

Mind over immunity

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ABSTRACT The central nervous system regulates the innate immune system by elaborating anti-inflammatory hormone cascades in response to bacterial products and immune mediators. We recently discovered that the central nervous system also responds via acetylcholine-mediated efferent signals carried through the vagus nerve. Nicotinic cholinergic receptors expressed on macrophages detect these signals and respond with a dampened cytokine response. Vagus nerve stimulators can mimic this response and can prevent lethal endotoxemia. This newly appreciated cholinergic anti-inflammatory pathway provides a neural substrate to study brain-immune interactions and might be harnessed for therapy of cytokine-mediated disease.—Tracey, K. J., Czura, C. J., Ivanova, S. *Mind over immunity*. *FASEB J.* 15, 1575–1576 (2001)

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WHEN WE SENSE lipopolysaccharide, we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all the tissues in the area. . . We live in the midst of explosive devices; we are mined. (Lewis Thomas, 1974)

The innate immune system, specifically macrophages and neutrophils, is the front line in the defense against invading pathogens. Invasive stimuli cause these cells to unleash an arsenal of mediators, including tumor necrosis factor (TNF) and other cytokines. This response activates coagulation, restricts blood flow to the affected area, and localizes infection or injury. The overwhelming majority of mammalian–bacterial interactions result in the eradication or containment of the pathogens without significant injury to the host. These ‘successful’ proinflammatory responses are usually kept in check by the restraining influence of anti-inflammatory mechanisms. Occasionally, however, the restraining effects of these regulatory mechanisms fail, and the cytokine cascades become as dangerous as the pathogens themselves. When this happens, the host can succumb to complications of systemic inflammation or sepsis. For instance, lethal endotoxemia initially induces the unchecked systemic overexpression of TNF and later HMG-1, leading to the death of the host (1, 2). This scenario of cytokine-mediated lethal shock and tissue injury has been likened to ‘friendly fire’ injury in military maneuvers.

It is widely known that the central nervous system (CNS) modulates the fight-or-flight response. For example, the sight of a charging lion stimulates adrenergic responses that increase cardiac output, mobilize energy supplies, and support other protective mechanisms necessary for survival. Recent evidence supports a comparable paradigm for the role of the CNS in modulating the response to microbial invasion. Cytokines, endotoxin, and other products of inflammation stimulate afferent neural signals in the vagus nerve that increase acute-phase responses, induce fever, and up-regulate the expression of interleukin (IL)-1 β in the brain (3–5). Afferent vagus neural signals are rapidly forwarded to the hypothalamic-pituitary axis, which releases adrenocorticotropin hormone; the resultant increase in glucocorticoid levels inhibits cytokine release by the innate immune system (6). Inflammation also activates the CNS to release melanocyte-stimulating hormone, another potent anti-inflammatory protein that inhibits cytokine synthesis (7). Thus, afferent neural signals alert the CNS to the presence of microbial threats or cytokine excess and reflexively stimulate an anti-inflammatory counter-response to prevent systemic inflammation.

We serendipitously discovered that efferent activity in the vagus nerve attenuates systemic inflammation (8, 9). Direct electrical stimulation of the vagus nerve during endotoxemia significantly attenuates TNF synthesis in tissue macrophages, reduces serum TNF levels, and prevents the development of lethal hypotension (8). In the absence of electrical stimulation, vagotomy alone significantly amplifies the TNF response to endotoxemia and shortens the time to onset of lethal shock. The molecular basis for the communication between the vagus nerve and the innate immune system is acetylcholine, the principal neurotransmitter of the parasympathetic nervous system (8, 9). Macrophages express cholinergic receptor activity; acetylcholine significantly inhibits LPS-induced TNF protein release through a post-transcriptional mechanism (8). Acetylcholine significantly inhibits the release of other proinflammatory cytokines, including IL-1 β , IL-6, and IL-18, but not IL-10, an anti-inflammatory cytokine. Other cholinergic agonists (nicotine and muscarine) also

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inhibit LPS-induced TNF release; macrophage cholinergic receptor activity is exquisitely sensitive to α -conotoxin, implicating nicotinic-type receptor activity in the transduction of the cytokine-inhibiting signal. Collectively, these observations implicate cholinergic signals from the CNS as direct and rapid modulators of the inflammatory response (8, 9). This mechanism has been termed the 'cholinergic anti-inflammatory pathway.'

It is plausible that vagus nerve stimulators can be developed for therapeutic use in treating inflammation. For instance, it may one day be possible to treat TNF-mediated disease (e.g., rheumatoid arthritis, Crohn's disease, endotoxemia) with vagus nerve stimulation as a replacement or supplement to anti-TNF strategies. The cholinergic anti-inflammatory pathway may be activated in placebo or acupuncture responses. In such cases there may not be a conscious awareness of the efferent activity in the vagus nerve, but it may be reasonable to train subjects to voluntarily modulate their immune response in a manner fashioned after the voluntary control of heart rate. Perhaps we should not be surprised that the brain possesses the capability to both detect and defuse the minefield of innate immunity. **FJ**

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