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 towards 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. The study by Okamoto et al. in this issue is exemplary in that regard (10).

Both, parasympathetic and sympathetic efferent nerves have been suggested to affect immune cells and inflammatory responses. The main parasympathetic neurotransmitter acetylcholine attenuated pro-inflammatory cytokine release including tumour 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 endotoxinemia reduced systemic TNF concentrations and prevented septic shock in rats (1). Human 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 antiinflammatory 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 while 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 beta-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 15). In macrophages, beta-2 adrenoreceptor stimulation elicits antiinflammatory and alpha-2 adrenoreceptor stimulation proinflammatory responses (14). This complexity together with species differences in immune regulation make 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. 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 obese persons. To address this issue, they studied lean and obese women 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 lean POTS patients, sympathetic predominance and circulating Interleukin-6 concentrations were increased compared with lean control women. In fact, these measurements were similar to those in obese women without POTS. Unlike in obese women with or without POTS, however, C reactive protein (CRP) was not increased in lean POTS patients. The authors suggest that autonomic mechanisms may have promoted interleukin-6 release from adipose tissue. Previously, beta-adrenoreceptor stimulation with isoproterenol was shown to increase interleukin-6 from isolated human adipocytes and in in vivo in human subjects (9).
Based on the dissociation between circulating interleukin-6, which stimulates hepatic CRP release, and CRP concentrations in lean POTS patients, Okamoto et al. 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-beta-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 obese persons, weight loss improves the imbalance between sympathetic and parasympathetic activity (16, 6) and may increase adipose tissue α7nAChR expression (2). Similarly to observations in animal models, sympathetic inhibition could improve the immunosuppression associated with strokes and, thereby, prevent infectious complications and deaths. Excessive sympathetic activity has also been reported in patients with ulcerative colitis, in which treatment with the alpha-2 adrenoreceptor clonidine significantly reduced sympathetic activity with associated
clinical and endoscopic improvements (5). Beneficial effects on systemic and local inflammatory response have also been reported with clonidine and dexmedetomidine administration in experimental severe necrotizing pancreatitis (13). We do not know whether these responses are mediated through sympathetic inhibition, parasympathetic activation (17), direct actions on immune cells, or combination of these mechanisms. Overall, all these studies provide an impetus for conducting larger scale studies in patients. However, recent experience with electrical vagus nerve stimulation, which failed to improve outcomes in heart failure patients, is a strong reminder that good ideas may not always turn into good treatments (20).

Disclosures

KCJ reports no conflicts of interest. JJ served as scientific advisor for Novartis, Boehringer-Ingelheim, Vivus, and Orexigen and receives research support from Boston Scientific and Boehringer-Ingelheim.

Author contributions

KCJ drafted and edited the manuscript. JJ revised and approved the final version of manuscript.
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