Neural control of the immune system

Eva Sundman and Peder S. Olofsson

Section for Anesthesiology and Intensive Care Medicine, Department of Physiology and Pharmacology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; and The Feinstein Institute for Medical Research, Laboratory of Biomedical Sciences, Manhasset, New York

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Sundman E, Olofsson PS. Neural control of the immune system. *Adv Physiol Educ* 38: 135–139, 2014; doi:10.1152/advan.00094.2013.—Neural reflexes support homeostasis by modulating the function of organ systems. 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 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.

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pharmacologically 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 (intracerebroventricularly) compared with intravenous dosing and that an intact vagus nerve is required for direct signals between nerves and splenic lymphocytes. Pattern recognition receptors are indicated as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors (NLRs).

The spleen is 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).
liorates colitis (26). VNS, as well as α7nAChR 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 α2δ-AChR 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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