Mechanisms of Bronchoconstriction from Nonimmunologic Environmental Stimuli*

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Asthma is characterized by repeated episodes of bronchoconstriction, often triggered by environmental stimuli. Since much of the therapy of asthma is aimed at preventing these episodes of bronchoconstriction, understanding the mechanisms by which environmental stimuli cause bronchoconstriction has obvious clinical importance. This review will discuss the general mechanisms by which inhaled agents can cause bronchoconstriction and what little is known about the specific mechanisms of action of non-immunologic stimuli.

Some of the well-recognized nonimmunologic stimuli to bronchoconstriction are listed in Table 1. These stimuli are all capable of causing marked bronchoconstriction in subjects with asthma, but have little effect on normal human subjects. Although at high concentrations some of these stimuli do produce measurable bronchoconstriction in animals, the relevance of these effects to realistic environmental exposures is uncertain. Thus, the major source of useful information on the mechanisms of action of these agents is experiments conducted on human subjects with asthma. The ethical and technical constraints of such experiments largely explain the limited nature of present understanding of these mechanisms. Three of the stimuli listed in Table 1 are virtually certain to cause clinically significant effects in patients with asthma. These three stimuli: exercise, fog (distilled water aerosol), and the air pollutant sulfur dioxide, have been the most extensively studied and form the basis of subsequent discussion in this review.

Exercise has been well recognized as a cause of clinically important bronchoconstriction in patients with asthma since at least the 17th century. Over the past ten years, studies from several laboratories have confirmed that the bronchoconstrictor effects of exercise can be mimicked by voluntary hyperpnea at an equivalent minute ventilation, suggesting that exercise-induced asthma is at least in part due to the local effects of exercise-induced hyperpnea on the airways. Studies reporting that hyperpnea-induced bronchoconstriction could be ameliorated by inhalation of warm humid air and potentiated by inhalation of cold dry air led to the suggestion that airway cooling might be the actual stimulus to exercise-induced bronchoconstriction. Recently, largely due to the pioneering studies of Anderson and co-workers, this notion has been questioned. In particular, the observation from three separate laboratories that the water content of inspired air was an important determinant of the magnitude of exercise or hyperpnea-induced bronchoconstriction, whereas the temperature was not, supported the hypothesis that exercise-induced bronchoconstriction might be due to airway drying rather than airway cooling. Recent evidence based on direct calculations of airway heat loss and airway water loss during hyperpnea with dry air at two widely different temperatures (−21°C and 39°C) suggests that neither heat loss nor water loss alone is likely to explain hyperpnea-induced bronchoconstriction and that it is therefore likely that both stimuli contribute to this effect.

The recognition that fog may be an important stimulus to bronchoconstriction is considerably more recent. Nonetheless, over the past ten years reports from several laboratories have shown that inhalation of an aerosol of water (the major constituent of natural fog) rapidly causes bronchoconstriction in most subjects with asthma. Distilled water aerosol causes bronchoconstriction on the basis of its low osmolarity since increasing the osmolarity of the inhaled aerosol by addition of dextrose or a variety of chemically unrelated solutes prevents fog-induced bronchoconstriction. Interestingly, inhalation of hyperosmolar aerosols is also a potent stimulus to bronchoconstriction. Although hyperosmolar aerosols are not generally encountered in the environment, this effect provides support for the notion that airway water loss can

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Mechanisms of Bronchoconstriction (Dean Sheppard)
stimulate smooth muscle contraction, since water loss from the airways during hyperpnea with dry air would be expected to increase the osmolarity of fluid at the lumenal surface of the airways.

The air pollutant sulfur dioxide (SO₂) has been suspected as an important cause of bronchoconstriction since at least the middle of this century, largely on the basis of the striking increase in the incidence of acute asthma attacks that accompanied episodes of severe SO₂ air pollution. Until recently, however, the failure to demonstrate acute effects of the concentrations of SO₂ found in polluted air on airway function had led some investigators to conclude that these clinical observations must be due to the effects of pollutants other than SO₂. Over the last five years, however, studies from several different laboratories have shown that concentrations of SO₂ as low as 0.4 ppm, well in the range encountered in polluted outdoor air and less than one tenth of the concentration presently allowed as an eight-hour average concentration in the workplace, can cause symptomatic bronchoconstriction when inhaled during moderate exercise by subjects with asthma. This effect of SO₂, like that of hyperpnea with dry air or inhalation of hypotonic aerosols, occurs after a brief period of exposure (as short as 3 min) and is maximal within a few minutes of the end of exposure.

**General Mechanisms of Bronchoconstriction**

Inhaled agents can stimulate contraction of airway smooth muscle by several different mechanisms, some of which are pictorially suggested in Figure 1. As shown in this drawing, any inhaled material (represented by shaded triangles) contacts several different populations of cells within or near the airway lumen before it can contact the airway smooth muscle itself. Although some inhaled stimuli (eg, agents such as methacholine) directly stimulate airway smooth muscle, the direct effects of many environmental stimuli (eg, distilled water aerosol) are likely to be dissipated within a short distance of the site of deposition within the airway lumen. These agents are thus likely to stimulate contraction of airway smooth muscle indirectly as a result of an effect on one or more population of cells at or near the lumenal surface of the airway. These indirect effects of inhaled agents can be roughly separated into neural effects, mediated by activation of afferent nerve endings and the ultimate release of bronchoconstrictor substances from nerves, and non-neural effects mediated by the stimulated release of bronchoconstrictor substances from other airway cells. Present evidence suggests that both neural and non-neural mechanisms contribute to the bronchoconstriction caused by each of the three environmental stimuli discussed in this review.

**Neural Mechanisms**

The best studied neural pathway for stimulating contraction of airway smooth muscle involves reflex activation of the parasympathetic efferent nerves that richly enervate the muscle. When activated, these nerves release acetylcholine which directly causes contraction of airway smooth muscle upon binding to muscarinic receptors. The roles of the reflex pathway in mediating the bronchoconstriction caused by environmental stimuli has been studied extensively by examining the ability of specific muscarinic antagonists such as atropine to inhibit these bronchoconstrictor effects. Evidence from studies of the effects of a range of doses of atropine suggests that this pathway plays an important role in the bronchoconstriction caused by dry air, by fog, and by sulfur dioxide in some subjects with asthma. However, on the basis of evidence accumulated from several different laboratories, it is clear that this muscarinic reflex cannot completely explain the bronchoconstrictor response to any of these stimuli, and in fact plays little or no role in the responses seen in many subjects.

Although the muscarinic pathway is by far the best studied, two other neural pathways could contribute to environmentally induced bronchoconstriction. The observation that alpha-adrenergic blockade can inhibit exercise-induced bronchoconstriction has led investigators to suggest that increased alpha-adrenergic activity may contribute to exercise-induced bronchoconstriction. However, adrenergic nerves are not prominent in the vicinity of airway smooth muscle and the observed effects of alpha-adrenergic antagonists may be due to effects on airway blood flow and consequent amelioration of heat and water loss from the airways.

Another possible neural mechanism of induced bronchoconstriction is the stimulated release of bron-
choconstrictor peptides (eg, substance P) from airway afferent nerve endings activated by retrograde stimulation via an axonal reflex. In addition to directly stimulating airway smooth muscle to contract, these peptides may stimulate the release of other bronchoconstrictor mediators from airway mast cells. Because no effective antagonists of these peptides have yet been developed for use in human subjects, the role of this pathway in the bronchoconstrictor response to environmental stimuli remains to be studied.

Non-neural Mechanisms

Each of the cell types depicted in Figure 1 is capable of releasing locally active chemical mediators that could lead to contraction of airway smooth muscle. Macrophages are present in the airway lumen throughout the tracheobronchial tree and are thus readily accessible to environmental stimuli. Pulmonary macrophages can be activated to secrete the platelet activating factor AGEPC, an agent with potent contractile effects on airway smooth muscle. Eosinophils are also present within the airway lumen and in the airway epithelium, and are present in increased numbers in patients with asthma. The role of eosinophils in asthma remains to be determined, but these cells are capable of secreting sulfadopeptide leukotrienes, another class of potent bronchoconstrictors. In addition, eosinophilic major basic protein, a constituent of eosinophils found in increased concentrations in the sputum of patients with exacerbations of asthma, appears to be capable of directly injuring the airway epithelium thereby potentially increasing access to the underlying smooth muscle of any bronchoconstrictor substance present in the airway lumen. Recently, it has been recognized that the airway epithelial cells themselves possess the intracellular machinery required to secrete mediators that might ultimately lead to contraction of airway smooth muscle. One of these mediators, 15-hydroxy-icosatetraenoic acid, has recently been shown to selectively stimulate mast cells to release leukotrienes. The location of these cells in large number at the lumenal surface of the airways makes them a likely initial site of response to environmental stimuli. However, because of the methodologic difficulties of studying the individual contributions of macrophages, eosinophils and epithelial cells to in vivo responses in human subjects, the roles of these cells in mediating the bronchoconstrictor response to environmental stimuli remain unexplored.

On the other hand, there is indirect evidence to suggest a role for the last cell type depicted in Figure 1, the airway mast cell. As Dr. Schulman has already discussed, mast cells clearly have the potential to release a host of bronchoconstrictors. The first line of evidence implicating mast cells in environmentally-induced bronchoconstriction comes from studies of the effects of cromolyn, a drug that has been shown in vitro to prevent the IgE-mediated degranulation of rat peritoneal mast cells. Treatment with cromolyn can prevent the bronchoconstriction caused by each of the environmental stimuli discussed in this review. However, cromolyn has been shown to have a number of effects other than mast cell stabilization, and the mechanism by which this drug prevents bronchoconstriction in human subjects has not been definitively determined. The protective effects of cromolyn cannot be explained on the basis of inhibition of a muscarinic reflex, since cromolyn adds significant protection against the bronchoconstriction caused by SO2 and by hyperpnea with dry air even after maximal muscarinic blockade.

The other line of evidence implicating airway mast cells in the response to environmental stimuli comes from measurements in venous blood of mediators thought to be released from mast cells after inhalation challenge. To date, both histamine and an as yet uncharacterized high molecular weight chemotactic factor thought to originate in mast cells have been found to increase in concentration in venous blood after induction of bronchoconstriction by exercise. However, the presence of these chemicals in the bloodstream does not prove that they originated in the airways and certainly does not establish a mechanistic link between their appearance and co-existent bronchoconstriction.

In summary, this review has discussed three nonimmunologic environmental stimuli that are probably causes of clinically significant bronchoconstriction in patients with asthma. All three stimuli cause bronchoconstriction in part by activating a muscarinic reflex, but this mechanism is unimportant in many patients. Each stimulus is also likely to stimulate release of some bronchoconstrictor mediator from one or more cell types at or near the lumenal surface of the airway. The precise cell(s) of origin and the bronchoconstrictor mediator(s) responsible for this non-muscarinic component of environmentally induced bronchoconstriction remain to be determined.

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