BACKGROUND INFORMATION
FROM
IMMUNOLOGY, A Short Course
2003, Wiley-Liss
Richard Coico, Geoffrey Sunshine, Eli Benjamini

THE IMMUNE SYSTEM HAS TWO PRIMARY FUNCTIONAL DIVISIONS

INNATE IMMUNITY	**ADAPTIVE or ACQUIRED IMMUNITY**
"Innate immunity is present from birth." "It operates against almost any substance that threatens the body." "Its principle role is to provide an early, nonspecific, first line of defense against pathogens." "Most microorganisms encountered daily in the life of a healthy individual are detected and destroyed within minutes to hours by innate defense mechanisms." p.11 "Innate immunity is an attribute of every living organism." p. 18 **PRIMARY PLAYERS**: Macrophages (monocytes), Neutrophils, Natural–Killer cells Dendritic Cells	"Under the circumstances in which an infectious organism is not eliminated by nonspecific innate immune mechanisms, adaptive immune responses ensue." p. 18 **PRIMARY PLAYERS**: T cells (mature in the thymus) B cells (mature in the bone marrow) T cells and B cells control the production of immunoglobulins (antibody production) The INNATE immune response produces proteins called cytokines that activate the elite fighters of the ADAPTIVE immune response. If a pathogen is ignored by the INNATE immune response, it will also be ignored by the ADAPTIVE immune response. THEREFORE The INNATE immune response is the primary controlling factor in immunity

It takes nerve to tell T and B cells what to do

Journal of Leukocyte Biology
Volume 79, June 2006

Nicholas W. Kin and Virginia M. Sanders
This article has 113 references

These authors are from the Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University

FROM ABSTRACT:

The existence of an association between the brain and immunity has been documented.

The nervous and immune systems communicate with one another to maintain immune homeostasis.

Activated immune cells secrete cytokines that influence central nervous system activity, which in turn, activates output through the peripheral nervous system to regulate the level of immune cell activity and the subsequent magnitude of an immune response.

This review focuses on the regulatory role for the peripheral sympathetic nervous system in modulating the level of cytokines and antibodies produced during an immune response.

We will also discuss how dysregulation of the line of communication between the nervous and immune systems might contribute to disease development and progression.

THESE AUTHORS ALSO NOTE:

"A basic function of the immune system is to clear foreign antigens such as viruses and bacteria to maintain host homeostasis and survival."

The innate immune system uses monocytes, macrophages, dendritic cells (DC), natural killer cells, basophils, eosinophils, and granulocytes.

The innate immune system "functions in an antigen-nonspecific manner, does not develop memory, and is considered the first line of host defense following antigen exposure."

The adaptive immune system uses T and B lymphocytes, "functions in an antigen-specific manner, and develops memory to allow for a faster and more robust response upon subsequent antigen re-exposure."

A reduced immune response leaves the host immuno-compromised.

An overtly robust or misdirected immune response results in the development of allergy/asthma or autoimmune diseases such as rheumatoid arthritis.

Therefore, survival of the host is dependent on precise regulation of the immune response.

The brain regulates both the innate and adaptive immune responses via two different pathways:

1) The hypothalamic-pituitary-adrenal axis (HPA) and the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the expression and release of adrenocorticotropic hormone (ACTH) from the pituitary, inducing the secretion of corticosteroids from the adrenal cortex.

2) Activation of the sympathetic nervous system (SNS) and the release of the catecholamine norepinephrine, neuropeptides Y, and endogenous opioids such as the enkephalins/ endorphins, as well as adenosine and adenosine 5 –triphosphate.

Other neuropeptides including calcitonin, gene-related peptide, somatostatin, vasoactive intestinal peptide (VIP), and Substance P are released by other nerve fibers within lymphoid tissue, and affect immune cell activity.

The brain maintains homeostasis by regulating both somatic functions and autonomic functions, such as heart rate, vascular tone, gastrointestinal motility, and respiratory rate. Through the peripheral nervous system, the brain transmits signals to the organ systems throughout the body.

The sympathetic nervous system (SNS) uses the neurotransmitter norepinephrine (NE).

The parasympathetic nervous system uses the neurotransmitter acetylcholine.

Almost every cell in the body has receptors for norepinephrine and acetylcholine.

“The SNS is often referred to as the system that precipitates a ‘fight-or-flight’ response, which is an evolutionarily conserved mechanism in vertebrates that functions solely to maintain homeostasis.”

Increased SNS activity increases the likelihood of host survival from assaults or stressful experiences.

“A bacterial or viral insult to the host activates the SNS to induce a change in immune cell activity to increase the likelihood of host survival.”

Activated [innate] immune cells secrete cytokines that influence the central nervous system (CNS). Pathways back to the peripheral SNS regulate the level of immune cell activity and the magnitude of an immune response.
[Very Important]

The immuno-neurological-immuno sequence includes:

1) The innate immune system is activated.
2) The activated immune system induces activation of the SNS.
3) The sympathetic nerve fibers penetrate the parenchyma of primary and secondary lymphoid organs.
4) Norepinephrine is released from the sympathetic nerves after antigenic challenge.
5) Immune cells express a specific receptor that binds norepinephrine.
6) Stimulation of these receptors by norepinephrine regulates the level of immune cell functional activity.
7) This sequence plays a role in disease prevention, but also plays a role in disease development.

In 1919, a study showed that stress and/or fatigue reduces the immune systems ability to eliminate pathogens, indicating a relationship between neurological/hormonal activity and susceptibility to infection and disease.

The mechanisms by which the brain could communicate with immunological function include:

1) Activation of the HPA axis causes the secretion of CRH and ACTH, culminating in the secretion of corticosteroids from the adrenal cortex.

2) Activation of the SNS involves the release of the neurotransmitter norepinephrine from nerve terminals in the close vicinity of cells within most organ systems.

The rate of neurons to the hypothalamus control the activation of the SNS.

1) Activated innate immune system cells produce proteins called cytokines (such as (interleukin (IL-1)).

2) These cytokines activate receptors on the peripheral vagus nerve which transmit signals to the brain.

3) The vagus nerve transmits signals from the brain back to the periphery via the neurotransmitter acetylcholine, which is anti-inflammatory, and regulates immune cell activity.

"The parenchyma of primary and secondary lymphoid organs are found to be innervated with sympathetic nerve fibers, including the bone marrow, thymus, splenic white pulp, and lymph nodes." **[Very Important]**

The SNS terminates in the parenchyma of secondary lymphoid tissues in the areas adjacent to CD4 T cells and in the vicinity of macrophages.

Lymphocytes express receptors that bind norepinephrine and corticosteroids, which regulate the level of immune cell activity.

"A change induced in any part of this bidirectional circuit by disease or a change in behavior might have profound consequences for the maintenance of immune homeostasis." **[Very Important]**

Cytokines released from activated innate immune cells also communicate directly with sympathetic nerves, causing a local release of norepinephrine within tissues without involving central brain functions [Important].

Severe infections which pose an immediate threat to survival, require participation of the CNS to orchestrate SNS mediated immune regulation.

Less severe infections require the participation of local neuroregulatory mechanisms only.

"The molecules released by the nervous system do not activate or impart any new activity to an immune cell but instead, regulate the magnitude of the activity induced by the immune system itself."

"Sympathetic nerves release norepinephrine within the microenvironment of CD4 T cells and B cells located in lymphoid organs."

"Sympathetic nerve fibers penetrate the parenchyma of primary and secondary lymphoid organs."

The sympathetic nerve terminal also releases neuropeptide Y, opioid peptides, and adenosine, which affect immune cell activity.

Elevated levels of norepinephrine from the SNS produces less IgG in response to infection.

CONCLUSION

"The magnitude of an adaptive immune response is regulated by the release of norepinephrine within the vicinity of activated CD4 T cells and B cells located within lymphoid tissue."

The released norepinephrine stimulates the adrenoreceptors expressed on the immune cells to regulate the level of gene activity.

"An insult to the host by an antigen will activate immune cells to produce cytokines that communicate with the brain or peripheral nervous system, which in turn, activate the SNS to release norepinephrine to regulate the activity of the immune cells responding to the insult."

"If the sympathetic neurotransmitter norepinephrine plays a role in modulating immune function, an age-related decline in lymphoid tissue innervation may contribute to the age-associated increase in the incidence of autoimmunity, cancer, and susceptibility to infection."

KEY POINTS FROM DAN MURPHY

1) The function of the immune system is to clear foreign antigens such as viruses and bacteria to maintain host homeostasis and survival.

2) There is a documented association between the brain and immune system function.

3) The nervous and immune systems communicate with one another to maintain immune homeostasis.

4) Dysregulation [chiropractic subluxation complex] of the line of communication between the nervous and immune systems contributes to disease development and progression. **[Very Important]**

5) The immune system is largely divided into two divisions:

A)) The Innate Immune System:
The innate immune system uses monocytes, macrophages, dendritic cells (DC), natural killer cells, basophils, eosinophils, and granulocytes. It functions in an antigen-nonspecific manner, does not develop memory, and is considered the first line of host defense following antigen exposure.

B)) The Adaptive Immune System:
The adaptive immune system uses T and B lymphocytes which produced antibodies, "functions in an antigen-specific manner, and develops memory to allow for a faster and more robust response upon subsequent antigen re-exposure."

6) A reduced immune response leaves the host immuno-compromised.

7) An overtly robust or misdirected immune response results in the development of allergy/asthma or autoimmune diseases such as rheumatoid arthritis.

8) Survival of the host depends on precise regulation of the immune response.

9) The brain regulates both the innate and adaptive immune responses via two different pathways:

A)) The hypothalamic-pituitary-adrenal axis (HPA) and the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the expression and release of adrenocorticotropic hormone (ACTH) from the pituitary, inducing the secretion of corticosteroids from the adrenal cortex.

B)) Activation of the sympathetic nervous system (SNS) and the release of the catecholamine norepinephrine, neuropeptides Y, and endogenous opioids such as the enkephalins/ endorphins, as well as adenosine and adenosine 5 –triphosphate.

10) The brain maintains homeostasis by regulating both somatic functions and autonomic functions, and by transmitting signals to the organ systems throughout the body.

11) The sympathetic nervous system (SNS) uses the neurotransmitter norepinephrine (NE).

12) The parasympathetic nervous system uses the neurotransmitter acetylcholine.

13) Activated innate immune cells secrete cytokines that influence central nervous system; pathways back to the peripheral SNS regulate the level of immune cell activity and the magnitude of an immune response. **[Very Important]**

14) The immuno-neurological-immuno sequence includes:

A)) The innate immune system is activated by an antigen.
B)) Innate immune cells produce cytokines.
C)) These innate system cytokines activate the sympathetic nervous system.
D)) The sympathetic nerve fibers penetrate the parenchyma of primary and secondary lymphoid organs.
E)) Norepinephrine is released from the sympathetic nerves.
F)) Immune cells express a specific receptor that binds norepinephrine.
G)) Stimulation of these receptors by norepinephrine regulates the level of immune cell functional activity.
H)) This sequence plays a role in disease prevention and in disease development.

15) Stress and/or fatigue increases the SNS release of norepinephrine which reduces the immune systems ability to eliminate pathogens.

16) The brain communicates with immunological function by:

A)) Activation of the HPA axis causes the secretion of CRH and ACTH, culminating in the secretion of corticosteroids from the adrenal cortex.

B)) Activation of the SNS involves the release of the neurotransmitter norepinephrine from nerve terminals in the close vicinity of cells within most organ systems.

17) Neurons to the hypothalamus control the activation of the SNS.

18) Innate immune system cytokines also activate the vagus nerve to the brain, transmitting back to the periphery the neurotransmitter acetylcholine, which is anti-inflammatory, and regulates immune cell activity.

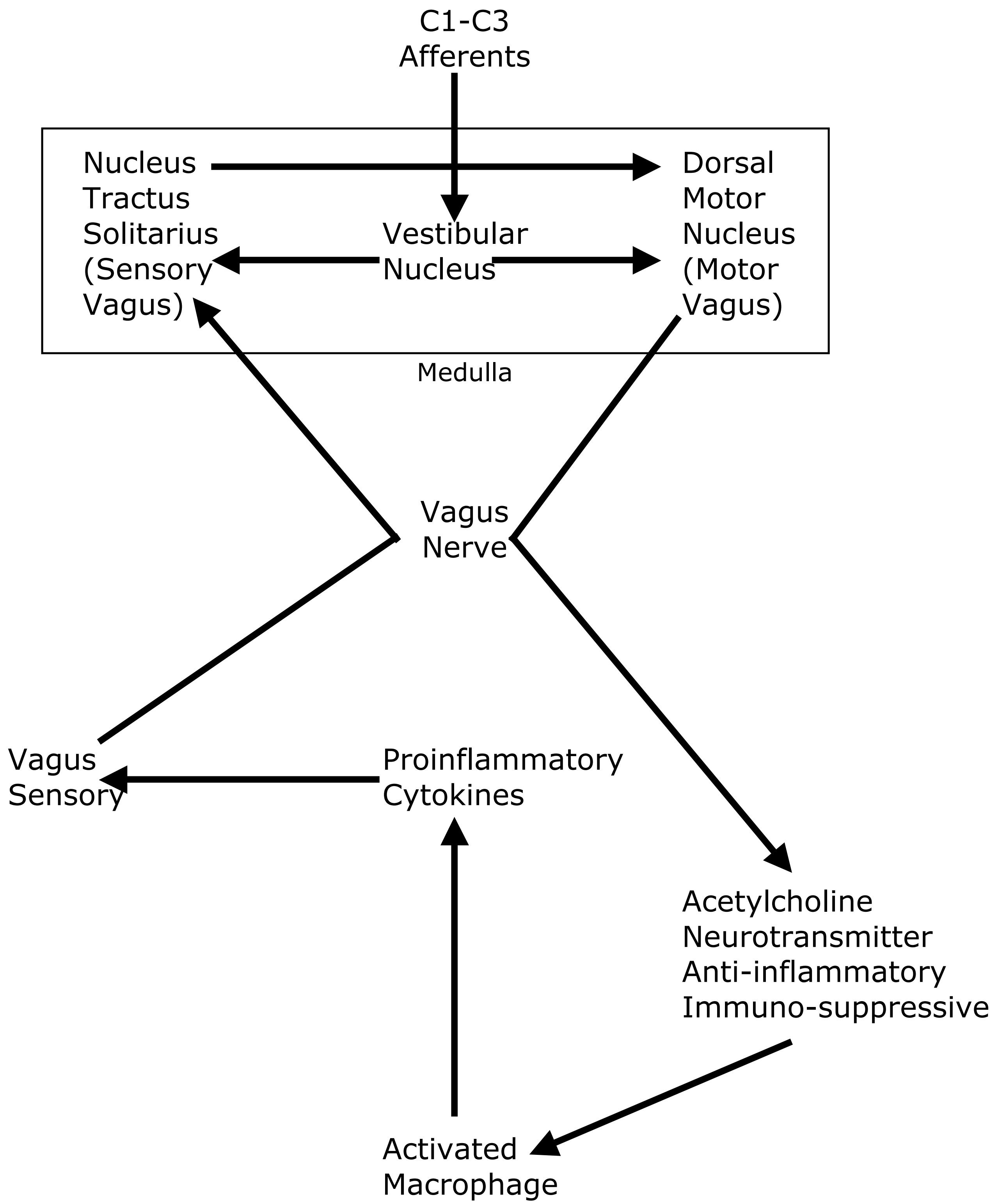
19) The parenchyma of primary and secondary lymphoid organs are innervated with sympathetic nerve fibers, including the bone marrow, thymus, splenic white pulp, and lymph nodes. **[Very Important]**

20) Cytokines released from activated innate immune cells also communicate directly with sympathetic nerves, causing a local release of norepinephrine within tissues without involving central brain functions. **[Important]**

21) Increased levels of norepinephrine from the SNS produces less IgG in response to infection. **[This is immunosuppressive]**

22) The magnitude of the normal immune response is determined by the level of SNS norepinephrine release and the level of SNS innervation of lymphoid organs.

Parasympathetic Neuroimmunology



Innate Immune Cell

Neuroimmunology