AR is expressed on both thymocytes and thymic epithelial cells that, when stimulated, exert a suppressive effect on cell growth, while, in contrast, the α AR is expressed on only thymic epithelial cells and exerts a positive effect on cytokine production.

1.4.2 Secondary Lymphoid Organs

1.4.2.1 Innate Immune Cells: DCs are potent APCs that play a critical role in regulating the initiation and intensity of an immune response [71]. Immune-mediated regulation of DC activity has been well studied, but the study of neurotransmitter-mediated regulation has not, even though sympathetic nerve fibers have been found to localize where DCs reside in both the skin [72, 73] and lymphoid tissues, where they are exposed to NE. BM-derived DCs (BMDCs) express the α_1 , α_2 , β_1 , and β_2 AR, and all receptors appear to induce functional

changes [74, 75]. Skin DCs express mRNA for α_2 AR, β_1 AR, and β_2 AR, although only the β_2 AR induced a functional change [76]. Splenic DCs also express a functional β_2 AR [77]. Thus, mature DCs appear to express both the α and β AR subtypes, although the ability of the receptor subtypes to be expressed and functional appears to depend on the tissue source.

Initially, functional studies using human peripheral blood monocytes and monocyte-derived macrophages revealed the expression of the β_1 AR and β_2 AR [78]. Moreover, there is evidence that in certain clinical conditions, e.g., in children with juvenile idiopathic arthritis, a functional α_1 AR is expressed on monocytes in the peripheral blood [79, 80]. Other studies reported that murine peritoneal macrophages express an α_2 AR, as determined functionally [81-83]. Therefore, monocytes and macrophages appear to express both the α and β AR subtypes, which is in contrast to lymphocytes that express the β_2 AR exclusively, as is discussed below.

1.4.2.2 Adaptive Immune Cells: Cells of the adaptive immune system, namely B and T cells, express the β_2 AR exclusively. On average, CD4⁺ and CD8⁺ T cells express approximately 200-400 binding sites per cell [84-86]. The β_2 AR is expressed on murine CD4⁺ naïve T and Th1 cells, but not on Th2 cells [87, 88], as determined at the level of gene and protein expression, as well as functionally. Data generated using human effector CD4⁺ T cells, however, are conflicting and include only functional data. For example, one study indicated that exposure to a β_2 AR agonist either inhibited Th1, but not Th2, cytokine production [89-92], changed the level of both Th1 and Th2 cytokines [93, 94], or had no effect [91, 95]. Thus, taken together, the data suggest that CD4⁺ naïve T and Th1 cells express the β_2 AR, but Th2 cells do not, and that an association may exist between the development of Th1 and Th2 cells and their ability to maintain or repress expression of the β_2 AR gene. The mechanism responsible for the differential expression of the β_2 AR on murine naïve, Th1, and Th2 cells is due to differences in histone and DNA modifications within the β_2 AR proximal promoter [96]. Specifically, chromatin precipitation revealed that H3K9 methylation, as well as the frequency of methylated CpG dinucleotides, increased in Th2 cells as compared to naïve and Th1 cells, effectively repressing β_2 AR gene expression. In contrast, CD4⁺ naïve T and Th1 cells showed H3K4 methylation and very low DNA methylation, effectively maintaining β_2 AR expression in these cells. Because these changes occurred in a manner equivalent to that reported for the respective cytokine promoters in these cells [reviewed in [97, 98]], the transcription factors activated by these cytokines may play a role in promoting the onset of chromatin modifications within the β_2 AR promoter of each effector subset. Thus, the results from these studies indicate that CD4⁺ naïve T or activated Th1 cells express a detectable level of the β_2 AR, while Th2 cells do not, and that this differential expression is due to differences in histone and DNA modifications within the β_2 AR proximal promoter.

Naïve and activated B cells express twice as many β_2 ARs as that expressed on T cells [50, 87, 88], suggesting that the B cell requires more receptors to bind the lower concentration of NE that diffuses into B cell regions from the PALS where the nerve terminals are located. Similar to CD4⁺ T cells, B cells express the β_2 AR exclusively. Although no radioligand binding studies have been done using T_{reg} cells, two studies identified expression of a functional β_2 AR on Foxp3⁺ T_{reg} cells that, when stimulated, increased intracellular cAMP

and PKA-activated CREB [44, 99], and mediated an anti-inflammatory response [44]. As far as we know, no radioligand binding or functional work has been done to quantify AR expression on Th17 cells. Therefore, the β_2 AR is expressed exclusively on the surface of T and B cells, and when stimulated, the level of intracellular cAMP and PKA activity increases.

1.4.3 Effect On Immune Cell Activity And Function—Stimulation of the ARs expressed on immune cells has been shown to play a role in regulating hematopoiesis, lymphopoiesis, thymopoiesis, lymphocyte homing, immune cell surface phenotype, and mature immune cell function. Below we will highlight the major findings.

1.4.3.1 Dendritic Cell: NE, in a β_2 AR-dependent manner, enhanced skin DC migration from the site of antigen to the draining lymph nodes during a contact hypersensitivity and stress-induced CD8⁺ T cell response [75, 100], suggesting that NE either exerts a chemotactic effect for directed migration or stimulates DC motility. However, when DCs that were exposed to antigen and a β_2 AR agonist *in vitro* were adoptively transferred to previously immunized mice, their ability to present antigen and elicit a delayed-type hypersensitivity was suppressed [76]. Likewise, DC-mediated cross-presentation of exogenous viral antigens to CD8⁺ T cells was inhibited [77, 101], via an effect on DC phagosomal antigen degradation, but without an effect on costimulatory molecule expression or endocytosis [101]. In contrast, NE, in an α_2 AR-dependent manner, enhanced the endocytosis of antigen by murine BMDCs [102].

NE suppressed IL-12 production by BMDCs, in a β_2 AR-dependent manner [101, 103] that involved an inhibition of NF- κ B translocation to the nucleus [101]. β_2 AR stimulation on both murine and human DCs reduced TLR-induced production of the inflammatory cytokines tumor necrosis factor- α (TNF α), IL-1 and IL-6 [104, 105], which was mediated partially by an inhibition of the NF- κ B and MAPK signaling pathways [104]. β_2 AR stimulation on DCs also affected NOD2 signaling, along with its cross talk with TLR-2, resulting in cytokine production that favored a slant toward Th17 differentiation [106] and promoted Th2-associated inflammation [107]. Thus, β_2 AR stimulation on a DC enhances migration to a lymph node, but suppresses antigen degradation and presentation and cytokine production, without affecting endocytosis or costimulatory molecule expression. In contrast, α_2 AR stimulation enhances endocytosis.

1.4.3.2 Monocyte/Macrophage: Endogenous NE in mice weakened innate immunity and predisposed mice to bacterial pneumonia [108], *E. coli* or *Pseudomonas aeruginosa* peritonitis [109], and *Klebsiella pneumoniae* peritonitis [131], the latter of which was due to a suppression of MCP-1 production by, and recruitment of, peritoneal macrophages during infection [110]. Likewise, NE decreased survival after a *Staphylococcus aureus* infection, resulting in higher peritoneal bacterial loads [111] and increased recovery time from a burn [133], even though there was an increase in mature monocyte progenitors [112] and macrophage maturation [113]. Cytokine genes in macrophages are major targets for NE action. After exposure to a β_2 AR agonist, proinflammatory TNF α production decreased [114-119], while anti-inflammatory IL-10 increased [120-122]. More recently, using a model of social disruption stress, NE mediated a decrease in plasma IL-6, TNF α , and

MCP-1 [123]. In contrast, after exposure to either an α_1 AR [124] or α_2 AR agonist [81, 125], proinflammatory TNF α production increased. Taken together, these data suggest that monocyte/macrophages express multiple AR subtypes, and that the inflammatory cytokine response is inhibited by β_2 AR stimulation, but enhanced by α_1 AR or α_2 AR stimulation, while the anti-inflammatory response is enhanced by β_2 AR stimulation. However, the concentration of NE may decide the functional effect on macrophages, as low concentrations of AR stimulation caused macrophages to become less phagocytic and produce less cytokine, while higher concentrations of AR stimulation enhanced these activities [126, 127]. Myeloid cell recruitment and migration to a site of injury is important and is influenced by NE. NE decreased survival during *Klebsiella pneumoniae* peritonitis in mice, primarily due to less MCP-1-dependent monocyte recruitment and a subsequent increase in bacterial load [110], which was also noted in a human microglial-like THP-1 cell line responding to amyloid beta peptide [128]. A recent study, using murine BM-derived macrophages cultured *in vitro* with M-CSF in the absence or presence of high (10^{-6} M) or low (10^{-8} M) concentrations of NE, found that a higher concentration of NE inhibited expression of MHCII and CCR2, proliferation, and migration toward MCP-1, but enhanced TNF α expression and phagocytosis, while the opposite results were obtained when the concentration of NE was lower [129]. Taken together, these findings suggest that NE regulates macrophage differentiation, proliferation and function, but that the effect may vary depending on the concentration of either NE released by a nerve terminal or an AR agonist administered therapeutically. In particular, these findings have implications for individuals with sepsis; e.g., burn patients who experience considerable stress and, at the same time, a rise in plasma NE concentration [130, 131].

1.4.3.3 T Cells: Early studies using unfractionated populations of T cells showed that exposure to either NE, a β_2 AR agonist, or a cAMP analog inhibited either mitogen- or anti-CD3 antibody-induced T cell proliferation [reviewed in [47]], due to a suppression of the expression of either the p55 and/or p75 chains of the IL-2 receptor [132, 133] and IL-2 production [134, 135].

1.4.3.3.1 CD4⁺ T Cells: Exposure *in vitro* to NE or a β_2 AR-selective agonist decreased IL-2 production by murine CD4⁺ naive T cells [136] and, under Th1-promoting culture conditions, induced naive T cells to differentiate into Th1 cells that produced an increased level of IFN γ upon restimulation, without affecting the number of Th1 cells that developed [137]. The effect on naïve T cell differentiation to a Th2 cell remains unknown, although Th2 functional responses were unaffected by exposure to NE or a β_2 AR-selective agonist, primarily because Th2 cells fail to express this receptor [87, 88]. *In vivo* studies indicated that NE stimulation of the β_2 AR was important for Th1 cell-driven responses, such as delayed-type hypersensitivity, e.g., NE increased ear swelling upon challenge with 2,4,6-trinitrochlorobenzene (TNCB) [138]. Another study found that NE in mice enhanced lymph node cell proliferation, but inhibited IL-2 and IFN γ production when activated by ConA *in vitro* [139, 140]. However, in mouse models exposed to Th1-promoting pathogens such as *Listeria monocytogenes* or *Mycobacterium tuberculosis*, NE increased the level of IFN γ produced by CD4⁺ T cells, as well as immunological protection [141]. These data suggest that NE and β_2 AR stimulation play a positive role in regulating the magnitude of CD4⁺

naïve T- and Th1 cell-mediated responses *in vivo* and *in vitro* by regulating the level of IFN γ secreted.

1.4.3.3.2 CD8⁺ T Cell: Few studies have been done to examine the effect of β_2 AR stimulation on CD8⁺ T cell activity, but a few findings have provided some insight. Exposure of mice to restraint stress to increase NE levels decreased the generation of a CD8⁺ T cell response to either HSV or influenza virus infection, which was partially mediated by a β AR-induced mechanism [142, 143]. Likewise, certain types of physical and psychological stress in humans elevated NE levels and induced an increase in CD8⁺ T cell number that was blocked by the administration of a β AR antagonist [144, 145]. Interestingly, acute administration of a β_2 AR agonist to healthy subjects for 7 days increased CD8⁺ T cell number, while, in contrast, chronic administration caused a decrease [146]. Quite the opposite, chronic exposure to a β_2 AR agonist in asthmatic individuals did not change the number of bronchial CD8⁺ T cells [147], while chronic exposure in HIV-infected individuals increased CD8⁺ T cell number [148], suggesting that a disease process may influence the effect from β_2 AR stimulation on a CD8⁺ T cell response differently. However, the timing of exposure to NE in relation to the stage of CD8⁺ T cell differentiation may be relevant. For example, if adrenergic ligands were added *in vitro* during the effector stage of the response to antigen, a decrease in CTL activity occurred [149, 150] due to a cAMP-induced decrease in the TCR-dependent release of cytotoxic granules [151], while NE exposure *in vivo* before sensitization with TNCB increased the generation of hapten-specific CD8⁺ T cell cytotoxicity upon TNCB challenge [138], suggesting that NE was required for the initiation stage of the response to antigen. Also, NE suppressed the antiviral CD8⁺ T cell response *in vivo* by enhancing the cross-presentation capacity of CD11c⁺CD8a⁺ DCs, suggesting that NE, via β_2 AR stimulation, suppressed the ability of DCs to activate CD8⁺ naïve T cells [77]. Thus, the role of NE and/or β_2 AR stimulation in modulating CD8⁺ T cell activity remains uncertain in both humans and animals, being both inhibitory and stimulatory, but these changes may be influenced by the time of β_2 AR stimulation in relation to the stage of CD8⁺ T cell differentiation or the time of AR stimulation in relation to T cell activation.

1.4.3.3.3 T_{REG} and TH17 Cells: In addition to Th1 and Th2 cells, the CD4⁺ T cell subset also includes T_{reg} and Th17 cells, although the role of NE and AR stimulation in regulating the activity of these cells is less understood. Exposure of T_{reg} cells to a β_2 AR agonist enhanced the *in vitro* suppressive activity of T_{reg} cells by not only increasing CTLA-4 expression on T_{reg} cells, but also increasing conversion of CD4⁺Foxp3⁻ cells into Foxp3⁺ induced T_{reg} cells, which led to a decrease in IL-2 mRNA levels in responder CD4⁺ T cells [99] and an increase in an anti-inflammatory response [44]. No work has been done to identify AR expression on Th17 cells, and this remains an important area of research.

1.4.3.4 B Cell: The role played by NE in regulating the magnitude of a B cell response has been another area of intense study. The reader is referred to the following comprehensive reviews of all of the early history in this area of defining the effects of NE and β_2 AR stimulation on B cell activity [reviewed in [49, 50]], with most findings indicating that NE increases the T cell-dependent antibody response [141, 152-158]. A few mechanisms

responsible for this increase *in vivo* include a NE/ β_2 AR-mediated increase in the level of CD86 expressed on the murine B cell surface, the level of serum antigen-specific IgG₁ produced, and the number of germinal centers formed [154]. When using a model system of purified splenic naive B cells cultured in the presence of CD40L and IL-4, researchers were able to perform more mechanistic studies that bypassed the involvement of macrophages, DCs, T cells, and antigen. Data showed that β_2 AR stimulation increased the amount of IgG₁ produced per B cell, without affecting the number of cells that switched to produce IgG₁, and more specifically, increased the rate of IgG₁ transcription, as determined by nuclear run-on [159-161]. These findings indicated that β_2 AR stimulation mediated the enhancing effect of NE in two ways. First, via a direct pathway from the β_2 AR to increase expression of the coactivator protein OCA-B and its binding to the 3'-IgH-enhancer region of the IgH locus, via a PKA and CREB-dependent mechanism [161], that regulated the rate of IgG₁ transcription [160]. And second, via an indirect pathway, in which NE and β_2 AR stimulation on a B cell upregulated expression of the costimulatory molecule CD86, which, when stimulated, activated another signaling pathway in the B cell that increased expression of the transcription factor Oct-2 and its binding to the 3'-IgH enhancer [161, 162]. Each effect separately caused the increase in IgG₁, but together, the increase was additive and involved a cooperative binding of the elevated levels of both OCA-B and Oct-2 to the 3'-IgH enhancer region [161]. For a more detailed description of how understanding the role played by the β_2 AR in enhancing the IgG₁ response led to the discovery of the signaling pathway activated by CD86, which was considered devoid of signaling ability in immune cells, please refer to the following review [163] and subsequent CD86 signaling studies [164-166].

These findings were confirmed *in vivo* when B cells alone were adoptively transferred to NE-depleted or NE-intact immunodeficient mice, and followed by the administration of anti-CD40 antibody, IL-4, an anti-CD86 Ab, and/or a β_2 AR agonist [154, 161]. The level of serum IgG₁ was increased almost 2-fold following β_2 AR stimulation and almost 3-fold following CD86 stimulation, and this level was further increased by almost 6-fold when both CD86 and the β_2 AR were stimulated. Likewise, the level of mature IgG₁ transcript and Oct-2/OCA-B transcript and protein produced by splenocytes from these mice positively correlated with the increased level of serum IgG₁ protein [161]. Therefore, the level of mature IgG₁ transcript and IgG₁ protein increased after β_2 AR and/or CD86 stimulation on a B cell, and this change appears to be associated with a similar increase in the level of Oct-2 and OCA-B transcript produced *in vitro* and *in vivo*. Thus, for the Th2/IL-4-dependent IgG₁ response, we now know the mechanism by which NE and β_2 AR stimulation exerts an enhancing effect. These findings also suggested that signaling pathways activated in a B cell through stimulation of an immunoreceptor (CD86) and a neuroreceptor (β_2 AR) converge to regulate the magnitude of an IgG₁ response.

Although one would have predicted that the mechanism responsible for the β_2 AR-mediated increase in the Th2/IL-4-dependent IgE response would be similar to that for the Th2/IL-4-IgG₁ response, it is not. Mice that were dominant-negative for CREB showed that the signaling intermediates used to induce the enhancing effects were quite different [167, 168]. Similarly to IgG₁, NE stimulation of the β_2 AR on a CD40L- and IL-4-activated B cell increased the rate of IgE mRNA transcription and the amount of IgE produced per cell,

without affecting class switch recombination [167]. As summarized in Figure 2, instead of activating CREB to produce these effects, β_2 AR stimulation increased IgE production in a p38 MAPK-, CD23-, and CD21/CD19-dependent manner [167], that was PKA-dependent, but CREB-independent [168]. Subsequent findings indicated that the mechanism regulating the β_2 AR-mediated increase in p38 MAPK phosphorylation involved the inactivation of hematopoietic protein tyrosine phosphatase (HePTP), which occurred in a PKA-dependent manner and subsequently allowed for an increase in p38 MAPK phosphorylation [168] to mediate an increase in CD23 and ADAM10 in the B cell [169]. It was subsequently determined that the β_2 AR-mediated and PKA/p38 MAPK-dependent increase in CD23 and ADAM10 expression occurred exclusively on B cell-derived vesicles, identified as exosomes, as opposed to on the cell surface [169]. Importantly, these vesicles were able to transfer the β_2 AR-associated enhancing effect on the level of IgE production to B cells unexposed to a β_2 AR agonist, suggesting a unique mechanism by which IgE production is regulated by exosomes released by B cells. Thus, β_2 AR-mediated enhancement of the IgG₁ response appears to use the PKA-dependent, CREB-mediated pathway to do so, while the enhancement of the IgE response appears to use the PKA-dependent, HePTP/p38 MAPK-mediated pathway.

2. SNS-Immune System Interactions in Health, and Disease

As discussed previously, NE-mediated regulation of immune cell activity is a mechanism by which immune homeostasis is maintained, assuring a healthy state. Therefore, any disruption of the communication between the nervous system and an immune cell, i.e., changes in lymphoid organ innervation, NE release, AR expression, and/or AR-induced signaling intermediate activation, may have health and disease implications. Even though the duration of any disruption may be short-lived, health consequences may often be long term. For example, chronic stress, which involves over-activation of the SNS and the release of higher quantities of NE, contributes to the pathology of many immune-mediated diseases [170]. Also, because of the bidirectional communication that exists between the nervous and immune systems, any disruption in one system may result in changes to the other. With a better understanding of the mechanisms by which the SNS affects immune cell effector function, we will be able to identify pharmacological targets that regulate the finely tuned balance between the maintenance of health and the development of disease. Below we will discuss some examples of how a disruption in this balance has contributed to, or has the potential to contribute to, disease severity and/or progression.

2.1 Asthma

Allergic asthma is a chronic inflammatory disorder of the airways that is triggered by specific allergens and is characterized by coughing, wheezing, shortness of breath, and chest tightness, which are primarily mediated by proinflammatory mediators released by mast cells, leading to bronchoconstriction. The clinical implication for the SNS-immune system interaction has considerable relevance to allergy and allergic asthma, which are both linked to an increase in IgE [193]. Not only is NE released during the response to antigen under normal physiological conditions [33], but it also participates in the generation of a normal level of antigen-induced IgE and lung pathology [167]. Paradoxically, β_2 AR over-

stimulation on a B cell enhances the level of IgE, in both *in vivo* and *in vitro* systems [159, 167, 169]. Thus, when an asthmatic individual is either stressed, causing an increase in NE release, and/or uses an inhaler, containing a β_2 AR agonist drug, the over-stimulation of the β_2 AR on a B cell may raise the individual's level of IgE higher than normal, placing the individual at a higher risk, especially because slight increases in the level of IgE correlate with the development of a more severe allergic asthma response to allergen [171]. In addition, the effects of continued use of a β_2 AR agonist in allergic asthma may be further exacerbated by a stress-induced release of more NE, which is of particular concern since stress is known to be positively associated with allergic asthma in humans [172, 173] and mice [174]. Thus, the use of a β_2 AR agonist for the treatment of allergic asthma may not only produce the desired effect to relieve bronchoconstriction, but also exert an unintended side effect related to a disruption in the SNS-immune system balance that involves an over-stimulation of the β_2 AR on a B cell, causing an increase in the level of IgE produced and, potentially, a worsening of the asthma symptoms. Such an imbalance may explain why current β_2 AR agonist therapies lose their efficacy over time, why there is an increase in a patient's risk of asthma-related death when using long-acting β_2 AR agonists [175], and why allergic asthma patients experience exacerbated asthma symptoms during times of stress.

2.2 Pneumonia

IgG₁ is especially important in thwarting the development of bacterial pneumonia, which is an infection of the lungs that leads to shortness of breath and death. Pneumonia is particularly deadly in susceptible populations, and it is the leading cause of death in patients who suffer from chronic lymphocytic leukemia [176]. Therefore, any therapy that would boost IgG production by B cells may provide an opportunity to increase protection and survival from pneumonia in susceptible populations. Notably, clinical findings have shown that a 2- to 3-fold increase in serum IgG correlates to a 3- to 9-fold increase in protection against *Streptococcus pneumoniae* and pertussis [177, 178], suggesting that increases of this magnitude in the level of antibody produced is potentially relevant clinically. Thus, a β_2 AR-induced increase in IgG₁ may prove to be helpful, perhaps via the administration of a β_2 AR agonist during pneumonia vaccination.

2.3 Viral Immunity

The SNS-immune system interaction is beneficial in defense against both microbial and viral infections. Acute stress, as modeled by a social disruption stress model in mice, is beneficial for the clearance of both microbial [179] and viral [180] infections, such as influenza. This enhancement in immunity is attributed to an increase in the expression of activation markers on innate immune cells, along with an increase in NK and CD8⁺ T cell activity [181]. Furthermore, the enhanced activation status of these innate immune cells is SNS-dependent, as β_2 AR antagonists prevented the enhancement [181]. Indeed, previous studies with macrophages determined that NE mediated a change in the pro-inflammatory cytokines TNF α , IL-12, IL-6, and IL-1 β [182, 183], which may also have contributed to establishing the level of anti-viral immunity. Furthermore, NE induced a change in CD4⁺ naïve T cell differentiation to induce the development of Th1 cells that produced a higher level of IFN γ [137], which is a potent antiviral factor that could also explain the enhanced antiviral immunity measured in the social disruption stress model for viral immunity.

In contrast, chronic stress is detrimental to the development of immunity resulting from vaccination and promotes viral pathogenesis. Those experiencing chronic stress have reduced numbers of lymphocytes in the blood and reduced leukocyte mobilization to the skin [184]. A recent meta-analysis of stress and vaccination-induced antibody titers confirmed that stress is negatively associated with the generation of viral immunity [185]. For example, stress reduced the immune response to several different viral vaccines, including those against hepatitis B [186], rubella [187], pneumonia [188], and influenza [189-191]. Also, chronic stress is associated with increased viral pathogenesis. In humans, stress is associated with HIV disease progression, increased viral replication, and immune suppression [192], loss of CD8⁺ T cell control of HSV-1 [193], and EBV reactivation [9]. The exact mechanism responsible for mediating the effects of chronic stress are often debated, but may involve both cortisol [213, 218] and NE [194, 195], as well as changes in receptor expression for both ligands. Thus, understanding the SNS-immune system interaction will provide an avenue for therapeutic intervention to improve both vaccination efficacy and the control of viral infection, development and progression.

2.4 Rheumatoid Arthritis

A number of clinical observations provide evidence for the involvement of a neuroimmune interaction in the pathogenesis of an inflammatory disease, such as rheumatoid arthritis (RA) [196-198], where the systemic level of IFN γ is elevated [199, 200]. This finding suggests a potential role for a SNS-induced, β_2 AR-mediated effect in this disease process, perhaps affecting naive CD4⁺ T cell differentiation into Th1 cells that secrete a higher level of IFN γ [137]. In this manner, Th1 cells secreting a higher level of IFN γ might accumulate within the synovial fluid to promote the inflammatory process. On a mechanistic level, SNS denervation in rats produced an earlier onset, and enhanced the severity, of arthritic changes [201], indicating that local changes in the sympathetic nerve input to the inflamed tissue modulates immune cell activity to play a key role in the development of arthritis [202].

2.5 Aging

Decreases in the level of splenic innervation have been reported in aged subjects and individuals with certain pathological conditions. For example, an age-related decrease in sympathetic innervation was observed in both the spleen and lymph nodes of aging rats, but not in the thymus [203-206]. This observation may explain the declining T and B cell responses [138, 207, 208] and cellularity of the white pulp [209, 210] that are associated with aging. Thus, disruption in the level of sympathetic innervation within lymphoid organs during the process of aging may translate into disruption in the rate of NE release during the course of the immune response. Also, one study reported an age-dependent decrease in both the number and affinity of β ARs expressed on the surface of spleen cells [211]. Thus, if NE plays a role in modulating immune function, an age-related decline in lymphoid tissue innervation and β AR expression [212-214], may contribute to the age-associated increase in the incidence of autoimmunity, cancer, and susceptibility to infection [210, 212, 215, 216]. On the other hand, if cytokines play a role in modulating the immune-to-brain communication pathway, then an age-related decline in immune function may contribute to an age-associated increase in behavioral and cognitive dysfunctions [217]. Although these

possibilities are speculative, they do emphasize the need for a better understanding of the mechanisms by which one system influences the functioning of the other.

2.5 Spinal Cord Injury and Immunosuppression

Spinal Cord Injury (SCI) has been linked to reduced immune function and mortality. Specifically, SCI below the level of the diaphragm is associated with increased rates of pneumonia, sepsis, and susceptibility to infection [218]. A condition known as autonomic dysreflexia (AD) results from SCI, causing the loss of a negative feedback loop that would normally control the level of sympathetic nerve output to the periphery [219]. As a result, the level of NE input to lymphoid organs is increased considerably. It has long been appreciated that patients with SCI are immunosuppressed after the acute phase of SCI, which is due to an early decrease in the number of T, B, and APCs [220] and a suppressed antigen-specific antibody responses [221], perhaps because the levels of NE were too high. Furthermore, this immune suppression was abrogated in the presence of β_2 AR antagonists [221, 222], establishing a link between the SNS and immune systems in SCI. Thus, SCI-associated AD, which is primarily a nervous system disorder, results in immune system dysregulation, illustrating further the importance of these two systems in maintaining overall homeostasis.

2.6 Stress and Wound Healing

Wound healing is another aspect of immunity that is affected through the neuroendocrine connection via stress. Psychological stress is associated with a decreased ability of wounds to heal, such as those that occur during surgical incisions [223], skin punctures [224], and burns [225]. The physiological mechanism responsible for mediating this phenomenon may lie in a β_2 AR disruption of the healing response to wounding, which depends on the release of cytokines and chemokines that recruit phagocytes to the site of injury that are important for tissue remodeling [226], especially since β_2 AR stimulation on macrophages, T cells, and B cells impacts cytokine and chemokine release. One study found that host resistance to *Listeria monocytogenes* was decreased following acute cold restraint stress involved the SNS and was mediated by the β_1 AR [227]. Importantly, sustained catecholamine release and cytokine production is detrimental in the long-term to not only the immune system, but also the cardiovascular system, up to three years following burn injury [130, 131, 228]. Recent work found that stress-induced suppression of wound-healing was attenuated in the presence of a β_2 AR antagonist, improving re-epithelialization in both rat [248, 251] and mouse [252-254] models of epithelial injury, as well as wound healing in human burn patients [229]. It is interesting to note that a β_2 AR antagonist is used quite often after initial burns to reduce tachycardia [230], and may play a role in suppressing immune system function that is needed for wound repair.

3. Summary

To date, a number of clinical examples support a role for a neuroimmune relationship in the etiology or progression of a disease state, emphasizing that an understanding of the cellular, biochemical, and molecular mechanisms by which NE regulates the level of immune cell activity will lead to the development of therapeutic approaches to alter the etiology and/or

progression of immune system-related diseases. For example, the level of immunocompetence may vary as a result of either a change in the level of locally secreted NE in lymphoid organs or a change in the level of expression of the β_2 AR on lymphocytes. Such NE/ β_2 AR-mediated changes in immunocompetence may not be immediately life threatening to an individual, but could alter long-term health status and quality of life.

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Abbreviations

TCNB 2,4,6-trinitrochlorobenzene

ARs	Adrenergic Receptors
APC	Antigen Presenting Cell
BM	Bone Marrow
BMDC	BM-derived DCs
CNS	Central Nervous System
CTL	Cytotoxic T Lymphocytes
DCs	Dendritic cells
G-proteins	GTP-binding proteins
GPCRs	G-protein coupled receptors
GRKs	G-protein coupled receptor kinases
Gα_i	inhibitory G-protein
HPA	Hypothalamic-pituitary-adrenal
NE	Norepinephrine
PALS	Periarteriolar lymphatic sheath
PKA	Protein Kinase A
RA	Rheumatoid arthritis
<i>scid</i>	severe combined immunodeficiency
SCI	Spinal Cord Injury
Gα_s	stimulatory G-protein
SNS	Sympathetic Nervous System
T_{reg}	Tregulatory
TNFα	Tumor necrosis factor-α

Highlights

- Sympathetic nerve fibers penetrate the parenchyma of lymphoid organs
- Antigen exposure leads to norepinephrine release from nerve terminals
- Norepinephrine binds to adrenergic receptors expressed on immune cells
- Adrenergic receptor signaling in immune cells modulates cell activity and function

Figure 1.

SNS signaling upon antigen exposure. Antigen introduction via injury or exposure allows for the release of inflammatory cytokines by phagocytic innate immune cells that stimulate the hypothalamus in the brain to activate preganglionic sympathetic neurons. Preganglionic sympathetic neurons synapse on postganglionic sympathetic neurons outside of the spinal cord and innervate lymphoid organs. NE is released from the sympathetic nerve terminals in the proximity of immune cells that express the β_2 AR. In addition to the autonomous ability of immune cells themselves to regulate their own activity, the effects induced after β_2 AR stimulation on immune cells provide a mechanism by which immune homeostasis is maintained.

Figure 2. Known mechanisms of IgG₁ and IgE regulation in B cells

(1) The IgG₁ increase that is mediated by β_2 AR stimulation follows the classical $G_s\alpha$ stimulatory pathway that results in phosphorylation of CREB and mediates transcription of downstream targets, including OCA-B, Oct-2, and IgG₁ (2) The β_2 AR-associated IgE increase is mediated through the PKA/HePTP/p38 MAPK pathway. The existence of these divergent pathways suggests a differential mechanism by which the enhancement of IgG₁ and IgE is regulated.