

Elaborate interactions between the immune and nervous systems
Review
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THIS AUTHOR NOTES:

“The immune system and the nervous system maintain extensive communication, including 'hardwiring' of sympathetic and parasympathetic nerves to lymphoid organs.” **[VERY IMPORTANT]**

These neurotransmitters modulate immune activity:

Acetylcholine

Norepinephrine

Vasoactive intestinal peptide

Substance P

Histamine.

Neuroendocrine hormones such as corticotropin-releasing factor [CRF], leptin and alpha-melanocyte stimulating hormone [MSH] regulate cytokine balance, which also modulate immune activity.

The immune system modulates brain activity, including body temperature, sleep and feeding behavior.

Immune system molecules modulate development of neuronal connections.
[IMPORTANT]

“The nervous system and the immune system mount a variety of essential, coordinated responses to danger.”

“Multiple anatomic and physiological connections exist between the CNS and the immune system, including 'hardwiring' of the autonomic nervous system via the vagal nerve and sympathetic nerve fibers to the main sites of the immune system in the liver, spleen, bone marrow, thymus, lymph nodes, skin and gastrointestinal system.” **[VERY IMPORTANT]**

Much is known about the interactions of the brain and immune system. **[Good]**

There are three types of interactions between the CNS and the immune system:

- 1) The CNS acts reciprocally with the immune system.
- 2) The CNS drives immunity. **[QUITE IMPORTANT]**
- 3) The immune system regulates the CNS.

“The brain modulates the immune system in response to environmental stress through the hypothalamic pituitary axis, orchestrating immune responses with CRF.”

Since the nervous system (brain) modulates the immune system response, the immune system must be able to communicate to the brain that it has encountered dangerous viruses, bacteria, or parasites. When the immune system encounters these dangers, it creates and releases soluble mediators that cross through holes (windows) in the blood brain barrier, at a location known as the circumventricular organs of the hypothalamus of the brain. **[This is good. Recall, other authors we have reviewed claim that dietary excitotoxins [[glutamate, aspartame]] also cross the blood brain barrier at the circumventricular organs of the hypothalamus, creating damage, resulting in inability to control appetite and inability to regulate fluid balance, both of which enhance weight gain].**

After detecting danger, immune system cells produce proteins called cytokines. The first immune system cytokine discovered interleukin 1 (IL-1), which breaches the blood-brain barrier at the circumventricular organs of the hypothalamus, alerting the hypothalamus that there is danger in the periphery.

Other immune system proteins (cytokines) that cross the blood brain barrier at the hypothalamus include tumor necrosis factor (TNF) and IL-6. These cytokines activate the febrile response through neurons in the preoptic area of the anterior hypothalamus. Fever, in turn, affects behavior, sleep, feeding and appetite.

There is a theory that suggests that these pyrogenic (pro-inflammatory) cytokines IL-1, IL-6 and TNF cause increased production of prostaglandin E2 in cells at the blood-brain interface. Prostaglandin E2 is synthesized through a cyclooxygenase-2-dependent pathway [of the omega-6 fatty acid arachidonic acid]. Prostaglandin E2 then crosses the blood-brain barrier and stimulates the temperature increase induced through the activity of preoptic hypothalamic neurons.

There is “evidence that afferent fibers in the vagal nerve may transport pyrogenic cytokines to the thermoregulatory centers in the hypothalamus.”

“Extensive parasympathetic and sympathetic inputs modulate immune activity through the AchR and adrenergic receptors.”

Neuroendocrine mediators such as leptin, alpha-MSH and CRF also modulate immune activity. CRF is released from the hypothalamic pituitary axis. Leptin is released from the hypothalamus in response to increases in body fat.

Increased CRF inhibits TH1 immunity, whereas increased leptin enhances TH1 immunity.

Immunologists divide the physiological functions of cytokines into convenient subsets, such as the T helper type 1 (TH1)/TH2 dichotomy.

TH1 cytokines, including interferon-gamma (IFN-gamma) and TNF, are associated with activation of many autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and juvenile diabetes.

TH2 cytokines, characterized by IL-4, IL-5 and IL-13, are associated with suppression of such diseases and the promotion of allergic responses, including asthma and food sensitivities.

The balance between TH1 and TH2 cytokines is important in the control of fever.

HARDWIRING OF THE CNS AND LYMPHOID ORGANS:

“The brain and the immune system communicate through neurotransmitters, cytokines and endocrine hormones.”

“The brain and the immune system are actually hardwired through the autonomic nervous system: the parasympathetic nervous pathways innervate lymphoid tissues via the neurotransmitter acetylcholine, and the sympathetic nervous pathways innervate lymphoid tissue via the neurotransmitter norepinephrine.” **[VERY IMPORTANT]**

“There is direct evidence of these rich neural connections with lymphoid tissue, including thymus and bone marrow as well as lymph nodes, spleen and gut-associated lymphoid tissue.”

Lymphocytes function is largely controlled by membrane receptors that accept the neurotransmitters acetylcholine from the parasympathetic nervous system and norepinephrine from the sympathetic nervous system. **[IMPORTANT]**

Lymphocytes also have receptors for the neurotransmitters vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide, calcitonin gene-related peptide (CGRP), substance P, histamine and serotonin.

Lymphocytes also have receptors for neuroendocrine mediators, including CRF, alpha-melanocyte-stimulating hormone (alpha-MSH) and leptin.

Immune responses directed at neurological targets (autoimmunity) include multiple sclerosis, Rasmussen encephalitis, epilepsy, myasthenia gravis, narcolepsy and anorexia.

“The parasympathetic neurotransmitter acetylcholine potently modulates several classical immune reactions via the vagus nerve.”

“In an animal model of arthritis, paw swelling after injection of the inflammatory chemical carageenan could be suppressed by vagal nerve stimulation.”

Vagal nerve stimulation releases the neurotransmitter acetylcholine which can suppress the systemic septic shock.

“The sympathetic nervous system can alter the TH1/TH2 balance through stimulation of the beta-adrenergic receptor.”

“Sympathetic nerve stimulation enhances production of TH2 cytokines while inhibiting TH1 cytokine production.”

In rheumatoid arthritis there is evidence of loss of sympathetic innervation in the joints, and this may contribute to the pathological effects of TNF on the synovium.

“The sympathetic nervous system is involved in the transmission of prions from peripheral sites such as the gastrointestinal system to the brain.”
[This is mad cow disease].

Leptin, a molecule produced in response to levels of fat stores and that thereby regulates body weight, is a potent stimulator of TH1 immunity. Sympathetic inhibition blocks the leptin-induced changes in T and B cell function, suggesting that leptin mediates its effects on immune cell function through the sympathetic nervous system and stimulation of the α -adrenergic receptor.

Two other hypothalamic peptides that reduce appetite are CRF and α -MSH. Both of these hormones are important in immunity. CRF is released from the hypothalamus in response to environmental stress and activates the pituitary to produce adrenocorticotropic hormone (ACTH), which in turn activates the adrenals to produce corticosteroids. Increased CRF inhibits TH1 immunity.

“Given the existence of hardwiring of the nervous system to the immune system through neurotransmitters and neuroendocrine mediators, it has been possible to demonstrate modulation of the immune response with behavioral experiments in which animals are stressed.”

“Placement of animals in restraints induces stress in the animals, activating CRF and adrenocorticoids.”

"Bulimia and anorexia and perhaps some psychiatric disorders may have at least part of their pathogenesis in autoimmunity."

"The immune response has an adaptive component and an innate component."

The adaptive immune response is central to myasthenia gravis multiple sclerosis, Rasmussen encephalitis and stiff-man syndrome.

The innate immune response is responsible for neurodegenerative diseases Alzheimer and Parkinson, including the presence of the innate response molecules MHC and TNF.

Some of the quintessential molecules of adaptive immunity are expressed in both the nervous system and the immune system.

Many molecules function in both the immune system and the nervous system. The MHC, which is the most essential molecule in the regulation of genetic control of the immune response, is important in neural development.

We now know the immune synapse is dynamic and elaborately organized with a plethora of molecules at the interface between T cells, antigen and the MHC molecules.

"The immune system and the nervous system are linked functionally and anatomically."

The nervous system and the immune systems influence each other and interact with each other.

KEY POINTS FROM DAN MURPHY

- 1) The immune system and the nervous system have extensive communication, including 'hardwiring' of sympathetic and parasympathetic nerves to lymphoid organs, including the liver, spleen, bone marrow, thymus, lymph nodes, skin and gastrointestinal system.
- 2) Immune system molecules modulate development of neuronal connections.
- 3) The nervous system and the immune system work together in a coordinated response to protect the body from infection.
- 4) The CNS drives immunity.
- 5) The brain also modulates the immune system through the hypothalamic pituitary axis with CRF.

- 6A) When the immune system encounters dangers, it creates and releases cytokines that cross through holes in the blood brain barrier at a location known as the circumventricular organs of the hypothalamus of the brain.
- 6B) This triggers the hypothalamus to initiate appropriate responses in the immune system, through the hypothalamic-pituitary-adrenal-axis and responses in the autonomic nervous systems.
- 6C) [Dietary excitotoxins like glutamate and aspartame also cross the blood brain barrier at the circumventricular organs of the hypothalamus, creating damage, resulting in inability to control appetite and inability to regulate fluid balance, both of which enhance weight gain].
- 7) Immune system cell pro-inflammatory cytokines increased production of prostaglandin E2 in cells at the blood-brain interface. Prostaglandin E2 then crosses the blood-brain barrier and stimulates the temperature increase induced through the activity of preoptic hypothalamic neurons. . Prostaglandin E2 is synthesized through a cyclooxygenase-2-dependent pathway [of the omega-6 fatty acid arachidonic acid].
- 8) Afferent vagus nerve fibers transport pro-inflammatory cytokines to the thermoregulatory centers in the hypothalamus.
- 9) The brain and the immune system communicate through neurotransmitters, cytokines and endocrine hormones.
- 10) Lymphocytes function is largely controlled by membrane receptors that accept the neurotransmitters acetylcholine from the parasympathetic nervous system and norepinephrine from the sympathetic nervous system.
- 11) The parasympathetic neurotransmitter acetylcholine modulates several immune reactions via the vagus nerve.
- 12) The sympathetic nervous system can alter the TH1/TH2 cytokine balance.
- 13) Sympathetic nerve stimulation enhances production of TH2 cytokines while inhibiting TH1 cytokine production. [This is important because Th1 enhances the fight against infection, while Th2 enhances the development of atopic disorders.
- 14) Some of the quintessential molecules of adaptive immunity are expressed in both the nervous system and the immune system. Many molecules function in both the immune system and the nervous system. The MHC, which is the most essential molecule in the regulation of genetic control of the immune response, is important in neural development.
- 15) The immune system and the nervous system are linked functionally and anatomically.