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Review

Neuroendocrine regulation of inflammation

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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.

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 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 1920s 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 1960s, studies by Solomon and Moos showed that a relationship existed between the psychological and immunological

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; $G\alpha_i$, inhibitory G-protein; HPA, hypothalamic-pituitary-adrenal; NE, norepinephrine; PALS, periarteriolar lymphatic sheath; PKA, protein kinase A; RA, rheumatoid arthritis; *scid*, severe combined immunodeficiency; SCI, spinal cord injury; $G\alpha_s$, stimulatory G-protein; SNS, sympathetic nervous system; T_{reg}, Tregulatory; TNFα, tumor necrosis factor-α.

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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 Fig. 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 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 h 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.*, $\geq 10^{-6}$ 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.