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Innervation of lymphoid organs: Clinical implications

Denise L. Bellinger [a,*], Brooke A. Millar [a], Sam Perez [a], Jeff Carter [a], Carlo Wood [a], Srinivasan ThyagaRajan [a], Christine Molinaro [a], Cheri Lubahn [b], Dianne Lorton [b]

[a] *Department of Pathology and Human Anatomy, Loma Linda University School of Medicine, 11021 Campus Street, Alumni Hall 325, Loma Linda, CA 92352, USA*

[b] *Hoover Arthritis Center, Sun Health Research Institute, Sun City, AZ 85351, USA*

Abstract

Host defense against pathogens is regulated by cross-talk between two major adaptive systems of the body—the nervous and immune systems. This bidirectional communication is essential for maintaining homeostasis. Sympathetic nerves that innervate lymphoid tissues provide one of the major outflows from the brain to regulate tissue repair and host defense. This review focuses on the role of (sympathetic nervous system) SNS in neuroimmune regulation, an area that has received much less attention than the other major immunoregulatory pathway, the hypothalamo–pituitary–adrenal (HPA) axis. Research over the past 25 years has demonstrated that norepinephrine (NE) fulfills the criteria for neurotransmission in lymphoid tissue, with both primary and secondary immune organs receiving an extensive supply of sympathetic nerves that directly contact with immunocytes. Under stimulation, NE released from terminals in secondary lymphoid organs interacts with adrenergic receptors (AR) expressed on immune cells to affect the development, trafficking, circulation, proliferation, cytokine production, and the functional activity of variety of lymphoid and myeloid cells. Our knowledge of the role of sympathetic nerves in modulating hematopoietic functions of primary lymphoid organs (bone marrow and thymus) and mucosal immunity are extremely limited. While the immune system is not absolutely dependent upon signals from the brain to function, sympathetic-immune modulation may drive host defense toward protection against, or progression toward, immune-related diseases. Additionally, signals from the (SNS) may enhance immune readiness during disease- or injury-induced 'fight-or-flight' responses. A better understanding of neural–immune interactions may foster the development of strategies for treating immune-mediated diseases, particularly where neuroimmune cross-talk may be dysregulated.

Keywords: Noradrenergic; Autonomic; Sympathetic innervation; Lymphoid organs; Immune modulation

1. Introduction

Increasing evidence indicates functional bidirectional communication between immune and nervous systems, although the mechanisms of this cross-talking are incompletely understood. Primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs are innervated by autonomic (mainly sympathetic) efferent nerves that provide a major pathway through which the brain can alter immune reactivity. In this paper, we review the anatomical studies revealing the origin, pattern of distribution and targets of sympathetic nerve fibers supplying lymphoid organs. Catecholamines of neural (as well as nonneural) origin are released in the lymphoid microenvironment for neuroimmune modulation. Neuropeptide Y (NPY), ATP, opioid peptides, and vasoactive intestinal peptide (VIP), under certain conditions, may be co-released with norepinephrine (NE) to modify noradrenergic (NA) signaling of immunocytes. Data demonstrating the expression of specific receptors for these neurotransmitters on immune cells in immune organs and mechanisms through which ligand binding to these receptors activates intracellular signaling pathways to alter immune responses are discussed. We also describe research indicating that changes in immune function and normal aging can influence the distribution of nerves and the expression of neural

* Corresponding author. Tel.: +1 909 558 7069; fax: +1 909 558 1432.
E-mail address: dbellinger@llu.edu (D.L. Bellinger).

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receptors in lymphoid organs, which in turn affects the ability of the sympathetic nervous system (SNS) to modulate immune function and may increase the risk for, or promote the progression of, certain types of immune-mediated diseases.

2. Neurotransmission in bone marrow

2.1. Sympathetic nerves supplying bone marrow

The bone marrow, a primary lymphoid organ, replenishes the adult immune system throughout life using a pool of lymphohematopoietic stem cells. Nerves that innervate bone marrow, as well as neuroendocrine interactions with bone marrow cells, are part of a brain-immune axis that is important for regulation of hemato- and lymphopoiesis. Efferent sympathetic autonomic nerves enter the nutrient foramina of long bones, course along blood vessels in the Haversian and Volkmann's canals to distribute to bone marrow [1–7]. Sympathetic nerves that distribute to bone contain NE, NPY, and VIP. NA sympathetic nerves provide the densest innervation of rat bone marrow. Sympathetic nerves containing NPY and VIP are less abundant than nerves immunoreactive for tyrosine hydroxylase (TH), the rate-limiting enzyme for NE synthesis, but displayed a similar pattern of distribution [2].

NA nerves closely appose hematopoietic and stromal cells in the bone marrow [2,4–9]. An electron microscopic study of bone marrow has revealed nerve terminals directly apposed to a particular type of stromal cell, the periarterial adventitial cell, an important source of growth factors and adhesion molecules [8]. Efferent nerves also appose sinus adventitial reticular cells and intersinusoid reticular cells, which interconnect with periarterial adventitial cells via gap junctions.

Collectively, these findings provide anatomical evidence for sympathetic regulation of hematopoiesis and lymphopoiesis in bone. In support of this functional role, temporal development of rat bone marrow innervation of the rat bone marrow correlates with the onset of hemopoietic activity [10]. The perivascular distribution of sympathetic nerves provides support for SNS regulation of vasomotor activities and the release of mature blood cells from the bone marrow. The close spatial relationship between these nerves with hematopoietic cells and stromal cells suggests a role in regulating hematopoiesis.

2.2. Presence of neurotransmitters in bone marrow

In mice, NE is present in the range of 1–3 ng/g bone marrow tissue in mice [11,12]. This is generally one to two orders of magnitude lower than is found in secondary lymphoid organs in the rat [13,14]. NE concentration in murine bone marrow exhibited diurnal variations, with peak values occurring at night [11]. High and low concentrations of NE were linked with high and low levels of their metabolites. NE, but not epinephrine (EPI), positively correlated with the proportion of cells in the G2/M and S phases of cell cycle [11]. Cold exposure increased NE turnover rate by 36%, while peritoneal *Pseudomonas aeruginosa* infection increased NE turnover rate by 131% in the bone marrow [15], demonstrating functionally dynamic responsiveness of sympathetic nerves in bone marrow to generalized stress.

2.3. Expression of receptors for neurotransmitters in bone marrow

Functional data (described below) and radioligand binding studies have demonstrated α-adrenergic receptor (AR) expression on bone marrow cells [16]. ^{3}H-labeled prazosin, an α_1-AR antagonist, binds to both bone marrow cell membranes and intact bone marrow cells with high and low affinity. A lymphoid/stem cell fraction expressed the high affinity binding site, but the cell subset that expresses the lower affinity site is not clear. Expression of β-AR have not been demonstrated on bone marrow cells using radioligand binding, northern blots or reverse transcription-polymerase chain reaction (RT-PCR) for mRNA, but in vivo and in vitro functional studies and studies examining β-AR signal transduction support their expression on bone marrow cells. A biphasic increase in intracellular bone marrow adenosine 3′,5′-monophosphate (cAMP) content was measured 1 and 15 min after mice were exposed to either NE, EPI, or isoproterenol (β-AR agonist) [17,18]. A rise in bone marrow cell cAMP content intracellularly also was measured in sublethally irradiated mice [19]. In both cases, the β-AR antagonist, propranolol, blocked the adrenergic drug effect, suggesting that β-AR stimulation mediated the increase in cAMP.

2.4. Functional and clinical significance of innervation of bone marrow

Cells of the immune system originate in the bone marrow. With the exception of T lymphocytes whose stem cells migrate to the thymus from the bone marrow to become mature, immuno-competent, immunocytes mature in the bone marrow. After differentiation in the bone marrow or thymus, cells of the immune system then use the blood vascular and lymphatic systems as conduits in order to patrol tissues. The process of blood cell production, hematopoiesis, occurs in multiple organs during embryonic and fetal development, including, yolk sac, liver, thymus, spleen, lymph nodes and red bone marrow. After birth, however, hematopoiesis is confined primarily to red bone marrow, with some lymphoid tissue contributing to production of lymphocytes. In children, nearly all the bone marrow is red marrow, while in adults red marrow is limited to skull, ribs, sternum, vertebrae, pelvis and proximal humerus or femur. With adulthood, yellow