Pulmonary and Antiallergic Drugs

Edited by
JOHN P. DEVLIN

Pulmonary and Antiallergic Drugs

Edited by
JOHN P. DEVLIN
Research and Development
Boehringer Ingelheim Ltd.
Ridgefield, Connecticut

A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

Library of Congress Cataloging in Publication Data:

Main entry under title:

Pulmonary and antiallergic drugs.

(Chemistry and pharmacology of drugs; v. 4)
"A Wiley Interscience publication."
Includes index.
1. Antiallergic agents—Testing. 2. Respiratory allergy—Chemotherapy—Evaluation. 3. Respiratory allergy—Animal models. I. Devlin, John P. II. Series. [DNLM: 1 Drug Evaluation. 2. Hypersensitivity—drug therapy 3 Hypersensitivity—physiopathology. 4. Respiration—drug effects. W1 CH36D v.4 / WD 300 P982] RM371.P85 1985 615'.72 84-11905
ISBN 0-471 87395-0

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Contributors

MARTIN K. CHURCH

Southampton General Hospital
Southampton, United Kingdom

JOHN P. DEVLIN

Boehringer Ingelheim Ltd.
Ridgefield, Connecticut

JAMES E. FISH

The Johns Hopkins Medical Institutions at the
Good Samaritan Hospital
Baltimore, Maryland

ARMIN FÜGNER

Boehringer Ingelheim KG
Ingelheim, West Germany

KARL D. HARGRAVE

Boehringer Ingelheim Ltd.
Ridgefield, Connecticut

ROBERT M. NACLERIO

The Johns Hopkins Medical Institutions at the Good Samaritan Hospital
Baltimore, Maryland

R. ROBERT SCHELLENBERG

University of British Columbia
St. Paul's Hospital
Vancouver, Canada

Preface

The intention of this volume is not only to present to the reader an outline of the state of the art in the development of pulmonary and antiallergic drugs, but also to provide directives into the practical aspects of this endeavor. An effort has been made in all chapters to provide foresight into the direction of research and to stimulate exploratory probes into areas that are promising but ill-defined.

The etiology of asthma and allergic rhinitis is unknown; however, our understanding of the pathophysiology and the biochemical mechanisms involved has advanced dramatically in the past 15 years. These advances are reviewed and their significance evaluated by Drs. Schellenberg and Church in Chapters 1 and 2, respectively. They permit a clearer definition of targets in drug development but, in concert with clinical experiences with new drug candidates, have revealed serious limitations in the *in vivo* pharmacological models of allergy. Critical evaluations of these models, the significance of species variation, and the potentials they hold for future development are provided by Dr. Fügner in Chapter 3. In this same period the effort in drug design in allergy has been immense, but unfortunately the progress has only been modest. Nevertheless, the advances in our understanding of the biochemical and pathophysiological pathways referred to above offer a wealth of promising directives in novel drug development. The evolution of the numerous drug classes applied in allergy and the events leading to the emerging renaissance in drug design are outlined by Drs. Devlin and Hargrave in Chapter 4.

Concern has also been raised as to the validity of the clinical techniques employed in new drugs evaluations. The early detection of efficacy in human models is of paramount importance; Drs. Naclerio and Fish review the techniques, advances, and problems in this area in Chapter 5.

Introduction

The term *allergy* was coined in 1906 by Baron von Pirquet to describe the altered reaction (Greek: *allos ergon*) of an individual to a second challenge of an *antigen* and to resolve the paradoxical relationship between the terms immunity and hypersensitivity. With usage, allergy has come to be applied exclusively to *hypersensitivity reactions;* however, even with this restriction a broad range of disease entities is encompassed. Subdivisions have been proposed which are based on the chronology of the response (*immediate* or *delayed*), the type of *immunoglobulin* involved, and the degree of *cellular mediation*. With these classifications in mind we can define *allergic asthma, rhinitis,* and *conjunctivitis* as examples of immediate hypersensitivity that are mediated through the reaction of an antigen (e.g., pollen, house dust, animal dander) with the antibody immunoglobulin E (*IgE; reaginic antibody*). Specific to this group of disorders is the term *atopy*, which identifies the inherent tendency of certain individuals to respond to an antigen with an immediate hypersensitivity reaction.

The cellular event that forms the basis for the clinical significance of the antigen–IgE interaction is the release of *mediators* from specialized cells in tissue (*mast cells*) and those in or recruited from the circulation (*basophils*). This event is central to all immediate hypersensitivity reactions. The manifestations of the allergic response—bronchoconstriction, sneezing, red and itchy eyes—are the consequences of the local effects of these mediators of allergy. A large number of such substances have been identified (e.g., histamine, arachidonate metabolites); the reader is referred to Table 1.1 (Chapter 1) and discussion in Chapters 1 and 2 of this volume for further information on this topic.

The high affinity that IgE possesses for receptors on mast cells and

basophils underscores the specificity of this interrelationship. The specific antigen interacts with cell-bound IgE in a manner that is believed to involve a cross-linkage of adjacent IgE-receptor units. This event, which is illustrated in Figure I.1, initiates a series of biochemical processes that ultimately result in the release of the mediators from intracellular storage sites (*granules*) and from the stimulation of *de novo* biosynthesis. Many of the individual biochemical events involved in this activation have been studied in detail. Unfortunately the order in which they occur and their interdependencies are still subjects of much speculation. Sequences have been proposed but convincing experimental support is lacking (see Chapters 1 and 2).

Mediator release from mast cells and basophils may also be induced through processes that do not involve IgE–antigen interaction. This *nonimmunological pathway* of cell activation does not fit into the classical definition of allergy and has received comparatively little attention in relation to the clinical activation of the allergic response. Experimentally, the end result, that is, the release of the mediators of allergy, is essentially the same. In *in vitro* systems, release induced by *nonimmunogenic secretogogues* (e.g., substance P, neurotensin, complement fragments) has been demonstrated, but significance in a pathophysiological sense,

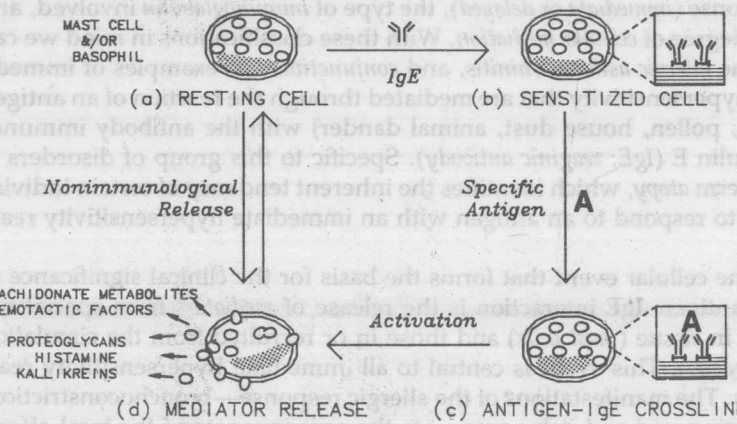

Figure I.1 The mediator release process: (*a*) The resting mast cell or basophil; (*b*) the binding of IgE (specific for the antigen "A") to receptor sites on the cell surface (insert); (*c*) cross-linkage of adjacent IgE-receptor complexes by antigen A (insert) with subsequent initiation of the cellular response; (*d*) the extrusion of the mediator containing granules, mediator release, and the initiation of *de novo* biosynthesis.

while indicated (exercise-induced asthma, cold urticaria, etc.), has not been clearly established. Another nonimmunological feature of note is that asthmatics are considerably more sensitive to inhaled histamine and acetylcholine challenge than normals. This *hyperreactivity* (see Chapter 1) suggests the involvement of inherent or acquired abnormalities in nervous control mechanisms.

The representation of the human allergic reaction in experimental animal models is a formidable task but one which is of fundamental importance in drug design and development. Despite the assertion (q.v.) that all allergic disorders share the same central event in the induction phase, a single animal model has yet to be described that accurately reflects this feature in a pharmacological sense. The reasons for this difficulty lie in the variation in drug response seen between mast cells and basophils and the apparent heterogeneity among mast cells from different tissue sources (see Chapters 2 and 3). The variations seen among different species, as well as in the response of different tissues to the mediators released, complicate this situation further. Model design and species selection are topics that have demanded considerable attention (see Chapter 3).

While significant gaps exist in our understanding of the allergic response, our current awareness does permit a number of rational targets in drug design, as well as a basis for uncovering the modes of action of the legacy of drug groups that were established through folk medicine and trial and error. The primary goals that have been set (see Chapter 4) address the possibility of interference in the activation of the secretory cells (prophylaxis) and in the blockade of the end-organ effects of the mediators of allergy (symptomatic relief).

The goal of the drug discovery process is the demonstration of improved efficacy in the therapeutic management of allergic disorders in humans. The problems faced in the pharmacological representation, which have been described, are compounded further in the clinical evaluation step (Chapter 5). This aspect involves not only the species jump to humans and the anticipated variations in the biological response, but also induces new variables such as the heterogeneity of the patient population, compliance, and the appearance of side effects that hitherto had not been observed.

The discovery and development of antiallergic and pulmonary drugs are entering a period of renaissance. The challenge is a formidable one; however, it is conceptually clear and the rewards are considerable.

J. P. D.

We conclude that critical evaluations of the biochemical, pharmacological and clinical techniques in allergy reveal serious gaps in their relevance to the actual disease situation. Closing these gaps is the present challenge before us and the theme of this volume.

JOHN P. DEVLIN

Ridgefield, Connecticut
November 1984

Contents

ONE

Pathophysiology of Allergic Diseases

R. ROBERT SCHELLENBERG
University of British Columbia
Pulmonary Research Laboratory
St. Paul's Hospital
Vancouver, British Columbia

Supported by the Medical Research Council Grant #MA-8017 and the British Columbia Lung Association

1 INTRODUCTION

In outlining a number of allergic disorders, I shall examine the pathophysiology of disease states primarily from the standpoint of which chemical mediators are involved in the specific conditions, what are the interactions of various cell types producing these mediators, and what physiologic or pathologic stimuli can activate these cells to release the mediators in question. No attempt is made to deal in depth with the specific pathological findings nor the physiological changes in parameters (for example, pulmonary mechanics) characteristic of these diseases, because these have been well documented in standard texts (1, 2) and review articles. By taking this approach it is hoped that further insight can be gained into the underlying mechanisms of the diseases so that one has a more rational approach to the development of therapeutic manipulations that may be beneficial in these disease states. The biochemical steps involved with the formation and degradation of these mediators as well as the modulatory steps involved are dealt with in Chapter 2. Since there are numerous components to complex diseases such as bronchial asthma, I shall also delineate a number of the processes involved which must be considered in the development of therapeutic modalities.

2 CLINICAL AND MORPHOLOGIC MANIFESTATIONS OF ALLERGIC DISEASES

2.1 Systemic Anaphylaxis

Anaphylaxis represents the most dramatic and potentially fatal form of immediate hypersensitivity. It is an acute reaction to released mediators from mast cells or basophils which have pathologic effects in a number of body organ systems. These include the cardiovascular system, manifested by systemic hypotension and cardiac arrhythmias; the respiratory system, with upper respiratory tract obstruction or bronchospasm; the gastrointestinal system, with nausea and vomiting, cramping and diarrhea; the skin, with itching, urticaria, and angioedema; and the peripheral nervous system, with paresthesias. The manifestations of major concern are those of cardiovascular collapse or upper airways obstruction, as these are the causes of death in fatal anaphylaxis.

"Anaphylaxis" is usually utilized to denote IgE-mediated reactions, whereas similar manifestations by non-IgE mechanisms are referred to as

"anaphylactoid reactions." There is evidence for release of histamine during human anaphylaxis (3) and presumably other mast cell mediators are released. Intravenous infusion of histamine can induce most of the manifestations of anaphylaxis. The cardiac effects of histamine and leukotrienes (discussed in Section 2) could account for arrhythmias and abnormal ventricular function, which can occur in anaphylaxis. Considerable data are now available regarding the cardiac effects of leukotrienes in many species, supporting the demonstration of the role played by these mediators in cardiac anaphylaxis (4). It is assumed that the same mediators are involved in anaphylactoid reactions due to other stimuli, a number of which are discussed in Section 4. It remains a possibility that cell types other than mast cells and basophils may be involved in these reactions. A potential mediator, besides histamine, that could cause the clinical manifestations is platelet activating factor, which can be derived from other cell types (see Section 3.5).

Causes of anaphylaxis include numerous allergens, especially those rapidly introduced into the circulation, such as insect venom and injected drugs. Although anaphylaxis is rarely caused by aerosolized antigens, it is a well-recognized complication of immunotherapy with allergens. Recently, cases of anaphylaxis following exercise have been described (5, 6), some of which occur only after ingestion of specific foods that by themselves do not evoke symptoms (7, 8).

Pathological changes noted with fatal anaphylaxis are varied, and in many cases no specific abnormalities are found. Presumably this relates to the severity of the reaction and thereby the time available for the development of such changes as hemorrhagic or nonhemorrhagic pulmonary edema, ischemic changes of the myocardium, tubular damage in the kidney, or visceral congestion. Laryngeal edema is detected in approximately one quarter of individuals dying from anaphylaxis. It has been suggested that the finding of eosinophilic infiltration in lung, liver, or spleen suggests this diagnosis (9).

2.2 Urticaria and Angioedema

Urticaria consist of extremely itchy, raised, blanched wheals surrounded by erythema in patchy distribution. Angioedema consists of edematous swellings of various sizes and distribution. In addition to involving the skin, the edema can involve the upper respiratory tract or the gastrointestinal tract. Angioedema may be painless or have associated burning pain or itching. Patches of typical urticaria and angioedema may occur simultaneously. Individual lesions rarely last more than a few hours and once they have resolved, the previously involved

skin does not develop new urticarial lesions for two to three days, suggesting desensitization of mast cells or a depletion of mediators causing these lesions. Histopathological features of urticaria are dilatation and engorgement of the blood vessels in the superficial dermis, widening of the dermal papillae, flattening of the rete pegs, swelling of collagen fibres, and slight perivascular cellular infiltrate (much more pronounced in chronic urticaria lesions than acute). Lesions in angioedema involve the deep dermis and subcutaneous tissues.

The known causes of urticaria and angioedema include a variety of systemic disorders, allergic etiologies, physical stimuli, and hereditary deficiencies. For further discussion of these causes, refer to the reviews by Mathews (10) and by Kaplan (11). It should be mentioned that for the majority of cases, especially those involving protracted recurrent or chronic urticaria, a specific etiological factor cannot be determined.

It has been demonstrated that histamine is released by stimuli inducing urticarial lesions (11). Because of its known physiological effects and the therapeutic usefulness of antihistamines, it is likely that histamine is the major mediator of these reactions. As discussed in Section 3, it can be noted that a number of the chemical mediators have significant effects upon vascular permeability plus vascular smooth muscle contractility, suggesting that mediators in addition to histamine may be involved in these responses. As there are numerous stimuli for mediator release, a number of which do not involve IgE-mediated mechanisms, it is conceivable that certain stimuli cause urticaria or angioedema through mast cell-independent release of mediators, but there is no evidence to support such mechanisms. It is more likely that such stimuli evoke release of histamine and other mediators from mast cells by non-IgE mediated mechanisms (discussed in Section 4).

2.3 Allergic Rhinitis

Allergic rhinitis is manifested by the nasal symptoms of rhinorrhea, itching, sneezing, and obstruction. It is commonly associated with conjunctival redness, itching, and tearing. The conspicuous changes noted in pathological studies are those of marked nasal mucosal edema, prominent mucous glands and goblet cells, and altered staining properties of mucopolysaccharides. Some individuals have polypoid lesions of the nasal mucosa.

The data to date suggest that mast cells and basophils account for the manifestations of this disease, and histamine, leukotrienes, chemotactic factors, prostaglandins, and kininogenase have all been demonstrated in the nasal secretions or from polypoid tissues. As discussed under this

specific mediators (Section 3), a number of these mediators are capable of altering blood vessel permeability, stimulating mucus secretion, and attracting the eosinophils to the local site.

In addition to the triggering of mediator release from mast cells by allergen interaction with IgE, symptomatic exacerbations may be produced by a number of irritants, such as noxious fumes and cold air. In addition, individuals with allergic rhinitis appear to have airways reactivity intermediate between normals and asthmatics when they undergo bronchoprovocation testing with agents such as methacholine (13).

2.4 Bronchial Asthma

Asthma is a disease characterized by airways obstruction that is reversible, either spontaneously or following drug therapy. Symptoms primarily consist of shortness of breath, wheezing, and cough with sputum production. The frequency and duration of symptoms are highly variable and to some degree are dictated by environmental factors as well as many physiologic factors such as exercise and stress. A major distinguishing component of individuals with asthma is hyperresponsiveness or hyperreactivity of their airways. Numerous studies have examined this property, which is discussed in Section 2.4.3.

Pathological findings in persons dying from severe bronchial asthma have been well documented (14, 15). These consist of mucoid plugging and cellular debris in the lumen, sloughing of epithelial cells from the lumenal surface, thickening of the basement membrane, increased size and number of mucus glands, infiltration by migratory cell types with a predominance of eosinophils, and hypertrophied smooth muscle. In considering these findings it is clear that there are numerous components that are altered in asthma which may play a crucial role in the physiologic alterations noted. Such changes must be considered when managing individuals with this disease and in particular when attempting to define steps in the pathological process that can be modulated by therapeutic agents. The following discussion deals with these components in more detail.

2.4.1 Mucociliary Function

A major component in asthmatic attacks is the plugging of small, and in more severe cases large, airways by mucus. Although it is conceivable that patients with asthma have abnormal ciliary function, at least during acute attacks, this has not been specifically documented. What has been shown is that abnormalities do occur in tracheal mucus velocity (a test of

overall mucus transport which does not differentiate ciliary function from changes in mucus properties). Wanner and his colleagues have demonstrated a decrease in tracheal mucus velocity with antigen bronchoprovocation in both allergic dogs (16) and humans (17). By use of inhibitors of histamine and slow-reacting substances (17), Wanner et al. concluded that it is primarily slow-reacting substances (leukotrienes) which mediates these changes. Other studies have examined the effect of mediators on mucus secretion in animal and human airways *in vitro* (see Fig. 1.1). They found that cholinergic and α-adrenergic agonists, the mediators of parasympathetic and sympathetic nervous stimulation of mucous gland secretion (18, 19), histamine, plus numerous cyclo-oxygenase and lipoxygenase products of arachidonic acid act as mucus secretagogues. The most potent appear to be leukotrienes C_4 and D_4 (20) and the mono-HETEs (21). These latter studies have not examined the relative effect of these agonists upon secretion by serous *versus* mucous cells which could lead to differing viscoelastic properties.

In addition to the absolute quantity of mucus produced, changes in the viscoelastic properties may be of equal importance in terms of the ease of clearing of the excess mucus produced. Since 95% of airways mucus is made up by water, changes in this water content could alter the transport clearance of the mucus. The water content of the mucus itself in periciliary fluid appears to be dependent upon active transport of chloride ions from the epithelial cells with the accompanying passive transport of water (22). Methacholine, histamine, epinephrine, and PGE_1 all increase chloride transport into the lumen (23), thereby enhancing fluid production in the airways. Thus, a number of stimuli may have effects not only on the amount of mucus produced, but also the viscoelastic properties that alter clearance properties. For example, both histamine and leukotrienes increase mucus secretion, but histamine increases tracheal mucus velocity whereas leukotrienes decrease this parameter of mucociliary function (16).

2.4.2 Bronchial Mucosal Permeability

Although pathological studies of severe asthma have demonstrated sloughing of the epithelial lining of airways, thereby allowing access of chemical mediators, antigens, and so forth to underlying structures, it has been suggested that an early event in the induction of an asthma attack must be the alteration of the epithelial barrier. The tight junctions between epithelial cells restrict passage of large molecular components such as antigens. Since the bulk of the mast cells, as well as the irritant receptor nerve endings, lie below the tight junctions, our present under-