Autonomic-mediated immunomodulation and potential clinical relevance

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 interactions1-7 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 medulla13 (figure 2). The PVN not only initiates endocrine and autonomic responses but may also modulate the responses of neurons of the NTS and ventrolateral medulla.

GLOSSARY

a7nAChR = α7 subunit-containing nicotinic receptor; ACh = acetylcholine; ACTH = adrenocorticotropic hormone; β2AR = 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; NFkB = nuclear factor kappa B; NPY = neuropeptide Y; NTS = nucleus of the solitary tract; PGE2 = prostaglandin E2; PVN = paraventricular nucleus; RVLM = rostral ventrolateral medulla; TNFα = tumor necrosis factor-alpha.

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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-1\(\beta\) and TNF\(\alpha\), may 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, \(^2\) 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.

**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
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.\textsuperscript{1,15}

Catecholamines exert pleiotropic effects on the activity of immune cells, acting primarily via $\beta_2$ adrenergic receptors (adrenoceptors)\textsuperscript{1,4,5} (table). These receptors are expressed on macrophages, naive CD4\textsuperscript{+} cells, Th1 helper cells, and B cells. Although murine Th2 cells appear not to express detectable levels of $\beta_2$ adrenoceptors, the presence of these receptors in human Th2 cells is still controversial.\textsuperscript{4,5} $\beta_2$ adrenergic receptor expression in immune cells is variable and regulated by a number of different factors, including cell activation, cytokines, neurotransmitters, and hormones.\textsuperscript{1} Stimulation of the $\beta_2$ 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.\textsuperscript{1,3} $\beta_2$ adrenergic receptor-activated elevation of cAMP levels inhibit nuclear factor kappa B (NFkB) activation in dendritic cells, macrophages, and monocytes. This leads to suppression of the production and release of proinflammatory (type
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 β2 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 β2 adrenoreceptors, catecholamines increase production type 2 cytokines, such as IL-4. Activation of β2 adrenoreceptors also increases Th2 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.1,6 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.1,15,19

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 endotoxiaemia.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

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Function</th>
<th>Effect of β2 adrenoreceptor</th>
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</thead>
<tbody>
<tr>
<td>Interleukin (IL)-1</td>
<td>Antigen presenting cells (APC), endothelium</td>
<td>Major proinflammatory cytokine, endogenous pyrogen</td>
<td>Decrease</td>
</tr>
<tr>
<td>IL-2</td>
<td>T-helper (Th) Th0 and Th1, natural killer [NK] cells</td>
<td>Proliferative factor for lymphocytes</td>
<td>Decrease</td>
</tr>
<tr>
<td>IL-12</td>
<td>APC</td>
<td>Major inducer of Th1 response</td>
<td>Decrease</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>APC</td>
<td>Major proinflammatory cytokine</td>
<td>Decrease</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Th1, NK</td>
<td>Potent activator of macrophages and inhibitor of Th2 functions</td>
<td>Decrease</td>
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<tr>
<td>IL-3</td>
<td>T cells</td>
<td>Hemopoietic factor</td>
<td>Decrease</td>
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<tr>
<td>IL-10</td>
<td>APC, Th2</td>
<td>Potent inhibitor of Th1 and macrophage functions</td>
<td>Increase</td>
</tr>
<tr>
<td>IL-6</td>
<td>APC, Th2</td>
<td>B-cell differentiation factor; induction of active phase proteins</td>
<td>Increase (APCs)</td>
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<td>IL-8</td>
<td>Monocytes, endothelium</td>
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</tr>
<tr>
<td>Transforming growth factor-β</td>
<td>Many cells</td>
<td>Potent inhibition of Th1 and macrophages</td>
<td>Increase (fibroblasts)</td>
</tr>
</tbody>
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**Table Effects of β2 receptor stimulation on cytokine production**
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 anti-inflammatory 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 onset23 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 IL-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 immuno-suppression 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 β2 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 β2 adrenergic receptor agonists have a protective effect.31 There is increased expression of β2 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.33 In vitro studies show that peripheral mononuclear cells from patients with MS have reduced dopamine release in response to mitogens34; therapy with β-interferon elicited upregulation of catecholamine production and β1 adrenergic and dopamine receptor expression in these cells.35 Impaired function of sympathetic co-transmitter 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
**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 β2 adrenoceptor or Y1 receptor stimulation may have a beneficial immunomodulatory role in MS and other disorders, and that blockade of β2 adrenoceptors 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.

**REFERENCES**


33. Lucin KM, Sanders VM, Jones TB, Malarkey WB, Popovich PG. Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. Exp Neurol 2007;207:75–84.


for adrenoceptor-mediated mechanisms in fine tuning of T-cell development. Auton Neurosci 2008;144:1–12.


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