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Review

Autonomic regulation of cellular immune function

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ABSTRACT

The nervous system and the immune system (IS) are two integrative systems that work together to detect threats and provide host defense, and to maintain/restore homeostasis. Cross-talk between the nervous system and the IS is vital for health and well-being. One of the major neural pathways responsible for regulating host defense against injury and foreign antigens and pathogens is the sympathetic nervous system (SNS). Stimulation of adrenergic receptors (ARs) on immune cells regulates immune cell development, survival, proliferative capacity, circulation, trafficking for immune surveillance and recruitment, and directs the cell surface expression of molecules and cytokine production important for cell-to-cell interactions necessary for a coordinated immune response. Finally, AR stimulation of effector immune cells regulates the activational state of immune cells and modulates their functional capacity. This review focuses on our current understanding of the role of the SNS in regulating host defense and immune homeostasis. SNS regulation of IS functioning is a critical link to the development and exacerbation of chronic immune-mediated diseases. However, there are many mechanisms that need to be further unraveled in order to develop sound treatment strategies that act on neural–immune interaction to resolve or prevent chronic inflammatory diseases, and to improve health and quality of life.

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1. Introduction

Immune function can be altered by classical behavior conditioning paradigms. Repeatedly pairing an immune stimulus with a non-immune type of stimulus (associative training)subsequently results in the non-immune stimulus producing a similar effect on immune function as the immune stimulus (reviewed in Cohen et al., 1994; Riether et al., 2008). Learning and memory are required for behavioral conditioning, indicating mediation of conditioning effects via the central nervous system (CNS). Moreover, behavioral conditioning can alter inflammation and disease outcomes (Ader and Cohen, 1982; Bovbjerg et al., 1987; Giang et al., 1996), indicating an important role for CNS-to-immune system (IS) regulation in health and illness. Although, all neuroendocrine hormones can affect immunity, there are two major pathways that mediate CNS-to-IS signaling, the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenocortical (HPA) axis. Both pathways are regulated centrally by limbic and autonomic circuits known to mediate the effects of stressor on body functions. Here, we review the central autonomic circuits that influence SNS-to-IS signaling, and how they affect immune function. A large body of research indicate that sympathetic activation either pharmacologically or through physical or psychosocial stressors can significantly alter immune function (Kemeny and Schedlowski, 2007), with consequences for mental and physical health. Lesioning, stimulating, or blocking the activity of specific autonomic/limbic brain regions/nuclei known to regulate autonomic/neuroendocrine outflow also alters measures of immune function (reviewed Felten et al., 1991). Finally, experimentally manipulating of the autonomic outflow from the CNS to immune organs, can affect such functions as delayed-type sensitivity reactions, natural killer (NK) cytotoxicity, cytokine secretion, lymphocyte proliferation, and antibody production (reviewed in Bellinger et al., 2008b; Elenkov et al., 2001). The effects of these manipulations are generally reproducible, dose-dependent when adrenergic ligands are used, and reversible by blocking the sympathetic manipulative actions of the treatment. It is clear from these findings that the CNS regulates the functions of lymphoid tissues via the autonomic nervous system (ANS).

The ANS plays a critical role in physiological regulation under basal conditions and in response to acute and chronic stressors. The ANS, particularly the SNS, regulates the homeostatic and host defense functions of the IS. Foreign substances, termed antigens, and tissue damage are perceived by the brain as stressors, and therefore activate the SNS, which, in turn, regulates host defense mechanisms. Psychological and physical stressor activate the HPA and SNS to modulate homeostasis of the IS, induce inflammation, and affect the IS's ability to heal wounds and fight infections. In this paper, we review the regulation of the IS by the SNS.

Both arms of the ANS, the PaSNS and SNS, are classically "two-neuron chain circuits" consisting of a pre- to postganglionic neuron connection. Central autonomic circuits between the forebrain, limbic system, and certain hypothalamic regions/nuclei and brainstem nuclei impinge on these two-neurons circuits, comprising the brain–ANS–immune axis. Postganglionic sympathetic neurons from specific sympathetic ganglia innervate immune organs and tissues (Fig. 1); however, evidence is lacking for parasympathetic innervation of immune organs (discussed in Bellinger et al., 2013). Vagal afferents, as well as other visceral afferents, convey immune signals to regions of the brain that regulate sympathetic outflow to immune organs (reviewed in Bellinger et al., 2013). Additionally, preganglionic sympathetic neurons supply the adrenal medulla, which releases the catecholamines, norepinephrine and epinephrine into the circulation. Thus, the SNS can have both localized and systemic effects on immunity. These pathways provide the anatomical substrate for SNS-immune cross-talk. Afferent visceral fibers, including those in the vagus nerves, are an important route for conveying information concerning tissue damage or antigen exposure, and subsequent immune activation, to the CNS. Additionally, circulating cytokines provide a slower route of communication with the brain. Many different cytokines can interact with the brain at circumventricular organs (CVOs), which lack a blood–brain barrier. Alternatively, they can be actively transported into certain regions of the brain (reviewed in Dantzer, 2001). Immune activation also induces the production of proinflammatory cytokines centrally (Rothwell, 1991; Watkins and Maier, 2000; Neumann, 2001; Felderhoff-Mueser et al., 2005).

While multiple neuromediators are released from sympathetic nerves, norepinephrine is the major neurotransmitter that regulates cells of the IS, and most research has focused on noradrenergic regulation. Cells of the IS respond to noradrenergic signaling via the cell surface expression of α- and β-adrenergic receptors (ARs) (Fig. 1). Research is beginning to unravel the mechanisms through which the intracellular signaling pathways used by α- and β-ARs communicate with the signaling pathways used to regulate immune functions.

Here, we discuss our current understanding of the brain–SNS–immune axis, and sympathetic regulation of immune cell development and immune function. We present an overview of findings indicating that activation of β_2-AR signaling pathways suppresses T-helper (Th)1 responses and cellular immunity, and drives Th2 responses important for humoral immunity. Adrenergic regulation of more recently characterized Th17- and Treg-cells is also presented. Under chronic conditions where the IS fails to eliminate the threat and/or to restore immune homeostasis, dysregulation of the SNS can promote inflammation and boost cellular and humoral immunity contributing to the damaging effects of localized and systemic inflammation. Additionally, we describe SNS regulation of immune cell development in the bone marrow (BM) and thymus, although it is not well understood. Most limited is our understanding of the effects of sympathetic outflow on mucosal immunity, and effects on effectors cells of the innate IS. Research reviewed here underscores the need for better understanding central mechanism that influence sympathetic outflow, and α_1- and β-AR-mediated regulation of immune function in order to develop early-intervention therapeutics aimed at recovery of sympathetic-immune dysregulatory mechanisms under certain physiological conditions and disease states.

2. Central regulation of autonomic outflow to immune organs

Central descending sympathetic pathways that regulate sympathetic nerve activity (SNA) in lymphoid organs are best defined for the spleen. The spleen is innervated by neurons in the superior mesenteric