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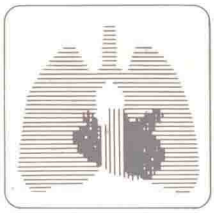

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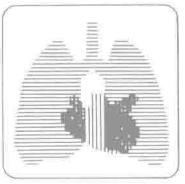

Advances in the use of inhaled corticosteroids

Symposium Proceedings

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Introduction

Distinguished participants, ladies and gentlemen,

In my capacity as President of the Hong Kong and Macau Chapter of the American College of Chest Physicians, I would like to welcome you all to this symposium on Advances in the Use of Inhaled Corticosteroids. This symposium has been organized jointly by the American College of Chest Physicians (HK and Macau Chapter) and Astra Pharmaceuticals, and is being attended by over 100 specialists from 15 countries and cities in four continents. I must take this opportunity to thank Astra Pharmaceuticals for making this meeting possible.

Bronchial asthma is a common disease, and the last 10 to 15 years have witnessed important advances in our understanding and management of the disease. Our concepts of the pathogenesis of bronchial asthma have changed profoundly with the elucidation of the arachidonic acid cascade and the involvement of secondary effector cells such as eosinophils and neutrophils.

Systemic corticosteroids have played a valuable role in the treatment of asthma, and their mode of action is now better understood. Their usefulness, however, has been limited by systemic side-effects. The introduction of inhaled corticosteroids in the early 1970s has proved to be one of the main advances in the treatment of asthma. As new topical corticosteroids are being introduced, the need for a symposium to review progress in this field is long overdue.

This symposium has a compact and comprehensive programme of four sessions over two days, covering the pathophysiology of asthma, the pharmacokinetics and clinical pharmacology of glucocorticosteroids, the clinical aspects of inhaled corticosteroids in general and of inhaled budesonide in particular. I am sure this symposium will serve as a forum for exchange of knowledge and experience in this rapidly advancing field, and I trust you will find the symposium stimulating and productive. Thank you.

W.K. Lam
President
American College of Chest Physicians
(Hong Kong and Macau Chapter)

Basic mechanisms in allergic asthma

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EARLY AND LATE ASTHMATIC REACTION

Upon controlled exposure to allergen in the laboratory, an asthmatic may develop airflow obstruction within 10-15 minutes. This early asthmatic reaction (EAR) is short-lived and easily reversible. It is most likely to be due to bronchospasm. Five to eight hours later, EAR may be followed by another episode of airflow obstruction. This late asthmatic reaction (LAR) lasts much longer (16-24 hours), and sometimes lasts for weeks.

LAR is now attracting more attention, because it is realised that asthmatic symptoms resemble LAR rather than EAR, and more importantly LAR is associated with development of non-specific bronchial hyperresponsiveness (BHR),[1] which is a characteristic feature of asthma. LAR was originally thought to be due to Arthus type 3 reaction based on findings of IgG and C_3 deposits on skin. Now it is found that IgG actually blunts LAR[2] and inflammation of airways due to chemical mediators is more important. This is supported by the observation that the sputum of asthmatics contains clusters of airway epithelial cells, eosinophils and neutrophils, and the airway walls are intensely inflamed.[3]

After LAR, broncho-alveolar lavage reveals a mixture of eosinophils and neutrophils in humans[4] and bronchial biopsy shows an increase in inflammatory cells in allergic sheep.[5] A number of chemical mediators have also been detected in peripheral blood after LAR, such as histamine, neutrophil chemotactic factor (NCF), thromboxane B_2, prostaglandins, leucotriene D_4, platelet factor 4 and cationic basic protein.[6-10] These mediators have been shown to cause not only bronchospasm, but also mucosal oedema and mucous plugging of airways (Table 1).[11] Hence, chemical mediators are responsible not only for EAR, but also for LAR.

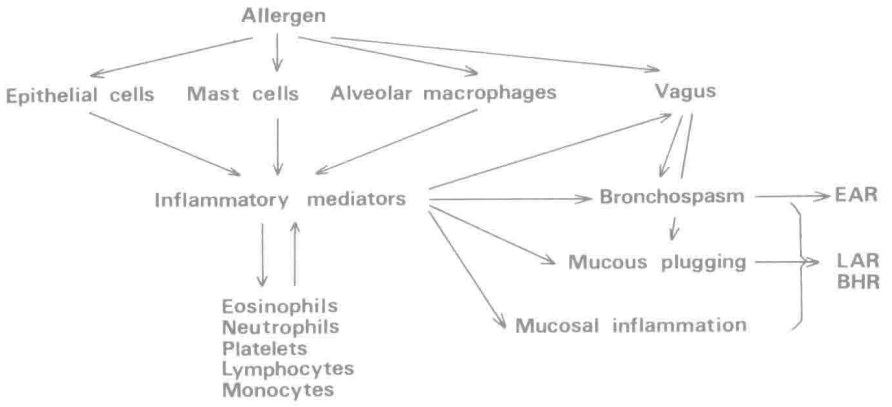

Fig. 1. Scheme for proposed mechanisms in allergic asthma. EAR = early asthmatic reaction; LAR = late asthmatic reaction; BHR = bronchial hyperresponsiveness.

TABLE 1

Spectrum of asthmatic reactions induced by inflammatory mediators

	Hist	PG	LT	HETE	Tx	PAF	NCF	ECF	Others
Bronchospasm	+	+	+		+	+			Bradykinin, ACH
↑ Mucus	+	+	+	+					PGF-A, MMS, ACH
Desquamation (epithelium)									O_2^-, H_2O_2, BP
Cellular infiltrate			+	+		+	+	+	IF-A
Mucosal oedema	+	+	+			+			Bradykinin
Basement membrane thickening									O_2^-, Enzymes

Hist = histamine; PG = prostaglandins; LT = leucotrienes; HETE = hydroxyeicosatetraenoic acid; Tx = thromboxanes; PAF = platelet activating factor; NCF = neutrophil chemotactic factor; ECF = eosinophilic chemotactic factor; ACH = acetylcholine; PGF-A = prostaglandin generating factor of anaphylaxis; MMS = macrophage mucus secretagogue; BP = basic proteins; IF-A = inflammatory factor of anaphylaxis.

Recent findings have allowed us to hypothesize the events after allergen exposure in asthmatics (Fig. 1).[12] This involves a primary effector system of cells to initiate asthma. The resultant mediator release induces asthma by a direct action and also indirectly by recruiting secondary effector cells. Multiple mechanisms are likely to be operative, and these may vary from one patient to another.

THE PRIMARY EFFECTOR CELLS

Primary effector cells initiate asthma on exposure to allergen.

Mast cells

Mast cells have been known for a long time to be important in allergic asthma. Now, attention has been directed towards mucosal mast cells rather than the connective tissue mast cells since the former is different in structure and function from the latter and is strategically more important in initiating asthma. It has been found recently that extrinsic asthmatics contain more mast cells on broncho-alveolar lavage than controls.[13] Furthermore, these mast cells are unstable, leaking histamine more readily on incubation with anti-IgE. Whether this is a primary phenomenon or is secondary to asthma is unknown. Having unstable and more mast cells in bronchial lumen would facilitate activation by allergen with subsequent mediator release. The inflammatory mediators would then open up the tight epithelial junctions, allowing an influx of allergen into submucosa where more mast cells are available for amplification of response.

Alveolar macrophages

Alveolar macrophages are cells that have attracted attention because they are found to possess receptors for IgE.[14] In addition, they release NCF, eosinophil chemotactic factor (ECF), prostaglandins, leucotrienes, thromboxanes and platelet activating factor (PAF) upon exposure to allergen.[14] By virtue of their situation in the lungs, we may speculate that they also participate in initiation of asthma.

Vagal reflex

Atropine is known to inhibit antigen-induced bronchoconstriction in asthmatics, thus implying a cholinergic mechanism.[15] The most superficial nerve endings lie less than 1 μm from the airway lumen where

they are well sited to respond to intraluminal irritation with reflex bronchoconstriction.[16] There may also be local effects via activation of axon reflexes with release of neuropeptides such as substance P, neurokinins and calcitonin gene-related peptide, which may cause bronchospasm and airway inflammation.[17] In addition, mediators such as histamine and bradykinin may also activate vagal reflex.

Airway epithelium

The airway epithelium is often regarded merely as a physical barrier. In fact, it is metabolically active and has been shown to release an arachidonic acid metabolite, 15-HETE, which is a chemotactic factor for neutrophils.[18] Although there is no evidence of activation of epithelial cells by allergen, it is conceivable that any epithelial irritation may lead to mediator release and contribute to development of asthma.

INFLAMMATORY MEDIATORS

New sources of mediators

Formerly, only mast cells were known to release chemical mediators.

TABLE 2

Cellular sources for inflammatory mediators

	Histamine	ECF	NCF	PG	LT	HETE	Tx	PAF	Others
Mast cells	+	+	+	+	+		+	+	PGF-A
Alveolar macrophages		+	+	+	+		+	+	
Epithelial cells						+			
Eosinophils					+			+	Basic proteins
Neutrophils					+			+	
Platelets						+		+	
Lymphocytes		+	+						
Monocytes			+				+		

ECF = eosinophilic chemotactic factor; NCF = neutrophil chemotactic factor; PG = prostaglandins; LT = leucotrienes; HETE = hydroxyeicosatetraenoic acid; Tx = thromboxanes; PAF = platelet activating factor; PGF-A = prostaglandin generating factor of anaphylaxis.

Now, alveolar macrophages, airway epithelial cells, eosinophils, neutrophils, platelets, lymphocytes and monocytes are found to release a variety of potent inflammatory mediators to sustain asthma (Table 2).[14, 18–21] Even vascular endothelium, smooth muscle and fibroblasts may elaborate prostaglandins.[22] This may have important therapeutic implications, as drugs designed to act on mast cells alone may not be effective to control asthma.

New mediators

Inflammatory mediators other than histamine have resumed more importance now as they are longer acting and more potent. In addition, they cause inflammation not only by direct action, but also by recruiting inflammatory cells. Of the new mediators, three groups have attracted most attention.

Arachidonic acid metabolites

Arachidonic acid derived from membrane phospholipids is metabolized by two pathways. The first involves cyclo-oxygenase with formation of prostaglandins, thromboxane and prostacycline. The second involves lipoxygenase with formation of hydroxyeicosatetraenoic acids (HETEs) and leucotrienes (LT, SRS-A). In asthmatics, LTD_4 is 140 times more potent than histamine in causing bronchoconstriction.[23] The prostaglandins and leucotrienes induce airway inflammation and mucous plugging.[22]

Platelet activating factor

Morley et al. proposed that platelet activating factor (PAF or PAF-acether) plays a vital role in asthma as its administration to experimental animals and man produced an impressive spectrum of inflammatory reactions and it has been shown to be released in vivo.[20] Furthermore, many anti-asthmatic drugs such as cromoglycate, theophylline, ketotifen and steroids modify PAF-induced bronchoconstriction.

Chemotactic factors for inflammatory cells

Chemotactic factors include ECF, NCF, LTB_4 and HETEs. They mobilize inflammatory cells into lungs from circulation and contribute significantly to asthma.

SECONDARY EFFECTOR CELLS

Secondary effector cells perpetuate asthma by inducing inflammation of airways.

Eosinophils

Although eosinophils contain enzymes which inactivate histamine and leucotrienes, they release proteins (major basic protein and eosinophilic cationic protein) which are cytotoxic, causing much epithelial desquamation.[19] In addition, they produce leucotrienes and PAF. The abundance of eosinophils in the airways of asthmatics suggest that they are important in the pathogenesis of asthma.

Neutrophils

Neutrophils have been shown to be the most conspicuous leucocyte of the inflammatory response and were necessary for the subsequent development of BHR.[24] When activated, neutrophils can metabolize arachidonic acid with formation of inflammatory mediators such as leucotrienes, PAF and proteolytic enzymes.

Platelets

Plasma platelet factor 4 levels were elevated during allergen-induced asthma, which implied platelet activation.[25] Platelets have been found to release PAF and HETE.

Lymphocytes

When stimulated by chronic exposure to antigen, T-lymphocytes elaborate interleukin 3 which forms more mucosal mast cells from bone marrow precursor cells.[26] Lymphocytes are present in large numbers in chronic inflammation. T-lymphocytes have been shown to elaborate inflammatory mediators such as NCF.[21]

Monocytes

Monocytes behave as alveolar macrophages in the lungs.

SUMMARY

Inhalation of allergen will activate intraluminal mast cells, alveolar macrophages, vagal nerves and possibly airway epithelial cells. Vagal stimulation will lead to reflex bronchospasm, whereas inflammatory mediators released from mast cells and macrophages may make the epithelial barrier more permeable, allowing an influx of allergen into submucosa of airways where more mast cells are available for amplication of allergic response.

Inflammatory mediators cause asthma by a direct action and also indirectly via recruitment of secondary effector cells such as eosinophils, neutrophils, platelets and lymphocytes. These inflammatory cells also elaborate potent mediators such as leucotrienes, HETE, thromboxanes, PAF and cytotoxic proteins to perpetuate the asthmatic response. The resulting inflammation of airways is responsible for development of late asthmatic response and non-specific bronchial hyperresponsiveness.

Anti-inflammatory agents such as corticosteroids are, therefore, important in the control of asthma, as they reduce airway inflammation in clinical asthma.

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Airway hyperreactivity and asthma

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INTRODUCTION

The general field of asthma research has been impeded by a lack of suitable definitions that ensure that all workers in the area mean the same thing when they use similar words. Bronchial reactivity research is certainly no exception. My brief is to try to put into some perspective the relationship between normal airway calibre control, abnormal variations in airway calibre and the clinical condition of bronchial asthma. Some definitions are necessary and the following are put forward for the purpose of clarification.

Airway reactivity and bronchial reactivity

Airway reactivity refers to the property of the respiratory tract which enables it to alter its luminal diameter in response to a number of stimuli. *Bronchial reactivity* confines the consideration to below the trachea.

Airway hyperreactivity and bronchial hyperreactivity

Airway hyperreactivity implies an excessive response to the same or additional stimuli and bronchial hyperreactivity refers to an excessive narrowing of the bronchial tree to those stimuli.

Bronchial asthma

Bronchial asthma has defied precise definition largely because of the variable and well recognized clinical associations. Most would accept that a subject who has acute episodic breathlessness associated with large variations in airway resistance either spontaneously or after a recognized exposure has bronchial asthma and, thus, 'reversible airflow obstruction' remains a useful functional definition.

Since this discussion is related to bronchial asthma, it is bronchial hyperreactivity that we must consider and leave aside questions about upper respiratory tract hyperreactivity.

BRONCHIAL REACTIVITY AND HYPERREACTIVITY

Normal bronchial calibre is influenced by several factors (Table 1) and, as a general statement, patients with bronchial asthma show an abnormality in bronchial calibre regulation which results in excessive airway narrowing in response to a variety of stimuli. Common stimuli used to demonstrate this property are inhalation of cold air,[1] exercise,[2] inhaled antigen,[3] inhaled histamine[4] and inhaled methacholine.[5,6] It is unlikely that each agent operates by identical pathways but the overall response by patients with asthma to different stimuli is remarkably similar in terms of induced airflow obstruction. Not all individuals respond to the same extent to different challenges and the demonstration of this varying hyperreactivity raises the probability that there may be distinctly different mechanisms of hyperreactivity.

Thus, there may be a predominantly mucosal response with inflammatory oedema and mild or no bronchial smooth muscle contraction. On the other hand, bronchial smooth muscle contraction may be the sole or major response.

Clinical asthma is often considered to be the result of one or several external triggers (e.g. exercise, atopy, fumes) operating in a subject with endogenous bronchial hyperreactivity. This is clearly an oversimplification but the analogy has a modern counterpart with the several possible mediator releasing systems now recognized.[6] It is possible that, even in

TABLE 1

Regulation of bronchial calibre

Mechanical forces	–Inflation volume
	–Transpulmonary pressure
Neural factors	–Vagal constrictor
	–Sympathetic dilator
	–? Purinergic pathways
Humoral factors	–Catecholamines
	–Preformed mediators
	–Synthesized mediators
	–Local gas tensions