

The Sympathetic Nerve An Integrative Interface between Two Supersystems: The Brain and the Immune System

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FROM ABSTRACT:

The brain and the immune system are the two major adaptive systems of the body.

During an immune response the brain and the immune system "talk to each other" and this process is essential for maintaining homeostasis.

Two major pathway systems are involved in this cross-talk: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS).

This overview focuses on the role of SNS in neuroimmune interactions, an area that has received much less attention than the role of HPA axis.

Evidence accumulated over the last 20 years suggests that norepinephrine (NE) fulfills the criteria for neurotransmitter/neuromodulator in lymphoid organs.

Thus, primary and secondary lymphoid organs receive extensive sympathetic/noradrenergic innervation. **[WOW!]**

Under stimulation, NE is released from the sympathetic nerve terminals in these organs, and the target immune cells express adrenoceptors.

Through stimulation of these receptors, locally released NE, or circulating catecholamines such as epinephrine, affect lymphocyte traffic, circulation, and proliferation, and modulate cytokine production and the functional activity of different lymphoid cells.

Although there exists substantial sympathetic innervation in the bone marrow, and particularly in the thymus and mucosal tissues, our knowledge about the effect of the sympathetic neural input on hematopoiesis, thymocyte development, and mucosal immunity is extremely modest. **[WOW!]**

In addition, recent evidence is discussed that NE and epinephrine, through stimulation of the 2-adrenoreceptor-cAMP-protein kinase A pathway, inhibit the production of type 1/proinflammatory cytokines, such as interleukin (IL-12), tumor necrosis factor-alpha, and interferon-gamma by antigen-presenting cells and T helper (Th) 1 cells, whereas they stimulate the production of type 2/anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta.

Through this mechanism, systemically, endogenous catecholamines may cause a selective suppression of Th1 responses and cellular immunity, and a Th2 shift toward dominance of humoral immunity.

On the other hand, in certain local responses, and under certain conditions, catecholamines may actually boost regional immune responses, through induction of IL-1, tumor necrosis factor-alpha, and primarily IL-8 production.

Thus, the activation of SNS during an immune response might be aimed to localize the inflammatory response, through induction of neutrophil accumulation and stimulation of more specific humoral immune responses, although systemically it may suppress Th1 responses, and, thus protect the organism from the detrimental effects of proinflammatory cytokines and other products of activated macrophages.

The above-mentioned immunomodulatory effects of catecholamines and the role of SNS are also discussed in the context of their clinical implication in certain infections, major injury and sepsis, autoimmunity, chronic pain and fatigue syndromes, and tumor growth.

[This knowledge may be used in] the treatment of experimental models of autoimmune diseases, fibromyalgia, and chronic fatigue syndrome.

THESE AUTHORS ALSO NOTE:

INTRODUCTION

A. Overview

The brain and the immune system are the two major adaptive systems of the body, or the "supersystems."

"Although the immune system has been often regarded as autonomous, the last two to three decades provided strong evidence that the central nervous system receives messages from the immune system and vice versa messages from the brain modulate immune functions." **[IMPORTANT]**

"The brain and the immune system are involved in functionally relevant cross-talk, whose main function is to maintain homeostasis."

Two pathways link the brain and the immune system:

- (1) The autonomic nervous system (ANS) via direct neural influences.
- (2) The neuroendocrine humoral outflow via the pituitary.

The end-products of the hypothalamic-pituitary-adrenal (HPA) axis are adrenal glucocorticoids.

These adrenal glucocorticoids are immunosuppressive and anti-inflammatory.

The sympathetic nervous system (SNS) innervates all lymphoid organs and the catecholamines (CAs), the end products of SNS, modulate several immune parameters.

The primary and secondary lymphoid organs are extensively hardwired by noradrenergic [sympathetic] nerve terminals.

The immune system is tuned by norepinephrine (NE) released locally from nonsynaptic varicosities or circulating epinephrine secreted by the adrenal medulla.

"The SNS provides another major integrative and regulatory pathway between the brain and the immune system."

"CAs, similar to glucocorticoids, have been often regarded as immunosuppressive," but their effects are different locally versus systemically, and their effects may change under various physiologic conditions and duration (acute versus chronic).

The main sympathetic neurotransmitter is nor-epinephrine (NE).

The main sympatho-adrenal hormone is epinephrine (adrenaline). It works at the sympathetic-immune interface. Epinephrine (adrenaline) comes from the adrenal medulla.

B. Historical Perspectives

Adrenaline (epinephrine) was the first hormone to be isolated from tissue, about 100 years ago.

Noradrenaline (norepinephrine) is a by-product in the synthesis of adrenaline.

Leukocytosis occurs after subcutaneous injection of the adreno-medullary hormone epinephrine in humans.

There is a decrease in the phagocytic activity of leukocytes during the periods of greatest psychological stress.

In the 1930s, Hans Selye described involution of the thymus in animals exposed to stressors.

In the 1930s, physiologists like Walter Cannon called Selye's stress response "fight or flight" reaction.

Cannon's "flight or fight" response is an adaptive response to stress caused by the secretion and actions of sympathetic CA.

Cannon emphasized the "generalized" sympathetic response, was the "wisdom of the body" that occurs during stress.

Norepinephrine (NE) is the major neurotransmitter released from sympathetic nerves.

In the 1950s, research showed a 400% increase in "stress-lymphocytes" (splenic natural killer cells) within 10 min after subcutaneous injection of epinephrine.

In the 1970s and 1980s, it became clear that classic hormones and newly described cytokines are involved in functionally relevant cross-talk between the brain and the immune system.

The immune response induces an increase of plasma corticosteroid levels, which alters the activity of hypothalamic noradrenergic neurons, and reduces the content of NE in the spleen.

In the 1970s, functional epinephrine (adrenaline) hormone receptors on lymphocytes were found. Adrenergic [sympathetically derived NE and epinephrine] agents attaching to the lymphocyte receptor would modulate lymphocyte proliferation.

"In the 1970s and 1980s, the first comprehensive morphological studies provided evidence that both primary and secondary lymphoid organs are innervated by sympathetic/noradrenergic nerve fibers."

The immune system function is altered by stressful stimuli or by specific neurological lesions.

Stress increases the susceptibility to autoimmune diseases.

ANATOMY AND PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

A. Organization of the Autonomic/Sympathetic Nervous System

"The ANS regulates the function of all innervated tissues and organs throughout the vertebrate body with the exception of skeletal muscle fibers."

The ANS "forms the major efferent component of the peripheral nervous system, containing integrative neuronal connections and even complete reflex arcs."

"The ANS is largely autonomous (independent) in that its activities are not under direct conscious control."

The ANS consists of three components:

- (1) The sympathetic (noradrenergic) with cell bodies in the spinal cord.
- (2) The parasympathetic (cholinergic) systems with cell bodies in the brainstem.
- (3) The enteric system, which lies within the wall of the gastrointestinal tract.

"The most extensive and physiologically most diverse component is the SNS, which sends axons to all parts of the body."

"The enteric system, which contains a similar number of neurons as the spinal cord, regulates intestinal functions; this system is modulated by projections from the sympathetic and the parasympathetic systems."

"The sympathetic division originates in nuclei within the brain stem and gives rise to preganglionic efferent fibers that leave the CNS through the thoracic and lumbar spinal nerves ('thoracolumbar system')."

Postganglionic sympathetic fibers run to the tissues innervated.

"Most postganglionic sympathetic fibers release NE; they are noradrenergic fibers; i.e., they act by releasing NE."

"The adrenal medulla contains chromaffin cells, embryologically and anatomically homologous to the sympathetic ganglia in that they are derived from the neural crest."

"The adrenal medulla, unlike the postganglionic sympathetic nerve terminals, releases mainly epinephrine, and to a lesser extent NE (the ratio is 4:1)."

"The chromaffin cells of the adrenal medulla are innervated by typical preganglionic sympathetic nerve terminals, whose neurotransmitter is acetylcholine."

"The principal end products of the SNS are NE and epinephrine, called CAs."

The HPA axis and SNS are activated by certain cytokines, such as IL-1, TNF-alpha, and IL-6.

Immune cells express mostly beta-adrenoreceptors

CAs are synthesized from tyrosine.

Tyrosine is converted to dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase (TH) and finally to dopamine (DA).

Dopamine is converted to NE in the vesicle by dopamine-hydroxylase (DBH).

In the adrenal medulla, NE is further converted to epinephrine.

B. Role of Sympathetic Nervous System and Hypothalamo-Pituitary-Adrenal Axis in Maintaining Basal and Stress-Related Homeostasis

"Living organisms survive by maintaining an immensely complex dynamic equilibrium of the internal milieu or homeostasis, a term coined by Walter Cannon."

"The systemic sympathetic and adrenomedullary system and the HPA axis are the peripheral limbs of the stress system, whose main function is to maintain both basal and stress-related homeostasis."

"At rest CAs maintain homeostasis as major regulators of fuel metabolism, heart rate, blood vessel tone, and thermogenesis."

"When homeostasis is disturbed or threatened by internal or external challenges, both the SNS and HPA axis become activated, resulting in increased peripheral levels of CAs and glucocorticoids that act in concert to keep the steady state of the internal milieu."

"In the 1930s, Hans Selye defined this reaction as general adaptation syndrome or stress response."

The immune response can activate the stress system.

Certain cytokines, particularly tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6 activate both the SNS and the HPA axis.

Centrally, the two principal components of the general adaptational response are:

(1) Corticotropin-releasing hormone (CRH).

The CRH system starts in the paraventricular nucleus (PVN) of the hypothalamus.

(2) Locus ceruleus-NE (LC-NE)/autonomic (sympathetic) nervous system.

The LC-NE/sympathetic systems are located in the brain stem. [pons]

"Functionally, the CRH and LC/NE/sympathetic systems seem to participate in a positive, reverberatory feedback loop so that activation of one system tends to activate the other system."

There are projections of CRH-secreting neurons from the lateral PVN of the hypothalamus to the sympathetic systems in the hindbrain, and conversely.....

There are projections of catecholaminergic fibers from the LC-NE system, via the ascending noradrenergic bundle, to the PVN in the hypothalamus.

“Activation of the LC-NE system leads to release of NE from an extraordinarily dense network of neurons throughout the brain, resulting, centrally, in enhanced arousal and vigilance, and peripherally, in increased sympathetic output, i.e., increase of the release of NE from the varicose sympathetic nerve terminals and epinephrine from the adrenal medulla.”

AUTONOMIC/SYMPATHETIC INNERVATION OF LYMPHOID ORGANS: NONSYNAPTIC COMMUNICATION

“Many organs of the body, such as the heart and the gastrointestinal tract, receive both sympathetic (noradrenergic) and parasympathetic (cholinergic) innervation.”

“It is usual, however, for one type of innervation to predominate over the other.”

“Lymphoid organs, similar to blood vessels, receive predominantly sympathetic/noradrenergic and sympathetic/neuropeptide Y (NPY) innervation.”

“Histofluorescence studies done since the late 1960s have firmly established the presence of noradrenergic [sympathetic] nerve fibers in the lymphoid organs of all species studied.”

A. Innervation of the Thymus

Postganglionic sympathetic nerve fibers innervate the thymus cortex, where immature thymocytes reside and develop.

The distribution of mast cells within the thymus parallels the distribution of noradrenergic [sympathetic] fibers.

B. Innervation of the Spleen

“The splenic nerve contains approximately 98% sympathetic nerve fibers, and most studies suggest that the innervation of the spleen is predominantly sympathetic.”

“Noradrenergic [sympathetic] postganglionic innervation originates mainly in the superior mesenteric/cealic ganglion, and the nerve fibers enter the spleen around the splenic artery, travel with the vasculature in plexuses, and continue along the trabeculae in trabecular plexuses.”

“Macrophages and B cells residing in the marginal zone and the marginal sinus, the site of the lymphocyte entry into the spleen, also receive NE innervation.”

C. Innervation of Lymph Nodes and Tonsils

In lymph nodes, noradrenergic [sympathetic] fibers enter at the hilus with the vasculature, and distribute either into a subcapsular nerve plexus or travel with blood vessels through the medullary cords."

Noradrenergic [sympathetic] fibers also supply paracortical and cortical zones which are T cell-rich regions.

"In the human palatine tonsils, noradrenergic [sympathetic] fibers distribute along the vasculature to form dense perivascular plexuses and single fibers traveling in parafollicular areas."

D. Innervation of the Bone Marrow

"Data on bone marrow innervation are rare compared with that on other lymphoid tissues."

"Generally nerves enter the marrow accompanying arteries, travel with the vascular plexuses deep in the marrow, arborize in surrounding parenchyma, and end among hemato- and lymphopoietic cells."

"Most of the nerves supply the arterial component of the marrow's circulation, but there is a substantial innervation of the sinusoidal parts and parenchymal elements where they may influence hematopoiesis and cell migration." **[WOW]**

Studies indicate that the development of the innervation of bone marrow occurs late in fetal life, just before the onset of hemopoietic activity.

E. Innervation of Mucosa-Associated Lymphoid Tissues

"Gut-associated lymphoid tissue (GALT) and bronchus-associated lymphoid tissue (BALT) receive both sympathetic and peptidergic innervation."

"The [sympathetic] nerve network within mucosal tissues is very extensive."

"It has been calculated that the number of nerve cell bodies present in the gastrointestinal tract is equivalent to that found in the spinal cord."

In GALT, including Peyer's patches that represent clusters of lymphoid nodules in the intestines, noradrenergic [sympathetic] fibers arborize profusely in the interdomal region of the lamina propria.

"Nasal mucosa receives tonic discharges from the sympathetic nerves but not from the parasympathetic nerves."

"Recent evidence suggests that sympathetic nerve stimulation may up-regulate immunoglobulin (Ig)A secretion in the submandibular glands."

Mucosal immune responses tend to bias toward T helper (Th) 2 responses.

Since CAs and the mast-cell product histamine mediate a Th2 shift, sympathetic innervation of mucosal membranes may contribute to the dominance of the Th2 responses observed in these tissues. [i.e. allergies, hay fever, etc.]

F. General Pattern of the Autonomic/Sympathetic Innervation of Lymphoid Organs

"Sympathetic/noradrenergic and sympathetic/NPY postganglionic nerve fibers innervate both the smooth muscle of the vasculature and the parenchyma of specific compartments of primary and secondary lymphoid organs."

Therefore, "it is possible that both NE and NPY, released from these sympathetic fibers, play a role in controlling blood flow to these organs and may influence lymphocyte traffic."

"Some noradrenergic [sympathetic] fibers are present in the parenchyma of lymphoid organ tissue that are not associated with blood vessels."

"Thus, NE released from perivascular or parenchymal nerve fibers may affect lymphoid cells and exert an immunomodulatory role."

"Noradrenergic [sympathetic] innervation of lymphoid tissue appears to be regional and specific; generally, zones of T cells, macrophages, and plasma cells are richly innervated, while nodular and follicular zones of developing or maturing B cells are poorly innervated."

"The main target cells of the noradrenergic [sympathetic] innervation appear to be immature and mature thymocytes, TEC, T lymphocytes, macrophages, mast cells, plasma cells, and enterochromaffin cells."

"Noradrenergic [sympathetic] nerve fibers, particularly in the thymus, are closely associated with mast cells in both perivascular and parenchymal zones, suggesting a possible humoral role for NE and histamine in the development of T cells in the thymus."

"Noradrenergic innervation is present early in the development, and their arrival generally precedes the development of the cellular compartment of the immune system suggesting a role for NE in maturation of the immune system."

G. Spatial Relationships with Peptidergic Innervation

"In addition to the autonomic/sympathetic innervation, all lymphoid organs also receive sensory peptidergic innervation that is confined mostly to the parenchyma." **[WOW!, VERY IMPORTANT]**

This conforms to the general scheme described for the peripheral innervation of other organs.

There is a close spatial relationship between peptidergic [sensory afferent] nerve fibers and mast cells, T cells and macrophages.

Apart from their direct immunomodulatory effects, NE released from postganglionic noradrenergic [sympathetic] nerve terminals or SP antedromically released from sensory nerves may exert an important indirect immunomodulatory effect on lymphoid organs.

H. Neuroimmune Connection in Nonorganized Lymphoid Compartments

“Neuromast cell connections and neuromacrophage connections, as well as neuro-T cell contacts, are not restricted to the preformed lymphoid organs and tissues, but are also regularly encountered in virtually all somatic and visceral tissues.”**[WOW!]**

“T cells, macrophages, and mast cells are regularly seen in any peripheral nerve and in both sympathetic and sensory ganglia.”

NONSYNAPTIC RELEASE OF NOREPINEPHRINE IN LYMPHOID ORGANS: PRESYNAPTIC MODULATION

A. Evidence for Neural Release of Norepinephrine (and Dopamine) in Lymphoid Organs

“Whereas endocrine signaling depends on blood-borne access of hormones to immune cells, neurotransmitter signaling depends on local availability of the specific neurotransmitter from neural release.”

“Neural release is achieved when the propagated electrical signal reaching the axon terminal triggers a depolarization that causes the release of the neurotransmitter, provided that Ca^{2+} is available.”

Sympathetic nerve terminals in the spleen are able to store, take up, and release NE in response to electrical field stimulation.

Most splenic NE is of neuronal [sympathetic] origin.

The noradrenergic axon terminals in the spleen are able to take up DA from the circulation, convert it in part to NE, and release it as both DA and NE in response to neural activity.

B. Norepinephrine Is Released and Affects Immune Cells Nonsynaptically

The synapse is the primary site of neuronal information processing.

"Thus, the chemical substances are released by depolarization from the axon terminals across the synaptic cleft (about 15-100 nm) and act on the postsynaptic membrane equipped with receptors."

"It is clear that, in contrast to some regions of the CNS and particularly to the neuromuscular junction, where classical synapses are observed, postganglionic neurons in the periphery innervating blood vessels, vas deferens, and smooth muscle terminate in a network of varicose areas (boutons en passant) that lack synaptic contact with their target cells."

"In the CNS the monoamines (NE, dopamine, serotonin) released from nonsynaptic varicosities into the extracellular space, diffusing far away from the release sites, make functional interactions with other neurons without making synaptic contacts."

Differences between the classical synaptic and the nonsynaptic interactional response is speed.

Such "slow" tuning effects would appear to be useful in controlling autonomic functions and the balance between the sympathetic and parasympathetic nervous system.

Although some occasional "synaptic-like" contacts have been described in the spleen, most of the ultrastructural studies reveal that noradrenergic [sympathetic] fibers in lymphoid organs are confined to the connective tissue septa and do not make "classical" synaptic contacts with target cells.

The reticular system in the spleen immobilizes the immunocytes in spaces where noradrenergic [sympathetic] nerves terminate, providing an opportunity for the immunocytes and [sympathetic] nerves to meet each other.

It appears that in lymphoid organs NE is also released primarily nonsynaptically.

Therefore, "adrenoreceptors on immune cells are targets of remote control, and, thus, NE, may play a modulatory role in signal transmission at the sympathetic-immune interface."

C. Release of Neuropeptide Y and Its Action on Immune Cells

"NPY is a 36-amino acid peptide that acts as a neurotransmitter and neuromodulator in the CNS and the peripheral nervous system."

"NPY-positive nerve fibers are present in all lymphoid organs."

Both NE and NPY control blood flow and may affect lymphocyte traffic, and lymphoid cells might express NPY receptors.

SYSTEMIC AND LOCAL EFFECTS OF CYTOKINES ON SYMPATHETIC NERVOUS SYSTEM ACTIVITY

A. Systemic Effects: Long Feedback Loop between the Immune System and the Brain

In the 1970s it was shown that the immune system and its products can signal the CNS.

"During an immune response, certain cytokines, such as IL-1, IL-6, and TNF-alpha can signal the brain, which through a complex CRH-dependent pathway, triggers activation of both the SNS and the HPA axis."

"The SNS, similar to the HPA axis is involved in a long feedback loop between lymphoid organs and CNS."

"The afferent limb of this loop seems to operate by blood-borne cytokines that, via circulation or through the afferents of the vagus nerve activate the central components of the stress system."

[Very important, because the afferent fibers of the vagus terminate in the medullary nucleus tractus solitarius.

The nucleus tractus solitarius is monosynaptic post-synaptic from the vestibular nucleus.

The vestibular nucleus is fired with chiropractic adjustments.]

"The efferent loop consists of the SNS, its projections to lymphoid organs and the release of NE from the sympathetic nerve terminals in these organs."

"These effects depend upon intact splenic sympathetic innervation."

"Distinct functional pathways exist within the ANS and SNS, i.e., ANS consists of a set of subdivisions, innervating different effectors, each of which is controlled by specific reflex mechanisms related to the function of the effector."

Inflammatory/immune response may actually activate different pathways of SNS, as compared with other stressors or stimuli.

Each immune response may have its own specific central neurochemical and peripheral neuroendocrine "signature".

[This implies that stimulation of the SNS may inhibit or stimulate the immune response, depending upon a host of local and systemic variables.]

B. Local Effects of Tumor Necrosis Factor-alpha and Interleukin-1

"The above-mentioned data suggest that systematically administered TNF-alpha and IL-1 trigger centrally the sympathetic output that results in an increase of NE turnover in several lymphoid and nonlymphoid organs in the periphery."

The local effect of these cytokines is often different than their CNS effects.

For example, TNF-alpha inhibits the stimulation-evoked release of NE from the hypothalamic median eminence (ME).

"The ME is a hypothalamic structure not protected by the blood-brain barrier; here neurosecretory projections, such as CRH from the PVN, terminate and control hormone secretion from the anterior pituitary."

EXPRESSION OF ADRENORECEPTORS ON LYMPHOID CELLS: SIGNAL TRANSDUCTION

A. Expression and Distribution of Adrenoreceptors on Lymphoid Cells

"NE and epinephrine mediate their effects on target cells via stimulation of two principal receptors: alpha and beta adrenergic receptors (ARs)."

"Virtually all lymphoid cells express beta-ARs, with the exception of T helper (h) 2 cells."

Different ARs on Th1 cells vs Th2 cells may provide a mechanistic basis for differential modulation of Th1 and Th2 functions by CAs.

B. Signal Pathways and Molecular Aspects of Catecholamines Actions

"NE and epinephrine transduce their biological information through stimulation of adrenergic receptors (ARs)."

ROLE OF SYMPATHETIC INNERVATION IN IMMUNE SYSTEM DEVELOPMENT AND HEMATOPOIESIS

A. Immune System Development

"Clear distinction should be made between the role of SNS in immune system development and the effect of CAs on immune responsiveness."

Postnatally, studies show progressive increased innervation of lymphoid organs by noradrenergic [sympathetic] fibers.

“With normal aging the thymus progressively degenerates and becomes infiltrated with adipose tissue.”

“Noradrenergic [sympathetic] innervation over the course of thymic involution does not decline, but rather persists, even though one of its presumed targets, thymocytes, are lost.”

With the shrinkage of this organ, noradrenergic [sympathetic] nerve fibers are confined to a smaller volume of tissue, giving the appearance of hyperinnervation.”

“Thus, unlike secondary lymphoid organs, the microenvironment of the aged thymus is capable of maintaining noradrenergic nerve fibers.”

“Progressive loss of noradrenergic [sympathetic] innervation and the loss of T-lymphocytes and macrophages in the spleen continues throughout the lifespan of the aged.”

“With the normal aging process, a decline in the T cell-mediated immune functions is well documented.”

This phenomenon may be linked to the decline in noradrenergic [sympathetic] innervation of secondary lymphoid organs.

“The early presence of noradrenergic innervation in specific compartments of the thymus and the spleen during critical periods of development points toward a role of NE in the maturation/development of the immune system and ‘shaping’ of the immune responsiveness.”

Neonatally sympathectomized rats express alterations in T and B cell proliferation and NK cell activity.

Neonatal sympathectomy also results in reduced immunoglobulin (Ig) M production throughout development.

B. Hematopoiesis

“The bone marrow compartment contains the principal hematopoietic tissue and is the site of proliferation and maturation of multipotent stem cells into mature blood cells of different lineages.”

Bone marrow contains a substantial amount of CAs.

“The SNS neural input of the bone marrow may be implicated in the regulation of hematopoiesis.” **[VERY IMPORTANT]**

Environmental conditions (cold exposure) and infectious agents elevate central sympathetic outflow release of NE to the bone marrow.

“These findings indicate that the noradrenergic innervation of the bone marrow is functionally dynamic and is responsive to generalized or immunological stress.”

“In vivo, myelopoiesis, and in particular the production of granulocytes and macrophages, are under a sympathetic inhibitory tone, whereas lymphocyte formation appears to need adrenergic [sympathetic] stimulation.”

C. Thymocyte Development

The thymic cortex (a site where immature thymocytes develop and differentiate to mature thymocytes or T lymphocytes) receives rich sympathetic innervation.

Thymocytes mature and differentiate into T cells in the thymus under influences that include sympathetic NE.

SYMPATHETIC CONTROL OF LYMPHOCYTE TRAFFIC AND CIRCULATION

“Lymphocyte migration, circulation, and traffic are under the influence of the CNS and the SNS plays a significant role in this process.” **[IMPORTANT]**

Infusion of both epinephrine and NE [sympathetic CAs] in humans induces a transient increase of total lymphocytes and a marked (between 400 - 600%) increase of NK cell numbers.

Acute psychological stress or physical exercise induce a transient increase in lymphocyte numbers, in particular the NK cell number.

[NOTE: ACUTE AND TRANSIENT]

“A short term, acute increase of sympathetic activity or a single infusion of adrenergic [sympathetic] agents might have the opposite effect on NK cell numbers, than does prolonged sympathetic activity”:

- (1) In short term increase of sympathetic activity, CAs increase NK cell numbers and activity by acutely mobilizing NK cells from depots.
- (2) In the long term(chronic) increase of sympathetic activity, CAs decrease the number of lymphocytes, and particularly of NK cells in the peripheral blood.

In humans, long term chronic increase of plasma epinephrine levels [from the sympathetics] reduce the percentage of NK cells in peripheral blood.

One possible mechanism by which "CAs modulate lymphocyte distribution is that the SNS, which directly innervates the vascular smooth muscle, regulates the regional blood flow, and thereby changes the delivery of lymphocytes to postcapillary venules of tissues, and the opportunity for lymphocytes to enter tissue."

"Perhaps the lymph flow is also under sympathetic control." **[WOW]**

"Electrical stimulation of regional sympathetic nerves results in increased lymphatic pumping, which in turn has marked effects on lymphocyte output."

Different lymphocyte subpopulations have different sensitivity to CAs effect on lymphocyte distribution, probably because of differences in ARs expression.

As an example, B lymphocytes have many ARs, while Th cells have substantially fewer ARs and are only modestly affected by CAs.

MODULATION OF LYMPHOCYTE PROLIFERATION AND K⁺ CHANNEL CONDUCTANCE

"Potassium channels play a critical role in the modulation of T cell calcium signaling and subsequent regulation of proliferation.

NE is able to inhibit the voltage-dependent K⁺ currents from thymocytes, and these K⁺ channels are involved in the processes of lymphocyte activation, proliferation and differentiation.

MODULATION OF CELLULAR AND HUMORAL IMMUNITY BY CATECHOLAMINES

A. T Helper 1 / T Helper 2 Paradigm: Role of Type 1 and Type 2 Cytokines

Immune responses are regulated by APCs (antigen-presenting cell), as follows:

(1) Innate immunity

Includes monocytes/macrophages, dendritic cells, and other phagocytic cells.

(2) Acquired (adaptive) immunity

Includes T helper (Th) lymphocyte, with subclasses Th1 and Th2.

Th1 cells secrete cytokines IFN-gamma, IL-2, and TNF-beta, which promote cellular immunity. (pro-inflammatory)

Cellular immunity provides protection against intracellular bacteria, protozoa, fungi, and several viruses.

Th2 cells secrete cytokines IL-4, IL-10, IL-13, and IL-9, which promote humoral immunity. (anti-inflammatory)

Humoral immunity provides protection against multicellular parasites, extracellular bacteria, some viruses, soluble toxins, and allergens.

Systemically, post-ganglionic sympathetic nerve release of NE, circulation derived release of epinephrine from the terminals in blood vessels and lymphoid organs, and epinephrine secreted from the adrenal medulla [these are sympathetic CAs], do the following:

- (1) Inhibit Th1 pro-inflammatory cellular immunity.
- (2) Stimulate Th2 anti-inflammatory humoral immunity.

“Naive CD4+ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells.”

Cytokines produced by cells of the innate immune system are the most important factor known to influence the differentiation of these Th0 cells toward Th1 or Th2.

IL-12, TNF-alpha, and IFN-gamma are synergistic, and are the major pro-inflammatory cytokines that drive chronic delayed type inflammatory responses through monocytes/macrophages **[INNATE]** and natural killer (NK) cell driven Th1 cellular immunity.

“Th1 and Th2 responses are mutually inhibitory.”

IL-12, TNF-alpha and IFN-gamma promote Th1 cellular immunity response and inhibit Th2 response.

IL-4 and IL-10 promote Th2 humoral immunity by stimulating the growth and activation of mast cells and eosinophils, and switching B cell immunoglobulin to IgE, and inhibiting Th1 responses.

IL-4 and IL-10 are the major anti-inflammatory cytokines.

B. Effects of Catecholamines on the Production of Type 1 and Type 2 Cytokines

“An increasing body of evidence suggests that CAs inhibit selectively Th1 functions, and favor Th2 responses, rather than causing generalized immunosuppression, as previously believed.”

“CAs appear to suppress Th1 activities and cellular immunity and to boost Th2 and humoral responses.”

CAs appear to up-regulate the production of type 2 cytokines, especially IL-10.

IL-10 is one of the most potent anti-inflammatory cytokines, and is potentiated by NE and epinephrine sympathetic CAs.

“Catecholamines also appear to exert tonic inhibition on the production of pro-inflammatory cytokines in vivo.”

Excessive exercise, immobilization stress, or surgery increase sympathetic CAs production. **[Immobilization Stress!]**

Systemically, CAs inhibit type 1 and stimulate type 2 cytokine secretion, respectively; however, in local responses the effect of CAs may be different.

“CAs may actually boost local cellular immune responses in a transitory fashion.”

“Whereas CAs suppress Th1 responses and pro-inflammatory cytokine secretion and boost Th2 responses systemically, they may differ in how they affect certain local responses.”

“CAs appear to have a dual effect on NK cells.”

“CAs (mostly epinephrine) mediate an acute, short lasting, and transient increase of NK cells numbers due to their mobilization from depots.”

On the other hand, chronically, CAs appear to mediate an inhibition of NK cell activity.

“Stress [chronic], which is accompanied by increased levels of peripheral CAs, inhibits several components of cellular immunity and particularly NK cell activity.”

“It appears that NK cells are the most ‘sensitive’ cells to the suppressive effect of stress, and not surprisingly, NK cell activity has become a bona fide index of stress-induced suppression of cellular immunity.”

Peripheral, circulating monocytes differentiate into macrophages.

TNF-alpha and IL-12 stimulate the activity of activated macrophages and NK cells, which are the major component of cellular immunity.

Excessive production of TNF-alpha and IL-12 play a key role in the inflammatory activity and the tissue damage observed in organ-specific autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

“Anatomically, a close spatial relationship between sympathetic and [sensory] peptidergic nerve fibers on one hand, and macrophages and mast cells on the other hand, is frequently observed. Neuromacrophage and neuromast cell connections are

not restricted to the preformed lymphoid organs and tissues, but are also regularly encountered in virtually all somatic and visceral tissues." **[WOW!]**

ROLE OF GROWTH FACTORS IN SYMPATHETIC NERVOUS SYSTEM DEVELOPMENT AND MODULATION OF THE IMMUNE RESPONSE

Nerve growth factor (NGF) is best characterized as a neurotrophic factor for the development and differentiation of sympathetic neurons in both developing and adult animals.

"NGF is synthesized by cells of immune system lineage, its level increases during inflammatory responses."

PHYSIOLOGIC CONTROL OF THE SYMPATHETIC-IMMUNE INTERFACE:

"The physiologic regulation of the sympathetic-immune interface appears to be a rather complex phenomenon, exerted at different levels."

"At the level of sympathetic nerve terminals, presynaptic receptors regulate the output of NE released in lymphoid organs and blood vessels."

CLINICAL IMPLICATIONS

A. Infections

"A major factor governing the outcome of infectious diseases is the selection of Th1 versus Th2 predominant adaptive responses during and after the initial invasion of the host." [Th1 response is the best response for most bacterial and viral infections].

"Thus, hyperactive SNS or stress-related increases of CA levels through induction of a Th2 shift may have a profound effect on the susceptibility of the organism to and/or may influence the course of an infection, the defense against which is primarily through Th1-driven cellular immunity mechanisms."

"*Helicobacter pylori* infection is the most common cause of chronic gastritis, which in some cases progresses to peptic ulcer disease."

"The role of stress in promoting peptic ulcers has been recognized for many years."

Thus, increased systemic CAs and glucocorticoid levels as stress-related mediators, may skew the local responses toward Th2 and thus allow the onset or progression of a *H. pylori* infection.

"The innervation (primarily sympathetic/noradrenergic) of lymphoid tissue may be particularly relevant to HIV infection, since lymphoid organs represent the primary site of HIV pathogenesis."

NE, the major sympathetic neurotransmitter released locally in lymphoid organs will directly accelerate HIV replication up to 11-fold in acutely infected human cells.

CAs may suppress cellular immunity and directly accelerate HIV replication.

"Psychological stress was found to be associated in a dose-dependent manner with an increased risk of acute infectious respiratory illness."

"Stress hormones (CAs and glucocorticoids) through their selective inhibition of cellular immunity [TH1 response] may play substantial roles in the increased risk of an individual to acute respiratory infections caused by common cold viruses."

B. Major Injury

"Major injury (serious traumatic injury and major burns) or major surgical procedures often lead to severe immunosuppression that contributes to infectious complications and, in some cases to sepsis, the most common cause of late death after trauma."

Following trauma, there are two patterns of response:

- (1) A sympatho-adrenal storm associated with stimulation of the HPA axis.
- (2) This phase is followed by a decrease in both sympathetic and HPA axis responses.

There is suppressed cellular immunity (Th1) and increased production of IL-10, causing a Th2 shift.

This systemic release of IL-10 triggered by SNS activation might be an important mechanism of immunosuppression after injury.

"Thus, high levels of systemic IL-10 documented in patients experiencing a 'sympathetic storm' due to acute accidental or iatrogenic brain trauma were associated with high incidence of infection."

"CA secretion triggered by major injury, via an induction of a Th2 shift, may contribute to the severe immunosuppression observed in these conditions."

This documents that in humans there is a sympatho-adrenal neuroendocrine pathway that cause systemic immunosuppressive response, affecting the incidence of infections and their complications, and "emphasize the importance of neurotransmitter/hormone-associated modulation of immunity." **[GOOD]**

C. Autoimmunity

Several autoimmune diseases are characterized by common alterations of Th1 versus Th2 balance, including rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus, autoimmune thyroid disease (ATD) and Crohn's disease, with the balance skewed toward Th1 and deficient in Th2 activity.

"The autonomic/sympathetic nervous system and HPA axis, both involved in stress responses, influence autoimmunity in a complex way."

The regulation of macrophage functions by the SNS is complex because the systemic effects of the SNS are different from certain local responses, and "particularly the effect of sympathetic innervation in the joints."

D. Fibromyalgia and Chronic Fatigue Syndrome

"Patients with unexplained chronic pain and/or fatigue have been described for centuries in the medical literature, although the terms used to describe these symptom complexes have changed frequently."

"The currently preferred terms for these syndromes are fibromyalgia and chronic fatigue syndrome (CFS)."

"Fibromyalgia is the second most common rheumatologic disorder, behind osteoarthritis."

These patients may have "a blunted sympathetic response to stressors."

"Several lines of evidence indicate that a dysregulation of the autonomic nervous system might play a role in fibromyalgia."

E. Tumor Growth

Systemic Th1 functions and cellular immunity are down-regulated during tumor growth.

Mice subjected to unilateral superior cervical ganglionectomy showed slowed growth of two breast cancers.

"In humans, the augmentation of the rate of tumor progression and cancer-related death has been associated with stress."

"CA-mediated suppression of cellular immunity may play a role in increased growth of certain tumors."

CONCLUSIONS

"The presence of sympathetic/noradrenergic nerve fibers in lymphoid organs, the release of NE from the sympathetic nerve terminals in these organs, and the expression of adrenoreceptors on lymphoid cells, which are able to respond functionally to stimulation, suggests that NE may meet the criteria for neurotransmitter/neuromodulator in lymphoid organs."

Similar to many organs in the periphery, the release of NE is subject to presynaptic modulation.

The axon terminals of the sympathetic nerve do not make synaptic contact with immune cells.

"NE released from sympathetic axon terminals diffuses far away from the release site; therefore NE transmits its signals nonsynaptically."

"Thus, the SNS may provide major integrative and regulatory pathway between the CNS and the immune system."

Sympathetic-immune interactions are complex.

"Endogenous CAs modulate the function of primary lymphoid organs, such as the bone marrow and the thymus."

"Evidence accumulated in the last decades indicates that, peripherally, both NE released from the nonsynaptic sympathetic nerve terminals in lymphoid organs and blood vessels and epinephrine released from the adrenal medulla are involved in fine tuning of immune responses."

Noradrenergic sympathetic nerve endings lie in close proximity to zona glomerulosa cells of the adrenal gland cortex, and modulate the secretion of steroids (through non-synaptic catecholamine norepinephrine (NE) secretion).

These noradrenergic sympathetic neurons take up DA and convert it into NE.

"The effects of CAs are quick, within minutes. This modulation might be ideally designed for quick adjustment of immune responsiveness."

"Another important role of CAs in the periphery might be a tonic inhibition of certain immune functions, and particularly, the production of type 1/pro-inflammatory cytokines."

"CAs appear to exert systemically differential, opposite effects on cellular and humoral immunity."

By inhibiting type 1 and potentiating type 2 cytokine production, CAs suppress cellular and boost humoral immunity.

The Th2-driving effects of CAs may have beneficial or detrimental consequences, depending on certain conditions.

The enhanced sympathetic CA driven Th2 response has the following consequences:

- (1) Has a protective role in infections.
- (2) Has a pathogenic role in allergy.
- (3) Reduces the pro-inflammatory tissue-damaging effects of macrophages and Th1 cells.

The excessive immune response caused by the activation of the stress system, and hence, through glucocorticoids and CAs, suppresses the Th1 response and causes a Th2 shift.

"The substantial Th2-driving force of endogenous CAs can be amplified to a great extent during certain conditions such as severe acute, subacute, or chronic stress."

"For example, in major injury, a condition followed by a sympathetic storm, these effects of CAs may contribute to serious infectious complications."

"Therefore, a defect in the sympathetic-immune interface, or an abnormal activity of the SNS in either direction, might contribute at a certain point to the pathophysiology of common human diseases, where a selection of Th1 (type 1) versus Th2 (type 2) responses plays a significant role."

"These include several infections, major injury and its complications, allergic (atopic) reactions, autoimmune/inflammatory diseases, and tumor growth."

"In summary, the immune system is not autonomous; the SNS and HPA axis may represent the major communication channels through which the CNS superimposes its control on the immune system."

"Better knowledge and understanding of the physiology and pathophysiology of the sympathetic-immune interface may help the development of new therapeutic strategies for common human diseases."

Abbreviations

CNS,	central nervous system;
Ab,	antibody;
APC,	antigen-presenting cell;
ANS,	autonomic nervous system;
AR(s),	adrenoreceptor(s);

ACTH,	adrenocorticotrophic hormone;
BALT,	bronchus-associated lymphoid tissue;
CAs,	catecholamines;
CFS,	chronic fatigue syndrome;
CRH,	corticotropin-releasing hormone;
DA,	dopamine;
DBH,	dopamine -hydroxylase;
DOPA,	dihydroxyphenylalanine;
GALT,	gut-associated lymphoid tissue;
HPA,	hypothalamo-pituitary-adrenal axis;
IFN,	interferon;
IL,	interleukin;
LC,	locus ceruleus;
ME,	median eminence;
MS,	multiple sclerosis;
NE,	norepinephrine;
NK,	natural killer cell;
NGF,	nerve growth factor;
NPY,	neuropeptide Y
PGE,	prostaglandin E;
PVN,	paraventricular nucleus;
RA,	rheumatoid arthritis;
SLE,	systemic lupus erythematosus;
SNS,	sympathetic nervous system;
SP,	substance P;
Th,	T helper lymphocyte;
TEC	thymic epithelial cells
TCR,	T cell receptor;
TH,	tyrosine hydroxylase;
TNF,	tumor necrosis factor;

COMMENTS FROM DAN MURPHY

This incredible article is 43 pages long and has 446 references. This article presents the best evidence I have seen linking the sympathetic nervous system to function of the immune system. In Gina Kolata's 1999 book FLU, she documents how the 1918 flu pandemic killed as many as 100 million people in about 6 months time. Although chiropractic was first licensed in Kansas in 1914, multigenerational chiropractic families and chiropractic historians will tell stories of chiropractic and osteopathic management of flu victims, and how their success directly enhanced subsequent licensure efforts. Some of the osteopathic evidence is presented in the May 2000 issue of the Journal of the American Osteopathic Association. Apparently, those who were adjusted (manipulated) suffered only 1/40th the death rate as compared to allopathically managed patients, and those under adjustment management tended not to get the flu. I present the following theory:

Subluxation reduces brain / cortical summation.

Reduced brain summation dis-inhibits the sympathetic nervous system.

Hence, the sympathetic nervous system is chronically overactive, releasing more catecholamines: norepinephrine from the post-ganglionic sympathetic efferents, and epinephrine from the adrenal medulla.

This increase in sympathetically derived catecholamines reduces the systemic type 1 (Th1) immune system response (causes a Th2 shift).

Since the Th1 response is primarily responsible for fighting infections, one cannot fight infections as well, increasing probability of death from infection, i.e. flu.

Chiropractic / osteopathic adjustments apparently reverse this sequence.

KEY POINTS FROM DAN MURPHY

- (1) The brain and the immune system talk to each other and this process is essential for maintaining homeostasis.
- (2) The most extensive and physiologically diverse component of the efferent nervous system is the sympathetic nervous system (SNS), which sends axons to all parts of the body.
- (3) The primary and secondary lymphoid immune organs receive extensive sympathetic/noradrenergic innervation, including:
Thymus, Spleen, Lymph Nodes, Tonsils, Bone Marrow, Mucosa-Associated Lymphoid Tissues (gut, bronchus, nasal).
- (4) The sympathetic nervous system (SNS) innervates all lymphoid organs. Catecholamines (CAs) from the SNS control immune function.
- (5) Norepinephrine (NE) is the major catecholamine neurotransmitter released from sympathetic nerves.
- (6) In general, CAs are primarily immunosuppressive, but their effects are different locally versus systemically, and their effects may change under various physiologic conditions and duration (acute versus chronic).
- (7) The sympathetic fibers also control blood flow to these immune organs which may influence lymphocyte traffic and therefore immune cell responses.

- (8) Immune cells, such as mast cell, macrophages, and lymphocytes have receptor sites that respond to sympathetic released catecholamines, altering their function.
- (9) The SNS plays a significant role in lymphocyte migration, circulation, and traffic.
- (10) Lymph flow is also under sympathetic neurological control.
- (11) The sympathetic nervous system is also critical in the neonatal development of the immune system organs, and in shaping immune responsiveness.
- (12) Systemically, sympathetic catecholamines cause a suppression of Th1 responses and cellular immunity, and a Th2 shift toward dominance of humoral immunity.
- (13) Th1 cellular immunity provides protection against intracellular bacteria, protozoa, fungi, and several viruses. **[FLU]**
- (14) Th2 humoral immunity provides protection against toxins, and allergens. [Gives one typical atopic / allergy symptoms]
- (15) Traumatic injury often leads to immunosuppression and enhanced infections because trauma recovery is marked by long-term decrease in both sympathetic and HPA axis responses.
- (16) Sympathetically driven imbalance in the Th1 versus Th2 response is also associated with autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, autoimmune thyroid disease, Crohn's disease, fibromyalgia, chronic fatigue syndrome, and tumor growth.
- (17) The SNS provides the major integrative and regulatory role between the CNS and the immune system.

[Removing the subluxation will:

reduce sympathetic activity, reduce catecholamine release, enhance the Th1 response which will improve infection fighting; and inhibit the Th2 response, which will reduce allergy / atopic disease signs and symptoms].