Review Article

Neuronal Modulation of Airway and Vascular Tone and Their Influence on Nonspecific Airways Responsiveness in Asthma

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Received 1 August 2012; Accepted 28 September 2012

Academic Editor: Ynuk Bossé

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The autonomic nervous system provides both cholinergic and noncholinergic neural inputs to end organs within the airways, which includes the airway and vascular smooth muscle. Heightened responsiveness of the airways to bronchoconstrictive agents is a hallmark feature of reactive airways diseases. The mechanisms underpinning airways hyperreactivity still largely remain unresolved. In this paper we summarize the substantial body of evidence that implicates dysfunction of the autonomic nerves that innervate smooth muscle in the airways and associated vasculature as a prominent cause of airways hyperresponsiveness in asthma.

1. Introduction

With the exception of airway smooth muscle, perhaps no other group of cells has as clear a role in the pathogenesis of asthma as the neurons comprising the afferent and efferent innervation of the airways and lungs. The symptoms of asthma—wheezing, dyspnea, chest tightness, cough, reversible airways obstruction, mucus hypersecretion, and airways hyperresponsiveness—all inextricably link the nervous system to this disease. It is thus remarkable that in the 440 pages of the National Heart, Lung and Blood Institute (NHLBI) guidelines on asthma, nerves are mentioned in just one sentence [1]. Nerves are not mentioned at all in the British Thoracic Society (BTS) guidelines for asthma [2]. Even the recent and potentially landmark study by Peters et al. [3], in which the anticholinergic tiotropium was found to be at least as good as steroids or β-agonists (perhaps better) for treatment of asthma, nerves are not mentioned in the article itself nor in the accompanying editorial [4]. In this brief review we summarize the large body of evidence supporting a primary role for airway autonomic nerve dysfunction in the hyperresponsiveness of the airway smooth muscle in asthma.

2. The Understated Role of Nerves in Asthma

Guidelines such as those produced by the NHLBI and BTS, in which immune cells including eosinophils are given a central role in asthma pathogenesis appropriately highlight the prominent feature of inflammation in the asthmatic lung. Inflammation may precipitate airways hyperresponsiveness [1, 5–8]. But the association between inflammation and airways hyperresponsiveness has probably been overemphasized [9–13]. The bias towards inflammation in asthma guidelines reveals the disproportionate influence immunologists, and allergists have had overdefining this disease for national and international medical organizations as well as their influence over the direction of asthma-related research. As asthma prevalence and asthma mortality rates have remained largely unchanged in the decades where inflammation has become a central theme in asthma research and therapy, it may be time for a new perspective on old concepts of the pathogenesis of reactive airways disease.

Given the strong case for neural dysfunction in asthma, it is surprising how little attention airway nerves receive in the published literature. The underemphasis on nerves in asthma and the exaggerated influence of inflammation in
asthma can be illustrated by comparing the scant references to neural mechanisms in this disease with the incessant discussions of eosinophils in asthma guidelines and in all of asthma-related literature. This is especially surprising, given how strong the evidence is in favor of neural mechanisms in asthma and how comparatively weak the evidence is supporting a role for eosinophils in this disease. Even the most ardent proponents might struggle to make a strong case for a role of eosinophils in asthma. There is no increase in the risk of asthma for patients with hypereosinophilic syndrome [14]. Nonasthmatic atopic patients develop a profound eosinophilia of the airways upon exposure to allergen but develop few if any of the symptoms of asthma [15, 16]. Many asthmatics have eosinophil levels in their airways and air spaces that are comparable to that of nonasthmatics [5, 6, 17]. Experimental therapies such as anti-IL-5 and recombinant IL-12 have a profound effect on circulating and airway eosinophil numbers and on allergen-induced recruitment of eosinophils to the airways but little or no effect on asthma symptoms in most patients and no effect on airways reactivity [18–21]. Even steroids, which markedly inhibit eosinophil function, survival and recruitment to the airways, have only modest effects on airways hyperresponsiveness [22]. And yet, in spite of what seems to be a clear role for the nervous system in asthma and at best a debatable role for eosinophils, nerves are mentioned in one sentence combined in the NHLBI and BTS guidelines while these same guidelines, cite eosinophils 85 and 43 times, respectively. This imbalance is pervasive in the published literature as well. Since 2001, several years after Leckie and colleagues reported their disappointing results with anti-IL-5, there have been over 4600 papers published with the keywords of “asthma” and “eosinophil” but less than 450 papers with the keywords “asthma” or “nerve”. Indeed, there have been more papers published with the keywords “eotaxin” and “asthma” over the past 10 years than papers with the keywords “asthma” or “COPD” and “nerves” combined.

The mechanisms of airways hyperresponsiveness are poorly understood. It seems all but certain that smooth muscle is central to regulating airways reactivity. However, studies of airways smooth muscle contractility in vitro, conducted using airways obtained from asthmatic and nonasthmatic lung donors, yield results that are somewhat varied [23–28]. Thus, an argument can be made that neither smooth muscle contractility (efficacy) nor responsiveness (potency) differs to any great extent between airways obtained from diseased or nondiseased patients. Bronchodilators are also largely equally effective in smooth muscle from asthmatics and nonasthmatics [29, 30]. The defect in asthma may therefore manifest only within the context of the intact body and lung.

If, however, we accept the evidence in support of the hypothesis that airway smooth muscle accounts in large part for the most defining pathophysiological features of asthma (reversible airways obstruction and airways hyperresponsiveness) it is then critical to determine what ultimately regulates airway smooth muscle contraction. Airway smooth muscle generates little myogenic tone and so contraction depends upon the actions of contractile agonists. Despite an extensive list of autacoids and neurotransmitters that can contract human airway smooth muscle, a survey of the published literature suggests that only 3 endogenously released ligands, acetylcholine, histamine, and the cysteinyll-leukotrienes, reliably contract human airway smooth muscle to any significant extent and in physiologically relevant conditions in the airways of asthmatics. What so clearly defines the role of the nervous system in regulating the airways hyperresponsiveness in asthma is the indisputable source of the acetylcholine that regulates airway smooth muscle tone and the profound effects of anticholinergics on the airways obstruction and airways reactivity that define this disease.

3. Autonomic Innervation of Human Airway Smooth Muscle

The autonomic nervous system plays a primary role in regulating airway smooth muscle tone. The highly regulated activity of these nerves allows ongoing input to the airway smooth muscle such that basal tone is regulated on a breath by breath basis. The origin of this ongoing drive depends upon centrally (i.e., brainstem) mediated activity established by both respiratory and reflexive inputs [31–34]. In most animals and in humans, stimulation of airway autonomic nerves evokes near maximal constricctions of the airways through the actions of acetylcholine released from postganglionic parasympathetic nerves. Alternatively, activation of airway autonomic nerves can reverse completely spasmogen-evoked bronchoconstriction through the actions of noncholinergic neurotransmitters such as nitric oxide (NO) and vasoactive intestinal peptide (VIP) and related peptides. It follows logically that dysfunction or dysregulation of airway autonomic nerves is likely to contribute to the pathogenesis of asthma and COPD (reviewed in [35]).

For years it had been widely assumed that noncholinergic neurotransmitters mediating relaxations of the airways were coreleased with acetylcholine from a single population of postganglionic parasympathetic nerves. It was further speculated that these noncholinergic cotransmitters served as a brake on the parasympathetic nervous system, preventing excessive constriction during periods of elevated autonomic tone. Our studies have revealed, however, that anatomically and physiologically distinct parasympathetic nerves mediate cholinergic contractions and noncholinergic (nitrergic) relaxations of the airways [36–38]. Importantly, reflexes differentially regulate these distinct parasympathetic pathways [34, 39]. The existence of two parasympathetic pathways with opposing actions on the bronchial muscularature changes entirely how autonomic nerve-dependent regulation of airway caliber should be viewed. Bronchospasm could be evoked by increases in cholinergic nerve activity or withdrawal of nitrergic neural activity. Conversely, increased nitrergic nerve activity or decreased cholinergic tone could elicit bronchodilatation. The role of the autonomic nervous system in disease must also now be viewed differently. With distinct neuronal pathways mediating contractions and relaxations of airway smooth muscle, dysfunction or dysregulation of either parasympathetic pathway could account for
4. Autonomic Dysfunction and Asthma

There is indisputable evidence supporting the hypothesis that dysregulation of airway cholinergic nerves contributes to the pathogenesis of airways obstruction and airways hyperresponsiveness. Cholinergic nerve-mediated obstruction of the airways is increased in asthma and COPD [28, 40]. Airways hyperresponsiveness is also associated with alterations in cholinergic nerve function. Anticholinergics markedly reduce (10–20-fold) or abolish airways reactivity to a wide variety of spasmogens and stimuli including prostanoids, histamine, bradykinin, capsaicin, hyperpnea, exercises and allergen (reviewed in [35]; Table 1). Airways hyperresponsiveness associated with extrapulmonary disorders may also be dependent upon alterations in airway autonomic control. Bronchospasm initiated by gastrointestinal reflux or airways obstruction associated with allergic rhinitis is prevented by anticholinergics. Similarly, in patients with upper respiratory tract infections, the marked increases in airways reactivity precipitated by the infection are reversed by atropine [41]. More recent studies suggest anticholinergics might be highly effective in treating asthma. Soon after the study of Peters et al. [3], which suggested that tiotropium was superior to steroids and β-agonists in controlling asthmatic airway function, 2 subsequent studies reported similar findings when using the ultra-potent and long acting anticholinergic [42, 43]. The reported effects of tiotropium on airway smooth muscle mass suggest that in addition to relieving functional obstruction, anticholinergics may play an important role in reversing airways remodeling [44].

Evidence suggesting that nitrergic parasympathetic nerves are dysfunctional in airways disease is circumstantial.
but compelling. In humans and in many animal species, adrenergic nerves are sparse or absent in the airways and without apparent influence over airway smooth muscle tone [45]. Consequently, nitrergic parasympathetic nerves represent the only functional relaxant innervation of airway smooth muscle. Importantly, in asthma, an inability to dilate with deep inspiration and not excessive smooth muscle constriction may underlie the pathogenesis of airways hyperresponsiveness [46]. In a preliminary report, inhibitors of NO synthase (NOS), which can inhibit relaxations mediated by airway nitrergic parasympathetic nerves, prevent the bronchoprotective effects of deep inspiration in normal patients [47]. Perhaps airway nitrergic nerves regulate airways reactivity by counteracting the actions of spasmogens through tonic, ongoing effects in the airways or by subserving a compensatory role with increased activity following challenge. Consistent with these hypotheses, NO synthase inhibitors exacerbate airways responsiveness to bradykinin in mild asthmatics, a compensatory mechanism that is lost in severe asthmatics [48]. Although the source of the nitric oxide was not determined in these clinical studies, experiments using animals and studies of human airway preparations indicate that parasympathetic nerves are one potential source [33, 49–52]. Pathological and molecular biological studies are also consistent with the hypothesis that dysregulation of airway noncholinergic nerves contributes to the pathogenesis of asthma and COPD. For example, arginase (which competes with neuronal NOS for the substrate L-arginine) activity is increased in models of asthma, thereby leading to a reduced capacity to produce neuronal NO [53]. Mutations in the gene encoding the neuronal isoform of NOS have been associated with asthma [54, 55]. These mutations are associated with a decrease in exhaled nitric oxide in asthma [56]. In fatal asthma, VIP-containing nerves have been reported to be sparse in the airways [57]. VIP and NOS are colocalized to airway ganglia [51]. All of these observations indicate that dysregulation of nitrergic parasympathetic nerves might contribute to the pathogenesis of airways diseases.

5. Autonomic Regulation of Vascular Tone in Asthma

Vascular beds in the airways play an important role in basal airway obstruction through the regulation of airway wall volume [58]. Mucosal edema is a prominent feature in the asthmatic airways, and this contributes significantly to airflow limitations [59]. The airway vasculature, however, can also directly modulate airway smooth muscle reactivity by regulating the clearance of bronchoactive agents from the airway wall. For example, animal studies have shown that vasoconstriction or reduced vascular perfusion of the airways significantly potentiates airway smooth muscle responsiveness to a variety of bronchoplastic agents [60–62] (Figure 2). In asthmatics, intravenous angiotensin II increases methacholine bronchoconstriction but does not alter bronchoconstriction evoked by endothelin, an autacoid that constricts airway vascular smooth muscle (while methacholine relaxes vascular smooth muscle; [63, 64]). The diuretic furosemide also reduces airways reactivity to exogenous stimuli in humans [27], perhaps via a vasodilatory action since it does not relax airway smooth muscle in vitro. Similarly, in vivo epinephrine (a nonselective adrenergic agonist that would evoke both bronchodilation and vasoconstriction) has no effect on reactivity yet in vitro (where the vasculature is no longer intact), it is more potent and efficacious than the β-adrenergic agonist albuterol at preventing airway smooth muscle constriction [65].

As is the case with airway smooth muscle, vascular smooth muscle possesses a baseline level of tone that is dependent upon ongoing activity of the autonomic nervous
system [61]. However, unlike the airway smooth muscle, va- 
sular tone is heavily dependent upon adrenergic sympathetic 
nerves acting via alpha-adrenergic receptors (reviewed in 
[66]). Neuropeptide Y also constricts the vascular smooth 
muscle secondary to sympathetic nerve activation, whereas 
activation of parasympathetic nerves evokes vasodilatation 
following the release of acetylcholine or nitric oxide and 
vasoactive intestinal peptide. In some species neuropeptide 
expressing sensory nerves can mediate vasodilatation via 
axon reflexes, although this is not likely a prominent 
mechanism of vasoregulation in humans.

6. Mechanisms of Autonomic Dysfunction

While it is clear that the nervous system is essential to the 
reactivity of the airways in asthma, it is unclear precisely what 
drives dysfunction of airway nerves in asthma. The simplest 
explanation might be that inflammation alters airway auto-
nomic function in asthma. Airways inflammation has been 
associated with enhanced cholinergic responses following 
altered prejunctional control mechanisms (such as the mus-
carinic M2 autoreceptor that normally prevents acetylcholine 
release from nerves) or by sensitizing neurotransmission 
through the parasympathetic autonomic ganglia (the synap-
tic relay between pre- and postganglionic neurons) (reviewed 
in [35]). Nitrergic relaxant nerve responses may also be 
diminished in the asthmatic airways. The synthesis or degra-
dation of the peptidergic and nitrergic neurotransmitters 
(or their substrates) utilized by nitrergic nerves may be 
perurbed in asthma via the actions of peptidases, free radical 
scavengers, and arginase. An alternative explanation is that 
the effects of airway inflammation are indirectly linked to 
autonomic nerve dysfunction. For example, sensitization and 
and altered activity of airway sensory nerves is a common feature 
in asthma. Sensory nerves provide direct inputs to airway 
autonomic pathways, both at the level of the brainstem and 
the autonomic ganglia, and it is therefore likely that altered 
sensory function contributes to changes in autonomic drive 
to the airways [35].

7. Conclusions and Future Directions

It seems possible that an overemphasis on the role of inflam-
mation in models of asthma, and less attention to the central 
role of airways hyperresponsiveness, has contributed to the 
frequent failure to translate promising therapeutic strategies 
discovered in animals into patients with asthma [67, 68]. 
Important insights into the mechanisms of inflammation 
in asthma have been established. In clinical studies, both 
leukotrienes and IL-5 induce pulmonary eosinophilia [69, 
70], whereas in asthmatics, leukotriene modifiers and anti-
IL-5 reduce eosinophil and basophil recruitment to the 
airways [19, 20, 28, 71]. The Th2 cytokines IL-4 and IL-13 
also seem to play a role in astmatic inflammation [1], but 
threaties targeting IL-5 [19–21], IL-4 [72], or IL-13 [73, 74] 
have provided little or no relief of asthma symptoms and 
little relief from airways hyperresponsiveness. By contrast, 
anticholinergics have proven remarkably effective at reducing 
the acute responses to allergen challenge and consistently 
decrease airways obstruction and airways reactivity in asth-
matics. There is much unknown about the innervation of the 
airways. Given its central role in the pathogenesis of asthma, 
efforts to fill the many gaps in our understanding of airway 
nervous control are warranted.

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