Neural control of the immune system

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A PRINCIPLE of mammalian physiology is that the nervous system supports homeostasis by modulating the function of organ systems. The basic organizational unit of the nervous system is the reflex arc, composed of sensory (afferent) neurons that project regulatory signals to target tissues. CNS integration of information allows for a purposeful and rapid adaptation to changing demands on the organism through autonomic reflexes. For example, the baroreflex regulates heart rate (HR) and blood pressure at the expense of optimal organ perfusion and delivery of O₂ and nutrients.

Although reflex physiology has been a field of extensive research, limited attention has been given to neural control of inflammation and immunity. However, recent advances in neuroscience and immunology have revealed that neural reflexes also regulate the immune system. Activation of the vagus nerve modulates leukocyte cytokine production and alleviates experimental shock and autoimmune disease, and recent data have suggested that vagus nerve stimulation can improve symptoms in human rheumatoid arthritis. These discoveries have generated an increased interest in bioelectronic medicine, i.e., therapeutic delivery of electrical impulses that activate nerves to regulate immune system function. Here, we discuss the physiology and potential therapeutic implications of neural immune control.

Nerves Sense Inflammation and Interact With Leukocytes

Inflammation is a key process in mammalian defense against pathogens and in wound healing. Molecular products of microbial invasion and tissue damage are detected by pattern recognition receptors (PRRs), which activate cells in the innate immune system, e.g. macrophages. This early response gives rise to a cascade of events aimed to clear pathogens and ultimately restore health, and includes the production of pro-inflammatory cytokines and recruitment of leukocytes. The initial process promotes the classic symptoms of localized inflammation, including swelling, redness, and loss of function, and may progress to include systemic responses mediated by the CNS, such as fever, anorexia, and fatigue.

Because excessive inflammation and cytokine production in itself can cause tissue damage, nonresolving inflammation, inflammatory diseases, shock, and even death, it is essential that the inflammatory response is tightly regulated and controlled. Multiple control mechanisms that balance proinflammatory mechanisms have been described, for example, release of inhibitory cytokines and soluble cytokine receptors as well as activation of regulatory lymphocyte subsets. Interestingly, PRRs (e.g., Toll-like receptors and nucleotide-binding oligomerization domain receptors) and receptors for cytokines and prostaglandins are also expressed by sensory neurons, which can provide a molecular mechanism for the CNS to acquire information on localized inflammation in the periphery. Indeed, sensory nerves can respond to the presence of microbial products independent of immune activation. Since sensory nerves form a dense network throughout the external surfaces of the body, it has been suggested that this innervation provides an anatomic basis for precise sensing by the CNS of pathogen invasion, tissue damage, and inflammation. Reciprocally, a range of immune cells express receptors for neurotransmitters, including dopamine, ACh, and norepinephrine, which can regulate leukocyte activity and differentiation. Autonomic nerves innervate lymphoid tissue and other organs and regulate immune responses. Hence, an anatomic and molecular framework for sensing and regulating immune system activity in a reflexive manner is in place.

The Inflammatory Reflex

Important insights into the neural control of inflammation have come from the study of a prototypical example of a neural immune-regulatory circuit termed the “inflammatory reflex.” In this reflex, afferent signals transmitted through the vagus nerve are processed in the CNS and culminate in efferent vagus nerve activity that regulates macrophage cytokine release in the spleen. Our current understanding of this reflex is based on a number of seminal discoveries. Watkins et al. and other research teams found that the fever response to low doses of IL-1β injected into the intraperitoneal cavity of rats requires an intact vagus nerve, because animals with a subdia-
phragmatically severed vagus nerve fail to develop a pyrexic response to the injected cytokine. Moreover, injection of IL-1β into the portal vein in rats gives rise to increased afferent activity in the vagus nerve and increased activity in the splenic nerve, but not when the hepatic branch of the vagus nerve had been ablated (41). Thus, signaling in the vagus nerve plays a role in the systemic response to cytokines. Tracey and colleagues (8) found that CNI-1493, a tetravalent guanylhydrazone with anti-inflammatory effects, is significantly more potent when given directly in the brain (intracerebroventriculicularly) compared with intravenous dosing and that an intact vagus nerve is required for its effect. These findings indicate that signals originating in the CNS can travel through the cholinergic vagus nerve and regulate inflammation in the periphery. Indeed, electrical stimulation of the vagus nerve significantly reduces systemic TNF levels and prevents shock in experimental endotoxemia, whereas surgical ablation of the vagus nerve has the opposite effect in this model (9).

The spleen is a major source of systemic TNF in endotoxemia, and it has been convincingly demonstrated that electrical vagus nerve stimulation (VNS) can significantly reduce cytokine production in the spleen. However, the vagus nerve does not directly innervate the spleen. It travels to the coeliac ganglion, where the adrenergic splenic nerve arises. Electrical stimulation of the splenic nerve reduces splenic cytokine production (28), and the splenic nerve is necessary for vagus nerve-mediated inhibition of TNF release from splenic macrophages (51). Furthermore, activation of cholinergic α7-nicotinic ACh receptors (α7-nAChRs) is required for vagus nerve-mediated inhibition of their TNF release (64). Given that nerve fibers in the spleen lack the machinery to produce ACh, how are signals in this conduit relayed to cholinergic receptors in the spleen?

**Specialized T Cells Are an Integral Component of the Inflammatory Reflex**

Despite the lack of splenic cholinergic innervation, the spleen is known to contain the neurotransmitter ACh (15). The source of this ACh has not been extensively studied. Pioneering work by Kawashima and colleagues (20, 21, 48) showed that some lymphocytes, including T cells, express the enzyme choline acetyltransferase (ChAT) and are capable of ACh biosynthesis. We discovered that electrical VNS fails to inhibit systemic TNF release in endotoxemia in T cell-deficient nude mice (52). Interestingly, lymphocytes are found in close apposition to adrenergic nerve endings in the spleen (19, 52), and T cell expression of adrenergic receptors is required for the integrity of the efferent arm of the inflammatory reflex (63). This proximity of nerves and ChAT+ lymphocytes in the spleen and the expression of adrenergic receptors on ChAT+ T cells (52) provides a basis for direct signals between nerves and splenic lymphocytes. Adoptive transfer of ChAT+, but not ChAT−, T lymphocytes to nude mice restores the inhibitory effect of VNS on TNF release (52). Collectively, these data support that the ACh production and release required for inhibition of TNF in the spleen is provided by ChAT+ T lymphocytes.

Macrophages in the spleen are a major source of systemic TNF in experimental endotoxemia (25, 51). Monocytes and macrophages express cholinergic receptors and respond to cholinergic agonists with reduced release of proinflammatory cytokines (4, 50). Expression of α7-nAChRs is, furthermore, essential for vagus nerve-mediated inhibition of TNF release in endotoxemia and required for the macrophage response to cholinergic agonists (64). Since α7-nAChRs are expressed in several organs, including the CNS and autonomic ganglia, it was conceivable that the cholinergic signal required for the integrity of the inflammatory reflex occurred outside the immune system and not in splenic macrophages. Experiments with chimeric mice created by bone marrow transfer demonstrated that α7-nAChR deficiency in nonbone marrow-derived cells did not abolish vagus nerve inhibition of cytokine production in endotoxemia. In contrast, α7-nAChR deficiency in bone marrow-derived cells, including leukocytes, abolished the inhibitory effect of VNS on TNF production (42). These observations indicate that signaling through α7-nAChRs on macrophages in the spleen is essential for the integrity of the inflammatory reflex.

Thus, electrical signals in vagus nerve fibers that terminate in the celiac ganglion (5) activate the splenic nerve to release norepinephrine, which, in turn, activates ChAT+ T cells in the spleen to release ACh and inhibit TNF release by activating α7-nAChRs on macrophages (Fig. 2).

**Therapeutic Effects of Electrical VNS**

Activation of signaling in the inflammatory reflex by electrical nerve stimulation or pharmacological means not only attenuates TNF production but can also treat a variety of diseases with an inflammatory component in animal models (for a review, see Ref. 2). For example, activation of the efferent arm of the inflammatory reflex reduces mortality after cecal ligation and puncture (CLP; a sepsis model), whereas disabling vagus signaling increases mortality (7, 24, 45). Central activation of the inflammatory reflex ame-
other immune diseases, including collagen-induced arthritis (2, 27, 62, 68, 69). In humans, analysis of HR variability (HRV) has been used as a measure of vagus nerve activity (53). Interestingly, HRV measurements upon hospital admission have a predictive value for outcome in human sepsis (1, 11, 46). Vagus nerve activity, as measured by HRV, is also a prognostic marker for ischemic cardiovascular disease (6, 14, 31, 35) and is reduced in autoimmune diseases, including rheumatoid arthritis (17, 32, 34, 54, 57). The findings on the correlation of HRV to disease do not establish causality of vagus activity for disease development but support the notion that modulation of vagus nerve signals may treat disease. Preliminary data from a phase II clinical trial of an implantable electrical vagus nerve stimulator in patients suffering from rheumatoid arthritis were recently presented (30). In this study, the stimulator was activated by the patient for <5 min/day by passing a magnet over the implanted device. Levels of disease activity score and C-reactive protein levels in blood were significantly reduced by the treatment and returned toward baseline levels when treatment was halted. These findings are encouraging, since they suggest that symptoms of rheumatoid arthritis and inflammation may potentially be controlled and treated by VNS in humans. Clinical trials of VNS as a treatment for other inflammatory diseases, e.g., Crohn’s disease, are also under way. It would be very interesting to investigate the potential of VNS for the treatment of other debilitating diseases with an inflammatory pathogenesis, including atherothrombosis (23, 33).

Other Immune-Regulatory Neural Reflexes

In addition to the vagus nerve circuit described above, a number of other neural immune control pathways have been described. Electrical stimulation of the sciatic nerve has been reported to improve outcome in experimental bacterial peritonitis (59). VNS reduces murine marginal zone B cell migration and antigen production in the spleen in response to blood-borne streptococci (37). VNS also reduces experimental inflammatory bowel disease in splenectomized animals, indicating that discrete innervation by the vagus nerve regulates the inflammatory response at different locations (36, 43). Furthermore, in experimental murine stroke, invariant natural killer T (iNKT) cell migration in the liver is arrested in response to adrenergic signals. This is a mechanism behind the increased susceptibility to fatal infections after stroke in mice, and blockade of the adrenergic nerve signaling restores iNKT migratory activity and reduces complications to infection in this model (67). In addition, Arima and colleagues (3) showed in experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis, that autoreactive T cells enter the CNS at a specific spinal cord location. In this case, CNS access for T cells depends on a reflex neural circuit originating in hindleg muscle contractions that autoreactive T cells enter the CNS at a specific spinal cord location (3). It is conceivable that some of the neural reflexes that regulate inflammation and immune cell activity can be therapeutically modulated for the treatment of clinical disease. Furthermore, monitoring of signals in the neuronal circuits that regulate immune system activity may
prove to be of diagnostic value in conditions with nonresolving inflammation.

Conclusions

Neural reflex circuits regulate and optimize organ function, including immune responses, in evolutionarily ancient animals and mammals. Developments in the field of neural immune control have spawned clinical trials focused on novel therapies for inflammatory disease, for example, drugs that modulate α2-1nAChR signaling and implantable nerve stimulators. The emerging field of bioelectric medicine holds promise, and it is possible that nerve stimulators will be part of the standard treatment for select inflammatory diseases in a not very distant future.

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