Consolidating roles of neuroimmune reflexes: specificity of afferent, central, and efferent signals in homeostatic immune networks

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Neural reflexes occupy a central role in physiological homeostasis. The vagus nerve is a major conduit for transmitting afferent and efferent signals in homeostatic reflex arcs between the body and the brain. Recent advances in neuroscience, immunology, and physiology have revealed important vagus nerve mechanisms in suppressing inflammation and treating rheumatoid arthritis and other autoimmune conditions. Numerous clinical trials indicate that there is significant benefit to vagus nerve stimulation therapy. Although many questions are still unanswered, it will be important, even necessary, to pursue answers that will be useful in guiding interventions to modulate immunological and physiological homeostasis.

Physiological homeostasis is fundamental to health. It is mediated by nervous system reflexes that continuously monitor and regulate the body's internal environment and adjust cellular and organ activities to operate in balance. Central to these regulatory mechanisms is the vagus nerve, a major information conduit transmitting signals between the body and brain. Recent advances in this field were discussed during a 5 day meeting entitled "Brain Body Physiology," at Cold Spring Harbor Laboratory's 88th Symposium in New York. Formal talks and informal discussions with meeting participants revealed important new mechanistic insights into homeostatic reflex arcs, the implications of their dysfunction, and the therapeutic potential for restoring homeostasis by electrically modulating neural activity in the vagus nerve and in the brain.

The story begins at the turn of the 20th century, when Santiago Ramón y Cajal memorialized, in beautiful ink drawings, the components of simple vagus nerve reflexes that control coughing and vomiting (Swanson et al. 2017). His contemporary and friend, Charles Sherrington, a physiologist who with Ramón y Cajal would share distinction as "fathers of neuroscience," proposed that simple reflexes cooperate to produce complex behaviors (Sherrington 2023). Together, their observations established that homeostasis is an emergent property of interacting neural networks and simple reflexes.

A simple reflex is initiated by input arising in the afferent or sensory arc, as feedback from the body to the brain. Brainstem nuclei receive this input and respond using corrective efferent signals that travel back through autonomic neurons, including the vagus nerve, and through neuroendocrine pathways, including the hypothalamic pituitary axis. Homeostasis is maintained or restored when reflexes are activated by input deviating from physiological set points established in the brainstem, which executes corrective signals to the body. For example, if blood pressure drops, baroreceptors send signals via the vagus nerve to neurons residing in brainstem nuclei, which then issue efferent autonomic signals to increase heart rate and constrict blood vessels, raising blood pressure. Dysfunction in these reflex networks is a hallmark of impaired homeostasis and illness.

Physiologists in the 20th century identified dozens of autonomic reflexes that establish homeostasis in the body's organ systems, except for the immune system. However, at the turn of the 21st century, a series of discoveries revealed an "inflammatory reflex" in the vagus nerve that inhibits inflammation (Tracey 2002). This established a new paradigm, indicating that specific efferent vagus neurons inhibit cytokine production in the spleen, colon, and other tissues. Extensive evidence derived from neuroscience, immunology, molecular genetics, and pharmacogenetics elucidated specific anti-inflammatory efferent signals. One pathway arises in cholinergic neurons in the brainstem dorsal motor nucleus (DMN) that project to the celiac superior mesenteric ganglion complex, the origin of catecholaminergic neurons that

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project to the spleen (Kressel et al. 2020). Laser stimulation of the DMN (using ChR2 optogenetics) induces compound action potentials in the splenic nerve, direct neurophysiological evidence that parasympathetic signals in the vagus nerve regulate sympathetic signaling in the splenic nerve. In the spleen, these neural signals effect the inhibition of a cytokine storm and the mobilization of anti-inflammatory T cells (Tregs) that express choline acetyltransferase, cells that we call T-ChAt (Olofsson et al. 2016). As discussed at the meeting, the inflammatory reflex spawned research in several important areas and raised new questions being actively pursued in dozens of research centers.

First, is the inflammatory reflex impaired in human autoimmune diseases, such as rheumatoid arthritis, where the immune system attacks the body's tissues, and can this dysregulation be reversed using vagus nerve stimulation (VNS)? VNS involves the implantation of a device that delivers electrical impulses to the vagus nerve, modulating its activity. This approach has been used clinically for over four decades, with more than 200,000 patients receiving VNS devices to manage epilepsy and depression. Recent clinical trials provide compelling data that stimulating the inflammatory reflex using VNS in humans inhibits the cytokine storm. Moreover, VNS also reduces disease severity in rheumatoid arthritis and inflammatory bowel disease, two conditions currently treated using immune-suppressing agents, including anti-TNF and anti-IL-1 treatments (Koopman et al. 2016). Because these agents are invasive (injectable) and labeled with black box warnings (because of their serious, life-threatening side effects), ongoing clinical studies are addressing the relative risks and benefits of using VNS instead of, or in addition to, drugs. Recently, SetPoint Medical (a company I cofounded), announced that a clinical trial in rheumatoid arthritis achieved its primary therapeutic end point in patients with severe disease that was unresponsive to available drugs, suggesting that another hurdle to clinical adoption has been overcome (https://www.businesswire.com/news/home/20240321236439/en/SetPoint-Medical-Accepted-into-FDA-Total-Product-Life-Cycle-Advisory-Program-for-Development-of-its-Neuroimmune-Modulation-Platform-for-the-Treatment-of-Multiple-Sclerosis).

Second, how does the brain, through its brainstem neurons and networks, regulate immunity? Charles Zuker and collaborators (Jin et al. 2024) discovered that cytokines produced during inflammation in tissues initiate the afferent arc of reflexes that modulates the activity of proinflammatory and anti-inflammatory responses. A specific population of vagus neurons responds to proinflammatory cytokines (TNF and IL-1), and a different population of neurons responds to anti-inflammatory cytokines (IL-10). Ablating vagus nerve afferent fibers that project into the brainstem nucleus of the solitary tract (NST) causes unregulated inflammation, whereas experimental activation of specific vagus fibers inhibits inflammation and stimulates anti-inflammatory responses. These results establish a critical role of NST neurons in establishing the inflammatory set point necessary to establish immune homeostasis.

Third, does the brain store memories or engrams of inflammatory events, and do these neural networks control inflammation in the body? Asya Rolls and collaborators (Koren et al. 2021) discovered that the development of inflammation in the colon or peritoneal cavity activates brain networks in the insular cortex and other regions. Importantly, using chemogenetic reactivation of neuronal ensembles previously activated during the period of experimental inflammation incites the onset of inflammation in specific tissues, even in the absence of an inflammatory stimulus. Because these signals are tissue- and network-specific, it now appears that "immunological memory" is not restricted to T and B cells but also includes the brain as a repository of immune information.

Thus, we have new paradigms for how the nervous system and immune system interact to maintain immunological homeostasis. When the brain is informed by afferent signals in the vagus nerve that the inflammatory internal milieu is deviating from set points, the brainstem neural networks produce coordinated efferent corrective signals, traveling through the vagus nerve and other autonomic nerves and via neuroendocrine pathways. These and other advances are encouraging dozens of laboratories to produce functional neural maps of immune control and response in the central nervous system. We are living in the era of the "immunological homunculus," but we have swapped out neurosurgeon Penfeld's handheld electrodes to stimulate brain tissues and correlate tissue locations with specific behavior in patients and instead use pharmacogenetic and optogenetic methods in mice to identify specific brain neurons modulating specific immune responses (Tracey 2007). Neuroimmunology today is arguably the most exciting field in all of science.

Moreover, the vagus nerve is readily accessible in the neck, and more than 200,000 patients over four decades have received surgically implanted vagus nerve pacemaker-like devices to treat epilepsy and depression. The procedure has been established as safe, especially in the treatment of resistant patients facing ongoing illness combined with side effects from ineffective, expensive, and other invasive alternative therapies. Numerous clinical trials indicate that there is significant benefit to vagus nerve stimulation therapy, so while progress continues along the reductionist path to defining afferent, central, and efferent signaling pathways in these networks at the molecular level, there is also a significant clinical need, if not demand, for new therapies. It will be important, even necessary, to interpret such progress in the light of how this coming knowledge will be useful in guiding interventions that modulate the emergent properties of immunological and physiological homeostasis.

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