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Published in:
Atherosclerosis

DOI:
10.1016/j.atherosclerosis.2006.10.009

Publication date:
2007

Document Version
Publisher's PDF, also known as Version of record

ELSEVIER

Atherosclerosis 195 (2007) e1–e9

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Review

Vagus–brain communication in atherosclerosis-related inflammation: A neuroimmunomodulation perspective of CAD

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Received 15 May 2006; received in revised form 19 September 2006; accepted 2 October 2006
Available online 13 November 2006

Abstract

The current understanding of the pathophysiology of atherosclerosis leading to coronary artery disease (CAD) emphasizes the role of inflammatory mediators. Given the bidirectional communication between the immune and central nervous systems, an important question is whether the brain can be "informed" about and modulate CAD-related inflammation. A candidate communicator and modulator is the vagus nerve. Until now, the vagus nerve has received attention in cardiology mainly due to its role in the parasympathetic cardiovascular response. However, the vagus nerve can also "inform" the brain about peripheral inflammation since its paraganglia have receptors for interleukin-1. Furthermore, its efferent branch has a local anti-inflammatory effect. These effects have not been considered in research on the vagus nerve in CAD or in vagus nerve stimulation trials in CAD. In addition, various behavioural interventions, including relaxation, may influence CAD prognosis by affecting vagal activity. Based on this converging evidence, we propose a neuroimmunomodulation approach to atherogenesis. In this model, the vagus nerve "informs" the brain about CAD-related cytokines; in turn, activation of the vagus (via vagus nerve stimulation, vagomimetic drugs or relaxation) induces an anti-inflammatory response that can slow down the chronic process of atherogenesis.

Keywords: Atherosclerosis; Coronary artery disease; Inflammation; Autonomic nervous system; Vagus nerve

Contents

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doi:10.1016/j.atherosclerosis.2006.10.009

1. Introduction

During the past decade, a shift in the understanding of the pathophysiology of coronary artery disease (CAD) has occurred with a major current emphasis on the role of inflammation [1]. Despite accumulating evidence, the implications of this knowledge are only beginning to be translated into clinical practice. Furthermore, recent progress in neuroscience and neuroimmunology provides important cues as for the role of the nervous system in modulating peripheral inflammation [2]. The implications of this modulation for major chronic illnesses (e.g., CAD, cancer) are only starting to be recognized [3,4]. Given such neuroimmune connections (see below), one important question thus can be: How does the brain "discover" and possibly modulate CAD progression?

The present article proposes a role for the vagus nerve in informing the brain about CAD-related peripheral inflammation and in modulating CAD-related inflammation. This approach introduces a potential new domain, namely the neuroimmunomodulation of atherogenesis. Though the separate elements of the proposed model are heavily researched and recognized on their own, the novelty of the present model is in integrating these fields and revealing their interrelationships. As we shall see, such integration has implications for clinical practice as well since intervening in one element can affect others. We briefly review the role of inflammation in CAD onset and progression, and the role of the vagus nerve in modulating inflammatory processes. We then review the neuroendocrine and behavioural modulators of vagal activity, and review studies that elicited changes in the activity of the vagus nerve in CAD and chronic heart failure (CHF). Finally, we provide an integrative model linking the vagus nerve to CAD-related inflammation and the brain, and propose future research and clinical directions.

2. The role of inflammation in CAD

Extensive reviews on the role of inflammation in CAD and the acute coronary syndrome (ACS) have been published in the past few years [1,5], beyond the role of other major risk factors. Furthermore, inflammatory markers have been related to other major CAD risk factors including obesity [6], smoking [7] and hypertension [8]. Briefly, the inflammatory response is pivotal in the development of CAD and in its progression to ACS. Development of CAD is characterized by enduring endothelial injuries and repair, to a large extent under the influence of the immune and inflammatory responses. When the endothelium is injured or is challenged by bacterial products, cholesterol, vasoconstricting hormones (e.g., norepinephrine), oxidative-stress products or pro-inflammatory cytokines, it responds with the expression of adhesion molecules. The adhesion molecules and chemokines include vascular cellular adhesion molecule 1 (VCAM-1) and interleukin-8 (IL-8), which encourage attraction of leukocytes to the intimal layer of the arteries [1]. The leukocytes (monocytes, T-cells), in turn, connect to the endothelium and to smooth muscle cells (SMC). The SMC migrate from the media to the intima, multiply there and thus increase the volume of the atherosclerotic lesion. This entire process can begin to limit the arterial lumen by a gradually increasing coronary occlusion. Due to various signals, SMC in the developing plaque produce matrix-metallo-proteinases (MMPs), which render geometric remodelling and destruction of the extra-cellular matrix in the atheroma [9]. Parallel to these processes, monocytes that have migrated into the coronary plaque and matured (macrophages) engulf oxidized low-density lipoprotein cholesterol (oxLDL), and become foam cells. These foam cells and their eventual necrosis produce the lipid-rich necrotic core of the atherosclerotic plaque.

Once the plaque has established, it can move through three stages that lead to ACS. The first stage is coronary plaque instability. Under the influence of macrophages and SMC, which produce MMPs, the extracellular plaque matrix may become unstable and prone to rupture [10,11]. One important factor, namely, macrophage migration inhibitory factor (MIF), influences accumulation of monocytes near the coronary plaque, thereby contributing to plaque instability. Indeed, blocking MIF in mice re-stabilized the plaque by altering its structure [12].

The second stage is plaque rupture, which occurs due to extra-plaque haemodynamic factors including shear stress, vasoconstriction, elevated blood pressure and cardiac output [13], as well as due to intra-plaque factors including angiogenesis and haemorrhage [14]. Pro-inflammatory cytokines (e.g., IL-1, IL-6, tumour-necrosis factor alpha, TNF-α), chemokines (e.g., IL-8), adhesion molecules (VCAM-1) and the ligation pair CD40-CD40L (co-stimulatory molecules between T-cells, monocytes and platelets) also increase the chances of plaque rupture via several mechanisms including the extra-plaque haemodynamic factors mentioned above [14]. For example, IL-1 can induce increased sympathetic output and blood pressure [15], both pro-rupturing factors. Another example is the enhanced expression of CD40L on platelets following inflammatory signals [16], which could secrete thromboxane A2, a potent vasoconstrictor. Following plaque rupture, the third and critical event of superimposed thrombosis occurs. This stage is under the influence of coagulation factors and under the influence of pro-inflammatory cytokines as well [17]. At this stage, an occlusive thrombosis may then lead to unstable angina or myocardial infarction (MI). Following ACS events, the processes leading to ACS may be enduring since pairing of platelet-leukocytes (which occur in the third stage) can induce further inflammation, increasing the chances of the first stages to reoccur [18]. This demonstrates the chronic inflammatory nature of atherosclerosis and the potential of recurrent ACS events.

3. The role of the vagus nerve in inflammation

The vagus nerve has received attention in cardiology mainly due to its parasympathetic effects on the heart [e.g., 19,20–22]. Imbalance of the sympathetic and parasympathetic (vagal) nerve systems have been associated with and may even precede various forms of cardiac diseases [e.g., 23]. In virtually all research on this subject, heart rate variability (HRV) and its components have been used as measures of sympathetic or parasympathetic activation [24].

In addition, the vagus nerve also plays an important role in peripheral inflammatory processes, which are relevant to CAD. The brain may be informed (or "learn") about peripheral inflammation either via direct immune penetration in brain regions lacking a blood–brain barrier, BBB [25], via prostaglandin signalling across the BBB following cytokine activation [26], or by an immune-to-nerve conversion of information at paraganglia of the vagus nerve which have receptors for IL-1 [27–30]. It is noteworthy that IL-1 and its associated markers have a prognostic role in ACS [31,32]. Thus, the vagus nerve is one of three major routes by which the brain is informed about peripheral inflammation. However, a few studies demonstrated that peripheral inflammation led to expected alterations in the brain (fever and elevated brain IL-1) with or without an intact vagus nerve [33,34]. Thus, the vagus nerve may be important in informing the brain mainly about relatively low concentrations of pro-inflammatory cytokines [33]. It is possible that the other two routes (direct BBB penetration and prostaglandin signalling) play a role in informing the brain about high levels of (systemic) inflammation. Detection of low, local concentrations of peripheral cytokines by the vagus nerve may be specifically relevant to local, CAD-related pro-inflammatory cytokines. Thus, the vagus nerve may "inform" the brain about CAD-related pro-inflammatory cytokines. One unknown issue is whether the neuroimmunomodulatory processes of the vagus nerve described below are sensitive to the severity of CAD since levels of pro-inflammatory cytokines do correlate with severity of CAD occlusion [35]. Future research needs to address this issue. The ascending pathway of the vagus nerve involves primarily the neurotransmitter acetylcholine. In contrast, the descending pathway uses mainly this neurotransmitter, in cardiac post-ganglionic neurones, yet nitric oxide may be released as a neurotransmitter as well [36].

Peripheral inflammation typically triggers symptoms of the sickness response that include reduced appetite, anhedonia, reduced sexual activity, hyperalgesia and fever. A major mediator of this response is brain IL-1 that is expressed by neurons and endothelial cells of the brain's blood vessels [37]. Brain IL-1 receptors were found to be expressed in regions involved in the sickness response such as the preoptic nucleus of the hypothalamus specifically coordinating the fever response [38].

What are the neuroimmune consequences of the arrival of ascending information concerning peripheral inflammation to the brain? Following activation of the nucleus of the solitary tract (NTS) in the brainstem, the major projectory nucleus of the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis is activated [39]. Activation of the HPA-axis produces high levels of cortisol, resulting in systemic anti-inflammatory effects [3]. This is a slow-acting and diffuse systemic anti-inflammatory pathway. However, a more rapid and localized response involves the descending vagal pathway, which is anti-inflammatory and uses cholinergic neurotransmission [3]. Though brain IL-1 has been shown to be involved in the cellular immunosuppressive consequences of peripheral inflammation [40], it is unclear whether this occurs via the slow or rapid routes. Nevertheless, via both of these anti-inflammatory routes, we propose that the vagus nerve may inhibit CAD-related pro-inflammatory cytokines and possibly even slow down CAD progression or prevent ACS. Thus, the vagus nerve may play a role in informing the brain about and in modulating CAD-related inflammation. The following sections will explain the modulators of vagal activity.

4. Neuroendocrine modulation of vagal activity

The autonomic nervous system consists of two branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), the latter innervating the heart via the vagus nerve. Both systems can counteract each other, work independently from each other, or work together [41]. Interactions between the sympathetic and parasympathetic nervous systems take place both in the central nervous system and the periphery. In the central nervous system, the integration of both branches occurs in several regions of the brainstem, the limbic system and higher cortical regions. Sympathetic and parasympathetic afferents interact in the NTS [42,43], which is a major visceral relay system in the brainstem. Regions in the limbic system, including the hypothalamus and the central nucleus of the amygdala, may also influence parasympathetic activity, since they are involved in the regulation of the baroreceptor reflex, in which both sympathetic and parasympathetic neurons participate [44]. Activity in the ventral part of the anterior cingulate cortex was found to correlate with an index of descending vagal activity, namely high frequency HRV [45]. Finally, a hormone that influences vagal activity is corticotrophin-releasing hormone (CRH), whose secretion is positively affected by sympathetic neurotransmitters [46]. Studies in rodent brains suggest that CRH in the central nucleus of the amygdala inhibits parasympathetic regulating activity in brainstem nuclei [47,48]. In the periphery, norepinephrine (NE), the post-ganglionic neurotransmitter of the SNS, inhibits the presynaptic acetylcholine release on post-ganglionic cardiac vagus nerve terminals [49], thus decreasing vagal activity. Neuropeptide Y (NPY) is co-transmitted with NE in response to sympathetic stimulation, and has an essential role in the crosstalk between the SNS and the immune system, via the Y2 receptor [50,51]. In the case of macrophages (relevant to CAD and ACS), NPY

potentiates the effects of norepinephrine on cytokine release (e.g., IL-6), depending on the adrenergic receptors involved [52]. Furthermore, NPY also inhibits vagal activity in the heart [53]. Thus, NPY (and NE) may potentially inhibit the immuno-modulating effects of the vagus nerve in relation to CAD-related inflammation.

5. Behavioural modulation of vagal activity

Several of the brain regions that interact with the vagus nerve are also associated with various behavioural factors and processes that predict CAD onset and progression. Transient mental states like depression are associated with increased activity in certain limbic regions and reduced cortical–limbic connectivity [54]. As mentioned above, limbic and cortical regions are associated with vagal activity [45]. Depression is also associated with reduced HRV [55], hence reduced vagal activity, and depression is an independent significant prognostic predictor in patients with CAD as revealed by a recent meta-analysis [56]. Recently, it was demonstrated that HRV was reduced in a group of MI patients with depression as opposed to post-MI patients without depression, independent of other clinical variables known to affect HRV [57]. In a following study by the same group, controlling statistically for HRV reduced the prognostic power of depression in post-MI patients, though it still remained significant [58]. These observations support the concept that reduced vagal activity may be one of the mechanisms underlying the detrimental effects of depression on post-MI prognosis. Similarly, anxiety and related constructs have been associated with increased activity in limbic regions and with a reduced regulatory cortical activity [59], though also illustrated by increased right-sided anterior cortical activity [60]. Anxiety is also associated with reduced HRV [61] and anxiety has predictive value in CAD as well [62,63]. These results indicate that anxiety and depression may influence vagal activity, which could affect both CAD-related inflammation and prognosis in CAD.

However, negative mood states may also be induced by peripheral inflammation, possibly by vagus nerve signalling. Administration of low concentrations of lipopolysaccharide (which induces peripheral inflammation) leads to depressed and anxious moods and behavioural withdrawal [64], part of the sickness response [37]. It is thus possible that these psychological responses may be induced by CAD-related inflammation as well. The constellation of negative mood and behavioural withdrawal, triggered by peripheral inflammation, may be especially salient for people with a Type-D personality, an emerging independent prognostic factor in CAD. Type-D refers to the combined traits of high distress and high social inhibition, and significantly predicts CAD prognosis, independent of known risk factors, e.g. [65–67]. Thus, it is possible that the vagus nerve, and its role in communicating information about and in modulating peripheral inflammation, may partly mediate the epidemiological links between psychological factors and CAD progression.

There is evidence that certain behavioural techniques including relaxation therapy can increase vagal activity (HRV), as recently examined in a meta-analysis [68]. There is also some evidence that relaxation interventions may influence pro-inflammatory cytokines [69]. Finally, a recent and unique study tested the effects of a "neuro-cardiac" HRV bio-feedback technique in which patients learned to alter their HRV using behavioural techniques while monitoring their own HRV. This intervention increased HRV in patients with coronary heart disease [70]. Thus, behavioural factors are associated with vagal activity, and behavioural interventions may modulate vagal activity, which in turn could influence its anti-inflammatory role. However, the effects of such behavioural interventions on vagal activity, on CAD-related inflammatory markers, and on prognosis in CAD patients have not yet been tested.

6. Electrical and drug activation of the vagus nerve in cardiac disease

The most direct manner for testing the role of the vagus nerve in CAD is by examining the effects of vagal stimulation in this disease. Two main types of vagal stimulation are vagus nerve stimulation (VNS) and administration of vagomimetic drugs. Zamotrinsky et al. [71] tested the effects of VNS on cardiac functions and angina care in patients with severe angina. Compared to angina patients that received usual treatment, VNS led to increases in the density of noradrenergic nerves and to increases in the density of microvascular vessels in the atria. Furthermore, VNS led to a reduction in taking vasodilators (glycerol trinitrate), reduction in heart rate and blood pressure, increases in left-ventricular ejection fraction and to improvements of ECG parameters. The investigators attributed these improvements only to reduced noradrenergic activity due to VNS. However, it is possible that some of these effects may have also been achieved by reducing CAD-related inflammatory markers in the coronaries, yet this was not tested. The results of Bernik et al. [72] may support such claims since they demonstrated that VNS reduced serum as well as myocardial levels of TNF-α in rats following aortic occlusion. TNF-α is a pro-inflammatory cytokine, and, together with its receptors, it has multiple roles in atherogenesis, ACS and prognosis, e.g. [73,74]. In another study using an animal model of chronic heart failure (CHF) [75], VNS was provided for six weeks to rats after an induction of a MI. The intensity of VNS was adjusted for each rat, to reduce heart rate by 20–30 bpm. Compared to sham-surgery controls, the VNS group had reductions in left-ventricular end-diastolic pressure and biventricular weight, and had significantly greater percentages of survival (86% compared to 50% in controls). The authors concluded that via prevention of pumping failure and cardiac remodelling, these effects were obtained. However, as commented by another group [76], the investigators did not examine whether their results stemmed from reductions in CAD-related pro-inflammatory

cytokines. Indeed, heart failure is associated with inflammation that causes remodelling of the left ventricle (especially after myocardial infarction, hence the link between CAD and CHF) [77]. Knowing that the cardiovascular effects of VNS may work through anti-inflammatory pathways is scientifically important but also has important clinical implications since the duration or manner of administering VNS may differ for altering haemodynamic versus inflammatory factors. It should be noted however, that one study in depressed patients [78] found that VNS led to increases in certain peripheral inflammatory markers (IL-6, TNF, and transforming growth factor, β). However, that study did not include a control group, participants where chronically depressed and on medication, factors which may have influenced these results.

Vagomimetic drugs have also been tested in CAD patients and animal models. A low dose of scopolamine induced vagal activation as assessed by HRV in patients with CHF [79]. However, no information was provided regarding subsequent morbidity. Similarly, low-dose atropine increased HRV in dogs with a healed MI [80]. Finally, Wang et al. [81] documented specific increases in several indices of HRV in post-MI patients receiving transdermal scopolamine compared to a placebo group. However, neither study reported effects of vagomimetic drugs on pro-inflammatory cytokines.

7. Integrative model—a neuroimmunomodulation approach to CAD

Based on integrated findings from neuroimmunology and cardiovascular research, we would like to introduce a neuroimmunomodulation approach to CAD. There is accumulating evidence concerning the anatomical routes and functional roles of neuronal innervations of the heart, which include afferent, efferent and inter-connecting neurones that act to provide cardiovascular stability [82]. As mentioned above, studies have also begun to document brain activity accompanying cardiovascular functions [42–48]. Pathological cardiac conditions including sudden death are thought to occur partly due to sympathetic overactivity and catecholamine toxicity [83]. In addition, following a MI, there is TNF-α induced endothelial leakage in the brain, specifically in the anterior cingulate. Given the role of this region both in autonomic/cardiovascular regulation and in mood, subsequent cingulate dysregulation may account for the adverse prognostic effects of distress in post-MI [84]. Thus, there is a constant communication between the heart and the central nervous system, which plays roles both in (ab)normal cardiovascular states and in mental states.

Along these lines, we would like to present an integrative model of the role of the vagus nerve in the communication and neuroimmunomodulation of pathological states in CAD. Fig. 1 depicts our hypothesized model concerning the role of the vagus nerve in "informing" the brain about and in modulating CAD-related pro-inflammatory cytokines. For the sake of being comprehensive, we also provide in the figure information concerning additional nuclei and routes relevant to the SNS. However, our main focus is on the PNS and specifically the vagus nerve. According to our model, the vagus nerve may inform the brain about inflammatory processes relevant to CAD or CHF since it transmits information to the brain about peripheral pro-inflammatory cytokines. Furthermore, activating the vagus nerve may then slow down progression of CAD or CHF since it activates two anti-inflammatory routes, namely the HPA axis and the vagal descending cholinergic route. These anti-inflammatory effects are of course in addition to the parasympathetic cardiovascular effects of vagal activation. Several observational studies in humans have found that parasympathetic activity in the heart, as indexed by HRV, is indeed inversely correlated with CAD-related pro-inflammatory cytokines such as IL-6 [85,86]. As suggested by Singh et al. [87], any agent or activity that may increase the cholinergic activity of the vagus may be beneficial due to these inhibitory effects on CAD-related pro-inflammatory cytokines.

Future studies need to test whether the proposed vagal neuroimmunomodulation plays a role in the more chronic process of atherogenesis or in the ACS or both. In addition, future studies should examine whether individual differences in either ascending or descending vagal activity (which modulate CAD-related inflammation) are risk-factors for the development and prognosis in CAD. Do people with little ascending vagal activity, hence, lacking certain heart-to-brain communication signals, show an increased prevalence of CAD? Future studies are also needed to test the effects of VNS, vagomimetic drugs and relaxation techniques on inflammatory mediators and progression of CAD and CHF, in randomized controlled trials. The effects of such interventions need to be especially examined among patients with low vagal activity (e.g., distressed patients), who are at risk of poor prognosis. Future studies should further examine whether the mechanism of action of such interventions in improving the prognosis in CAD or CHF works by reducing CAD-related pro-inflammatory cytokines. Hence, our proposed model provides a framework for examining neuroimmunological modulation in CAD and CHF and may have direct clinical relevance for treating these prevalent illnesses. To exemplify the clinical value of the proposed model, Table 1 depicts findings from the reviewed studies in humans and animals in which the effects of neuroimmunomodulation on health outcomes were tested.

8. Caveats to the model and future directions

The proposed model is based on converging evidence and requires direct testing. Specifically, future studies need to test whether the cardiological benefits of vagal activation may stem from its anti-inflammatory effects. This would not only reveal the mechanism of action of vagal activation in CAD

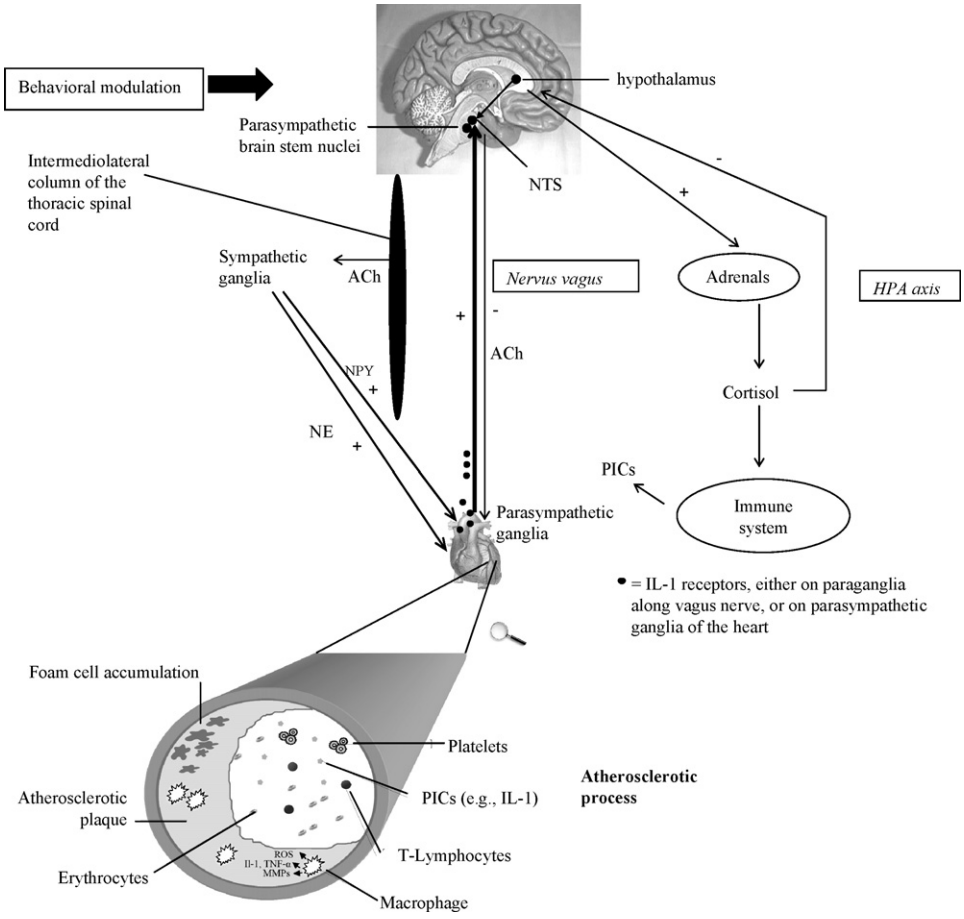

Fig. 1. The afferent and efferent pathways, which inform the brain about and modulate the inflammatory status of the heart and arteries, via the vagus nerve. Additional modulating systems are also indicated. *Note*: Ach, acetylcholine; NE, norepinephrine; NTS, nucleus tractus solitarius; PIC's, pro-inflammatory cytokines; IL-1, interleukin 1; NPY, neuropeptide Y. Parasympathetic brain stem nuclei include: the nucleus Edinger-Westphal, superior salivatory nucleus, inferior salivatory nucleus, and the dorsal vagal complex of the medulla.

but may also allow directing such clinical efforts to patients with elevated CAD-related pro-inflammatory markers. Second, the timeframe of the proposed mechanisms in unknown; in other words, future studies need to examine whether the neuroimmunomodulating effects of the vagus play a role in the more chronic processes of CAD development, in the ACS or in both. Third, the proposed model does not elaborate on the role of neuropeptides. These are important since the vagus nerve expresses receptors for neuropeptides [88] and NPY attenuates the secretion of acetylcholine in the vagus nerve [50,53]. Thus, future studies may need to investigate the role of neuropeptides to understand their interactions with the vagus nerve in relation to immunomodulation of CAD-related inflammation. Nevertheless, this model opens a new avenue linking the most basic cellular and inflammatory processes in CAD aetiology to the brain via a major part of the regulatory autonomic nervous system; namely, the vagus nerve.

Table 1
Studies demonstrating the effects of neuroimmunomodulation on health outcomes in humans and animals

Study	Subjects and disease	Intervention	Results
(a) Animals			
Bernik et al. [72]	Rats with induced MI	VNS	Reduced systemic & cardiac TNF-α
Li et al. [75]	Rats with induced MI	VNS	Improved cardiac health and survival
Halliwill et al. [80]	Dogs with healed MI	Atropine	Increased HRV
(b) Humans			
Zamotrinsky et al. [71]	Patients with severe angina	VNS	Increased adrenergic nerve density and microvascular circulation, improved cardiac functioning and reduced use of vasodilators
La Rovere et al. [79]	CHF	Scopolamine	Increased HRV
Wang et al. [81]	Post-MI	Scopolamine	Increased HRV

Note: MI, myocardial infarction; VNS, vagus nerve stimulation; HRV, heart rate variabiliy.

Acknowledgement

This work was supported by a VICI grant from the Netherlands Organisation for Scientific Research (NWO; grant no. 453-04-004).

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