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HYPOTHESIS

You may need the vagus nerve to understand pathophysiology and to treat diseases

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ABSTRACT

Can different pathophysiological mechanisms and risk factors leading to various diseases be linked with altered transmission of signals by one common pathway? The present article provides evidence for the hypothesis that adequate vagal nerve activity reduces the risk of major diseases, via common basic mechanisms and interim risk factors. These diseases include cardiovascular disease, cancer, Alzheimer's disease and the metabolic syndrome. Three basic mechanisms contribute to such illnesses: local oxidative stress and DNA damage, inflammatory reactions and excessive sympathetic responses, all of which are inhibited by vagal nerve activity. Efferent vagal activity that can be non-invasively measured by HRV (heart rate variability), derived from an ECG, is inversely related to all three basic mechanisms, to various risk factors (e.g. diabetes and dyslipidaemia) and, more broadly, to the diseases as well. Finally, vagal activity is proposed to moderate the effects of risk factors on developing such illnesses. By proposing an integrative neurobiological model of major diseases, identifying people at risk for, and treating patients with, such diseases may be done more efficiently. People with low HRV may be identified and subsequently treated by vagus nerve activation to possibly prevent or treat such illnesses. This proposed disease paradigm may have important preventative and therapeutic implications, whose clinical effects need to be investigated.

INTRODUCTION

CVD (cardiovascular disease), cancer and AD (Alzheimer's disease) are frequent causes of death worldwide. These diseases are causes of global mortality and reduced quality-adjusted life-years [1,2]. Furthermore, the MetS (metabolic syndrome), a cluster of risk factors, including obesity, elevated lipids, elevated glucose and blood pressure, can be seen as a disease on its own, as well as a risk factor for the other three major diseases [3,4]. These diseases not only influence well-being and longevity, but also have an immense economic impact [5]. A major challenge in clinical science is that these diseases are manifested differently, which makes screening, prevention and treatment complex, requiring lots of means and expenses. However, these illnesses share more common underlying pathophysiological mechanisms than is usually believed. How would biomedical sciences benefit if these diseases could be explained by one common factor linked to their multiple underlying pathophysiological mechanisms? How would public health authorities benefit from a rather simple, non-invasive and inexpensive screening method for identifying people at risk and for possibly preventing such diseases? How would clinicians and patients benefit from a safe type of treatment which may improve the prognosis of such diseases, in addition to routinely used treatments?

Key words: Alzheimer's disease, cancer, cardiovascular disease, heart rate variability, neuromodulation, vagus nerve.

Abbreviations: AD, Alzheimer's disease; CRP, C-reactive protein; CVD, cardiovascular disease; HRV, heart rate variability; IL-1, interleukin-1; MetS, metabolic syndrome; PSA, prostate-specific antigen; SNS, sympathetic nervous system; VNS, vagus nerve stimulation.

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We propose that the common pathway, unifying the aetiopathogenesis of the above-mentioned diseases, involves the vagus nerve. First, we hypothesize that low activity of the vagus nerve is a risk factor for the diseases (CVD, cancer and AD). Secondly, we theorize that inadequate vagal activity acts as a risk factor for these diseases by exacerbating their common underlying mechanisms (e.g. inflammation). Thirdly, we hypothesize that vagal activity moderates and statistically interacts with these underlying mechanisms and with disease risk factors (e.g. diabetes) in predicting the risk of these diseases.

These hypotheses led us to propose an integrative explanatory model linking high vagal nerve activity with a reduced risk of and improved prognosis in CVD, cancer and AD, via modulation of their aetiological mechanisms and risk factors. Furthermore, we hypothesize that, in the presence of risk factors, high vagal activity plays a protective role against these diseases. Consequently, activating the vagus nerve may in future serve as an additional treatment for such diseases, reflecting the protective role of this cranial nerve.

UNDERLYING MECHANISMS LEADING TO THE DISEASES

CVD, cancer and AD are characterized by morphological and functional abnormalities at the cellular level or by the formation of abnormal materials, including atherosclerotic plaque formation (in CVD) and β-amyloid plaques as well as neurofibrillary tangles (in AD), whose progress depends on key micro-environmental signals. Three basic mechanisms, namely oxidative stress and DNA damage, excessive inflammation, and excessive SNS (sympathetic nervous system) activity, play crucial roles in these diseases as well as in the MetS. To understand our hypothesis, we explain the role of the three mechanisms in these diseases, and thereafter their modulation by the vagus nerve.

Oxidative stress

Oxidative stress occurs when there is an imbalance between oxidants and antioxidants in favour of the former, a process subsequently leading to DNA damage. This is aetiological to coronary heart disease [6] via oxidation of LDL (low-density lipoprotein)-cholesterol and promotion of inflammation in the atherosclerotic plaques of coronary arteries [7]. Oxidative stress is pivotal in transformation of cells to malignant ones as it contributes to DNA mutations, especially if key tumour suppressor genes and pro-oncogenes are affected [8]. Oxidative stress is also increased in stroke and can lead to DNA damage in brain tissue [9]. In AD, oxidative stress induces neuronal apoptosis [10].

Inflammation

Inflammation refers to the recruitment of immune cells to a tissue that is under 'stress' from injury, irritation and infections, and, if excessive in extent and time, constitutes a major contributing factor to various chronic diseases. Inflammation has been shown to play pivotal roles in CVD, particularly in atherosclerosis, manifested by recruitment of immune cells (e.g. macrophages) to arterial lesions. Inflammation also promotes factors that lead to plaque rupture, such as plaque destabilization and elevated blood pressure, and promotes thrombosis [11]. In cancer, inflammation promotes escape from apoptosis by inhibiting tumour suppressors (e.g. p53) at early stages, and promotes angiogenesis (e.g. via vascular endothelial growth factor) and metastasis (via matrix metalloproteinases and adhesion molecules) at later stages [12,13]. In AD, inflammation may mediate the detrimental effects of β-amyloid peptides on brain neurons, leading to neurodegeneration [14].

Excessive SNS activity

SNS activity refers to increased activity in sympathetic nerves, and elevated plasma adrenaline (epinephrine) and noradrenaline (norepinephrine), also indexed by an increased heart rate and other stress markers. SNS activity plays roles in CVD by contributing to vascular wall injury due to inducing vasoconstriction and increasing blood pressure, eventually contributing to atherosclerosis and ischaemia [15]. In cancer, sympathetic neurotransmitters influence the direction of the metastatic pathway and their blockade may slow down metastasis [16]. In AD, there is diminished cerebral blood flow, possibly due to excessive SNS activity, which is counteracted by vagal enhancing medication [17].

These three aetiological mechanisms, namely oxidative stress and DNA damage, inflammation and excessive SNS activity, contribute to interim disease end points, such as hypertension, dyslipidaemia and diabetes mellitus [18], which are risk factors on their own for CVD, cancer and AD [19]. These interim disease end points can culminate in the MetS, another risk factor for these diseases [3,4,20]. Our main focus, however, is on the three diseases mentioned above. Can oxidative stress, inflammation and SNS activity, other known risk factors and diseases all be linked to the alteration of one common protective pathway?

HYPOTHESIS 1: ADEQUATE VAGAL ACTIVITY PREDICTS THE REDUCED RISK OF DISEASES AND IMPROVED PROGNOSIS

We consider low vagal activity to be a risk factor of diseases and poor prognosis. Activity of the efferent vagal pathways can be measured non-invasively via determination of HRV (heart rate variability). Evidence

from correlation studies shows that HRV is inversely correlated with the risk of, and with poor prognosis in, CVD [22,23]. Furthermore, HRV is positively correlated with longevity in cancer [24] and with better cognitive performance in AD [25] in some studies, independent of confounders. Finally, vagus activity is inversely related to the presence of components of the MetS and to the risk of having the MetS [26]. HRV is also inversely related to other interim risk factors (e.g. diabetes, hypertension and dyslipidaemia) for the above diseases. How can vagus nerve activity reduce the risk of these diseases?

HYPOTHESIS 2: THE VAGUS NERVE MODULATES THE PATHOPHYSIOLOGICAL MECHANISMS CONTRIBUTING TO DISEASES

Anatomically, the motor (efferent) pathways of the vagus nerve descend from the nucleus ambiguous and nucleus dorsalis nervi vagi in the brainstem to many visceral organs, including the lungs, heart, pancreas and gastrointestinal tract, bridging these organs with the CNS (central nerve system). Physiologically, the vagus has a communicative (mediating) and homoeostatic (modulating) role. The sensory (afferent) vagal pathways that terminate in the nucleus of the solitary tract transmit a wide range of signals to the brain, reflecting its mediating role. Importantly, experimental research has revealed that the vagus nerve informs the brain about peripheral inflammation that is signalled via vagal-paraganglia-expressing receptors for IL-1 (interleukin-1) [27].

Evidence exists for the modulatory role of the vagus in the three aetiological mechanisms in general and in the diseases we discuss specifically. VNS (vagus nerve stimulation) reduces oxidative stress [28] and specifically DNA fragmentation in CVD [29]. Furthermore, an acetylcholine agonist inhibited cell proliferation and increased the levels of the tumour suppressor protein p53 in experimental studies [30], which may have implications for preventing tumorigenesis. However, acetylcholine-enhancing drugs were found to promote tumour cell proliferation in other studies [31]. Nevertheless, we propose that the vagus nerve is a more complex homoeostatic system, which operates via multiple neurotransmitters and affects several systems (cardiovascular, neuroendocrine and immunological) [32], which may explain its proposed protective role. Concerning inflammation, the vagus nerve triggers modulatory anti-inflammatory effects at local and systemic levels: the descending vagus (operating via local α_7 nicotinic acetylcholine receptors on monocytes) and the systemic HPA (hypothalamic–pituitary–adrenal) axis [32]. In CVD patients, vagal activity is inversely correlated with inflammation [33] and, in an animal model of cerebral haemorrhage, cholinergic anti-inflammatory effects were found as well [34]. Finally, vagal activity normally counteracts the sympathetic nervous system [35], a finding specifically demonstrated in ischaemia [36].

HYPOTHESIS 3: THE ACTIVITY OF THE VAGUS NERVE INTERACTS WITH THE PATHOPHYSIOLOGICAL MECHANISMS AND RISK FACTORS IN PREDICTING DISEASE

In addition to conceptualizing decreased vagal activity as a risk factor for these three major diseases, the vagus nerve may also exert modulatory (interactive) effects. Activity of this nerve can statistically interact with two groups of variables. The first group includes the mechanisms described above, whereas the second includes other contributing risk factors (e.g. hypertension and diabetes). Low vagal activity may also interact with genetic susceptibility, which could explain why, in people with the same low vagal activity, some may develop AD, whereas others develop cancer or CVD. The hypothesized interaction could take the following form: in the presence of these additional risk factors (e.g. diabetes), high HRV is expected to reduce the risk of disease onset or of poor prognosis. Evidence for such an interaction was shown by Sajadieh et al. [37], who demonstrated the synergistic interaction of low HRV with high CRP (C-reactive protein) levels to contribute to future death and myocardial infarction. In that study, low vagal activity potentiated the effects of CRP on prognosis. Furthermore, we recently found that high vagal activity moderates the effects of cancer stage on the tumour marker PSA (prostate-specific antigen) in prostate cancer patients (M. De Couck, J. De Grève, D. Van Brummelen and Y. Gidron, unpublished work). In patients with low vagal activity, those with a severe cancer stage had higher PSA levels at 1 year compared with patients with milder stages. In contrast, in patients with high vagal activity, the cancer stage did not predict PSA levels at 1 year. Figure 1 depicts in a general schematic manner the protective interactive role of the vagus nerve, hypothesized to exist in all diseases described above. Theoretically, it is possible to have a risk factor, for example hypertension, and adequate vagal activity, possibly since the risk factor can result from other causes, such as genetics, environment or other acute diseases. High basal vagal activity is expected to moderate its negative effects, hence the interaction between HRV and the disease risk factor.

INTEGRATIVE MODEL

The evidence given above can be combined into one integrative model (see Figure 2). Adequate vagal activity can be understood as a protective factor in the risk and prognosis of CVD, cancer and AD. At the first stage, the

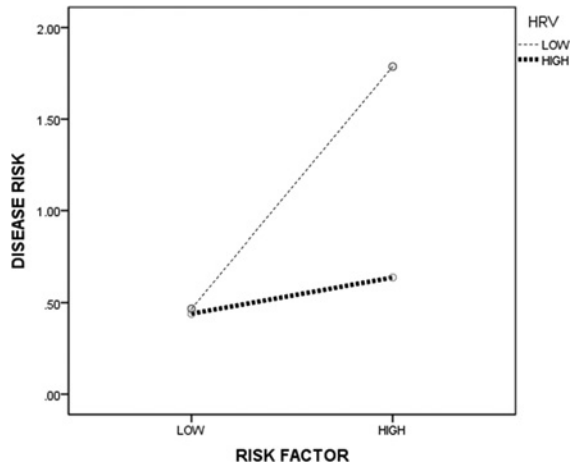

Figure 1 **A general scheme of the hypothesized interactive (protective) role of the vagus nerve, as evaluated by HRV, with risk factors in predicting general disease risk**

vagus nerve inhibits the basic underlying mechanisms, which are aetiological to these diseases. In addition to its neuroimmune homoeostatic role [38], we expand this to modulating oxidative stress and the SNS. Consequently, at the second stage, the risk of developing interim risk factors and the MetS is reduced by vagus nerve activity. All of these processes together lead to a reduced risk and better prognosis of the diseases.

It is important to note that the interim risk factors and the MetS are diseases on their own and can be seen as contributing risk factors for the development of CVD, cancer and AD. Furthermore, vagus nerve activity also interacts with the mechanisms and risk factors and is thus a moderator (see Figure 1). This understanding represents a new integrative model of the aetiology of these diseases (Figure 2).

CAVEATS AND FUTURE DIRECTIONS TO TEST THE HYPOTHESIS

The proposed model rests on converging evidence; however, we lack more longitudinal and experimental evidence linking vagal activation with reduced risk of these three diseases. Furthermore, no study has tested whether such activation inhibits the three mechanisms and risk factors, and thus leads to a lower risk of these diseases. In addition, it is important to keep in mind that there might be bi-directional effects between vagal activity and several of the mechanisms and risk factors. Yet, given the strong genetic component in vagal activity [39], the role of insufficient activity of this cranial nerve in preceding these underlying mechanisms and in contributing to the diseases cannot be easily dismissed. Furthermore, vagotomy was found to lead to worsening of such conditions, for example metastasis [40]. Finally,

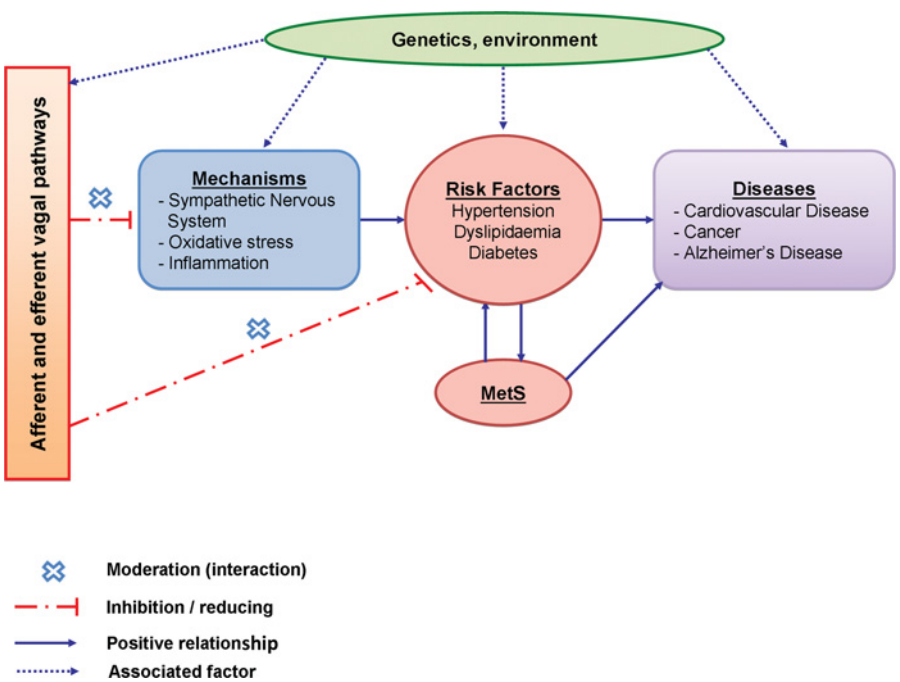

Figure 2 **Integrative model: vagal activity as a protective factor in the risk and prognosis of CVD, cancer and AD**

Table 1 Proposed studies for testing our hypothesis (examples and level of evidence)

RCT, randomized controlled trial.

Design	Detail	Level of evidence
Longitudinal studies	Does baseline HRV predict onset of diseases over 10 years? Does baseline HRV predict prognosis in diseases?	Medium
Moderation studies	Do baseline HRV and oxidative stress interact in predicting risk of the diseases?	Medium
Mediation analysis to test the pathophysiological mediators	Do biomarkers of inflammation, oxidative stress and SNS mediate the link between HRV and prognosis in diseases?	Medium/high
Experimental (RCT)	The effects of vagal-activating treatments (e.g. vagus nerve stimulation) on prognosis in diseases	High

studies need to examine the role of vagal activity in more acute diseases, such as infectious diseases, possibly revealing the limits of such a model. We have not described the relevance of this model to other diseases or pathological conditions. For example, our model is of relevance to chronic pain. The three pathophysiological mechanisms are related to chronic pain [41–43], and vagal activity is inversely related to pain [44]. Finally, vagal activation results in brain activity which is partly incongruent with the pattern observed in pain [45]. Future studies need to examine this model in relation to other conditions. Another limitation is that HRV may only partly represent the activity of the vagus nerve, since it may primarily reflect cardiac vagal activity. Nevertheless, there is evidence that HRV is strongly correlated with vagal activity [46]. HRV is also related to all of the variables described in our model, including peripheral oxidative stress, inflammation, SNS activity and to the disease end points.

Table 1 presents the studies that can be performed to test our hypotheses. Different study designs, details of such studies and the level of evidence as a result of their design rigor are shown. These include prospective and experimental studies, and we provide examples of such proposed studies. Measuring markers of the three pathophysiological mechanisms will shed light on their hypothesized role in the proposed model. Experimental studies testing the effects of vagal stimulation, such as HRV biofeedback or medication, on the mechanisms and disease end points would fully test this model. Once all levels of evidence have been observed, the scientific validity and clinical significance of the model could be determined.

CONCLUSIONS

Our hypothesized model explains results of epidemiological studies linking high vagal activity with lower risk of diseases. This hypothesized framework expands a previous model in cancer [47] to other diseases, all of which are the main causes of morbidity and mortality. The proposed integrative model can enable researchers and clinicians to understand the aetiopathogenesis of different diseases characterized by the alteration of common biological variables, identify people at risk and possibly treat patients with such diseases more efficiently. The non-invasive index of vagal activity, HRV, could be used in population surveys to easily identify people who may benefit from monitoring and preventative interventions to reduce illness burden and economic costs by vagal-activating interventions (e.g. vagus nerve stimulation).

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