Pathophysiology and Pharmacotherapy of Asthma: An Overview

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Received May 4, 1979, from the *Department of Biological Research, Section on Respiratory and Allergic Diseases, Smith Kline and French Laboratories, Philadelphia, PA 19101.* Accepted for publication July 27, 1979.

Abstract □ The pathophysiology of allergic and "nonallergic" asthma is presented, and several classes of antiallergic agents are discussed.

Keyphrases □ Antiallergic drugs—cromolyn sodium, adrenergic bronchodilators, corticosteroids, anticholinergic agents □ Pathophysiology—asthma, immunologically induced release of primary and secondary mediators, membrane permeability changes, calcium-ion dependency, antiallergic drugs □ Asthma—review of current theories, clinical evaluation, symposium, antiallergic drugs

Asthma is a disease marked by recurrent, quickly developing, bronchial obstruction leading to paroxysmal dyspnea. The condition results from a spasm of hypersensitive bronchial smooth muscle, generally in the segmental and smaller bronchi. The spasm is often accompanied by a mucosal edema and respiratory mucus hypersecretion. The principal types of the disease are allergic or extrinsic asthma and "nonallergic" or intrinsic asthma, the latter of uncertain origin (1). The prevalence of asthma is slightly higher in children than in adults; ~5% of all children in the United States below the age of 15 suffer from the disease (2).

An early clinical impression of the disease was accurately given by Dr. Michael Ryan, writing in "Observations on the History and Cure of the Asthma" (for review, see Ref. 3), who observed in 1793 that few diseases can be considered more formidable. The prospect of instant suffocation is so alarming as to weaken and depress a mind endowed even with the utmost fortitude and resignation. Dr. Ryan concluded that any remedy capable of permanent relief must be looked upon as of the utmost importance to mankind.

PATHOPHYSIOLOGY

The symptomatology of immediate-type allergic diseases, including extrinsic asthma and allergic rhinitis, presumably results from the immunologically (antigen) induced release of various pharmacologically active substances from mast cells, and basophilic leukocytes previously sensitized with an antibody generally of the immunoglobulin E class (4), and possibly from other cells as well. The substances thus released and referred to as primary mediators of anaphylaxis, *i.e.*, those released as a direct consequence of antigen–antibody interaction, include histamine, slow-reacting substance, eosinophil chemotactic factor, and platelet-activating factor (5). There are probably other primary mediators as well as secondary mediators released indirectly, such as some of the prostaglandins and kinins involved in the modulation of allergic processes (5). The sequence of biochemical events associated with mediator release is not clearly understood and has been the subject of a substantial research effort, particularly during the past decade (5).

Considerable evidence now supports immunoglobulin E (4) as the immunoglobulin class essential to acute allergic reactions, although some data indicate that such reactions also can be mediated by subclasses of immunoglobulin G-type antibodies. Immunoglobulin E may be synthesized locally in the respiratory tract or by the systemic immune system. It is a heat-labile glycoprotein of 198,000 molecular weight, which, as do the other immunoglobulin classes, contains two heavy and two light polypeptide chains linked by sulfhydryl bonds in fundamentally a Y-shaped structure. Presumably, the most significant biological property of the molecule is its ability to bind to homologous mast cells and basophils, thus sensitizing these cells for subsequent allergic reactions (4, 6). The Fc region of immunoglobulin E is that portion of the stem of the immunoglobulin molecule responsible for the highly specific binding to the receptors (4, 6) on the membranes of the tissue-fixed mast cells and blood basophils.

The remaining branched portion of the molecule, the Fab portion, contains the antigen binding sites thought to be made up of parts of the heavy and light chains. While not completely understood, evidence suggests that bridging of two cell-bound immunoglobulin E molecules by antigen (4, 6) is the initial step in a cascade of reactions resulting in mediator release. Presumably, an allosteric change in the structure of the Fc portion of the antibody then leads to the development of activated sites (7) on the mast cell or basophil membrane. Resulting changes in the charge distribution of the membrane are thought to increase the membrane permeability and alter the intracellular ionic milieu, initiating further biochemical steps of which relatively little is known (7).

It has been suggested that an early event in the release is an activation of a membrane-bound chymotrypsin-like proesterase (5). Esterase activation presumably requires calcium ion and results in an enzyme that can be inhibited by isofluorphate (diisopropyl fluorophosphate). Later in the sequence, there appear to be an energy-requiring step that can be inhibited by 2-deoxyglucose, an intracellular calcium-ion-requiring step capable of being suppressed by edetic (ethylenediaminetetraacetic) acid, and a step regulated by the relative levels of cyclic adenosine monophosphate and/or cyclic guanosine monophosphate. Presumbly, the mechanism of action of many compounds clinically effective in asthma is at the cyclic nucleotide step(s) (5).

Moreover, the cellular secretion of histamine, at least, may involve microtubules and microfilaments (7), although the supporting data are generally indirect and involve inhibition of histamine release by the alkaloid colchicine, thought to be an inhibitor of microtubule function. Conversely, heavy water, which is considered to stabilize microtubules, enhances histamine release. Little is known about the process of limiting immunological histamine release, although a series of feedback controls governed by the cyclic nucleotides and histamine itself has been suggested. Somewhat more is known about some mediators of anaphylaxis, which are thought to contribute collectively to the clinical syndrome of the disease (5, 6).

Histamine is β-imidazolylethylamine, and it is synthesized principally by a specific *l*-histidine decarboxylase enzyme. Histamine involved in hypersensitivity reactions of the immediate type appears to be stored in discrete mast cell (or basophil) secretory granules as a complex with heparin and protein. This stored amine undergoes slow turnover by comparison to the extra mast cell histamine of the GI mucosa and the central nervous system.

While still the subject of controversy, it is believed that the immunological, calcium-dependent release of histamine involves two processes, perhaps including the exocytosis of the subcellular cytoplasmic granules and the disassociation of histamine from the granule matrix (7). The heparin–protein complex of mast cell granules has ion-exchange properties, and exposure of the granule matrix to an altered ionic environment results in an exchange of histamine for sodium ions, which have an affinity for the binding sites. Once released, histamine presumably contributes to portions of the clinical syndrome of immediate hypersensitivity reactions. Apart from tissue uptake, histamine then apparently undergoes metabolism by one of two pathways. One, through methylation of the ring structure by imidazole-*N*-methyltransferase, yields methylhistamine, which is then oxidized through monoamine oxidase to methylimida-

0022-3549/80/0200-0236$01.00/0

zoleacetic acid. Alternatively, histamine can undergo an oxidative deamination by histaminase or diaminoxidase to imidazoleacetic acid. The products of this metabolism are excreted in the urine.

As with histamine, the mast cell has been implicated as a source of slow-reacting substance of anaphylaxis (5, 8), although other cell types also appear to serve that function. Two experimental systems that generate slow-reacting substance of anaphylaxis are the sensitized fragmented lung and peripheral blood leukocyte preparations. The material is measured by bioassay utilizing the guinea pig ileum, and it produces a sustained contraction in the presence of an H_1-antihistamine and an anticholinergic agent. While the chemical structure of slow-reacting substance of anaphylaxis has only just been disclosed, some information was available concerning its physicochemical and biological properties. Slow-reacting substance of anaphylaxis was thought to be an acidic lipid of ~400–600 molecular weight and presumably contained an esterified sulfate group. It was considered resistant to proteases and phospholipases but labile to arylsulfatases and oxidation (5, 8). Furthermore, it was thought that slow-reacting substance of anaphylaxis could be derived from arachidonic acid, perhaps through a lipoxygenase pathway, but it appeared to be more polar than, and could be separated from, conventional prostaglandins (8).

Recently (9), it was suggested that slow-reacting substance of anaphylaxis may be "identical" to leukotriene C, one of a group of compounds related to the prostaglandins identified by Samuelsson, Borgeat, and colleagues of the Karolinska Institute in Sweden. Leukotriene C contains the amino acid cysteine covalently linked to the 20-carbon fatty acid derivative of the prostaglandin precursor, arachidonic acid. While there have been occasional reports of a small amount of preformed slow-reacting substance of anaphylaxis in lung tissue, it is presumably formed *de novo* and released on immunological challenge.

Eosinophils occur in relatively large numbers in pulmonary tissues and mucosal secretions of asthmatics, although their role is not precisely understood (10). Investigations that demonstrated that neither relatively pure slow-reacting substance of anaphylaxis nor histamine was chemotactic for these cells provided the basis for discovery of eosinophil chemotactic factor of anaphylaxis, another preformed primary mediator. Eosinophil chemotactic factor has a molecular weight of ~500, and chromatographic and electrophoretic evaluation suggests that eosinophil chemotactic factor of anaphylaxis is a low molecular weight acidic peptide. Two tetrapeptides with amino acid sequence Val-Gly-Ser-Glu and Ala-Gly-Ser-Glu were recovered from extracts of human lung fragments and were shown to be chemotactic for eosinophils (5, 10). Whether these tetrapeptides are, in fact, eosinophil chemotactic factor remains to be determined conclusively.

Additionally, other pharmacologically potent materials have been shown to be released from previously sensitized lung tissues on immunological challenge. Prostaglandins of the E and F classes are presumably rapidly synthesized (5, 8) and released, and they affect bronchial smooth muscle in an opposing fashion: prostaglandin E_2 producing relaxation and prostaglandin $F_{2\alpha}$ producing contraction (8). Their pharmacological activities are probably mediated by intracellular messengers, the cyclic nucleotides, cyclic guanosine monophosphate, and cyclic adenosine monophosphate, and they themselves are considered as secondary mediators whose synthesis and release may be governed by histamine or slow-reacting substance of anaphylaxis.

In addition to the prostaglandins, other chemicals, yet poorly characterized, probably contribute to the symptomatology of allergic asthma. Platelet-activating factor is possibly a lipid material, released on an immunoglobulin E–antigen interaction on basophils or lung tissue (5). Platelet-activating factor induces aggregation of platelets and the subsequent release of serotonin, which can cause tracheobronchial smooth muscle contraction.

In addition to the direct spasmogenic effects of many mediators of anaphylaxis, parasympathetic reflexes mediated through the vagus nerve also may contribute to the bronchoconstriction in the human asthmatic. Furthermore, individuals with asthma disclose a substantial hyperresponsiveness of their airways to several pharmacological agents such as histamine, prostaglandins, and cholinergic agonists as well as to such nonspecific irritants as cold air and noxious gases. This hyperresponsiveness may enhance the pathophysiological effects of the mediators released on antigen exposure.

PHARMACOTHERAPY

Following an established diagnosis and evidence for the reversibility of airway obstruction, the process of selecting an appropriate course of pharmacotherapy may be initiated. Management of the acute bronchospasm has the first priority; when it is initially controlled, etiological factors can be determined. In status asthmaticus (1, 11), a severe continuous state of asthmatic dyspnea, hospital management is indicated. Treatment must provide rapid bronchodilation, perhaps best achieved in this instance with intravenous aminophylline.

For less severe clinical situations, new drugs have been introduced during the last decade (11–14). Still others have been reevaluated for their utility among various patient populations.

Cromolyn Sodium—In 1956, a Fisons Pharmaceutical Corporation research team (3) initiated a search for compounds having selective actions on smooth muscle. The team chose khellin, extracted from a Mediterranean plant, as the chemical prototype since its seeds had been used since ancient times as a smooth muscle relaxant. A series of chromone-2-carboxylic acids was developed, but the compounds were inactive as smooth muscle relaxants and as antagonists to chemical spasmogens. However, they did partially inhibit, but not reverse, antigen-induced bronchospasm in an asthmatic volunteer. The interest in chromones led to the bis-chromones (3); in January 1965, one of these bis-chromones, cromolyn sodium (disodium cromoglycate), was synthesized and tested. In January 1968, it was introduced into therapy in the United Kingdom.

Although the cellular events responsible for the release of the mediators of anaphylaxis is not clearly understood (5), inhibition of their release would seem to be effective therapy. Presumably, the effectiveness of cromolyn sodium (3) is based on its ability to inhibit the immunologically induced release of mediators from sensitized cells (15). The compound has no bronchodilator or anti-inflammatory activity, and it is not effective for the treatment of the acute asthmatic episode. Rather, it is a clinically effective, prophylactic antiallergic agent in a limited patient population consisting principally of children. The compound is poorly absorbed from the GI tract, so it is administered as a powder inhalation.

Although some inconvenience and a need for education are associated with its use, cromolyn sodium offers a rather substantial degree of safety, with only occasional cough or bronchospasm generally associated with its use. While enjoying broader use elsewhere, in the United States the compound is indicated as an adjunctive therapy in the management of patients with severe bronchial asthma (3). Cromolyn sodium is continued on a more chronic basis if it significantly reduces the severity of symptoms, allows for a reduction in or elimination of steroids, or allows for satisfactory management of individuals who have "intolerable" side effects to sympathomimetic drugs or the methylxanthines.

The clinical efficacy of cromolyn sodium as an antiasthmatic agent has prompted a significant worldwide research effort directed to the discovery of more potent, orally active antiallergic drugs (15).

In addition to cromolyn sodium, the pharmacological armamentarium for the management of asthma consists of several adrenergic bronchodilators (16) including epinephrine and isoproterenol and the new, β_2-selective adrenergic drugs, theophylline and its several preparations, both systemic and inhaled corticosteroids, and anticholinergic agents such as atropine and its derivatives (11–14, 16, 17). Concern as to potential side effects with some of these agents, as well as the relative inconvenience attendant to cromolyn sodium administration, suggests that an orally active prophylactic antiallergic agent with a rather broad therapeutic index would be of significant value.

Adrenergic Drugs—Adrenergic receptors have been pharmacologically classified into α, β-1, and β-2 types. Among various other activities, adrenergic agents can stimulate α-receptors and cause vasoconstriction, β-1 receptors and cause cardiac stimulation, and β-2 receptors and provide bronchodilation (13, 16).

The use of adrenergic drugs in asthma dates from the use of the herb *Ma Huang* in Chinese folk medicine. The active ingredient, ephedrine, was introduced into Occidental medicine in the 1920's. Ephedrine stimulates α- and β-adrenergic receptors and, apart from its direct actions, releases norepinephrine stores from peripheral sympathetic nerve endings. Tachyphylaxis can develop to its activity, and subsequent doses are less effective, presumably due to norepinephrine depletion.

Epinephrine and isoproterenol, the prototype β-adrenergic stimulant, have been used in the management of bronchospasm for many years. Their use is limited, however, by the occasional development of undesirable side effects of tremor and cardiac stimulation. Beyond their lack of selectivity for β-2 receptors, the compounds have a relatively short duration of action because of rapid tissue inactivation, in part due to catechol-*O*-methyltransferase.

In the mid-1960's, Lands and coworkers demonstrated that a substantial selectivity for β-adrenergic receptors could be realized by chemical modifications of the phenylethylamine moiety of catecholamines (16). More recent attempts to improve selectivity and metabolic

stability have involved altering the catechol structure (16). Thus, in the past few years, some relatively selective β-2 adrenergic agonists have been developed including salbutamol, carbuterol, terbutaline, metaproterenol, and isoetharine (11, 13). Many of these compounds provide prolonged bronchodilation after aerosol or oral administration while producing relatively few cardiovascular side effects at effective bronchodilator dose levels.

Methylxanthine Phosphodiesterase Inhibitors—Theophylline and its various salts (11–13) are presumably effective in asthma by preventing the intracellular conversion of cyclic adenosine monophosphate to 5′-adenosine monophosphate. By elevating cyclic adenosine monophosphate, theophylline is capable of inhibiting immunologically induced mediator release and of potentiating the effect of β-2 selective adrenergic agonists, which stimulate the production of increased concentrations of cyclic adenosine monophosphate. First introduced as a therapy for asthma in the 1930's, oral theophylline now is widely used because it provides effective bronchodilation with minimal side effects in many patients. Occasional side effects with oral administration and, perhaps more frequently, with rapid intravenous administration include insomnia, nervousness, and cardiac arrhythmias.

Corticosteroids—Generally, corticosteroids (11–13) of relatively short duration are highly effective for the clinical management of severe asthma. Such compounds as prednisone, hydrocortisone, and prednisolone provide excellent anti-inflammatory, antiallergic activity in asthma. When utilized in an alternate day therapy, they are less likely to cause adrenal suppression, osteoporosis, or other adverse effects.

Recently, a variety of inhaled steroids have been introduced, and beclomethasone or other compounds have been shown to be locally effective at relatively low doses that do not cause substantial systemic effects. Adrenal insufficiency has occurred in some individuals when transferred to these topical inhaled steroids from systemic dose forms. The mechanisms by which the corticosteroids are effective in allergic inflammation is unknown but may be related in part to adenyl cyclase and the relative levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate.

Anticholinergic Agents—In recent years, there has been a substantial renewal of interest in anticholinergic agents for the clinical management of asthma. It has been suggested that an imbalance of the autonomic nervous system function contributes to the disease. The characteristic hyperirritability of the airway smooth muscle may be due to a parasympathetic nervous system predominance (11–13, 17). Stimulation of subepithelial receptors of tracheobronchial tissue by particulate, gaseous, or immunological irritants can induce vagal reflex-mediated bronchoconstriction. The resulting increase in airway resistance can be reduced by atropine administration. Moreover, cholinergic agonists enhance immunologically induced mediator release, and atropine can inhibit such release, thus suggesting activity at sites other than the muscle. Recent interest has been shown in the bronchodilation produced by ipratropium bromide, an atropine-like investigational drug.

In addition to these classes of compounds, other agents have been studied, including the E-series prostaglandins and α-adrenergic antagonists (8, 13). Prostaglandins E_1 and E_2 are apparently effective bronchodilators in some individuals, but respiratory tract irritation and cough have precluded their extensive study. α-Adrenergic antagonists such as phentolamine may be useful, although the extent of α-adrenergic tone to tracheobronchial smooth muscle is relatively minor. The potential for adverse effects with these antagonists has limited their study.

The selection of appropriate therapy was reviewed recently (11–13, 17). In summary, a substantial number of individuals respond with effective bronchodilation and little adverse reaction to an oral theophylline preparation. Oral, relatively β-2-selective adrenergic drugs provide good bronchodilation, but adverse effects including tremor may limit their use. Asthmatics who fail to achieve adequate relief with either of these classes of drugs may benefit from cromolyn sodium. Individuals with persistent, severe disease likely will require corticosteroids, and aerosols of these agents may preclude the need for larger doses of systemic steroids. Many of the therapies can be combined, and often lower doses of each agent in combination may be *as* effective (and perhaps offer fewer side effects) as single-drug therapy.

The past decade has seen substantial progress in the understanding of cellular processes that presumably account for the clinical syndrome of allergic asthma. As even greater understanding develops, we can expect more sophisticated drugs to supplement the existing agents.

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ACKNOWLEDGMENTS

Presented as part of the Symposium on New Approaches to the Treatment of Asthma, APhA Academy of Pharmaceutical Sciences, Anaheim meeting, April 1979.