Trends in Cardiovascular Medicine 26 (2016) 1–11

Available online at www.sciencedirect.com

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Vagus nerve modulation of inflammation: Cardiovascular implications

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ABSTRACT

The vagus nerve modulates inflammatory responses in various organ systems. Emerging evidence indicates that the vagus can have profound and complex effects on cardiovascular function, remodeling, arrhythmias, and mortality by several mechanisms. In heart failure and during ischemia, an adverse inflammatory response can occur. The vagus nerve may modulate cardiovascular disease and outcomes by affecting inflammatory responses. Here, evidence for and components of the vagus inflammatory reflex are reviewed and evidence for and implications of effects of vagus activation on inflammation in the cardiovascular system are considered.

Introduction

The vagus nerve regulates sinus (i.e., heart) rate and AV nodal conduction. Traditionally, this is where the thinking ends when it comes to the vagus nerve and cardiovascular physiology. However, the vagus nerve modulates inflammatory responses in various organ systems and in animal models [1,2]. However, emerging evidence indicates that the vagus nerve can have profound and complex effects on cardiovascular function, remodeling, arrhythmias, and mortality by other mechanisms [3]. In heart failure and during ischemia, an adverse inflammatory response can occur. Thus, the vagus nerve may modulate cardiovascular disease and outcomes by affecting inflammatory responses [3–7].

Here, evidence for and components of the vagus inflammatory reflex are reviewed and evidence for and implications of effects of vagus activation on inflammation in the cardiovascular system are considered.

Organization of the parasympathetic nervous system

Cardiovascular parasympathetic innervation occurs centrally via the right and left vagus nerves. Effects can be rapid and/or phasic (e.g., respiratory variation) or prolonged and tonic (related to localized central processing or ganglionic gating) [8]. Selective neural and hormonal modulation occurs centrally, at local cardiac ganglia, and via intracellular signaling in specific target cardiac cells.

The vagus nerve has afferent and efferent pathways. Afferent sensory baro/mechanoreceptors located in the heart and major blood vessels and chemoreceptors in the carotid bodies transmit signals centrally to the nucleus tractus solitarius, hypothalamus, and brainstem tegmental nuclei, providing feedback from the cardiovascular system to the central nervous system. Efferent preganglionic extensions at medial medullary sites (nucleus ambiguus, nucleus tractus solitarius, and dorsal motor nucleus) are modulated by "higher centers" in the forebrain (hypothalamus, amygdala, and insular cortex), constituting the central autonomic network. All activity extends peripherally through the vagus to post-ganglionic neurons, located in ganglia (cardiac fat pads), activated via nicotinic receptors, and then, post-synaptically, via muscarinic end-organ receptors.

In the normal resting state, parasympathetic, not sympathetic, activity regulates the sinus node. Acute stress initiates the vagus withdrawal and sympathetic stimulation; long-standing physical activity enhances resting vagus activation and suppresses exercise-induced sympathetic tone. Vagus

The author has indicated that there are no conflicts of interest.

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http://dx.doi.org/10.1016/j.tcm.2015.03.016
1050-1738/

activation inhibits sympathetic activity pre-synaptically [9] and post-synaptically, thus nullifying sympathetic activation completely at rest. Abrupt vagus activation can inhibit sympathetic activation that may occur with exercise, blood loss, or hypotension due to a tachyarrhythmia. This is known as "accentuated antagonism." Likewise, sympathetic activation can inhibit parasympathetic activation.

The vagus nerve fibers co-exist. "A-" fibers are myelinated, the largest, and fastest conducting. Afferent fibers include slow-conducting unmyelinated C-fibers and small diameter A-delta fibers, whereas small, thin, non-myelinated post-ganglionic C-fibers and intermediate-diameter and intermediate-conducting pre-ganglionic myelinated B-fibers in efferent fascicles contribute to cardio-inhibition mediated at the level of the heart by muscarinic (M2) receptors.

Efferent fascicles contain large myelinated A-β fibers belonging to the laryngeal bundle and cardio-inhibitory A-δ fibers that excite post-ganglionic neurons in cardiac fat pads (autonomic ganglia) via nicotinic receptors, affecting ganglionic transmission and ultimately parasympathetic activation via local neurons. Vagus efferent activation, tonic or phasic, depends on where fibers originate (nucleus ambiguus or dorsal motor nucleus) [10]. Nerves from these two nuclei differ in morphology, conduction velocity, firing, and effect on cardiac function [11,12]. Neurons from the nucleus ambiguus are thinly myelinated, have strong effects on heart rate, and are more phasic, whereas the neurons in the dorsal motor nucleus are non-myelinated and have a smaller effect on heart rate but greater effects on AV conduction and contractility. The effects from the dorsal motor nucleus are more tonic.

Vagus innervates predominately the sinus and the AV nodes, but extensions are distributed throughout the heart in a non-uniform epicardial/endocardial and regional fashion and not directly parallel to sympathetic innervation. Post-ganglionic (efferent) parasympathetic cholinergic fibers affect cardiac tissue through cardiac muscarinic (M) receptors. M2 receptors predominate, although, M3 and M4 receptors have been identified in the heart with density varying by location, cell type, and disease.

In heart failure, defective parasympathetic cardiac control exists and the influence of vagus diminishes even at rest [13–15]. This may actually occur before, or in connection with, elevation in sympathetic "tone" [16,17]. In heart failure, cardiac parasympathetic control is attenuated, ganglionic transmission and nicotinic receptor number is reduced, muscarinic receptor density can increase, and acetylcholinesterase activity can decrease [18]. M2 receptor density and sensitivity may change in part due to M2 receptor antibodies associated with remodeling in heart failure [19] (significance unknown [20,21]). In heart failure, parasympathetic withdrawal is associated with a shift from M2 to M3 and/or M4 receptors on cardiac structures [22] and pro-inflammatory cytokines [23].

Local inflammatory responses

Pathogen- and danger-associated molecules recognized by toll-like receptors and nucleotide-binding oligomerization design domain-like receptors on immune cell surfaces release tumor necrosis factor (TNF-α), Il-6, IL-1β, IL-18, high mobility group box 1 (HMGB1) and other pro-inflammatory cytokines that influence the pathogenesis of sepsis, ulcerative colitis, rheumatoid arthritis, and inflammatory disorders. Chronic inflammation has been not only linked to insulin resistance, metabolic complications, obesity, and several non-cardiovascular consequences but also linked to myocardial damage, heart failure progression, and cardiovascular death.

TNF-α and HMGB1 released by activated immune or damaged tissue cells can cause organ damage and failure. During sepsis, HMGB1 promotes epithelial cell permeability, leading to multi-organ system failure, and can cause death. Release depends upon NLRP3 inflammasome activation that mediates pro-inflammatory cytokines IL-1β, IL-8, and capsace-1. Inflammasomes cause "pyroptosis," a form of pro-inflammatory programmed cell death [24].

Components of innate immunity include T-helper (TH) cell lymphocytes subclassed as TH-1 secreting interferon-γ, IL-2, and TNF-β, and TH-2 secreting IL-4, IL-10, and IL-13 [25]. These cytokines, in concert with activated macrophages and natural killer cells, become major constituents of cellular immunity. IL-12, TNF-α, and other cytokines stimulate nitric oxide synthesis and other inflammatory mediators, driving a chronic, delayed-type, inflammatory response.

Cholinergic response to inflammation

Work from the 1970s pointed to the importance of cholinergic stimulation on T-cell cytotoxicity. More recently, Borovikova et al. [26] described that acetylcholine or direct vagus nerve stimulation via a nicotinic pathway attenuates TNF-α, IL-1β, IL-6, and IL-18 release during endotoxemia in rats and prevents septic shock. Tracey delineated peripheral and central cholinergic anti-inflammatory pathways involving the α7 subunit of the nicotinic acetylcholine receptor (α7nAchR). This essential pathway regulates intracellular control of cytokine transcription and translation [27,28]. Inflammatory cells (T lymphocytes and B lymphocytes, monocytes, macrophages, and neutrophils) have α7nAchRs on their cell surfaces [29]. α7nAchR activation inhibits capase-1, HMGB1, and pro-IL-1β release. NLRP3 inflammasomes are inhibited by the α7nAchR [30].

JAK–STAT (Janus kinase–signal transducer and activator of transcription) factors signaling anti-inflammatory pathways for various cytokines depend on JAK2 activation by α7nAchR and subsequent STAT3 activation by mechanisms within macrophages that inhibit pro-inflammatory nuclear factor, NF-κB p65 [31,32]. In an animal model of intestinal manipulation, vagus stimulation affects STAT3 in macrophages and decreases surgery-induced inflammation [31]. When STAT1 and STAT3 were inhibited in rat peritoneal macrophages exposed to lipopolysaccharides, HMGB1 mRNA levels decreased [33].

The inflammatory reflex

Regulatory pathways of cytokine production have been elucidated [2,34], but cytokine production regulated by neural