

Asthma pathogenesis and allergen-induced late responses

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Increases in airway eosinophils occur during the late asthmatic response, 7 hours after allergen inhalation, and these can persist for 3 days. Also, increases in airway metachromatic cells occur which are most marked after 7 hours. These increases in airway cells are associated with increases in bone marrow progenitors, which are caused by an increased responsiveness of the bone marrow to IL-5 after allergen because of an increased expression of the IL-5 receptor on the progenitors. These studies suggest that after allergen inhalation, signals are sent from the airways to the bone marrow, which increase production of progenitors and make more cells available to be recruited into the airways. (*J Allergy Clin Immunol* 1998;102:585-9.)

The observation that allergen inhalation can cause symptoms of asthma several hours later that can last several days was originally made more than 100 years ago by Blackley,¹ who was investigating his own allergy to grass pollen. The first thorough description of the airway responses to inhaled allergen was made by Herxheimer² in the early 1950s, who identified 2 distinct components to the response to inhaled allergen, which he called the immediate and late reactions.

In the late 1960s, the first studies on the pathogenesis of allergen-induced airway responses were undertaken.³ Also about this time Altounyan⁴ described another important consequence of the inhalation of allergen in that exposure to grass pollen during the grass pollen season could increase airway responsiveness to inhaled histamine in sensitized subjects. Subsequently, Cockcroft et al⁵ demonstrated that the increase in histamine and methacholine responsiveness that occurs after inhalation of allergen occurs in association with the allergen-induced late asthmatic response.

It is now accepted that inhalation of allergens by sensitized subjects results in airway narrowing, which develops within 10 to 15 minutes of the inhalation, reaches a maximum within 30 minutes, and generally resolves within 1 to 3 hours (the early asthmatic response) (Fig 1). In some subjects in whom an early asthmatic response develops, the airway narrowing persists and either does not return to baseline values or recurs after 3 to 4 hours and reaches a maximum over 6 to 12 hours (the late asthmatic response) (Fig 1). The late asthmatic response need not necessarily be preceded by a clinically evident early

Abbreviations used

BAL: Bronchoalveolar lavage
cysLT: Cysteinyl leukotriene

response. Thus in a subset of sensitized subjects, the inhaled antigen does not cause an early response but is followed 3 to 8 hours later by a late asthmatic response (isolated late response).

The late asthmatic response has been described to occur in approximately 50% of adults,⁶ and between 70% to 85% of children,⁷ in whom an early asthmatic response develops. The explanation for the apparently higher prevalence in children is not known. Whether the development of a late asthmatic response is dependent on the individual's response to the allergen or also on which allergen is inhaled is unclear. Price et al⁸ have documented that in a small percentage of children studied, inhalation of 1 allergen caused both an immediate and a late asthmatic response, whereas inhalation of another allergen caused only an immediate response. This suggests that in some subjects the late response may be allergen specific.

The factors that might predict the development of a late asthmatic response have been examined by several investigators.⁹⁻¹¹ These were mainly indices of high circulating IgE antibody to the inhaled allergen, such as a high IgE RAST with the allergen and a low antigen concentration in the skin eliciting a late cutaneous response. Boulet et al⁹ have also demonstrated that if a late cutaneous response followed a small early cutaneous response (wheal <5 mm), then a late asthmatic response was more likely to occur after an early response. Thus an important determinant of whether a late asthmatic response will develop in an individual is the level of circulating IgE antibody, which may be considered the degree of sensitization against the allergen. The other major determinant of the late asthmatic response is the size of the early response.¹² Thus the greater the degree of airway narrowing during the early response, the more likely a late response will develop. The size of the early response is, in turn, not only dependent on the quantity of mediators released, but also on the degree of histamine or methacholine airway responsiveness of the subject.¹³

PATHOGENESIS OF THE LATE RESPONSE

Investigation of the pathogenesis of the late asthmatic response had been limited, until recently, to describing the physiologic consequences of inhaling allergen on airway function. This was because of the difficulty in gaining access to the sites of the cellular and biochemical

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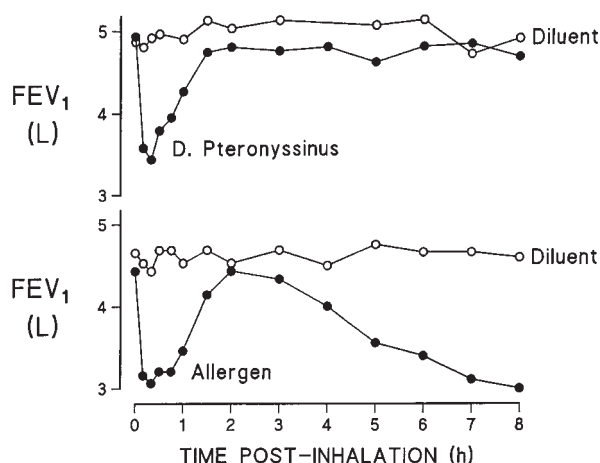


FIG 1. An isolated early asthmatic response after inhalation of house dust mite extract (*Dermatophagoides pteronyssinus*) (upper panel) and an early followed by a late asthmatic response after inhalation of house dust mite (lower panel). The control measurements (open circles) are made after inhalation of the diluent alone. The measurements made after allergen inhalation (closed circles) are made at the same time points as the control measurements.

events occurring in the airway. Other sites, however, such as the skin and the nose, were available for study where events akin to the late asthmatic response occur.

The late cutaneous response was initially thought to be an Arthus or type III immunologic reaction.¹⁴ However, Jerry Dolovich and colleagues¹⁵ clearly demonstrated that both the early and late cutaneous responses are mediated by IgE. The evidence for this is that the late cutaneous response to injected allergen is similar both temporally and in the histologic appearance to the response induced by injection of anti-IgE intradermally. Also, passive sensitization in the skin of nonatopic subjects can lead to an early and late cutaneous response (Prausnitz-Kustner reaction), which is abolished by removing IgE from the atopic serum. Lastly, although passive transfer of IgE into the skin of nonatopic subjects followed by injection of allergen caused a late cutaneous response, passive transfer of IgG did not.

Similarly, the early and late asthmatic responses appear to be IgE mediated. Bryant et al¹⁶ and Hill¹⁷ have shown that the early asthmatic response depends on the presence of IgE antibodies, as demonstrated by skin prick tests, and serum allergen-specific IgE antibodies. Subsequently, several investigators have demonstrated that the development of a late asthmatic response is related to high levels of allergen-specific serum IgE.^{6,9} Also, Kirby et al¹⁸ have shown that inhaled anti-IgE caused late asthmatic responses.

INFLAMMATORY CELLS AND LATE RESPONSES

The identification of stimuli that can cause transient asthma, such as inhaled allergens, have proven to be important in studies demonstrating a central role for air-

way inflammation in asthma pathogenesis. These studies initially examined numbers of cells and cellular differentials in bronchoalveolar lavage (BAL) fluid before and after allergen inhalation.^{19,20} These studies demonstrated an acute inflammatory response in the airways associated with the development of variable airflow obstruction, airway hyperresponsiveness, and asthma. de Monchy et al¹⁹ performed BAL during the late asthmatic response 6 to 7 hours after inhaling allergen and showed that numbers of eosinophils were increased in BAL fluid, with no significant change in any other cell type, including neutrophils. Metzger et al²¹ described increases in eosinophils, neutrophils, and lymphocytes 48 hours after local introduction of allergen into the airways. Also, Lam et al²² demonstrated an increase in eosinophils in BAL fluid from subjects with occupational asthma caused by red cedar, and Boschetto et al²³ described airway inflammation during the late response after administration of toluene diisocyanate, where the predominant cell type was the neutrophil. These studies have suggested that the stimulus that initiates the airway hyperresponsiveness determines the type of cellular response.

A more recent focus has been the examination of the state of activation of the inflammatory cells after allergen inhalation. These studies have identified that eosinophils are activated, as indicated by increased levels of eosinophil cationic protein and positive staining for the marker for cleaved eosinophil cationic protein (EG2), as early as 3 hours and persist for more than 24 hours in BAL fluid after allergen inhalation. This change preceded the increase in total number of eosinophils after allergen inhalation.²⁴

More recently, a less invasive method than bronchoscopy has been developed, which uses sputum induced by the inhalation of hypertonic saline to quantify and characterize inflammatory cells in asthmatic airways. Studies using this method have demonstrated that eosinophils and/or neutrophils increase markedly in sputum samples of asthmatic subjects undergoing a naturally occurring exacerbation of their asthma²⁵ as early as 7 hours after allergen inhalation, which can persist for 3 days after inhalation (Fig 2).²⁶ Also, increases in airway metachromatic cells occur after allergen inhalation, which are most marked 7 hours after inhalation.²⁶ These increases in airway eosinophils and metachromatic cells are associated with increases in circulating eosinophil progenitors measured as colony forming units 24 hours after inhaled allergen,²⁷ suggesting the inhaled allergen stimulates bone marrow production of these progenitors. This has recently been confirmed in a study in which bone marrow progenitors were directly measured in bone marrow aspirated 24 hours after allergen inhalation in subjects with mild asthma.²⁸ This study demonstrated an increased responsiveness of the bone marrow to IL-5 after allergen inhalation, which was associated with an increased expression of the IL-5 receptor on the progenitors.²⁹ Taken together, these studies suggest that after allergen inhalation, signals are sent from the airways to the bone marrow (possibly IL-5) that increase production

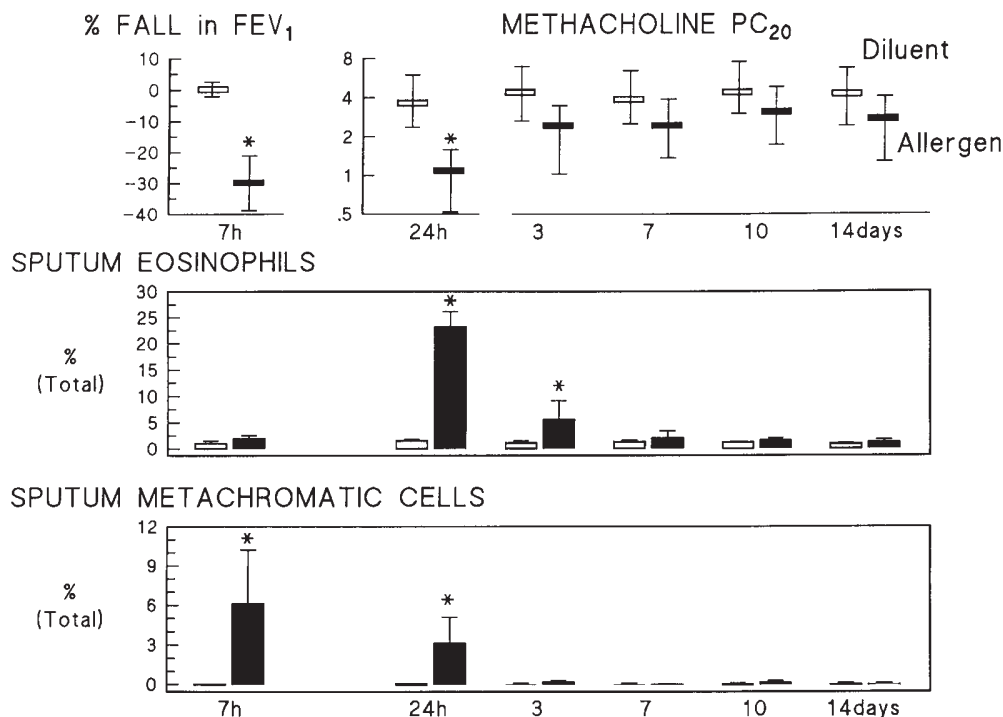


FIG 2. Increases in sputum eosinophils and metachromatic cells followed for 14 days after inhaled allergen in subjects who have allergen-induced dual asthmatic responses and methacholine airway hyperresponsiveness. The increases in metachromatic cells were maximal 7 hours after inhaled allergen, whereas the increases in eosinophils were maximal 24 hours after allergen.

of eosinophil/basophil progenitors by acting on progenitors more responsive to IL-5, thereby making more cells available to be recruited into the airways.

MEDIATORS AND LATE RESPONSES

The bronchoconstrictor mediators mainly responsible for allergen-induced early and late responses have been clarified. Considerable evidence is now available supporting a role for cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) (cysLTs) in the pathogenesis of allergen-induced responses. CysLTs are released from human lungs after allergen challenge *in vitro*,³⁰ whereas increases in cysLTs in BAL fluid³¹ and increases in urinary LTE₄³² have been observed after allergen challenge *in vivo*. CysLTs also increase microvascular permeability and stimulate secretion of mucus,³³ suggesting a possible involvement in the inflammatory process associated with the late asthmatic response. In recent studies pretreatment with specific cysLT₁ receptor antagonists (eg, ICI 204,219 [zifurlukast]³⁴ and MK-571³⁵) and LT biosynthesis inhibitors (eg, MK-0591³⁶ and Bayx1005³⁷) have partially attenuated both the early and late asthmatic response, providing further evidence for a role of cysLTs in the development of both the early and late asthmatic response (Fig 3). None of these studies with antileukotrienes have demonstrated complete protection against allergen responses. For example, BAYx1005 and MK-0591 inhibited the maximum percent fall in FEV₁

during the early response by 56.3% and 57.0%, respectively.³⁶ Treatment with BAYx1005 attenuated the maximum percent fall in FEV₁ during the late response by 47.4%,³⁷ with MK-0591 being comparably effective with a mean 50% and 54% reduction in the mean percent fall in FEV₁.³⁶

The residual allergen-induced bronchoconstriction not attenuated by antileukotrienes is likely mediated by histamine release. Increases in urinary histamine metabolites have been measured during both the early and late asthmatic responses.³⁸ In addition, pretreatment with a combination of an antileukotriene and an antihistamine attenuate the early and the late asthmatic response more than the antileukotriene alone.³⁹

Allergen-induced airway hyperresponsiveness and airway inflammation may also be mediated, in part, by cysLTs. Pretreatment with the cysLT₁ antagonist, pranlukast, significantly reduced allergen-induced methacholine airway hyperresponsiveness.⁴⁰ Also, the cysLT₁ antagonist, zifurlukast, reduced allergen-induced increases in airway inflammatory cells.⁴¹

Taken together, these studies have demonstrated that allergen inhalation by sensitized subjects causes histamine and cysLT release from airway mast cells, resulting in the early asthmatic response. Also, as a consequence of the early response, eosinophils and mast cells or basophils are attracted into the airways and activated. This results in further release of histamine and the

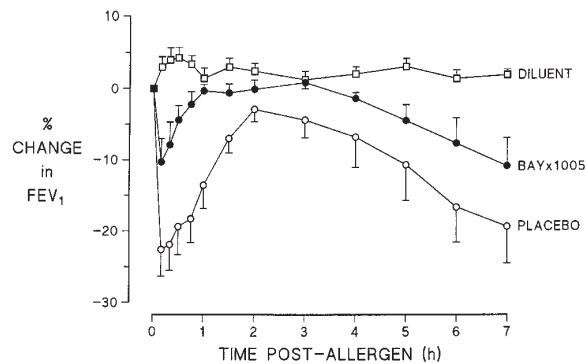


FIG 3. Mean ($\pm$ SEM) percent change in FEV₁ from baseline during the early and late asthmatic response to allergen inhalation after treatment with the leukotriene synthesis inhibitor BAYx1005 (closed circles) and placebo (open circles) and after inhaled diluent (open squares). * $P < .05$; ** $P < .001$. (From Hamilton et al. *Thorax* 1997;52:348-54.)

cysLTs, causing the late asthmatic response. Also, the bone marrow increases its responsiveness to IL-5, which causes increases in eosinophil and basophil production, which propagates the inflammatory response.

CONCLUSIONS

It has now been clearly demonstrated that allergic responses in the skin, nose, and airways can have a prolonged component, which, in most instances, is more important clinically and more difficult to treat than the early, relatively short-lived component of these reactions. By focusing on the late responses in the airways, the importance of airway inflammation in causing both late asthmatic responses and the increases in airway responsiveness after inhaled allergen has become clear. This, in turn, has identified the need to use antiinflammatory drugs, such as glucocorticoids, in treating exacerbations of asthma after exposure to inflammatory stimuli, such as inhaled allergen.

The use of the late asthmatic response as a laboratory model to study the pathogenesis of asthma does have limitations. For example, in many instances airway hyperresponsiveness and asthma are present in subjects who are not allergic to any identifiable allergen. In addition, inhalation of allergen or occupational exposure to a sensitizer can occasionally increase airway responsiveness without a measurable late response occurring. However, despite these limitations, it is likely that much of the morbidity suffered by allergic asthmatic subjects is a consequence of airway inflammation, which is manifest in many subjects as a late asthmatic response. Therefore continuing studies of the late response are likely to improve our understanding of the pathophysiology of asthma.

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