

**Autonomic innervation and regulation of the immune system  
(1987–2007)**

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FROM ABSTRACT:

Since 1987, only a few neuroanatomical studies have been conducted to identify the origin of innervation for the immune system.

These studies demonstrated that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons.

Neither the thymus nor spleen receive any sensory neural innervation; however, there is evidence that lymph nodes and bone marrow may be innervated by sensory neurons located in dorsal root ganglia.

There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ.

Thus, the primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system (SNS) and its main neurotransmitter, norepinephrine (NE).

Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system.

Innate immune cells express both alpha and beta-adrenergic receptor subtypes, while T and B lymphocytes express adrenergic receptors of the beta2 subtype exclusively.

Via these adrenergic receptors, NE is able to regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.

THESE AUTHORS ALSO NOTE:

There is a sympathetic input to the thymus from the upper cervical sympathetic chain ganglia.

“All primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons.”

“There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ.”

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#### INNERVATION OF THE THYMUS

“The sympathetic input to the thymus was identified as originating from sympathetic chain ganglia that extended from the superior cervical chain ganglia caudal to the T3 sympathetic ganglion.”

“The thymus gland unequivocally receives a substantial sympathetic innervation from cervical and upper thoracic sympathetic chain ganglia, and there is no neuroanatomical evidence for a parasympathetic or sensory input to the thymus gland.”

The sympathetic preganglionic neurons to the thymus arise from the intermediolateral cell column of the T1–T7 spinal cord, and from sympathetic premotor neurons located in the medulla oblongata, pons and hypothalamus.

“The sympathetic nervous system provides the only pathway for direct neural modulation of thymic immune function.”

#### INNERVATION OF THE SPLEEN

The prevertebral sympathetic ganglia associated with the celiac-mesenteric plexus provides a major sympathetic input to the spleen.

The splenic nerve is the final common pathway for neural input to the spleen.

There is no vagal or parasympathetic input to the spleen.

The sympathetic preganglionic neurons that innervate the spleen arise from the T1–T12 region of the thoracic spinal cord.

The spleen also receives its sympathetic innervation from many of the same nuclei in the brainstem, pons and hypothalamus that are activated by immune stimuli.

“Neuroanatomical and neurochemical evidence demonstrates that neural innervation of the spleen is entirely sympathetic in origin, and indicates further that there is no evidence for parasympathetic or sensory input to the spleen.”

#### INNERVATION OF LYMPH NODES

The presence and distribution of sympathetic catecholamine fibers in various lymph nodes has been well documented.

“Individual lymph nodes receive their sympathetic input from postganglionic neurons that are associated with supplying the sympathetic input to the particular region of the body where the immune organ is located.”

Lymph nodes are also innervated by afferent sensory neurons which helps to regulate the inflammatory immune response.

There is no neuroanatomical evidence for a parasympathetic input to lymph nodes.

#### INNERVATION OF BONE MARROW

“Same as for other immune organs, the sympathetic innervation of bone marrow is well established, and functional experiments have demonstrated that the sympathetic nervous system can regulate bone marrow function.”

All blood vessels receive a sympathetic nerve supply.

#### OTHER SITES OF NEUROIMMUNE REGULATION

“All regions of the body receive sympathetic input and all body surfaces that are potential sites of either microbial invasion or antigen challenge (skin, oral and gut mucosa, peritoneum, lungs) receive an extensive afferent neural innervation that is closely associated with cellular elements of the immune system.”

#### SUMMARY

“There is a predominate sympathetic (catecholamines) input to all components of the immune system, whereas afferent innervation of the immune system may be limited to lymph nodes and bone marrow.”

There is no neuroanatomical evidence for efferent vagal or parasympathetic innervation of the immune system.

## SYMPATHETIC REGULATION OF INNATE IMMUNITY

“Innate immunity represents the first line of defense against microbes.”

The innate immune system reacts quickly to microbes.

The primary cells of the innate immune system include macrophages and neutrophils (phagocytes), natural killer cells, and granulocytes, which include neutrophils, eosinophils, basophils, and mast cells.

These inflammatory cells produce a cascade of inflammatory cytokines, which help in bacterial killing.

These inflammatory cytokines also set the stage for subsequent engagement and actions by the adaptive immune system.

“Macrophages, and their specialized associates, dendritic cells, serve as antigen-presenting cells and provide a critical first step in the full engagement of the antigen-specific adaptive immune system.”

“Modulation of the early actions of the innate immune system have significant impact on the magnitude and quality of the specific adaptive immune response.”

Macrophages have the central role in the regulation of the innate immune system through their innervation and their production of inflammatory cytokines.

## SYMPATHETIC NERVES, NOREPINEPHRINE, AND THE REGULATION OF MACROPHAGES

“Norepinephrine (NE) is the primary transmitter released from sympathetic nerve terminals.”

NE is generally regarded as inhibitory for cytokine and innate immune responses.

“Activation of the sympathetic nervous system by either stress or central inflammatory stimuli inhibits splenic macrophage function.”

Inflammatory prostaglandins [PGE<sub>2</sub>] “activated the sympathetic nervous system,” and this proved to be immunosuppressive. **[Important]**

The sympathetic nervous system is activated by stressful stimuli.

“The immunosuppressive effect of stress on macrophage cytokine production was mediated entirely via the sympathetic nervous system.”

“In summary, activation of the sympathetic nervous system (noradrenergic nerves and adrenal medulla) exerts a potent anti-inflammatory action upon the innate immune system.”

“Numerous studies have shown a fundamental role for the sensory vagus nerve in transmitting neuroimmune afferent information from the abdominal cavity and viscera.”

The adrenal medulla and sympathetic nerves inhibit macrophage TNF-alpha production and systemic inflammation.

## SYMPATHETIC REGULATION OF ADAPTIVE IMMUNITY

NE may exert a suppressive effect on Th1/Th2 cell development and/or progression, but the effects on T and B cell function are variable.

## CONCLUSIONS

“It will also be important to understand how one’s level of immunocompetence might affect different components of the nervous system that exert an effect on immune cell activity, e.g., the level of innervation and/or locally secreted NE within lymphoid tissue and/or the level of expression for the beta-2 adrenoreceptor on immune cells.”

## KEY POINTS FROM DAN MURPHY

- 1) Since 1987, neuroanatomical studies of innervation for the immune system “demonstrate that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons.” **[Key]**
- 2) “There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ.”
- 3) “The primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system (SNS) and its main neurotransmitter, norepinephrine (NE).”
- 4) “Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system.” **[Key Point]**
- 5) Activation of the SNS “either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system.”
- 6) Norepinephrine (NE) from the sympathetic nervous system “is able to regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.”

- 7) There is a sympathetic input to the thymus from the upper cervical sympathetic chain ganglia.
- 8) "The primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system and its main neurotransmitter, norepinephrine."
- 9) "The sympathetic input to the thymus was identified as originating from sympathetic chain ganglia that extended from the superior cervical chain ganglia caudal to the T3 sympathetic ganglion."
- 10) "The thymus gland unequivocally receives a substantial sympathetic innervation from cervical and upper thoracic sympathetic chain ganglia, and there is no neuroanatomical evidence for a parasympathetic or sensory input to the thymus gland."
- 11) The sympathetic preganglionic neurons to the thymus arise from the intermediolateral cell column of the T1–T7 spinal cord, and from sympathetic premotor neurons located in the medulla oblongata, pons and hypothalamus.
- 12) "The sympathetic nervous system provides the only pathway for direct neural modulation of thymic immune function."
- 13) The sympathetic preganglionic neurons that innervate the spleen arise from the T1–T12 region of the thoracic spinal cord.
- 14) The spleen also receives its sympathetic innervation from many of the same nuclei in the brainstem, pons and hypothalamus that are activated by immune stimuli.
- 15) "Neuroanatomical and neurochemical evidence demonstrates that neural innervation of the spleen is entirely sympathetic in origin, and indicates further that there is no evidence for parasympathetic or sensory input to the spleen."
- 16) The sympathetic catecholamine fibers in lymph nodes is well documented.
- 17) "Individual lymph nodes receive their sympathetic input from postganglionic neurons that are associated with supplying the sympathetic input to the particular region of the body where the immune organ is located."
- 18) "The sympathetic innervation of bone marrow is well established, and the sympathetic nervous system can regulate bone marrow function."
- 19) All blood vessels receive a sympathetic nerve supply.
- 20) "All regions of the body receive sympathetic input and all body surfaces that are potential sites of either microbial invasion or antigen challenge (skin, oral and

gut mucosa, peritoneum, lungs) receive an extensive afferent neural innervation that is closely associated with cellular elements of the immune system.”

- 21) “There is a predominate sympathetic (catecholamines) input to all components of the immune system.”
- 22) “Innate immunity represents the first line of defense against microbes.”
- 23) The innate immune system reacts quickly to microbes.
- 24) The primary cells of the innate immune system include macrophages and neutrophils (phagocytes), natural killer cells, and granulocytes, which include neutrophils, eosinophils, basophils, and mast cells.
- 25) Inflammatory cytokines produced by the innate immune response set the stage for subsequent engagement and actions by the adaptive immune system.
- 26) “Modulation of the early actions of the innate immune system have significant impact on the magnitude and quality of the specific adaptive immune response.”
- 27) Macrophages have the central role in the regulation of the innate immune system through their innervation and their production of inflammatory cytokines.
- 28) Inflammatory prostaglandins [PGE2] “activated the sympathetic nervous system,” and this proved to be immunosuppressive. **[Important]**
- 29) The sympathetic nervous system is activated by stressful stimuli.
- 30) “The immunosuppressive effect of stress on macrophage cytokine production was mediated entirely via the sympathetic nervous system.”

#### COMMENTS FROM DAN MURPHY

This study is quite important for chiropractors for these reasons:

- 1) It documents that immune organs are innervated by the sympathetic nervous system and that immunity is largely controlled by the sympathetic nervous system.
- 2) We have reviewed studies that prove there are spinal cord reflexes between the mechanoreceptors of the spine and the sympathetic nervous system.
- 3) We have reviewed studies that document spinal adjusting influencing the sympathetic nervous system.
- 4) Chiropractic history has numerous reports of the benefits, including life-saving benefits, of chiropractic adjustments on patients with the flu, pneumonia, polio, otitis media, etc.