

Pharmacologic management of asthma

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Therapy for asthma has largely been focused on the end-organ effect of bronchoconstriction on airway smooth muscle. Xanthine derivatives such as theophylline were the initial oral bronchodilators used to manage asthma. Recent therapies directed at airway smooth muscle relaxation promote bronchodilation through stimulation of the β -adrenoreceptor.¹ The pharmacologic evolution of β -adrenergic agonists has led to the development of airway smooth muscle receptor-specific agents, agents that can be administered topically through aerosol inhalation, and agents that are long lasting. Epidemiologic studies have validated the safety of the long-acting β -adrenoreceptor drugs and established that tachyphylaxis, as measured by the direct bronchodilating effect of these agents after repeated use, is inconsequential.

More recently, the focus of asthma therapy development has been on modification of the inflammatory component of this disorder.² Oral corticosteroids cause substantial improvement in objective measures of lung function, but these agents are associated with considerable toxicity.^{3,4} The development of potent, highly lipid-soluble agents permits twice-daily dosage and may lead to a reduction in oral corticosteroid use in patients with corticosteroid-dependent asthma. Furthermore, inhaled corticosteroids provide an effective means of managing the pathology of inflammation with minimal adverse effects.

With the enhanced understanding of asthma pathophysiology, drugs now are being designed to act against different steps in the inflammatory process. Newer agents include those directed at antagonizing the effects of leukotrienes that are secreted from inflammatory cells. These include two classes: 5-lipoxygenase inhibitors and leukotriene receptor antagonists. A number of other therapies are currently in development. Some of these interventions (e.g., monoclonal antibodies) prevent adhesion of inflammatory cells to vascular endothelium in conducting airways. Other mechanisms of action of investigational agents include modification of T-helper (T_{H2}) cell interactions that trigger inflammatory activation, suppression of eosinophil development, and induction of eosinophil apoptosis in the bone marrow.

PATHOPHYSIOLOGY

A specific definition of asthma has been elusive because the clinician, the physiologist, the immunologist, and the pathologist all have different perspectives of this disorder. Nevertheless, it is generally agreed that asthma is a lung disease characterized by airway obstruction, airway inflammation, and increased airway responsiveness to a variety of stimuli.⁵ There are many different causes of asthma and many different factors that influence its development, including allergens, respiratory infections, exercise, environmental changes, and even aspirin in some patients.⁶

In response to an asthma trigger, the patient experiences an acute decrease in pulmonary function that is caused by smooth muscle contraction. Subsequently, a secondary decrease in pulmonary function (e.g., late-phase reaction) may occur 4 to 8 hours after the acute episode.⁶ The inflammatory response is mediated by a wide range of cell types, including eosinophils, T cells, and mast cells, among others (Fig. 1).⁶ The autonomic nervous system is secondarily involved in this process; it regulates airway smooth muscle tone, vascular tissues, and mucus secretion.⁷ In addition, structural changes in the airway epithelium and peripheral airways may contribute to bronchial hyperresponsiveness.⁸⁻¹⁰

The pathology of asthma has been investigated in postmortem studies. Certain features are notable, including occlusion of bronchial lumina with a mixture of mucus, serum proteins, and cellular debris; epithelial sloughing and remodeling; thickening of the epithelial basement membrane; edema and leukocyte (mainly eosinophil) infiltration of the submucosa; hyperplasia of mucous glands; and hypertrophy of bronchial smooth muscle.^{5,8,9}

With chronic asthma, a permanent change in the basement membrane of the airway lumen is observed.² These structural changes reflect collagen cross-linking that may be irreversible.⁵ In addition, it has been demonstrated that an excess of cells appears in the airway wall. These cells are often eosinophils that originate in the bone marrow and migrate to the conducting airways of the lung via molecular adhesion molecules that capture and direct them across the conducting airways. The presence of these cells is presumed to cause permanent remodeling of the airway smooth muscle. Thus there is a chronic, and probably irreversible, aspect to the asthma process.

B₂-AGONIST DRUG DEVELOPMENT

Early research into the pathophysiology of asthma suggested that asthma was a process of β -adrenergic deficiency or deficient response in sympathetic neural

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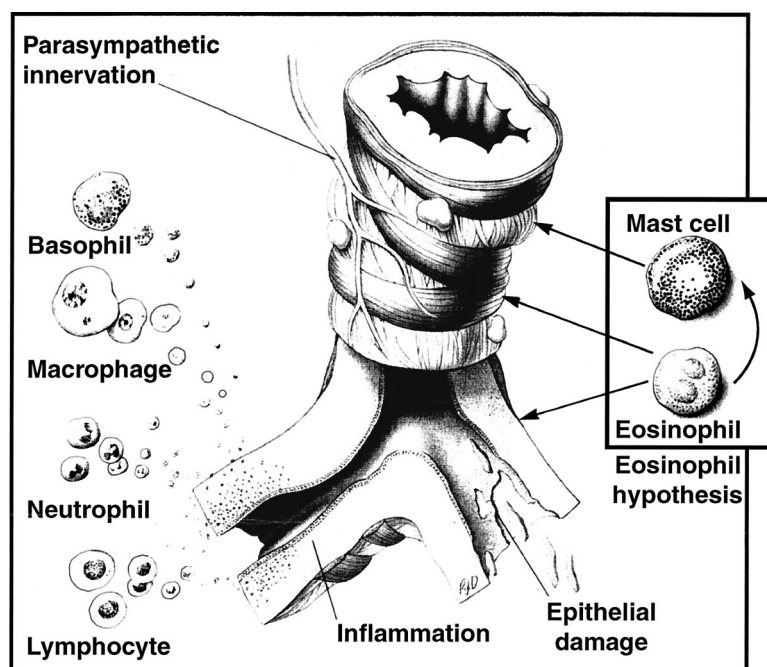


FIG. 1. The asthmatic process: a complex relationship between the inflammatory response and airway smooth muscle function. Reprinted with permission from Busse WW. *J Respir Dis* 1989;10:72–80.

regulation. The original drugs for asthma treatment (e.g., epinephrine) were nonselective β -adrenergic agonists designed to stimulate relaxation of the airway smooth muscle.¹¹ Bronchodilation is caused by stimulation of β_2 -adrenergic receptors.¹² β -adrenergic agonists function primarily by driving calcium through the adenylyl cyclase system into the sarcoplasmic reticulum of the muscle, thus making it less available to the contractile apparatus.¹³ In the absence of calcium, myosin light chain cannot be phosphorylated, and the smooth muscle cannot contract.

In an attempt to improve the bronchodilating properties of the original agents, isoproterenol was developed. It was the first drug to be used regularly by inhaler, but it has both β_1 - and β_2 -activity, thus inducing cardiac stimulation. In addition, isoproterenol is inactivated by catechol-O-methyltransferase, so its duration of action is short. Subsequently, albuterol and terbutaline were developed to overcome the problems associated with isoproterenol and its agonist, metaproterenol. These drugs are both highly β_2 -specific and have substantially longer durations of action than isoproterenol. Salmeterol and formoterol are the next generation of β_2 -specific agonists. They have longer durations of action (up to 12 hours) and provide steady-state bronchodilation.

ANTIINFLAMMATORY DRUG DEVELOPMENT **Antileukotriene therapies**

Metabolites of the arachidonic acid pathway, including the leukotrienes, are released by cells of the immune system and function as part of the inflammatory process. The leukotrienes induce some important features of

asthma, such as bronchospasm and increased bronchial hyperresponsiveness.¹⁴ Agents developed to date use two different mechanisms to combat the actions of the leukotrienes.¹⁵ The leukotriene D_4 receptor antagonists (e.g., zafirlukast) inhibit the effects of leukotrienes C_4 , D_4 , and E_4 on airway smooth muscle, while the 5-lipoxygenase inhibitors (e.g., zileuton) prevent the synthesis of leukotrienes.^{16–18} Zafirlukast and zileuton have demonstrated safety and efficacy in clinical trials and received approval for marketing by the United States Food and Drug Administration. Zileuton has been shown to cause substantial improvement in lung function in a significant subset of moderately severe asthmatic patients.

Future therapies

The future development of asthma therapies is focused not only at containing the infiltration of immune cells once they have invaded the airways but also at preventing the generation of these cells. Eosinophil infiltration of the airways results directly from adhesion of surface molecules on both the eosinophil and the vascular endothelium of the airway.¹⁹ The eosinophils possess an adhesion molecule not shared by neutrophils, designated as VLA-4, which binds specifically to an endothelial adhesion molecule, designated as VCAM-1. Monoclonal antibodies (small molecules) to these adhesion molecules are being developed to prevent eosinophils from invading the conducting airways. Other agents are being directed against hematopoiesis or to induce apoptosis in the bone marrow. Likewise, T_H2 interactions are being targeted to suppress inflammatory activation.

CONCLUSIONS

A variety of new agents are in development for the treatment of asthma because of an enhanced understanding of the pathophysiology of this disorder, particularly the inflammatory processes. Future therapies may be aimed at inhibiting the infiltration of eosinophils into airways or at inhibiting the generation of these cells. Gene therapies currently show little promise for treating this prevalent and generally nonmorbid disease.

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