Autonomic nervous system activity and inflammation: good ideas, good treatments, or both?

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THROUGH SYMPATHETIC AND PARASYMPATHETIC efferent nerves, the autonomic nervous system regulates and integrates many functions of the human body. Most people believe that psychological and physiological “stress,” which alters the balance between sympathetic and parasympathetic nervous system activity, can suppress the immune system, thereby setting off diseases. Indeed, immune cells express adrenergic and cholinergic receptors. Research in recent years suggests that autonomic nerves have an important role in sensing and controlling inflammation and in tuning immune responses. The underlying mechanisms have been delineated at the cellular level and in animal models. Overall, the literature suggests that neural mechanisms are important in the fine balance between inflammatory and anti-inflammatory responses. Tipping the balance toward excess suppression of inflammatory responses could raise the risk of infectious complications. Rampant inflammation would be deleterious as well. Yet, studies translating these concepts from animal to human physiology are scarce. In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Okamoto et al. (10) is exemplary in that regard.

Both parasympathetic and sympathetic efferent nerves have been suggested to affect immune cells and inflammatory responses. The main parasympathetic neurotransmitter acetylcholine attenuated proinflammatory cytokine release including tumor necrosis factor (TNF) in lipopolysaccharide-stimulated human macrophage cultures (1). The observation that nicotine was more effective than muscarine in inhibiting TNF release implicated nicotinic acetylcholine receptors. Electrical vagus nerve stimulation during lethal endotoxemia reduced systemic TNF concentrations and prevented septic shock in rats (1). Macrophages express α7-nicotinic acetylcholine receptor (α7nAChR) subunit, and its knockdown makes macrophages less responsive to nicotine-mediated TNF inhibition (19). In α7nAChR knockout mice, endotoxin produces excess proinflammatory cytokine release. Moreover, macrophages from these animals fail to respond to cholinergic agonists (19). Finally, genetic α7nAChR deletion exacerbates inflammation and fibrosis in experimental glomerulonephritis (18). The mechanism may also be involved in more modest inflammatory responses such as the low-grade inflammation associated with obesity, which predisposes to cardiovascular and metabolic complications. Indeed, selective pharmacological α7nAChR stimulation in a mouse model of type 2 diabetes ameliorated inflammatory and metabolic abnormalities (7). Increased α7nAChR expression on peripheral blood mononuclear cells was associated with better control of inflammation, disease severity, and clinical outcome in septic patients (3).

The idea that a cholinergic anti-inflammatory pathway directly affects inflammatory responses is overly simplistic. Instead, efferent parasympathetic vagal nerves may promote norepinephrine release from sympathetic splenic nerves. Norepinephrine then induces acetylcholine release from specific T cells, thereby inhibiting TNF production in α7nAChR expressing splenic macrophages (12).

In rats given intravenous endotoxin, bilateral section of splenic sympathetic nerves profoundly attenuated inflammatory cytokine release, whereas bilateral vagotomy was ineffective (8). The authors suggested that sympathetic rather than parasympathetic nerves comprise the efferent arc of the anti-inflammatory neural pathway. Indeed, immunosuppression following experimental strokes has been attributed to sympathetic nervous system activation (11). Nonselective β2-adrenoreceptor blockade and pharmacological ablation of the sympathetic nervous system with 6-hydroxidopamine attenuated stroke-induced immunological abnormalities, prevented infections, and improved survival (11). Surprisingly, increased parasympathetic activity following experimental strokes in mice was also linked to pulmonary infectious complications which were ameliorated with vagotomy or genetic α7nAChR deletion (4).

The issue is further complicated by the fact that the sympathetic nervous system may elicit pro- as well as anti-inflammatory responses in a context-dependent fashion [reviewed in Straub et al. (15)]. In macrophages, β2-adrenoreceptor stimulation elicits anti-inflammatory and α2-adrenoreceptor stimulation proinflammatory responses (14). This complexity together with species differences in immune regulation makes it difficult, if not impossible, to extrapolate findings from animals to patients. Will a change in autonomic activity promote or attenuate inflammatory responses and, if so, does this depend on the clinical context (i.e., diagnosis)?

Okamoto et al. (10) investigated the highly complex cross talk between autonomic nervous system, obesity, and inflammation in patients. Obesity is associated with low-grade systemic inflammation and autonomic nervous system imbalance with raised sympathetic and reduced parasympathetic activity. The authors hypothesized that the inflammation may be mediated through this autonomic imbalance in persons with obesity. To address this issue, they studied women, who were lean and obese, with and without a diagnosis of the postural tachycardia syndrome (POTS) (10). POTS, which served as human model of sympathetic overactivity and parasympathetic withdrawal, is a chronic condition associated with tachycardia with upright posture. First, the authors showed that in patients who were lean with POTS, sympathetic predominance and circulating interleukin-6 concentrations were increased compared with women in the lean control group. In fact, these measurements were similar to those in women who were obese but without POTS. Unlike in women who were obese and with or without POTS, however, C-reactive protein (CRP) was not increased in patients who were lean with POTS. The authors suggest that
autonomic mechanisms may have promoted interleukin-6 release from adipose tissue. Previously, β-adrenoreceptor stimulation with isoproterenol was shown to increase interleukin-6 from isolated human adipocytes and in vivo in human subjects (9).

Based on the dissociation between circulating interleukin-6, which stimulates hepatic CRP release and CRP concentrations in patients who were lean with POTS, Okamoto et al. (10) speculate that the site in which interleukin-6 is produced may be important. Interleukin-6 may have to be produced in visceral adipose tissue directly draining into the portal circulation to elicit CRP release. The idea that norepinephrine/epinephrine are important in sustaining low-grade systemic inflammation is supported by exceedingly rare patients with dopamine-β-hydroxylase deficiency, which is required for converting dopamine to norepinephrine. Interleukin-6 levels were low in these patients.

Obviously, studies in patients have their limitations, and confounding variables, such as differences in physical activity between groups, cannot be ignored. Nevertheless, the study provides novel insight in interactions between autonomic nervous system and inflammation in human beings and generates new ideas for mechanistic studies. The idea that through modulation of the autonomic nervous system, pro- as well as anti-inflammatory clinical responses could be attained is fascinating. Lifestyle interventions, medications, and devices could be repurposed or developed to target inflammation. In cardiovascular and metabolic diseases, measures to attenuate sympathetic activity may alleviate systemic inflammation. In persons with obesity, weight loss improves the imbalance between sympathetic and parasympathetic activity (16, 6) and persons with obesity, weight loss improves the imbalance promoting atherogenesis. Lessons from postural tachycardia syndrome and obesity.

REFERENCES


