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THE NEUROIMMUNE REFLEX: VAGUS NERVE–MEDIATED CONTROL OF INFLAMMATION AND ITS TRANSLATIONAL THERAPEUTIC POTENTIAL

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Inflammation is one of the main causes of many chronic diseases, but recent studies have indicated that immune responses are not regulated only by biochemical signals but also by direct neural input. The vagus nerve has been identified as an important neuroimmune interface that controls systemic inflammation through a reflex mechanism known as the inflammatory reflex. In this review, we evaluate fundamental studies and recent improvements in understanding the cholinergic anti-inflammatory pathway (CAP) and explore its potential applications.

Experimental studies have shown that stimulating the vagus nerve reduces the production of proinflammatory cytokines, especially tumor necrosis factor (TNF). This effect is mediated by acetylcholine released from the vagus nerve, which binds to α7 nicotinic acetylcholine receptors (α7nAChR) on immune cells (de Faria et al., 2025). The underlying circuit is a classical reflex arc. Afferent (sensory) vagal fibers detect peripheral inflammatory signals such as TNF, interleukin-1β (IL-1β), and bacterial lipopolysaccharides. These signals are sent to the nucleus tractus solitarius in the medulla oblongata. After integration, efferent (motor) fibers release acetylcholine, completing the reflex. This pathway is rapid, localized, and reversible, and is fundamentally distinct from slower humoral anti-inflammatory mechanisms.

Obesity is an excellent example of how reflexes can fail. As obesity is associated with chronic inflammation due to increased fat tissue mass, macrophage recruitment, and metabolic endotoxemia, it gradually results in decreased vagus nerve function. Reduced vagus nerve function is associated with several factors, including leptin resistance, elevated SOCS3 (Suppressor of Cytokine Signalling 3) protein production, and decreased α7nAChR expression within the hypothalamus. Genetic deletion of α7nAChR has been demonstrated to increase insulin resistance in response to a high-fat diet (Gerritsen & Band, 2018). While their genetic deletion has been demonstrated to increase the insulin resistance in response to a high-fat diet (Gerritsen & Band., 2018) Therefore, this anti-inflammatory pathway fails to inhibit cytokine secretion. Eventually, adipose tissue inflammation interferes with insulin action and causes the development of insulin resistance, which is the driving feature of type 2 diabetes mellitus.

Clinically, the vagus nerve is being targeted using both implantable and noninvasive devices. One implantable stimulator, called the SetPoint System, received approval from the United States Food and Drug Administration in 2025 for treating rheumatoid arthritis. This approval was based on the RESET-RA clinical trial, which showed that one minute of daily stimulation allowed 75% of patients who had not responded to other treatments to remain free of biologic or targeted synthetic DMARDs (Tesser et al., 2025). Another non-invasive method is Transcutaneous Auricular Vagus Nerve Stimulation (TaVNS), which is an ear-worn device that lowers systemic cytokines and helps manage diseases such as rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, and postoperative inflammation (Han et al., 2026). Both types of devices work by activating the cholinergic anti-inflammatory pathway, the body's natural nerve-based mechanism for controlling inflammation.

Remarkably, everyday lifestyle practices also enhance vagal tone naturally, without any device. Slow diaphragmatic breathing (5–6 breaths per minute) and cold-water face immersion trigger the vagus-dependent diving reflex, increasing heart rate variability and suppressing cytokine release. According to Bretherton et al. (2023), regular aerobic exercise increases heart rate variability and vagal tone. Compared to sedentary individuals, those who consume probiotic-rich diets and fibers show higher production of short-chain fatty acids from microbial fermentation in the gut, which helps protect the gut lining and improve vagal tone to suppress inflammation.