Autonomic Neuroscience: Basic and Clinical 182 (2014) 95–101

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

# Neural regulation of inflammation in the airways and lungs

Alice E. McGovern, Stuart B. Mazzone *

*Laboratory of Respiratory Neuroscience and Mucosal Immunity, School of Biomedical Sciences, The University of Queensland, St Lucia, QLD 4072, Australia*

ARTICLE INFO

*Article history:*
Received 26 October 2013
Accepted 12 December 2013

*Keywords:*
Neuro-immune
Autonomic
Asthma
Immune synapse
Airway reflexes

ABSTRACT

Many pulmonary diseases are characterized by inflammatory pathologies which in turn are responsible for obstruction, mucus hypersecretion, dyspnea, cough and other clinical symptoms of lung disease. Understanding processes that regulate inflammation will therefore provide insights into mechanisms that contribute to pulmonary dysfunction. The airways and lungs are densely innervated by autonomic and sensory nerves which might regulate aspects of pulmonary inflammation. In this review we provide a critical appraisal of the available literature on the topic of neuro-immune interactions in the airways and ask the question 'how strong is the evidence that pulmonary nerves regulate inflammation?'



## 1. Introduction

Inflammation is a hallmark pathology in many acute and chronic pulmonary diseases and inflammatory processes underpin development of the classic symptoms experienced by patients, including coughing, sneezing, dyspnea, excessive mucus production and wheezing (the latter principally a consequence of bronchoconstriction due to airway smooth muscle hyperreactivity and airway wall edema due to 'leaky' vasculature). Within this diverse range of clinical symptoms, it is not difficult to identify that inflammation and the airway nervous system interact in ways that underpin disease pathophysiology. Thus, coughing and sneezing are neural reflexes, dyspnea is a sensation of difficulty breathing dependent upon neural processing in the brain and mucus glands, bronchial smooth muscle and the airway vasculature are all under the control of autonomic nerves. Indeed decades of work in animals and humans has clearly shown that both dysfunction of airway nerves, as well as persistent changes in their structure and/or phenotype (plasticity) occur as a consequence of inflammation. However, what is less clear is whether the pulmonary nervous system in turn contributes to the regulation of immune cells within the airways and lungs, and hence whether neural mechanisms alter (enhance or suppress) inflammation, thereby contributing to the pattern of disease. Of course the specific nuances of the inflammatory processes that occur in the lungs differ from disease to disease, and are beyond the scope of this review. Rather, here we explore the broader issue of whether or not pulmonary nerves can alter inflammation and modify the pathogenesis of airway disease.

## 2. Neural innervation to the airways and lungs

In the following section we provide a brief overview of the neural innervation to the airways to help explore the topic of this review. Readers are referred to several excellent in depth reviews of airway innervation if additional details are required (Canning, 2006; Canning and Spina, 2009; Brouns et al., 2012). In all mammals, the airways are densely innervated by nerve fibers, which can be found diffusely throughout the parenchyma of the airways and lungs and in particular in association with the epithelia, airway smooth muscle, vasculature and glands. These nerve fibers are derived from a variety of sources, but principally represent either autonomic motor neurons or sensory neurons originating from vagal or spinal nerves (Kummer et al., 1992; McGovern and Mazzone, 2010; McGovern et al., 2012). Autonomic motor neurons have ongoing activity as a consequence of central autonomic drive or as a result of peripheral events such as lung inflations resulting in reflex activation of autonomic outflow (Mitchell et al., 1985; Kesler and Canning, 1999). This basal activity establishes a baseline level of bronchomotor tone, vasomotor tone and mucus secretion, which is critical for optimizing normal lung function. Some pulmonary sensory nerves also have a baseline activity which correlates with the pulmonary cycle. This sensory activity contributes to feedback control of respiratory rhythm generation in the brainstem and helps set the baseline activity in autonomic motor nerves (Kesler and Canning, 1999). Interactions between sensory and motor pathways through central and peripheral reflexes can additionally modulate (increase and decrease) the autonomic neural activity (Mazzone and Canning, 2002a).

### 2.1. Sympathetic and parasympathetic pathways

The efferent innervation to end organs within the airways and lungs is derived from both intrinsic and extrinsic origins. Sympathetic

* Corresponding author. Tel.: +61 7 3365 1074; fax: +61 7 3365 1766.
*E-mail address:* s.mazzone@uq.edu.au (S.B. Mazzone).

1566-0702/$ – see front matter 
http://dx.doi.org/10.1016/j.autneu.2013.12.008

(noradrenergic) and parasympathetic (cholinergic) postganglionic nerve fibers can be identified in the airways where they play functional roles in the regulation of airway and vascular smooth muscle tone and mucus gland secretion in most mammals (Kummer et al., 1992; McGovern and Mazzone, 2010; McGovern et al., 2012). One notable exception is the human airways, which have negligible sympathetic innervation of their bronchial smooth muscle, instead relying on circulating catecholamines for the bulk of their sympathetic relaxant control of bronchial tone (Richardson and Béland, 1976). Humans (and several other species including guinea pigs) also have a non-cholinergic relaxant parasympathetic innervation that contributes to the neural regulation of airway tone via the release of nitric oxide and peptidergic transmitters, rather than via typical parasympathetic acetylcholine-mediated mechanisms (Canning and Undem, 1993).

The organization of sympathetic pathways projecting to the airways is largely conventional, with preganglionic neurons residing in the intermediolateral cell column of the spinal cord and postganglionic neurons having their cell bodies in both the superior cervical and stellate sympathetic ganglia (Kummer et al., 1992; McGovern et al., 2012). Within the airways the postganglionic sympathetic fibers can be defined by their stereotypical expression of tyrosine hydroxylase and/or neuropeptide Y, but may also express other transmitter systems that are not unique to sympathetics (such as nitric oxide synthase (NOS), vasoactive intestinal peptide (VIP) and ATP). Parasympathetic preganglionic neurons are almost exclusively located in the nucleus ambiguus in the brainstem, although a small number of neurons can also be located in the dorsal motor nucleus of the vagus nerves (McGovern and Mazzone, 2010). At least two populations of postganglionic parasympathetic neurons have been defined, the classical cholinergic neurons that are intrinsic to the airway wall and a second population of non-cholinergic postganglionic neurons (which express NOS and VIP) that originate either within the airway wall or in the myenteric plexus of the adjacent esophagus (depending on the species in question) (Fischer et al., 1998). A third parasympathetic pathway has been identified in guinea pigs consisting of a specialized subset of esophageal cholinergic neurons which selectively project into airway parasympathetic ganglia (Mazzone and McGovern, 2010). Whether esophageal cholinergic neurons innervate airway autonomic ganglia in other species is not known.

### *2.2. Vagal and spinal sensory pathways*

By far the dominant sensory innervation to the airways is derived from vagal origins, with only a small population of cells originating from lower cervical and upper thoracic spinal dorsal root ganglia (DRG) (Kummer et al., 1992; McGovern et al., 2012). Subtypes of sensory neurons can be defined based on different criteria, including their origin (nodose versus jugular vagal ganglia, DRG etc.), physiological responsiveness (chemoreceptor versus mechanoreceptor), termination sites (extrapulmonary versus intrapulmonary), molecular expression patterns (as one example only, TRPV1 positive versus TRPV1 negative) or the reflex responses that they initiate (stretch receptor reflex, cough reflex, apnea etc.) (Mazzone, 2005; Brouns et al., 2012). Despite this wide range of defining characteristics, it is generally accepted that sensory neurons can be loosely classified as being either capsaicin-sensitive unmyelinated (or lightly myelinated) nociceptors which typically express neuropetides, or low threshold mechanosensors which are myelinated, glutamatergic and unresponsive to the direct actions of capsaicin. Capsaicin is an agonist at the TRPV1 receptor and in many species elicits nociceptor-dependent responses by inducing reflexes via the central nervous system and/or the peripheral release of neuropeptides (e.g., substance P and calcitonin gene-related peptide) onto airway and vascular smooth muscle, glands and autonomic ganglia, via classic axon or peripheral reflexes. Several other activators of nociceptors (but not all) can initiate peripheral transmitter release providing an important means by which sensory nerve terminals are involved in the peripheral regulation of end organs and cells within the airways and lungs. Whether mechanoreceptors can release glutamate from their peripheral terminals in the airways is not known, although their peripheral terminals do express the molecular machinery associated with release sites and some observations are perhaps consistent with this possibility (Brouns et al., 2006). The brainstem termination patterns of airway sensory neurons has broadly been described, and input via these pathways can evoke widespread changes in physiology, not just limited to pulmonary and respiratory control (Widdicombe and Lee, 2001; McGovern et al., 2012). Thus, the activation of an airway sensory pathway may modify extrapulmonary populations of cells (via the CNS), an important consideration when trying to ascribe a role for pulmonary nerves in modulating the immune system.

## 3. The neuro-immune synapse: Do airway nerves and immune cells interact spatially?

A classical view of neuro-immune interactions would predict that neurons can (and do) communicate with resident and/or infiltrating immune cells within the airways to modify their behavior (Fig. 1). Such cell-to-cell communication would presumably be mediated by chemical signals between the two cell types and this would be facilitated by a spatial organization whereby nerve fiber terminals and immune cells are located in close proximity. In the nervous system this type of spatial arrangement (a synapse) is a major mechanism for cell-to-cell communication and this is obviously how neurons communicate with not only other neurons but also effectors such as muscle, glandular, and epithelial cells. Structural entities resembling a synapse have been reported between nerve terminals and immune cells in lymphoid tissues and in in vitro culture systems (Felten and Olschowka, 1987; Suzuki et al., 2004; Dustin, 2012; see Bellinger and Lorton in this issue

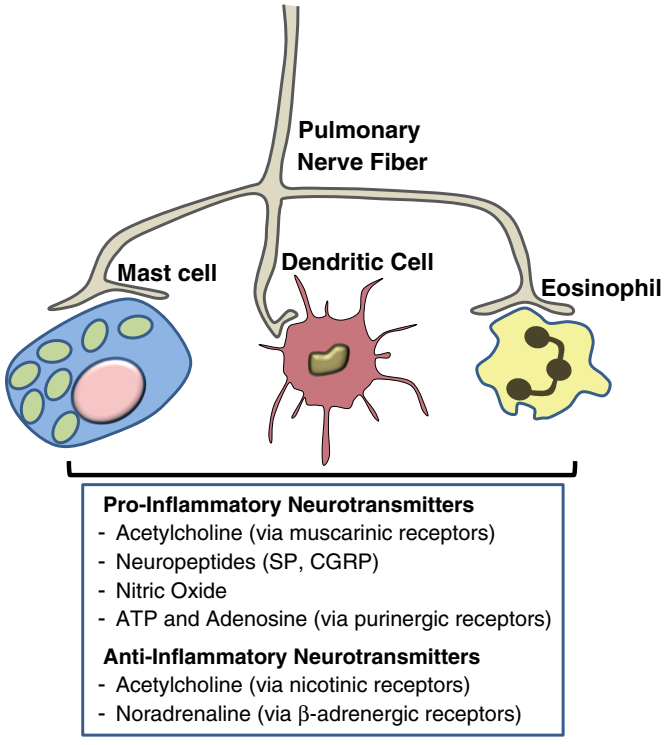


**Fig. 1.** A classical view of neuro-immune modulation in the airways. In this scenario airway sensory and/or autonomic motor nerve fibers form close contacts (possibly synapses) with resident or infiltrating immune cells. There is strong evidence that neurotransmitter molecules can regulate immune cell function, producing both pro-inflammatory and anti-inflammatory actions. However, the evidence for this type of neuro-immune arrangement in the airways is not strong.