exchange during hyperpnea in asthmatic patients demonstrate that the largest heat and water losses occur from the mouth and pharynx, and not within the thorax. Fifty to 60 percent of the total transfers take place between the lips and the glottis, and the remaining quantity is distributed longitudinally over the rest of the tracheobronchial tree. The central airways (glottis to the anterior segmental bronchi) account for 14 to 15 percent of the transfers, and the peripheral units (subsegmental bronchi to alveoli) account for the remainder. The water losses within the intrathoracic airways at the end of 4 minutes of exercise are quite small, and average only a few μl per liter, and even without considering any form of active replacement they result in trivial alterations in the tonicity of the mucosal fluids. It does not matter how ventilation is increased. Voluntary hyperventilation and exercise both produce the same effects when matched for appropriate variables.

Since the mouth and pharynx have a constant source of saliva (a hypotonic fluid) bathing them, this type of distribution allows the upper airways to act as a thermal reservoir permitting large volumes of frigid and/or dry air to be inhaled for prolonged periods without materially influencing the fluid balance of the lower airways. These new observations on the distribution of heat and water fluxes within the intrathoracic airways of exercising and hyperventilating asthmatics do not support the theory that airway dehydration is a catalyst for exercise-induced asthma. Based on both in vivo and in vitro data, the changes in tonicity that occur with all forms of hyperpnea, even in extreme climatic conditions, are far too small to have physiologic consequences. In the most severe circumstances, surface osmolalities in the central airways increase only 10 to 15 percent (from 300 to 340 milliosmols); yet, to induce isolated human mass cells and basophils to secrete just 10 percent of their histamine content in vitro, osmolalities in excess of 600 are required.

In addition to providing new insights into the factors involved in respiratory heat exchange in health and disease, the intrathoracic temperature data recently obtained in asthmatic patients have suggested a new pathogenetic mechanism for exercise-induced asthma. It is now recognized that airway cooling is insufficient to produce obstruction. A thermal gradient must exist at the end of exercise, and airway cooling must be followed by abrupt rewarming for bronchial narrowing to develop. If the gradient is large, as when cold air is inhaled at high levels of ventilation, or if rewarming is facilitated by breathing hot humid air in the recovery period, the severity of the obstruction is amplified. If the gradient is small, as when room air is inhaled at low minute ventilations, or if rewarming is attenuated by slowly lowering ventilation after hyperpnea, the severity of the obstruction is reduced. These observations have led to the speculation that the bronchial circulation is thermally reactive and, like the vessels of the skin, can develop a rebound or reactive hyperemia when subjected to sudden rewarming. Under these circumstances the airway narrowing in exercise-induced asthma may derive from hyperemia and edema of the airway wall induced by a sudden increase in blood supply to the bronchi.

Direct measures of the posthyperpnea temperatures that develop in asthmatic patients and normal subjects offer strong support to this possibility. Accumulated data demonstrate that the airways of asthmatic patients rewarm twice as fast as those of normal people during exercise. Since asthmatic patients have hyperplastic and hypertropic vasculature in their airway walls, the differences between them and normal individuals may relate to differences in the relative size and reactivity of their submucosal capillary beds.

The mechanism that controls the rate of rewarming is not known, but it may involve such factors as the neurotransmitters of the sympathetic nervous system or those of the nonadrenergic, noncholinergic nervous system. Regardless of mechanism, it is becoming more apparent the exercise-induced asthma may be a vascular phenomenon, and further research into this possibility may yield exciting new answers regarding the pathogenesis of this condition.

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The Airway Nonadrenergic Noncholinergic Inhibitory Nervous System*

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The airways of many mammalian species, including guinea pig, cat, chicken, cow, sheep, monkey, baboon, and man, are innervated by a nonadrenergic, noncholinergic (NANC) inhibitory system. Other species, such as dog, pig, and rat, do not possess an airway NANC inhibitory system. In primates, the NANC system appears to be the principal inhibitory innervation to the airways. Activation of NANC nerves results in airway smooth muscle relaxation under in vitro conditions and manifests as a bronchodilatory response in the intact lung. The role of the NANC inhibitory system in normal or diseased human airways is currently unknown;

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however, the observation that the NANC system may be the sole inhibitory innervation in human airways alludes to a potentially important function.2

Electrical field stimulation of intramural nerves in guinea pig and feline isolated central airway segments elicits a biphasic smooth muscle response comprising an initial contraction followed by a prolonged relaxation.3,4 The contractile phase is abolished by inhibitors of muscarinic cholinoreceptors, whereas the relaxant phase is partially attenuated by β-adrenoceptor antagonists. The relaxation response remaining after β-adrenoceptor blockade is defined empirically as being the NANC inhibitory response. In human isolated airways, the relaxation phase induced by electrical field stimulation is completely insensitive to antagonists of β-adrenoceptors, demonstrating the primary NANC innervation of these tissues.5 Several distinguishing features of the airway NANC inhibitory system have been documented in in vitro studies. For example, NANC inhibitory responses may be elicited in tissues in which neuronal acetylcholine stores have been depleted6 or neuronal catecholamine release has been blocked,7 indicating that the NANC system operates independently of autonomic nerves (ie, NANC neurotransmitter release is not dependent upon prior or concomitant release of a classic neurotransmitter). However, the neural origin of NANC relaxation responses has been confirmed by showing that they may be abolished by the nerve toxin, tetrodotoxin.8 Tetrodotoxin-insensitive NANC inhibitory responses have been observed in experiments where long pulse durations of electrical stimulation have been used.8 The significance of these latter responses, which may involve the release of an epithelium-derived factor,9 remains to be established.

Specific receptor and enzyme inhibitors have been used in an attempt to determine the nature of the NANC neurotransmitter. From such studies, it is evident that NANC relaxation responses are not reliant upon the generation of cyclooxygenase or lipoxygenase products of arachidonic acid metabolism nor do they involve an action of neurotransmitter on either histamine or 5-hydroxytryptamine receptors.10 Acute capsaicin-induced depletion of endogenous tachykinins abolishes the recently described NANC excitatory responses in the guinea pig trachea but does not affect NANC inhibitory responses. Further, inhibition of tissue neutral endopeptidase which potentiates NANC excitatory responses in guinea pig trachea does not alter NANC inhibitory responses.11 Thus, tachykinins appear neither to modulate nor to mediate the actions of the NANC inhibitory system.

Treatment of the guinea pig trachea with vasoactive intestinal peptide (VIP) antibody has been reported to attenuate NANC relaxant responses,12 suggesting a role for VIP as the NANC neurotransmitter. Further evidence in favor of this contention rests in (1) the presence of immunoreactive VIP in nerves within airway smooth muscle,13 (2) a positive correlation between the quantity of VIP released and the magnitude of NANC relaxation,14,15 (3) the ability of VIP to mimic the airway smooth muscle relaxation response that attends stimulation of NANC nerves.16 However, definitive evidence for VIP as the NANC neurotransmitter awaits the development of a specific antagonist for VIP receptors. Currently available VIP receptor antagonists—eg, [pCl-D-Phe₆, Leu⁷]-VIP and [nAc-Tyr⁴, D-Phe⁶]-GRF—are ineffective in blocking the actions of VIP in airway smooth muscle.17

Airway NANC inhibitory innervation has been demonstrated under in vitro conditions. In anesthetized, mechanically ventilated cats in which airway tone has been elevated, electrical stimulation of the distal end of cut cervical vagus nerves elicits a biphasic bronchomotor response similar to that described for electrical stimulation of isolated airway preparations—ie, initial cholinergic bronchoconstriction followed by prolonged NANC bronchodilation.18 In these animals, NANC and sympathetic adrenergic inhibitory responses arising as a result of efferent vagal and sympathetic nerve stimulation, respectively, may be readily distinguished from one another on the basis of their time course (ie, the bronchodilatory response to sympathetic stimulation is of shorter duration than that induced by NANC stimulation). Autonomic ganglionic blockade with hexamethonium abolishes NANC bronchodilation in vitro, indicating that this response results from stimulation of preganglionic nerves.19 This result also excludes the possibility that NANC inhibitory responses emanate from antidromic impulse propagation in afferent nerves, since action potentials in such nerves do not traverse a hexamethonium-sensitive ganglion.

In vitro experiments have provided important clues as to the pattern of innervation of NANC inhibitory nerves. In studies where changes in respiratory mechanics are observed, stimulation of efferent NANC nerves elicits a proportionally larger fall in airway resistance than in lung elastance.20 To the extent that resistance and elastance reflect the tone of central and peripheral airways, respectively, these results suggest that NANC inhibitory innervation is most dense in central airways. Direct visualization of airway caliber in cats using Tantalum bronchography has confirmed this distribution pattern and has indicated that the NANC inhibitory influence extends to airways larger than 1 mm in diameter, with the greatest effect occurring in airways 2 mm in diameter.13 In vitro studies corroborate the pattern of innervation suggested from these in vitro experiments. For example, in human airways the magnitude of NANC relaxations in bronchi is greater than that in bronchioles.14 Similarly, the inhibitory effects of NANC nerve stimulation do not appear to extend beyond the trachea in the guinea pig.1 This central predominance of innervation observed for the NANC inhibitory system is similar to that described previously for adrenergic and cholinergic innervation of airway smooth muscle.

Recent studies in the cat and in man have shown that the NANC inhibitory system may be activated reflexively. Mechanical stimulation of the larynx21,22 or chemical stimulation of airway afferent C-fibers23 elicits biphasic bronchomotor responses similar to those observed following efferent vagal nerve stimulation, with the bronchodilatory phase being NANC in nature. These responses may be attributed to activation of a central reflex because blockade of vagal nerve conduction abolishes them. Bronchoconstrictor responses to aerosolized methacholine or 5-hydroxytryptamine are enhanced by blockade of vagal nerve conduction in cats treated with inhibitors of cholinergic and adrenergic nerve function,24,25 indicating that NANC inhibitory nerves may function to regulate airway reactivity to aerosolized bronchoco-
strieeper agonists. Together, these data suggest a role for the NANC inhibitory nervous system in preventing or attenuating bronchospasm.

The functional significance of the airway NANC inhibitory system remains to be defined. It has been suggested that a defect in the function of airway NANC inhibitory innervation may contribute to the elevated airway reactivity observed in asthmatic individuals. The observation that ganglionic blockade does not enhance the airway reactivity of normal subjects would argue against such a contention, but since efferent autonomic nerve impulse traffic from the central nervous system to the airways would be blocked. However, bronchomotor responsiveness in normal subjects may be affected by nervous (e.g., adrenergic and NANC) and non-nervous (e.g., arachidonic acid metabolites) inhibitory influences. Non-nervous influences may be sufficient to regulate airway reactivity under conditions of autonomic blockade. As such, inhibition of both neural and non-neural influences may be necessary to induce a state of bronchial hyperreactivity in normal subjects. In addition, a local reflex may exist in the lung to regulate airway responsiveness, such that an axo-axonal connection would exist between afferent nerves and postganglionic NANC inhibitory nerves. This local reflex would allow the conduction of action potentials from afferent nerves to efferent NANC nerves without the involvement of the central nervous system and peripheral autonomic ganglia. Precise determination of the role of the NANC inhibitory system in the regulation of bronchomotor tone under physiologic and pathophysiologic conditions requires the use of a specific NANC inhibitory receptor antagonist, which has yet to be developed.

Aside from effects on airway smooth muscle, the NANC inhibitory system may regulate other lung functions, such as mucus secretion, mediator release or pulmonary vascular tone, and epithelial or endothelial permeability. Exploration of these other possible regulatory roles of the NANC system may provide valuable insights into the normal and abnormal physiology of the lung.

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Neurohumoral Regulation of Airway Contractile Responses

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Bronchomotor tone is the net product of moment-to-moment interactions across the autonomic nervous system, circulating humoral influences, and endogenous production of locally secreted mediators.

Some degree of airway smooth muscle contraction exists in all individuals. In normal persons, it appears to result largely from parasympathetic innervation to the airway. Endogenous bronchomotor tone theoretically is antagonized physiologically by inhibitory parasympathetic reflexes and by circulating epinephrine. Direct innervation to human airways by sympathetic nerves is insignificant. The homeostatic role of sympathetic secretion in regulating bronchomotor tone is not known.

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