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Perspective

The Anti-Inflammatory Cholinergic Pathway & Cardiometabolic Dysfunctions

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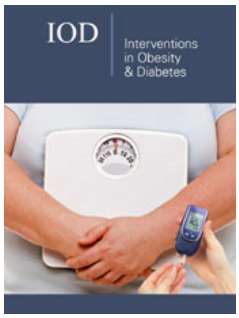

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Perspective

The Vagus Nerve (VN) is the main component of the Parasympathetic Nervous System (PNS) and is composed of sensory afferent and motor efferent fibers. It has various functions, including reducing heart rate, motility, and gastrointestinal secretion. The VN also plays a fundamental role in regulating the Cholinergic Anti-Inflammatory Pathway (CAP), a mechanism that modulates the immune system's inflammatory response [1]. The CAP is integrated into the Central Nervous System (CNS), where the afferent Vagus Nerve (VN) is activated by cytokines in the presence of a pathogen or tissue damage [1,2]. After activation, the signal transmitted by the afferent pathway reaches the nucleus of the solitary tract (NTS), which is in the bulbar region of the brainstem. The NTS is interconnected with the dorsal motor nucleus, where the efferent motor fibers of the VN originate. These fibers connect to the ganglia and organs of the periphery. When they produce and release Acetylcholine (ACh), they bind to the α7 subunit of the nicotinic ACh receptor (nAChRα7), which is present in macrophages. This process attenuates the production of inflammatory cytokines [3]. The results of Borovikova et al.'s [4] study showed that rats treated with Lipopolysaccharides (LPS), endotoxins found in the cell walls of Gram-negative bacteria, exhibited elevated TNF-α levels in their blood and liver. These effects were exacerbated in the absence of the VN [4]. Similarly, van Westerloo et al. [5,6] observed high concentrations of TNF-α, IL-1β, and IL-6 in peritoneal tissue fluid and heart blood samples in models of septic peritonitis and endotoxemia in vagotomized rodents. Furthermore, a significant reduction in TNF-α, IL-1β and IL-6 was observed in animals following nicotine administration or electrical stimulation of the Vagus Nerve (ENV) [5,6]. These results indicate that nicotine, as a nicotinic acetylcholine receptor agonist, interacts with the α7 receptor and that ENV increases ACh levels. Both factors contribute to the attenuation of cytokine formation in macrophages [4-6]. These studies suggest the importance of the VN in controlling the CAP pathway.

Tracey's group also demonstrated that the spleen, a lymphoid organ, appears to be essential for the CAP pathway [3]. One study reported that the spleen was responsible for producing approximately 90% of circulating TNF-α when the isolated organ was exposed to LPS. Furthermore, the group demonstrated that ENV decreased the concentration of TNF-α in the spleens of rats treated with LPS. As the spleen receives sympathetic innervation, the group hypothesized that some of the efferent ENV fibers connect to the superior celiac-mesenteric ganglion, which is in the subdiaphragmatic region [7]. In the ganglion, ACh binds to the α7 receptor when released, which is the same subtype found in mononuclear cells of the immune system. Thus, the efferent VN synapses with the sympathetic splenic nerve. The latter originates from the ganglion and innervates the spleen. After being activated by ACh, the splenic nerve contributes to the release of norepinephrine [7]. In turn, norepinephrine

interacts with β-adrenergic receptors in a subset of T cells (TCD4+ memory T cells) in the white pulp region of the spleen, producing ACh. In the same location, binding of ACh to the α7 receptor reduces levels of inflammatory cytokines [7]. Therefore, it is possible that, in the inflammatory models discussed above, vagotomy may have negated the decrease in systemic levels of inflammatory cytokines originating from spleen macrophages [3].

Together, the studies demonstrated the beneficial effects of ENV and pharmacological stimulation on the activation of the CAP pathway via peripheral α7 cholinergic receptors. However, it has been found that this pathway can be controlled by the M1AChR subtype of the muscarinic ACh receptor when centrally acting PNS agonist drugs are used. This receptor is expressed in cholinergic neurons in various regions of the brain, such as the cerebral cortex and CNS. Evidence suggests that central activation of the M1AChR is crucial for signalling the peripheral inflammatory response [8]. Other drugs, such as those used to treat Alzheimer's disease which have an inhibitory effect on Acetylcholinesterase (AChE) - an enzyme present in neurons of the peripheral nervous system of the brain which is responsible for the degradation of ACh - have been investigated. One such AChE inhibitor is galantamine, an alkaloid with the molecular formula $C_{17}H_{21}NO_3$ obtained from the bulbs of flowers such as Galanthus woronowii or other species of the Amaryllidaceae family. Reduced TNF-α expression were observed in rodents with sepsis that were treated with galantamine [9].

It is worth noting that inflammation has been associated with obesity- and Metabolic Syndrome (MS)-related complications. Consuming processed food while being obese can worsen metabolic dysfunctions associated with low-grade chronic and systemic inflammation. This is characterized by moderate levels of inflammatory mediators that can compromise autonomic and cardiovascular function [10,11]. Evidence suggests that inflammation and oxidative stress both contribute to the development and progression of metabolic dysfunctions such as lipogenesis, which leads to increased adipose tissue and local and systemic insulin resistance, resulting in autonomic imbalance [10-12].

Previous study by our group have shown that fructose overload in rats (a model of MS) increases TNF-α in cardiac tissue, resulting in increased insulin resistance, Blood Pressure (BP) and cardiac and vascular sympathetic modulation [13]. By the 15th and 30th days, increased levels of inflammatory cytokines were observed in both adipose tissue and the spleen [14]. These impairments were prevented by aerobic exercise training, a well-known non-pharmacological approach that improves autonomic regulation [15]. More recently, we found that fructose consumption by parents resulted in an increase in Blood Pressure (BP), autonomic imbalance based on baroreflex sensitivity analyses, and metabolic dysfunction in their offspring [16]. These results indicate a transgenerational effect in the complex relationship between cardiometabolic and autonomic changes. In this sense, reports in the literature have associated inflammation with metabolic dysfunction and reduced vagal activity, suggesting the involvement of the CAP pathway in this condition [2,10]. To investigate the role of the CAP pathway in metabolic dysfunction, Satapathy et al. demonstrated the effectiveness of galantamine in mitigating metabolic abnormalities in an obesity model [17]. Galantamine treatment reduced pro-inflammatory cytokines, weight, and adipose tissue, while improving insulin sensitivity and resistance in animals. Recently, we demonstrated that galantamine treatment improved insulin tolerance, increased vagal modulation, and decreased sympathetic/vagal balance, sympathetic vascular modulation, and BP variability in the offspring of fructose-overload-subjected parents, compared to untreated fructose offspring. Additionally, we obtained correlations between vagal modulation and insulin resistance and BP, suggesting that galantamine treatment improved cardiovascular autonomic modulation, which was associated with the amelioration of cardiometabolic dysfunction in the offspring of parents who had been exposed to chronic fructose consumption [18]. In a clinical study involving MS patients treated with galantamine, we observed an improvement in insulin sensitivity, alongside decreased concentrations of leptin, adiponectin, and TNF-α, as well as, autonomic imbalance, and greater activation of the CAP pathway [19].

In summary, these findings reinforce the idea that autonomic imbalance can modulate the inflammatory response via the CAP pathway, thereby playing a significant role in the development and progression of cardiometabolic dysfunction. These findings underscore the therapeutic potential of vagal modulation as a novel strategy for managing obesity and MS.

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