Autonomic Neural Regulation of the Immune System
Implications for Hypertension and Cardiovascular Disease

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The autonomic and the immune systems play major roles in the pathogenesis of cardiovascular disease and hypertension. To date, those 2 systems have been studied extensively but independently by cardiovascular biologists and by immunologists. The notion that the autonomic system can modulate the immune system and thereby influence the pathogenesis of cardiovascular disease and hypertension and their clinical outcome is novel and critical.

In this brief review we focus on that interaction and an integrated understanding of the neuro-immune axis. We also highlight recent progress and future research directions.

The main theme is that dysregulation of the autonomic system enhances the inflammatory response of the innate and adaptive immune systems leading to the initiation or acceleration of pathological processes and worsening of cardiovascular risks. The therapeutic potential of restoring an optimal autonomic control of the immune system is very promising.

Both components of the neuro-immune axis may be involved in its disruption. One is the autonomic nervous system, which may be dysregulated or imbalanced with increased sympathetic and decreased parasympathetic activity. The other is the immune system itself, which may be abnormally sensitive to the modulatory influence of the autonomic system. These 2 components are briefly described below.

**Autonomic Dysregulation in Chronic Hypertension**

The complexity of cardiovascular mechanisms that contribute to hypertension has been challenging. The roles of vascular and renal abnormalities are undeniable. Changes in vasomotor tone, sodium retention, and renal renin release are all well established. For decades the contribution of the sympathetic nervous system to chronic hypertension was not fully appreciated. Its importance is now well recognized.1–5 In a 1982 review, we described the neural sites and mechanisms involved in exaggerated sympathetic nerve activity (SNA) in several animal models, as well as in human hypertension.1 Moreover, there has been a surge of data highlighting the damaging cardiovascular effects and the increased mortality and morbidity associated with exaggerated SNA in a variety of cardiovascular diseases.6–10 In the Cannon Lecture of 2009 titled, “In Search of Autonomic Balance: the Good, the Bad, and the Ugly,” the parasympathetic nerve activity was portrayed as good, the sympathetic activity as bad, and the generation of reactive oxygen species by the renin-angiotensin-aldosterone system as the ugly.11 Although an essential role of the kidney has been established in angiotensin II (Ang II) hypertension,12 the renin-angiotensin-aldosterone system can initiate and maintain a state of sympathetic overactivity through its action on central neurons in the subfornical organ of the forebrain.13

In addition, the decrease in baroreceptor reflex activity1,2,3,11 and increase in chemoreceptor activity,3,5,14,15 often seen in hypertension and heart failure, enhance the excessive SNA and suppress the parasympathetic nerve activity. This combination increases cardiovascular risks not only in hypertension but also in several other cardiovascular disease states8,9,16 (Figure 1).

**Sensitivity of the Immune System to Autonomic Modulation**

A hallmark study demonstrated that vagal nerve stimulation protected mice from lipopolysaccharide-induced sepsis and was associated with a decrease in the secretion of tumor necrosis factor-α.17 In later studies, this effect was shown to be mediated by the α7-nicotinic acetylcholine (ACh) receptor.18 The suppression of the immune responses has been coined the “cholinergic inflammatory reflex,” drawing an analogy to the vago-vagal neural reflex.19 These studies set the stage for further exploration of the autonomic regulation of the immune system in cardiovascular disease. The enhanced inflammatory response in hypertension or other cardiovascular diseases may, thus, be attributed to the loss of the inhibitory parasympathetic influence or an increased sympathetic influence. It could also be because of abnormal sensitivities of excitatory or inhibitory receptors on the immune cells.

**Interactions of the Neuro-Immune Circuit in Cardiovascular Disease**

The interactions of the nervous system, immune system, and cardiovascular disease can be visualized as a triangle (Figure...
The triangle reflects the convergence of the neural and immunologic mechanisms in cardiovascular disease. It can be either a “death triangle” with excessive sympathetic and renin-angiotensin-aldosterone system (RAAS) activities that enhance the inflammatory immune response and increase mortality or a “survival triangle” with enhanced parasympathetic activity, which has been shown to suppress the inflammatory immune response and prolong survival.

Stimulation of Carotid Sinus Nerves and Vagal Nerves in Animal Models

In a canine model of rapid pacing-induced heart failure, electric carotid sinus nerve stimulation resulted in an increased survival benefit by suppressing the sympathetic and enhancing the parasympathetic arms of the autonomic nervous system. Similarly, stimulation of the right vagus nerve in a rat model of ischemic cardiomyopathy resulted in a 90% survival 4 months after coronary artery ligation compared with only a 50% survival in rats without vagal stimulation. Taken together, these studies indicate a beneficial effect of autonomic balance that not only spans different animal models and etiologies of heart failure but also shows that the effects are long lasting. In the rat model, the survival extended beyond the vagal stimulation time period. The mechanism of protection transcends the direct hemodynamic effect.

An important question in evaluating the role of SNA in hypertension is whether increased SNA contributes to the initiation of hypertension. In other words, do the impaired baroreceptor reflex and enhanced chemoreceptor reflex induce the development of hypertension or do they simply sustain a hypertensive state? In the spontaneously hypertensive rat (SHR), a genetic model of hypertension, there is evidence of an increase in SNA to several vascular beds before the onset of hypertension. We have shown that, in the prehypertensive state, when the SHR is 5 weeks of age, there is a significant increase in gene expression of the acid-sensing ion channel 2 and Ca^{2+}-activated potassium channels in glomus cells, which would explain their reduced mechanosensitivity and decreased excitability in SHRs before the onset of hypertension.

The
Clinical Trials of Carotid Sinus and Vagus Nerve Stimulation

The translational significance of the animal studies is now being tested in patients. The unexpected but significant beneficial influence of nerve stimulations on cardiovascular mortality and morbidity led to the implementation of major clinical trials involving the direct electric stimulation of the carotid sinus nerves in patients with drug-resistant hypertension and recently in patients with heart failure. 27-30 Also, results of vagus nerve stimulation in experimental models are leading to clinical trials in patients with advanced heart failure. 30-32

Inflammatory/Immune System Causes Cardiovascular Damage

In parallel with the recognition of the powerful influence of the autonomic nervous system on cardiovascular risks is an equally powerful recognition of the functional and structural damages that ensue from inflammation of the cardiovascular system. 33 This is evident in a variety of cardiovascular diseases. In atherosclerosis, plaques contain immune cells (lipid-laden macrophages, T cells, and dendritic cells). In heart failure, cytokine “storms” and the enhanced innate immune response with toll-like receptor (TLR) activation in macrophages and dendritic cells cause cardiac dysfunction.

In hypertension, such associations include early reports in 1976 that thymectomy in mice prevents the development of deoxycorticosterone acetate/salt hypertension. 34 The neonatal thymic transplants from Wistar-Kyoto normotensive controls into SHRs delays the onset of hypertension in the SHRs to >32 weeks. 35 The immune dysfunction in the SHRs involves a mononuclear immune cell subpopulation that induced dysfunctions of T lymphocytes. 36 Moreover, the administration of the immunosuppressive agents, cyclophosphamide and mycophenolate, was shown to stop the progression of hypertension in SHRs. 37

Although, Ang II is known to induce hypertension in experimental models, it also induces upregulation of interleukin (IL) 1-β, tumor necrosis factor-α, monocyte chemoattractant protein 1, and intercellular adhesion molecule 1. 38 Elevated levels of intercellular adhesion molecule 1 and IL-6 have also been documented in apparently healthy men. 39 These findings are significant because IL-6 causes myocardial hypertrophy, fibrosis, and apoptosis in experimental models of hypertension and appears to be involved in the pathogenesis of hypertension. 40 Moreover, IL-6 knockout mice are refractory to Ang II–induced hypertension. 41

Another model that confirms the dependence of Ang II–induced hypertension on the immune system is the immune-deficient RAG−/− mouse. In this model, the pressor response to Ang II infusion was blunted. 42 It was restored to the high levels seen in the C57BL/6 control mouse by the adoptive transfer of T lymphocytes. The transfer of B lymphocytes did not restore the pressor response. 42

The possibility that a latent activation of the innate immune system may exist in the prehypertensive state and initiate the development of hypertension is suggested by 2 observations. One is our early result in the young prehypertensive SHR that indicates a significant enhancement of cytokine release from splenocytes in response to activation of TLRs, which induce the transcription of cytokines. 43 This prehypertensive enhancement of cytokine release may explain the increase in regional sympathetic activity reported in the prehypertensive phase of SHR by Cabassi et al. 25

The other observation by Harrison et al 44 proposes that, in the prehypertensive state, an initial stress that may be of neural origin causes some vascular damage and the release of endogenous “neoantigens.” These activate the innate immune system and the release of cytokines, which, in turn, activate the T lymphocytes and the adaptive immune system, resulting in inflammatory consequences and hypertension.

Autonomic System Is a Powerful Regulator of the Immune System

The neurogenic origin of hemodynamic changes in hypertension is well accepted. 2,11,45 However, the concept that the autonomic nervous system exerts long-term effects on the cardiovascular system in pathological states through the regulation of the immune system is novel. It represents a major shift in our thinking about the mechanisms of cardiovascular actions of the autonomic nervous system. The shift is from accepting the primacy of the direct hemodynamic effects to the recognition that the more chronic functional and structural pathological processes are mediated through the interaction of the autonomic and the immune systems. There is strong evidence to support the direct sympathetic innervation of immune organs. 36 Immunomodulation by cholinergic and adrenergic agonists has also been shown, strengthening the functional significance of this anatomic association. 47

Three sets of experimental observations have been selected to illustrate the influence of autonomic regulation on the immune system.

First is the evidence that an increase in central sympathetic nerve activation by intracerebral ventricular infusion of Ang II enhances the immune response. 48 Although Ang II is responsible for a variety of actions that contribute to the development of hypertension, its central actions activate the peripheral sympathetic nervous system and affect the immune responses. A direct in vivo link among central Ang II, the increase in splenic SNA, and the enhanced splenic cytokine (IL-1β, IL-2, IL-5, IL-16, and transforming growth factor-β1) gene expression was convincingly demonstrated, as shown in Figure 3. Selective splenic denervation caused a significant suppression of the enhanced centrally driven, sympathetically mediated immune response to intracerebral ventricular infusion of Ang II, whereas the increase in renal sympathetic discharge was preserved. 48

Second is the evidence that vagus nerve activity restrains the inflammatory system. A compelling indication of a suppressive influence of resting vagal tone is the demonstration of a marked increase in nuclear factor κB-activation in the colon by photon emission tomography 4 weeks after subdiaphragmatic vagotomy (Figure 4A). 49 The colon is
densely populated with lymphoid tissue. A significant increase in nuclear factor κB, most likely in the innate immune cells, is the ultimate product of cellular inflammation and a major determinant of gene expression of cytokines. In a parallel experiment, vagotomy increased significantly the cytokine production including interferon-γ, tumor necrosis factor, and IL-6 in CD3/CD28 (CD4) T lymphocytes from the murine spleen (Figure 4B).50 In addition, activation of nicotinic cholinergic receptors has also been shown to play a role in B-lymphocyte maturation.51 Recently, studies have shown that T lymphocytes can synthesize and release ACh, thus serving as effectors of the vagal nerve circuit.52

Third is the evidence that vagal nerve stimulation exerts a protective anti-inflammatory effect and abrogates the detrimental responses in heart failure and endotoxic shock. In a canine model of pacing-induced heart failure, vagus nerve stimulation improved left ventricular ejection fraction, decreased cardiac size, and increased baroreflex sensitivity, when compared with the sham unstimulated animals.53 This functional improvement was associated with a significant reduction of the clinically used biomarker of inflammation, C-reactive protein, at 4 weeks and its nearly total suppression at 8 weeks.53

Vagus nerve stimulation was also protective in a murine model of sepsis.17 It attenuated the hypotension or shock induced in mice by endotoxin. It also suppressed serum, as well as hepatic tumor necrosis factor-α.17 These anti-inflammatory effects were later determined to be mediated by the activation of α7 nicotinic ACh receptors on macrophages.18

Recent Progress and Future Directions
Some of the most recent work and ideas for future directions in the area of inflammation/immunity relevant to hypertension cover the communications between the nervous system and the immune system. These occur at both a central and peripheral level.54

Tonic Suppressive Vagal Influence on the Immune System

Figure 4. A, Subdiaphragmatic vagotomy induces pronounced nuclear factor κB (NFκB) activation in the colon in vivo over a period of 4 weeks (w) postvagotomy. Adapted with permission from O’Mahony et al.49 B, Vagotomy results in a significant increase in gene expression of interferon (IFN)-γ, tumor necrosis factor (TNF), and interleukin (IL)-6 in isolated splenic murine CD4⁺ T lymphocytes. Adapted with permission from Karimi et al.50
Central Interaction
At the level of the central nervous system, circulating cytokines, or cytokines released from astrocytes and microglia, may activate specific nuclei in the hypothalamus or brain stem and induce an increase in SNA and hypertension. Alternatively, the migration of innate immune cells, such as macrophages and monocytes or T regulatory or cytotoxic lymphocytes, from the circulation to the central nervous system may induce an inflammatory response and a similar neuronal activation.

An intriguing hypothesis, proposed by Zubcevic et al,45 is that hypoperfusion of the brain stem may evoke hypertension. The hypothesis is based on the analogy that hypertension in the giraffe is an essential adjustment to maintain the cerebral circulation. The link between brain hypoperfusion and hypertension may be an inflammation of the brain microvasculature triggered by increased expression of adhesion molecules on the endothelium, which attracts leukocytes and lymphocytes.45,55 Inflammation of the brain microvasculature causes localized ischemia. The transduction mechanisms that evoke sympathoexcitation and hypertension might include vascular-glial-neuronal signaling pathways that require further exploration.56 The proposition is that long-term control of blood pressure may need to be viewed in the context of maintenance of cerebral blood flow by a process that involves central inflammatory/immune mechanisms.

Peripheral Interaction
A second level of communication occurs between the autonomic nervous system and the peripheral immune system. The spleen and the gut are the organs with the most dense reservoirs of immune cells. They represent the innate and the adaptive immune systems. The innate immune cells that recognize pathogenic antigens and release cytokines have adrenergic, cholinergic, and angiotensin receptors. When activated, these “autonomic receptors” may certainly alter the immunologic response.

The work of Tracey and colleagues18,19 has focused on the vagus nerve-dependent circuits that control innate immunity. He proposed the “inflammatory reflex” as a hypothesis to explain a negative feedback regulation of cytokine release. The vagus nerve is the mediator of both the afferent and efferent signals of the reflex. Vagal afferents, which are widely distributed in most visceral organs, including the heart and gut, may be activated by cytokines released as a result of tissue injury or inflammation. The reflex is then centrally mediated through the nucleus tractus solitarius and the dorsal motor nucleus of the vagus and activates the vagal efferents. These, in turn, suppress cytokine release from macrophages in the spleen or the gut. This feedback requires ACh signaling through α7 nicotinic receptors (Figure 5).18 The release of ACh in the spleen during vagal stimulation is puzzling, because the splenic nerve fibers lack the enzymatic processes for ACh synthesis. The recent discovery that a memory phenotype T-cell population in the spleen produces ACh and is integral to the inflammatory reflex resolves this question.52 Thus, this T lymphocyte is a component of the peripheral neural control of innate immunity and a possible therapeutic target in inflammatory states and autoimmune diseases.

Dysregulation of Neuro-Immune Interactions
In pursuit of the relevance of this nicotinic modulation of innate immune cells in an animal model of genetic hypertension, we studied the SHR.43 We tested the hypothesis that there is a heightened innate immune response and cytokine release from splenocytes of prehypertensive SHRs compared with their Wistar-Kyoto controls.

The transcriptional regulation of cytokine expression occurs through activation of TLRs on innate immune cells. TLRs are the primary innate immune receptors that detect “pathogen-associated molecular patterns” from bacteria, fungi, or viruses (eg, lipopolysaccharide, flagellin, and CpG-containing DNA).57 They also recognize products of cellular damage from the host as “damage-associated molecular...
The important concept that emerges from this brief review is that hypertension is indeed an immunologic disease (Figure 5). Different types of T lymphocytes define the nature of the immune response as either protective or cytotoxic. For example, T-regulatory cells, which release IL-10 and adenosine, suppress cytotoxic T cells (CD8* cells) and prevent auto-immune disease. In contrast, the recently identified T-helper 17 cells, which release IL-17, are cytotoxic against endogenous antigens causing severe autoimmune disease. The same T-helper 17 lymphocytes release IL-22, which is effective against exogenous microbial antigens.

The migration of T lymphocytes to renal or vascular tissues would contribute to the inflammatory and pathological process in hypertension. This positive feedback interaction between the activation of the innate and adaptive immune systems supports the notion that hypertension is in part an immunologic disease profoundly regulated by the autonomic system. Harrison et al44 reinforced the role of IL-17 specifically as the cytotoxic cytokine in renal and vascular tissues. CD8* cells are the responsible lymphocytes that release IL-17 in this model, and CD4* cells may be protective. The mechanisms by which the T lymphocytes migrate to the end organs were explored.60 An initial neural stimulus to the target organ, possibly an increase in SNA, may provoke an initial tissue damage. A mild “borderline” elevation of arterial pressure may initiate a vascular tension that may induce the expression of matrix metalloproteinase 12. This then may function as a neoantigen that activates an innate immune response and creates the chemoaffecting environment that results in migration of the cytotoxic T lymphocytes.

Conclusions and Implications

The important concept that emerges from this brief review is the realization that autonomic balance is not only an essential determinant of acute circulatory adjustments to stresses. It is a powerful regulator of pathological processes that define cardiovascular mortality and morbidity. We are now able to measure noninvasively this autonomic balance, to intervene therapeutically with drugs and direct nerve stimulations in human and animal models, and to confirm the strong association among autonomic balance, cardiovascular risks, and cardiovascular pathology.

A second important concept is the realization that the immune system, which is a major determinant of most cardiovascular pathological processes, can be modulated extensively by the autonomic system. This means that our notion of autonomic control of the circulation needs to be expanded beyond its hemodynamic influence and extended into its influence on cellular and structural pathological processes. These are accentuated by the proinflammatory activation of the innate and adaptive immune systems.

Our biggest challenge resides in the complexity of the immune system, its cellular components, and the multiplicity of cytokines that they generate. We need to define their origin and sites of action, the processes that determine their damaging influences, and, more importantly, the interventions that block or reverse those influences. On the other hand, a better understanding of the autonomic control of cardiovascular immune processes is extremely promising. We have tools to quantify that autonomic influence and tools to modulate it.

Our take home message from this review is as follows: the pronounced influence of the autonomic imbalance on cardiovascular morbidity and mortality is not simply a function of hemodynamic effects. Recent studies have revealed that a major determinant of the pathological process results from autonomic dysregulation of the inflammatory/immune system.

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References


