Autonomic-mediated immunomodulation and potential clinical relevance

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There is an active bidirectional communication between the immune system and the nervous system. Cytokines released from immune cells provide signals to neurons of the hypothalamus and brainstem, which trigger endocrine and autonomic responses that, in turn, inhibit the immune response. Both the sympathetic and the vagal efferent pathways participate in this anti-inflammatory and immunosuppressant action. Neurally mediated immunosuppression is adaptive and limits the extent of local or systemic inflammation. However, when activated in the setting of acute stroke or other forms of CNS injury, this response may lead to profound downregulation of both innate and adaptive immunity and predispose to infections, which are a major cause of morbidity and mortality in these patients. There are several excellent reviews focused on the various mechanisms involved in brain-immune interactions[1-7] and more recent publications focus on the consequences of immunodeficiency triggered by CNS injury.[8,9] Some relevant concepts on mechanisms and effect of autonomic activation on immune responses and the potential clinical implications are reviewed here.

IMMUNE SIGNALING TO THE CENTRAL AUTONOMIC NETWORK

Macrophages and monocytes respond to various stimuli by releasing proinflammatory cytokines, including tumor necrosis factor-alpha (TNFα), interleukin (IL)-1 beta (IL-1β), IL-6, IL-12, and interferon gamma (IFNγ); these mediators are both effectors of inflammation and signal molecules to the nervous system. There are at least 2 pathways by which the brain senses inflammation: a neural pathway and a humoral pathway (figure 1).[2]

Neural pathway. The sensory afferents in the vagus nerve have a major role in transmitting neuroimmune afferent information from the abdominal cavity and viscera. Immunogenic stimuli activate peripheral vagal afferents by action of IL-1β or other proinflammatory cytokines released from dendritic cells, macrophages, and other immune cells associated with these afferents.[10] Vagal afferents from the nodose ganglion terminate in the nucleus of the solitary tract (NTS), a component of the dorsal vagal complex of the medulla, which also includes the area postrema and the dorsal motor nucleus of the vagus. Ascending projections from the NTS, either directly, via a relay the parabrachial nucleus, or via catecholaminergic cells located in the ventrolateral medulla, reach the hypothalamus, amygdala, and insular cortex (figure 1). Somatic sensory fibers innervating the skin, mucosal surface, joints, and muscles also respond to immunologic stimuli and transmit this information, via the dorsal horn, to the NTS, parabrachial nucleus, and ventrolateral medulla.

A major target of the ascending pathways conveying signals from the immune system is the paraventricular nucleus (PVN) of the hypothalamus.[11] The PVN has an essential role in the coordination of endocrine and autonomic outputs that mediate stress responses, control metabolism, and regulate immune functions.[12] The PVN contains neurons that synthesize and release corticotropin-releasing hormone (CRH), which activates the hypothalamo-pituitary-adrenal axis, and autonomic neurons that activate the sympathetic outflow to peripheral tissues and to the adrenal glands. This PVN sympathoexcitatory pathway activates preganglionic neurons either directly or via a relay in the rostral ventrolateral medulla[13] (figure 2). The PVN not only initiates endocrine and autonomic responses but may also modulate the responses of neurons of the NTS and ventrolateral me-

GLOSSARY

α7nAChR = α7 subunit-containing nicotinic receptor; **ACh** = acetylcholine; **ACTH** = adrenocorticotrophic hormone; **β_2AR** = beta 2 adrenergic receptor; **cAMP** = cyclic adenosine monophosphate; **CRH** = corticotropin-releasing hormone; **Epi** = epinephrine; **IFNγ** = interferon gamma; **IL-1β** = interleukin IL-1 beta; **IL-1R** = interleukin-1 receptor; **MS** = multiple sclerosis; **NE** = norepinephrine; **NFκB** = nuclear factor kappa B; **NPY** = neuropeptide Y; **NTS** = nucleus of the solitary tract; **PgE_2** = prostaglandin E_2; **PVN** = paraventricular nucleus; **RVLM** = rostral ventrolateral medulla; **TNFα** = tumor necrosis factor-alpha.

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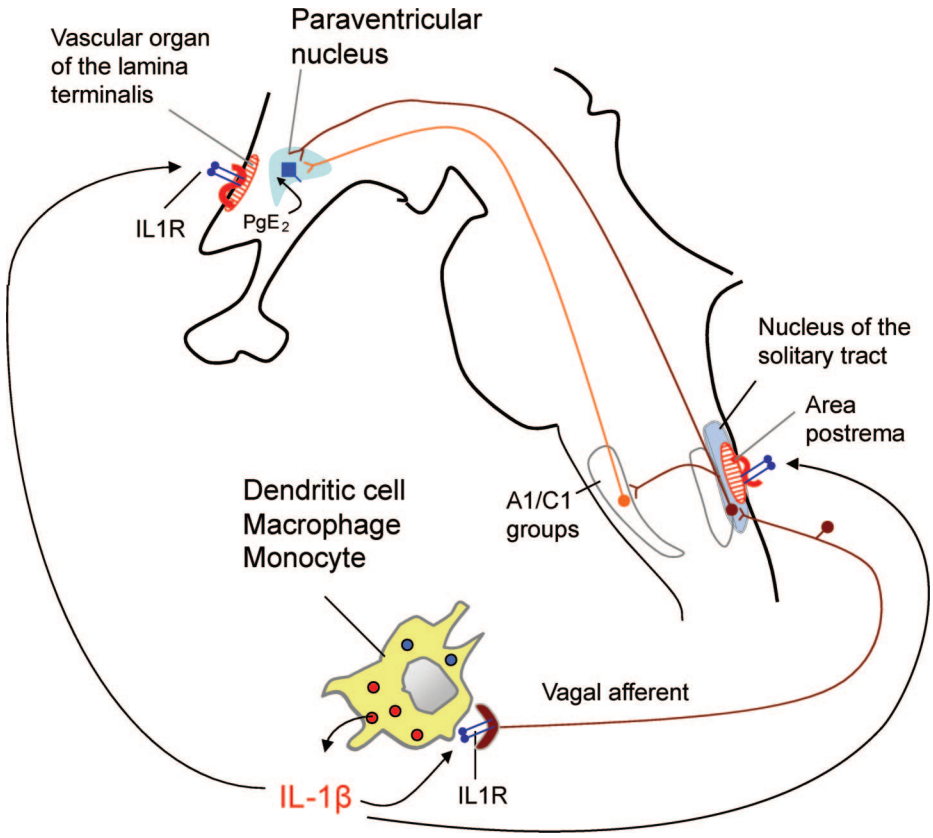
Figure 1 Immune signaling to the CNS



Proinflammatory cytokines, including interleukin (IL)-1β, released during inflammation provide signals to the CNS via neural and humoral pathways. IL-1β or other proinflammatory cytokines activate vagal afferents that terminate in the nucleus of the solitary tract. Ascending projections from this nucleus or from catecholaminergic A1/C1 cells located in the ventrolateral medulla reach the hypothalamus, including the paraventricular nucleus. Circulating proinflammatory cytokines may also enter the brain either through carrier-mediated mechanisms or via receptors in the capillary endothelium of circumventricular organs, including the area postrema and the vascular organ of the lamina terminalis, triggering release of soluble mediators such as prostaglandin E_2 (PgE_2), which provides signals to neurons in the preoptic area (not shown) and paraventricular nucleus. IL-1R = interleukin-1 receptor.

dulla to immune challenges.[13] The dorsal motor nucleus of the vagus receives inputs from both the NTS and the hypothalamus, and provides preganglionic vagal efferent fibers to the visceral organs (figure 2).

Humoral pathway. Circulating proinflammatory cytokines, such as IL-1β and TNFα, may enter the brain either through carrier-mediated mechanisms or via the capillary endothelium of circumventricular organs, including the area postrema and the vascular organ of the lamina terminalis.[2] Cytokines can bind to receptors at the endothelial surface of brain capillaries and trigger synthesis and release of soluble mediators such as prostaglandin E2 and nitric oxide, which diffuse into the brain parenchyma.[14] Both at the levels of the medulla and hypothalamus, there is the potential for integration of signals from cytokine receptors in the capillary endothelium of circumventricular organs with those from vagal and other sensory afferents. There is also evidence that several cytokines may be released from ependymal cells of the choroid plexus or brain endothelial cells in response to systemic immune challenges.[2] Cytokines released from immune cells at the site of CNS inflammation may reach receptors in all areas involved in neural-immune interactions, including peripheral tissues, vagal ganglia, spinal cord, brainstem, and hypothalamus directly, via diffusion in the extracellular space and CSF, or via the bloodstream.

AUTONOMIC CONTROL OF IMMUNE RESPONSES

Sympathetic nervous system. The sympathetic nervous system provides the primary pathway for the neural regulation of immune function. Sympathetic influences are primarily mediated by release of norepinephrine (NE) from postganglionic fibers innervating the peripheral lymphoid organs and via circulating epinephrine secreted by the adrenal medulla. There is a robust sympathetic innervation of primary and secondary lymphoid organs.[15] Sympathetic nerve fibers innervate both the vascular

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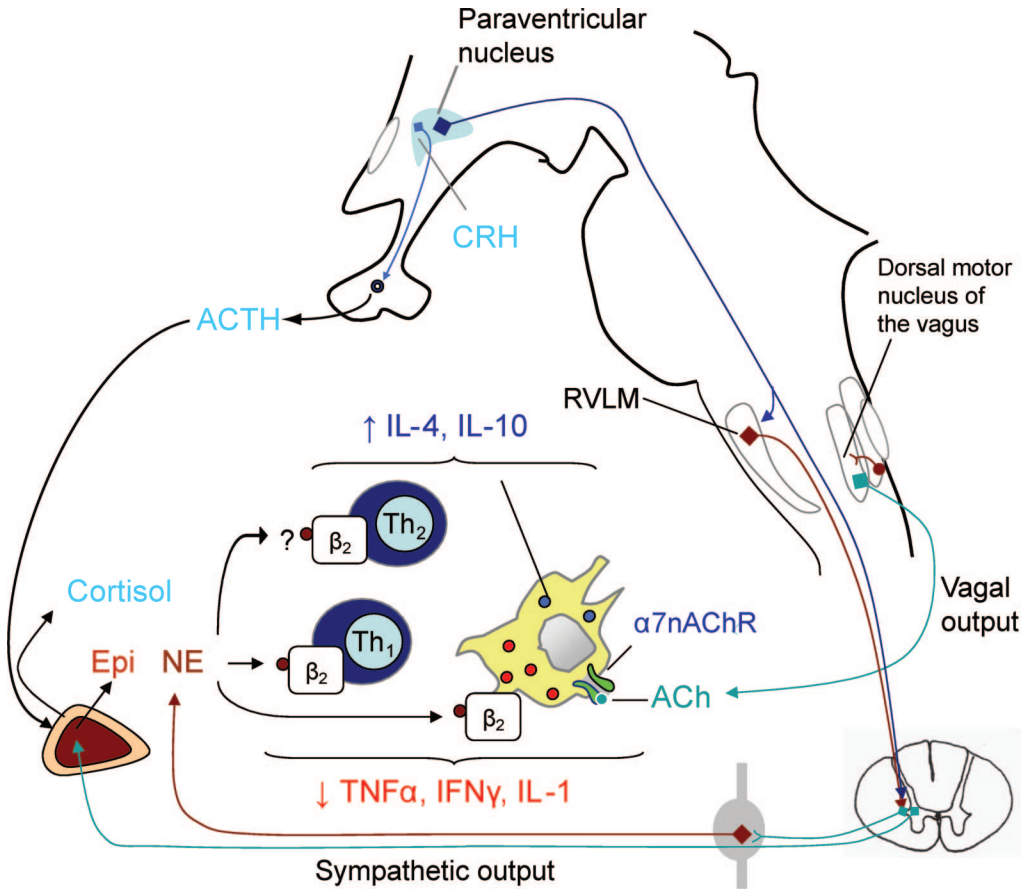
Figure 2 Autonomic control of immune responses



The sympathetic system is the primary pathway for the neural regulation of immune function. Projections from the paraventricular nucleus to preganglionic neurons in the spinal cord, either directly or via a relay in the rostral ventrolateral medulla (RVLM), trigger sympathetic influences mediated by norepinephrine (NE) released from postganglionic fibers and epinephrine (Epi) secreted by the adrenal medulla. Catecholamines, acting via beta 2 adrenergic receptors (β_2AR), inhibit innate immune responses, including production and release of tumor necrosis factor-alpha (TNFα), interleukin (IL)-1β, IL-6, and IL-12, and upregulate production of the antiinflammatory IL-10 by dendritic cells and macrophages. β_2 adrenoreceptors also inhibit production of interferon (IFN)γ and IL-2 by Th1 cells and, in some cases, may enhance production of IL-4 by Th2 cells. Vagal efferents originating in the dorsal motor nucleus of the vagus release acetylcholine (ACh), which inhibits production of TNFα, IL-1β, and IL-18 by macrophages via α7 subunit-containing nicotinic receptors (nAChRs). Brain-triggered immune immunodepression also involves activation of the hypothalamo-pituitary adrenocortical system. ACTH = adrenocorticotrophic hormone; CRH = corticotropin-releasing hormone.

smooth muscle and the parenchyma of the thymus, spleen, lymph nodes, bone marrow, and mucosa-associated lymphoid tissue. Noradrenergic innervation of lymphoid tissue appears to be regional and specific; in general, 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.[1,15]

Catecholamines exert pleiotropic effects on the activity of immune cells, acting primarily via β_2 adrenergic receptors (adrenoceptors)[1,4,5] (table). These receptors are expressed on macrophages, naive $CD4^+$ cells, Th1 helper cells, and B cells. Although murine Th2 cells appear not to express detectable levels of β_2 adrenoceptors, the presence of these receptors in human Th2 cells is still controversial.[4,5] β_2 adrenergic receptor expression in immune cells is variable and regulated by a number of different factors, including cell activation, cytokines, neurotransmitters, and hormones.[1] Stimulation of the β_2 receptors results in activation of adenylyl cyclase, thus increasing intracellular cyclic adenosine monophosphate (cAMP) and subsequent activation of protein kinase A. Studies in vitro and in vivo indicate that the sympathetic nervous system exerts a potent anti-inflammatory action by inhibiting the activity of macrophages and other cells associated with the innate immune system.[1,3] β_2 adrenergic receptor-triggered elevated cAMP levels inhibit nuclear factor kappa B (NFκB) activation in dendritic cells, macrophages, and monocytes. This leads to suppression of the production and release of proinflammatory (type

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Table Effects of β_2 receptor stimulation on cytokine production

Cytokine	Source	Function	Effect of β_2 adrenoreceptor
Interleukin (IL)-1	Antigen presenting cells (APC), endothelium	Major proinflammatory cytokine, endogenous pyrogen	Decrease
IL-2	T-helper (Th) Th0 and Th1, natural killer (NK) cells	Proliferative factor for lymphocytes	Decrease
IL-12	APC	Major inducer of Th1 response	Decrease
Tumor necrosis factor-α	APC	Major proinflammatory cytokine	Decrease
Interferon-γ	Th1, NK	Potent activator of macrophages and inhibitor of Th2 functions	Decrease
IL-3	T cells	Hemopoietic factor	Decrease
IL-10	APC, Th2	Potent inhibitor of Th1 and macrophage functions	Increase
IL-6	APC, Th2	B-cell differentiation factor; induction of active phase proteins	Increase (APCs)
IL-8	Monocytes, endothelium	Chemotactic for neutrophils	Increase
Transforming growth factor-β	Many cells	Potent inhibition of Th1 and macrophages	Increase (fibroblasts)

1) cytokines such as TNFα, IL-1β, IL-6, and IL-12 while upregulating production of antiinflammatory (type 2) cytokines such as IL-10 by these cells. IL-10 potently inhibits the proinflammatory and antigen-presenting capacity of dendritic cells, macrophages, and monocytes and thus the differentiation of naive $CD4^+$ T cells to Th1 cells.[1,3,4,5]

Many in vitro studies indicate that NE may exert modulatory effects on T and B cell functions. Catecholamines or β_2 adrenoreceptor stimulation inhibits $CD4^+$ cell proliferation by decreasing IL-2 receptor expression and production of type 1 cytokines, such as IFNγ and IL-2, by Th1 cells. In Th2 that express β_2 adrenoreceptors, catecholamines increase production type 2 cytokines, such as IL-4. Activation of β_2 adrenoreceptors also increasesTh2 dependent production of IgG1 antibodies by B cells.[1,4,5] However, the precise role of the sympathetic system in modulation of $CD4^+$ or $CD8^+$ T-cell activity in vivo remains uncertain and may be influenced by the baseline level of sympathetic activity, timing of receptor stimulation, and stage of cell differentiation.[1,4,5] For example, in the setting of local injury, the sympathetic system may boost regional immune responses.[16] Postganglionic sympathetic fibers innervating the lymphoid organs also release neuropeptide Y (NPY), which is a negative regulator of T cell antigen-presenting cell function. This peptide, acting via Y1 type receptors, inhibits secretion of IFNγ and enhances IL-4 secretion in vitro, suggesting that it shifts the Th1/Th2 balance toward Th2 phenotype.[17-19]

The vagus nerve and the cholinergic antiinflammatory pathway. Experimental studies point to the existence of a "cholinergic anti-inflammatory pathway," which may have a role in fast and localized modulation of immune function.[6,7] Vagal efferent stimulation inhibits endotoxin-induced production of proinflammatory cytokines such as TNFα, IL-1β, and IL-18 by macrophages. These effects are primarily mediated by α7 subunit-containing nicotinic acetylcholine receptors expressed in these cells.[7,20] Although there is lack of neuroanatomic evidence for vagal efferent input to immune organs,[1] vagal efferents are distributed throughout the reticuloendothelial system and other peripheral organs and may provide for coregulation of cytokine-producing cells such as Kupffer cells in the liver, which are the major source of cytokines in endotoxemia.[7] The inflammatory-sensing and the inflammation-suppressing functions of the vagus may thus provide for an "inflammation reflex" that produces a rapid anti-inflammatory response.[6,7]

CEREBRAL LATERALIZATION OF IMMUNE MODULATION Lesion studies suggest that there is a lateralization of the cerebral influence on immune functions. In experimental animals, left cerebral lesions produce immune deficits by reducing lymphocyte proliferation, NK cell activity, T-cell mitogen-induced responses, and antibody production, whereas right cerebral lesions increase T-cell activity and mitogen-induced responses.[21] A study in patients undergoing surgical resection for treatment of epilepsy supports the possibility of cerebral lateralization of the control of immune functions in humans.[22] Consistent with experimental findings, left hemisphere resections were associated with a decrease in total T cells and helper T cells whereas right hemisphere resections elicited an increase in the numbers

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of these cells. However, further studies are necessary to confirm the existence and characterize the mechanisms of lateralized hemispheric influence on immune responses.

CLINICAL CORRELATIONS **Acute CNS injury-induced immunodeficiency.** Experimental and clinical evidence indicate that acute CNS injury, including stroke, traumatic spinal cord injury, and brain injury, is associated with rapid and temporary immunodeficiency, which may be an important contributory factor for the increased susceptibility to infections in these conditions.[8,9] This acute CNS injury-induced immunodeficiency syndrome is characterized by lymphopenia and functional deactivation of Th-1 and NK cells, monocytes, and macrophages, and is associated with increased production of the antiinflammatory IL-10 cytokine. Experimental studies indicate that a catecholamine-induced suppression of Th1 function and IFNγ secretion by T and NK cells is the major cause of impaired antibacterial defense in these conditions.

Stroke-immune immunodepression and poststroke infections. Several studies demonstrate that catecholamine-induced T-cell lymphopenia and long-lasting T-cell dysfunction are common manifestations of human stroke that are detectable within few hours of stroke onset[23] and precede development of infection.[24] These abnormalities include decreased IFNγ and TNFα production and increased IL-4 and IL-10 production, which correlate with indices of sympathoadrenal activation, such as elevated levels of plasma metanephrine,[23] and the risk of poststroke infection.[25] The Preventive Antibacterial Therapy in Stroke (PANTHERIS) trial was a randomized, double-blind, placebo-controlled trial designed to investigate whether preventive short-term antibacterial therapy reduced the incidence of stroke-induced infections compared with standard therapy.[26] This study supported previous observations that there is rapid T lymphopenia and long-lasting T-cell dysfunction, including suppression of IFNγ and increased IL-10 levels in stroke patients. There was a trend toward greater decline in $CD4^+$ cell counts and higher levels in urinary NE early after stroke in patients who developed infections.[26] There was no significant difference in lymphocytic IFNγ production between patients with or without poststroke infections. Preventive administration of moxifloxacin did not influence the time course of infection in the setting of stroke-induced immunosuppression; early increase of plasma lL-10 levels were found in patients who were more likely to develop infections despite preventive antibacterial therapy.[26] The potential role of sympathetic activation in stroke-related immunosuppression is also supported by the result of a retrospective study showing that patients who had been on β-blocker treatment had significantly reduced risk of poststroke pneumonia and early mortality compared to patients not receiving such treatment.[27]

Spinal cord injury. Spinal cord injury is associated with impaired immune function that contributes to a significant increase in mortality due to infections. A significant reduction in circulating monocytes and T- and B-lymphocytes was detected within 24 hours after spinal cord injury and reached minimum levels within the first week.[28] Although treatment of these patients with high-dose methylprednisolone could have contributed to these findings, they are consistent with those in experimental models.[29] A cross-sectional, paired cohort study revealed decreased NK cell number and cytotoxicity in spinal cord injured patients compared to controls; this effect was similar in patients with lesions above or below T6 level.[30] However, in an experimental model of contusive spinal cord injury, high level (above T3) but not low level (below T3) lesions produced an increased NE level and a β_2 receptor-dependent decreased number of NK, T- and B lymphocytes, and antibody synthesis in the spleen.[29] This suggests that the degree of sympathetically induced immunosuppression may vary with the level of spinal cord injury.

Multiple sclerosis. It has been suggested that involvement of the sympathetic system may contribute to immune regulation in multiple sclerosis (MS).[31] Chemical sympathectomy increases the severity of experimental allergic encephalomyelitis, an experimental model of MS, whereas β_2 adrenergic receptor agonists have a protective effect[31] There is increased expression of β_2 adrenergic receptors in peripheral mononuclear cells of patients with MS, which appears to correlate with disease activity.[32] Whereas this may support a role of the sympathetic system in MS pathogenesis, there is also evidence that immune cells are able to synthesize catecholamines, which may act as local chemical signals regulating the development, function, and survival of these cells.[5,33] In vitro studies show that peripheral mononuclear cells from patients with MS have reduced dopamine release in response to mitogens[34]; therapy with β-interferon elicited upregulation of catecholamine production and β_2 adrenergic and dopamine receptor expression in these cells.[35] Impaired function of sympathetic cotransmitter NPY may contribute to immune dysregulation in MS. This peptide is cleaved by CD26, a surface peptidase that is upregulated in lymphocytes of patients with MS; the resulting NPY fragment is inactive on Y1 receptors and thus unable to shift the Th1/Th2 balance.[17]

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PERSPECTIVE Brain–immune interactions have a critical homeostatic role in limiting the degree of inflammation that may be damaging to tissue. However, autonomic and endocrine responses may also have a deleterious immunodepressant effect in the setting of acute CNS injury, predisposing to infection. Intriguing experimental and clinical findings suggest that there is a lateralization of hemispheric control of immune responses, that stimulation of β_2 adrenoceptor or Y1 receptor stimulation may have a beneficial immunomodulatory role in MS and other disorders, and that blockade of β_2 adrenoreceptors may protect against infections in the setting of acute CNS injury. Although these experimental observations are of high potential clinical relevance, they have to be confirmed in larger studies and well-designed clinical trials.

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