Respiratory Physiology & Neurobiology 178 (2011) 387–394

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Review

# Inflammation and cardiorespiratory control: The role of the vagus nerve[☆,☆☆]

Julian F. Thayer[a,b,*], Adrian Loerbroks[b], Esther M. Sternberg[c]

[a] The Ohio State University, Columbus, OH, USA
[b] Mannheim Institute of Public Health, University of Heidelberg, Mannheim, Germany
[c] National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

*Article history:*
Accepted 20 May 2011

*Keywords:*
Neural–immune
Vagus
Heart rate variability
Immune
Respiration
Asthma

ABSTRACT

Inflammation and immunity have been implicated in a wide variety of diseases and disorders ranging from asthma to cardiovascular disease to hemorrhagic shock. In this review we will briefly consider the evidence for the neural concomitants of immunomodulation. First, we will briefly review the anatomy and physiology of the cardiorespiratory system. Then we will review the anatomy and physiology of neural–immune communication. The nucleus of the solitary tract is a site of integration of both the afferent and efferent neural regulation of the cardiorespiratory as well as the immune system. Then we will provide an overview of what is known about neuroimmunomodulation from both animal and human studies including neuroimaging and clinical studies. Finally, we will discuss a possible role of this neural circuitry in asthma related health disparities.



## 1. Introduction

The respiratory and cardiovascular systems are inextricably linked (Richter and Spyer, 1990). One pathway by which these two important systems are connected is via the autonomic nervous system (ANS). Therefore any discussion of the autonomic-neural modulation of immune function may fruitfully include some mention of the interplay between the respiratory and cardiovascular systems. There are at least two reasons why this is so. First, measures of heart rate variability (HRV) have been used to index autonomic vagal activity. Importantly HRV has been used in numerous studies of neural–immune interactions. Furthermore, there is much discussion in the literature concerning respiratory influences on indices of HRV. As such consideration of the respiratory system is integral to the proper use and understanding of HRV as a measure of autonomic vagal activity and thus of neural–immune interactions. Second, diseases of the respiratory system such as asthma have been linked with immune function and inflammation. Importantly, these diseases have cardiovascular consequences associated with their increased mortality and morbidity. Therefore a greater understanding of the relationships between the respiratory and cardiovascular systems may help to illuminate the underlying causes of the disease burden associated with respiratory diseases. In addition, this enhanced understanding of the relationships among the respiratory, cardiovascular, and immune systems may help to explain some known health disparities in respiratory diseases such as asthma.

### 1.1. The cardiorespiratory system

One important function associated with both respiration and the cardiovascular system is the maintenance of the appropriate balance of oxygen and carbon dioxide within the body and tissues of an organism. This balance needs to be matched to the environmental demands placed upon an organism and as such is a dynamic process involving an intricate interplay among a number of physiological systems. Whereas prior thinking in this area suggested separate respiratory and cardiovascular systems more modern work proposes that these systems have a high degree of overlap and might be more fruitfully conceived as a single cardiorespiratory system (Richter and Spyer, 1990).

The complete exposition of this complex system is beyond the scope of the present review. However several aspects are relevant to an understanding of the neural–immune communication. First, neuroanatomical studies find a close relationship between the cardiovascular and the respiratory afferent and efferent neurons. On the afferent side a major site of convergence is the nucleus of the solitary tract (NTS). Here both respiratory and cardiovascular vagal afferents from the lungs and the heart respectively are integrated (Richter and Spyer, 1990; Spyer, 2009). On the efferent side, in addition to the NTS, there are vagal neurons within the nucleus

☆ This paper is part of a special issue entitled "Inflammation and Cardio-Respiratory Control", guest-edited by Frank L. Powell and Yu Ru Kou.

☆☆ This work was supported by an Alexander von Humboldt Senior Research Award to Julian F. Thayer.

* Corresponding author at: The Ohio State University, Department of Psychology, 1835 Neil Avenue, Columbus, OH 43210, USA. Tel.: +1 614 688 3450; fax: +1 614 688 8261.
*E-mail address:* Thayer.39@osu.edu (J.F. Thayer).

1569-9048/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.resp.2011.05.016

ambiguus (NA) that are important for the generation of both respiratory and cardiovascular rhythms (Richter and Spyer, 1990).

Parasympathetic neurons are also implicated in the control of the airways (Lewis et al., 2006; Spyer, 2009). Vagal afferents from the lungs and airways are important in the reflex control of respiratory activities (Widdicombe, 1986). In addition parasympathetic efferents (primarily from the NA) are the major source of control of bronchial tone via both cholinergic and non-adrenergic non-cholinergic (NANC) fibers (Lewis et al., 2006). Broncoconstriction is due primarily to parasympathetic cholinergic activity whereas broncodilation is due mainly to parasympathetic NANC mechanisms (Lewis et al., 2006). Importantly there appears to be no sympathetic innervation of airway smooth muscle and sympathetic innervation is restricted to the airway vasculature (Lewis et al., 2006). This parasympathetic control of the airways is important for an understanding of asthma as we will see later.

Like many organs in the body, the heart is dually innervated. Although a wide range of physiologic factors determine cardiac functions such as heart rate (HR), the ANS is the most prominent. An extensive body of research has been directed at identifying the pathways by which this neural control is achieved. For example, Benarroch (1993, 1997) has described the central autonomic network (CAN). The output of the CAN has connections to the sinoatrial node of the heart via the stellate ganglia and the vagus nerve as well as the respiratory motorneurons. Importantly, the output of the CAN is under tonic inhibitory control via GABAergic neurons in the NTS. The NTS has direct connections to the NA and the dorsal vagal motor nucleus (DVN) (see Thayer and Lane, 2009 for a complete description of these pathways). These connections are via interneurons between the NTS, NA, and DVN traversing the intermediate reticular zone and provide input to the cardiovagal and respiratory motor neurons (see Fig. 6, Benarroch, 1993). In addition the NTS is a site where the afferent and efferent vagus meet (see Fig. 1).

Importantly, when both cardiac vagal (the primary parasympathetic nerve) and sympathetic inputs are blocked pharmacologically (for example, with atropine plus propranolol, the so-called double blockade), intrinsic HR is higher than the normal resting HR (Jose and Collison, 1970). This fact supports the idea that the heart is under tonic inhibitory control by parasympathetic influences. Thus, resting cardiac autonomic balance favors energy conservation by way of parasympathetic dominance over sympathetic influences. In addition, the HR time series is characterized by beat-to-beat variability over a wide range, which also implicates vagal dominance as the sympathetic influence on the heart is too slow to produce beat to beat changes (Saul, 1990). Low HRV is associated with increased risk of all-cause mortality, and low HRV has been proposed as a marker for disease (Task Force, 1996; Thayer and Lane, 2007; Thayer et al., 2010b). Importantly tonic activity of the vagus nerve appears important for both respiratory and cardiovascular tone.

### *1.2. Is it necessary to control measures of HRV for respiration?*

Given the close relationship between the respiratory and cardiovascular systems it should not be surprising that functional relationships between these systems have been proposed. In the HRV literature it has been proposed that measures of HRV need to be "corrected" for respiration if they are to be used to accurately assess vagal function (Grossman, 1992). However there is continuing debate about whether respiration should be routinely

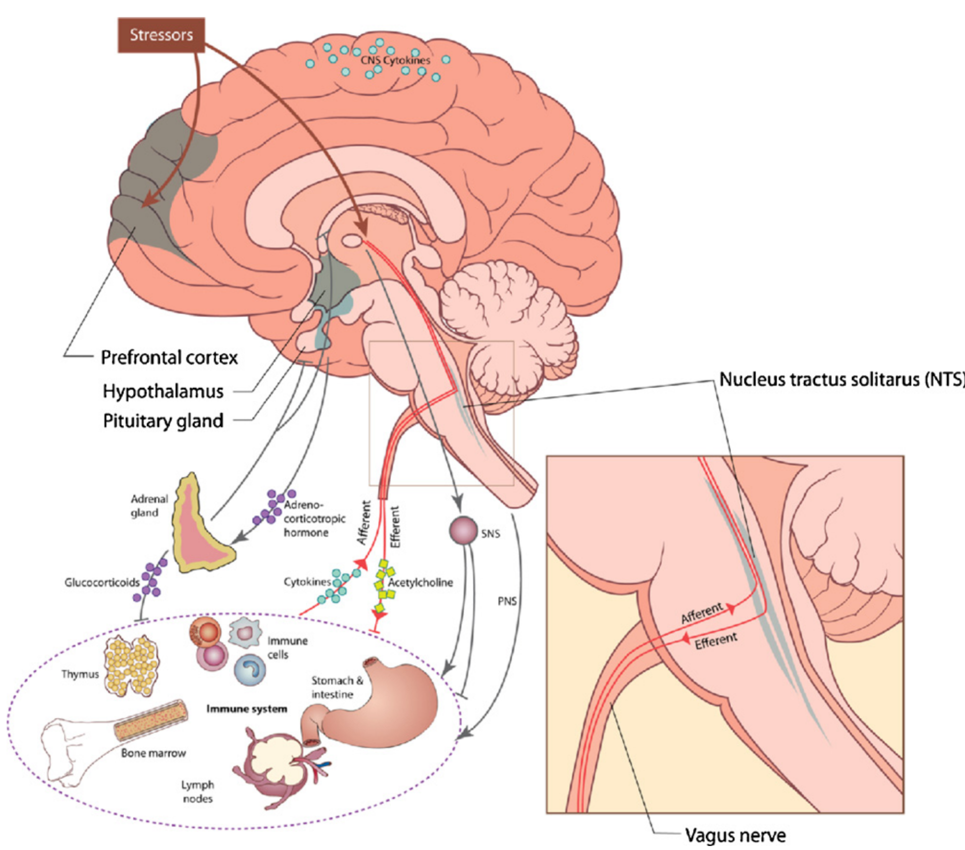


**Fig. 1.** Schematic illustration of the connections between the brain and the immune system. Signalling between the immune system and the central nervous system (CNS) through systemic routes, the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS), and the peripheral nervous system (PNS) are shown. The afferent and efferent vagus meet at the nucleus of the solitary tract (shown in the insert).