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 report to the central nervous system (CNS) and motor (efferent) 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 to optimize organ perfusion and delivery of O2 and nutrients (58).

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 clinical trials (9, 30, 43).

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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 (60). Our current understanding of this reflex is based on a number of seminal discoveries. Watkins et al. and other research teams (10, 49, 65) 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-
The spleen is a major source of systemic TNF in endotoxemia (25, 51). Monocytes and macrophages express cholinergic receptors and respond to cholinergic agonists with reduced release of proinflammatory cytokines (4, 50). Expression of α7nACHRs is, furthermore, essential for vagus nerve-mediated inhibition of TNF release in endotoxemia and required for the macrophage response to cholinergic agonists (64). Since α7nACHRs 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 α7nACHR deficiency in nonbone marrow-derived cells did not abolish vagus nerve inhibition of cytokine production in endotoxemia. In contrast, α7nACHR deficiency in bone marrow-derived cells, including leukocytes, abolished the inhibitory effect of VNS on TNF production (42). These observations indicate that signaling through α7nACHRs on macrophages in the spleen is essential for the integrity of the inflammatory reflex.

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-
VNS, as well as α2-nAChR agonist administration, ameliorates a range of experimental autoimmune 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. These nervous signals promote vascular chemokine (C-C motif) ligand 20 expression, which, in turn, facilitates T cell entry into the CNS. Disease development in this model was prevented by inhibition of the afferent nerve signals originating in soleus muscle contractions that reach the spinal cord at this specific lumbar 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 α4nAChR signaling and implantable nerve stimulators. The emerging field of bioelectronic 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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