Airway Obstruction and Inflammation

Present Status and Perspectives

Symposium on Airway Obstruction and Inflammation
Florence, November 30–December 2, 1988

Airway Obstruction and Inflammation

Present Status and Perspectives

Volume Editors
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Preface

The Proceedings of the Congress 'Airway Obstruction and Inflammation Present Status and Perspectives' which took place in Florence from November 30th to December 2nd, 1988 are collected in this volume. The Congress focused on basic problems, clinical aspects and therapies for asthma. A round table was dedicated to the epidemiologic and nosological standpoints of bronchial obstruction in Europe. The order and the contents of each oral presentation and original contributions have been strictly observed. After the updatings on 'the state of arts' of the main physiopathologic and immunologic problems, significant and original works carried out by Italian investigators are reported. The results of a multicenter study performed in 32 Italian centers testing the combination of ipratropium bromide with fenoterol in the long-term treatment of chronic obstructive pulmonary diseases are also reported. The Florentine congress was an excellent occasion to discuss for the first time the above-mentioned complete results in a large assembly of European pneumologists.

We are indebted to Boehringer Ingelheim, Florence, for sponsoring this congress and permitting the publication of this volume.

D. Olivieri
S. Bianco

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Neural Regulation of the Airways: The Vasculature

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Introduction

All airway functions are to some extent under nervous control. This includes the control of airway caliber, where most attention has been focused, as well as secretion [3], muco-ciliary clearance [8, 35], epithelial ion transport, epithelial permeability [25], airway vascular tone [13], and vascular permeability [17, 25–27]. A major impetus for the study of the nervous control of the airways has been to better understand the pathogenesis of asthma. Although there are some demonstrable abnormalities in the neural control of airway smooth muscle tone in asthma, they can account for only a very few of the features of airway hyperreactivity. Because these other aspects of airway function can contribute to the development and manifestation of hyperreactivity, it is important to look beyond the direct neural control of the smooth muscle, and examine the neural control of some of these other airway functions. There has recently been an increased interest in the airway vasculature, and it is on the neural control of this structure that this discussion will focus.

The Nervous Systems of the Lung

The basic schema of the innervation of the airways is shown in figure 1. The predominant neural pathway for the control of the airway smooth muscle tone and secretion is through cholinergic nerves. These

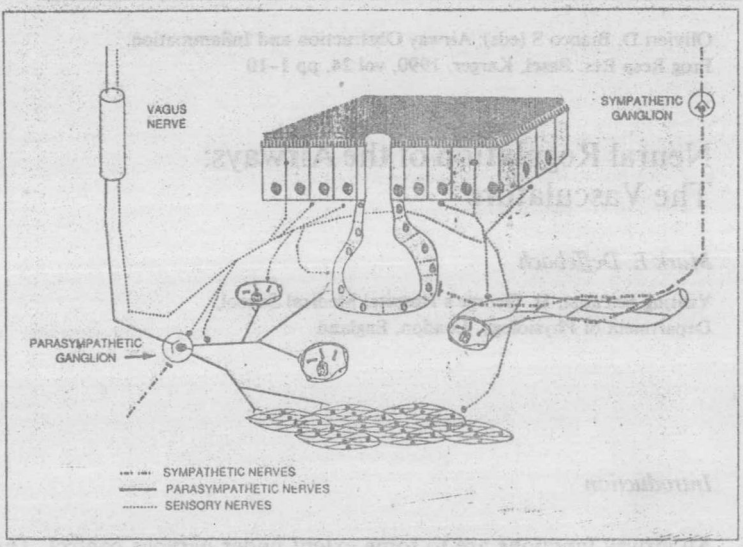

Fig. 1. General schema of the nervous supply to the airways. The parasympathetic nerves synapse in ganglia located within the airway wall, while the sympathetic ganglia are located in the cervical and thoracic region. Sensory nerves have endings in the subepithelial region with projections to many airway structures alone with the afferent fibers ascending with the vagus nerve.

nerve fibers reach the lung by way of the vagus nerve, with the superior and recurrent laryngeal nerves supplying the upper and lower trachea. They terminate in the parasympathetic ganglia, which are located within the airway walls. Here, neural transmission can be altered by a number of factors, including adrenergic nerves [4], sensory nerves, neuropeptides [33], opiate agonists [28], and even acetylcholine itself [5]. Post-ganglionic fibers terminate at the smooth muscle and glands where acetylcholine release can induce smooth muscle contraction and stimulate secretion. These cholinergic mechanisms appear to establish a resting smooth muscle

Table 1. NANC mediators in the lung

Neuropeptide	Associated nerves
VIP efferents	parasympathetic
PHI (PHM)	parasympathetic
Galanin	parasympathetic
NPY	sympathetic efferents
Sub P	sensory nerves
NKA	sensory nerves
NKB	sensory nerves
CGRP	sensory nerves

tone in asthmatics and patients with chronic airflow obstruction, and to a lesser extent in normals.

Adrenergic nerves originate in the upper thoracic spinal cord and synapse in the cervical and thoracic ganglia. The long post-ganglionic fibers intermingle with other nerves and blood vessels in the airway wall. The primary structures innervated by the sympathetic nerves are blood vessels, glands, and the parasympathetic ganglia. Despite the presence of β receptors on the airway smooth muscle, there is very little adrenergic innervation of the muscle in man. Although a precise role for adrenergic nerves in the lung remains to be defined, the most important roles appear to involve control of parasympathetic ganglionic transmission, secretion, and vascular tone.

A third class on neural mediators controlling airway function are the neuropeptides, often referred to as the nonadrenergic noncholinergic (NANC) system. This system utilizes a family of small peptides as transmitters, a partial listing of which is shown in table 1. The NANC system lacks the characteristic anatomic distinctions seen with the cholinergic (primarily parasympathetic), and adrenergic (primarily sympathetic) systems. Instead these neural transmitters are associated with both efferent and afferent nerves, and are localized to many airway structures, including glands, parasympathetic ganglia, and blood vessels [16] (table 1). The physiologic importance of the NANC system remains unclear. The first in vivo demonstration of its activity in man was reflex relaxation of pre-constricted airways [15, 22]. This has led to the hypothesis that this system is important in antagonizing the effects of the constrictor cholinergic system.

Recent studies however, cause one to question the importance, and specificity of this role. In humans, infusion or inhalation of vasoactive intestinal peptide (VIP) is unable to relax pre-constricted airways [6, 24], despite the observation that in vitro VIP can directly relax airway smooth muscle [1]. The cardiovascular effects predominate in the in vivo studies. Most of the other neuropeptides show bronchoconstriction in vitro, with neurokinin A (NKA), and substance P being the most potent. Even here their physiologic importance as a mediator of bronchoconstriction is questioned because in normal subjects and asthmatics inhalation or infusion of substance P does not result in bronchoconstriction, but does have profound cardiovascular effects [10, 12]. Furthermore, capsaicin, which among other effects causes release on sensory neuropeptides (including substance P and NKA), given in vivo to human subjects results in a transient bronchoconstriction which is due to a cholinergic reflex, and not a direct effect of the neuropeptides released [9]. Thus, the NANC system, although potent in vitro, may not have a major role in controlling the airway smooth muscle. As discussed below, however, it may be important in regulating other airway structures, including the airway vasculature.

Nervous Control of the Vasculature

The blood vessels of the airways form 2 venous networks, with a very dense submucosal plexus. The vascular bed is supplied with adrenergic nerves, as shown by histochemical and electron microscopy studies [23]. The structural relationship of cholinergic nerves and the blood vessels is not as clear however, although cholinergic nerves are seen in the vessel walls. The physiology of the neural control of the circulation has only been studied in experimental animals, and the results of the studies described must be extrapolated to man with caution.

The physiologic effects of sympathetic nerves are primarily mediated through vasoconstricting α receptors [19], although the neuropeptide NPY is associated with sympathetic nerves and is vasodilatory [30]. The effects of parasympathetic nerves appear to be more complex. Administration of atropine or ligation of the vagus nerves have little or no effect on resting vascular tone, suggesting that cholinergic nerves exert few tonic effects in the circulation but acetylcholine and methacholine, given either intravascularly or by inhalation, increase the airway blood flow [11]. Stimulation of parasympathetic nerves gives a more complicated picture however.

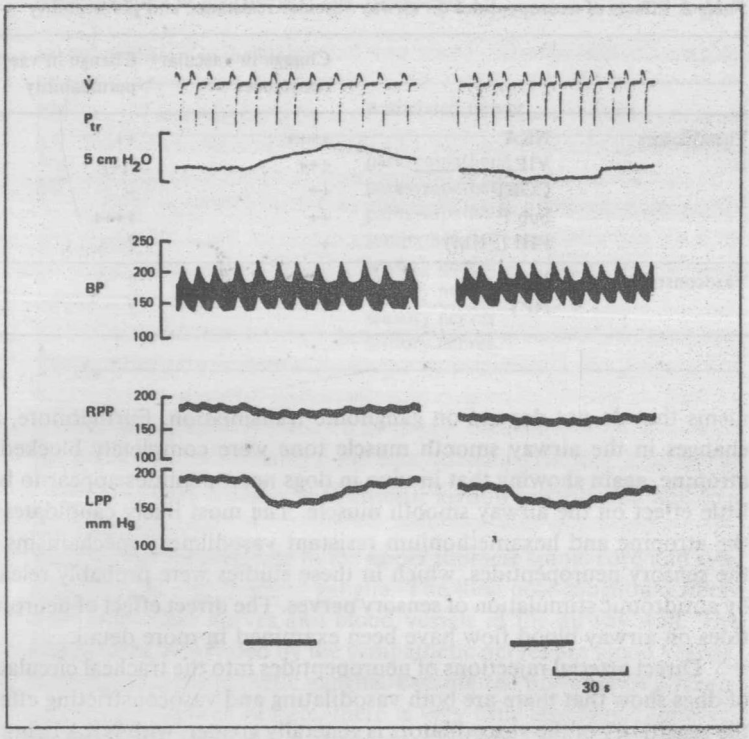

Fig. 2. Electrical stimulation of the superior laryngeal nerve in a spontaneously breathing dog before (left) and after (right) atropine. From top down: V = airflow; P_{tr} = tracheal lumen pressure (reflecting smooth muscle tone); BP = systemic blood pressure; RPP and LPP = right and left tracheal perfusion pressures. Both tracheal arteries are perfused with autologous blood at constant flow; a fall in the tracheal perfusion pressure therefore reflects a fall in vascular resistance. The atropine-resistant vasodilation is due to NANC mechanisms. From ref. [13].

Electrical stimulation of the superior laryngeal nerves in the dog causes tracheal vasodilation, but this is only halved by pretreatment with atropine (fig. 2). The remaining vasodilation is again decreased by half by pretreatment with the ganglionic blocker hexamethonium [13]. These studies show that all stimulations of the parasympathetic nerves are vasodilatory, and that cholinergic mechanisms in the parasympathetic ganglia and post-ganglionic fibers are involved, as well as noncholinergic vasodilatory mecha-

Table 2. Effects of neuropeptides on airway vascular resistance and permeability

		Change in vascular resistance	Change in vascular permeability
Vasodilators	NKA	++++	++
	VIP	+++	?(–)
	CGRP	++	–
	Sub P	++	++++
	PHI (PHM)	+	?
Vasoconstrictors	Bombesin	+	?
	NPY	+	?

nisms that do not depend on ganglionic transmission. Furthermore, any changes in the airway smooth muscle tone were completely blocked by atropine, again showing that in vivo in dogs neuropeptides appear to have little effect on the airway smooth muscle. The most likely candidates for the atropine and hexamethonium resistant vasodilatory mechanisms are the sensory neuropeptides, which in these studies were probably released by antidromic stimulation of sensory nerves. The direct effect of neuropeptides on airway blood flow have been examined in more detail.

Direct arterial injections of neuropeptides into the tracheal circulation of dogs show that there are both vasodilating and vasoconstricting effects; the sensitivity of the vascodilators is generally greater, with NKA being the most potent (table 2). Even at the highest doses there were no significant changes in the airway smooth muscle tone [13, 30]. Capsaicin, which has multiple effects including release of sensory neuropeptides, caused a vasoconstriction followed by vasodilation, perhaps reflecting release of both vasodilatory and constrictor neuropeptides [14, 29, 30]. Even with intraarterial injection of capsaicin there was surprisingly little effect on the smooth muscle. More recently, perfusion of the tracheal circulation with capsaicin, in order to deplete the sensory neuropeptides, was able to diminish the atropine-resistant vasodilation that occurs with superior laryngeal nerve stimulation [29]. Thus in dogs, neuropeptides, either released endogenously by nerve stimulation or capsaicin, or by direct injection, show a much greater potency for the vasculature than for the airway smooth muscle. It is therefore likely that these mediators are physiologically more important in the control of airway blood flow than in controlling the smooth muscle.

Neurogenic Inflammation

The studies cited above have concentrated on the control of vascular tone, and thus blood flow. Recently, studies have also examined the effects of neuropeptides on vascular permeability, a property of the vasculature that may have great importance for asthma. In guinea pigs, substance P, NKA, and capsaicin all increase vascular permeability when administered either intravascularly or onto the tracheal surface[17, 18, 26, 27]. The larger airways are more sensitive to these effects. Nerve stimulation after pretreatment with ganglionic and cholinergic inhibitors, which in rodents has been shown to release sensory neuropeptides [32], also results in increased vascular, and possibly epithelial, permeability [17, 20, 27]. The histologic picture after these stimuli does not merely show changes in vascular permeability, but also includes endothelial attachment of leukocytes followed by neutrophil infiltration of the perivascular tissues [20, 21]. This sequence of events, that is increased vascular permeability with cellular infiltrate following exposure to neural mediators or nerve stimulation, is referred to a neurogenic inflammation. Although it has been convincingly demonstrated in the airways of rats and guinea pigs, it remains to be seen if this occurs in other mammalian airways. Neurogenic inflammation has been demonstrated in human skin however, and does appear to involve similar mediators as the process in rodent airways [7]. Most recently, the presence of airway inflammation, by way of naturally occurring viral airway infections, was shown to greatly enhance susceptibility to the effects of neurogenic inflammation induced by capsaicin and substance P in rats [21]. The airway inflammation due to irritants such as cigarette smoke also may involve sensory neuropeptides [31].

NANC Mechanisms and Asthma

The possibility that airway blood flow, vascular permeability, and possibly some aspects of inflammation may all be influenced by the NANC nervous system in human airways raises some interesting questions as to how the NANC system may be important in asthma. To consider first the effects on blood flow. Mucosal blood flow participates in the delivery and clearance of both endogenous and exogenous active substances. For example in sheep, cold air induced bronchoconstriction could be reversed by increasing the bronchial blood flow [34]. Thus any disturbances of the

control of mucosal blood flow may contribute to the development and resolution of bronchoconstriction. The mucosal blood flow may also be important in the delivery of heat and water to the airways during cold dry air ventilation, a stimulus to which asthmatics are very sensitive. An exaggerated vasodilatory response to cold dry air ventilation may explain the finding that rewarming of the airways is more rapid in asthmatics than in normals [11]. This could be a manifestation of an exaggerated NANC vascular response in already inflamed airways. An exaggerated NANC response in the presence of viral induced airway inflammation could also explain the development of exercise-induced bronchoconstriction and other features of nonspecific airway hyperreactivity in nonasthmatic subjects during and after upper respiratory infections [2].

In summary, the airway circulation may play an important role in the pathogenesis of asthma, and understanding the regulation of the circulation is important in understanding the disease. In critically evaluating the mechanisms, and potential treatment strategies, of asthma, the neural control of the circulation needs to be carefully considered. These processes, although not directly involved in the control of the airway smooth muscle, may influence airways resistance, and appear to be important in one of the fundamental features of asthma, inflammation.

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