EFFECT OF GASTRO-OESOPHAGEAL REFLUX ON BRONCHIAL HYPERREACTIVITY

THESIS

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CONTENTS

ABBREVIATIONS

ATP	Adenosine triphosphate
BSM	Bronchial smooth muscle
B.A.	Bronchial asthma
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
C.I.U.	Cumulative inhalation unit
ECF-A	Eosinophil chemotactic factor of anaphylaxis
FEV1	Forced expiratory volume at the first second
FVC	Forced vital capacity
FEF	Forced expiratory flow
FRC	Functional residual capacity
GER	Gastro-oesophageal reflux
GIT	Gastrointestinal tract
Ig	Immunoglobulin
LT	Leukotriene
LES	Lower oesophageal sphincter
MDI	Metered dose inhaler
NCA	Neutrophil chemotactic activity
NANC	Non adrenergic - noncholinergic
PG	Prostaglandin
PAF	Platelet activating factor
PEFR	Peak expiratory flow rate
PD20	Provocative dose at which FEV1 decreases by 20%
SRS-A	Slow reacting substance of anaphylaxis
TLC	Total lung capacity
VIP	Vasoactive intestinal peptide
VC	Vital capacity

INTRODUCTION AND AIM OF THE WORK

Bronchial hyperreactivity is a non-specific tendency of the smooth muscle of the tracheobronchial tree to contract to an excessive degree in response to a variety of stimuli.

This increased contraction of smooth muscle results in a decrease in the caliber of airways that can be measured in the pulmonary function laboratory. (Pratter & Irwin, 1984).

Gastro-oesophageal reflux is a condition characterized by heart burn, regurgitation of acid in the mouth, retrosternal pain and dysphagia associated with insufficiency of the lower oesophageal sphincter with or without hiatal hernia. (Anderson et al., 1986).

Many authors have proposed that there is a relationship between gastro-oesophageal reflux and bronchial hyper-reactivity. The possible mechanism in patients with gastro-oesophageal reflux is the recurrent (micro-) aspiration of acid into the respiratory tract causing changes in the bronchomotor tone and consequent broncho-constriction. (Anderson et al., 1986).

Another possible mechanism is that the vagal nerve might mediate bronchoconstriction in patients with reflux when stimulated by acid in the oesophagus. (Mansfield and Stein, 1979).

The aim of this work is to study the relationship between bronchial reactivity and gastro-oesophageal reflux.

REVIEW OF LITERATURE

PATHOGENESIS OF ASTHMA

Introduction:

Asthma covers a broad clinical spectrum ranging from mild, readily reversible, bronchospasm, to severe chronic intractable obstruction to airflow. The disease is difficult to define since reversibility of airways obstruction may be impossible to demonstrate on certain occasions, for instance, the mild episodic asthmatic may be free of symptoms and have normal lung function for prolonged periods of time, whereas in acute severe athma, airways obstruction may take several days before any reversibility can be demonstrated. The disease is almost invariably accompanied by some degree of non-specific bronchial hyperreactivity but whether this is a primary feature or secondary to other factors such as bronchial inflammation remains uncertain. (Kay & Warwick, 1985).

It is an inflammatory disease of the airways that is chronic and persistent. Like other inflammatory diseases, asthma is characterized by the recruitment of inflammatory cells, vascular congestion, increased vascular permeability, increased tissue volume, and the presence of an exudate. Asthmatic inflammation in atopic patients may be distinguished from other inflammatory diseases by a characteristic pattern of early mast cell activation, eosinophil infiltration, fibroblast proliferation and collagen deposition, selective T-cell activation, epithelial sloughing, and mucus hypersecretion. (Howarth et al., 1990).

Airway narrowing in asthma can result from :

- Contraction of airway smooth muscle.
- Vasodilatation of bronchial vessels particularly of the vascular plexus lying between the smooth muscle and mucosa of airway lumen.
- Oedema of the submucosal tissues.
- Hypersecretion of mucus into the airway lumen. (Weiss et al., 1985).

At least five mechanisms have been proposed to account for these features:

1. <u>Mast cell activation</u> occurs when inhaled allergens cross-link monomer IgE previously bound to the surface of sensitized mast cells, thereby activating the cell to degranulate, with release of pre-formed mediators (e.g. histamine and heparin, and both neutrophil and eosinophil chemotactic factors). Activation also triggers both the cyclo-oxygenase and lipo-oxygenase pathways of the metabolism of the arachidonic acid present within the cell membrane.

The cyclo-oxygenase pathway leads to the formation of prostaglandins, notably PGD_2, a potent bronchoconstrictor, whereas the lipo-oxygenase pathway leads to the formation of leukotrienes, particularly LTC_4 and LTD_4, which again are both very potent long acting constrictors of bronchial smooth muscle. (Mygind, 1986).

However, lumenal or submucosal mast cells are sparse, even in bronchial lavage or in sections of bronchial walls from asthmatics. It is also not clear how large molecular weight allergens (e.g. those in the house mite faecal pellet, or grass pollens) contained in these large particles reach the sensitized mast cells which lie in the submucosa.

Furthermore, IgE receptors are also present on the surface of alveolar macrophages, and of course macrophages are much more abundant than are mast cells in the lung lining fluids. (Mygind, 1986).

Mediators of hypersensitivity

Pre-formed and membrane derived:

Following the combination of allergen with IgE on the mast cell surface, a complex series of events occurs which resutls in the release of mediators of hypersensitivity of two types. (Ishizaka, 1981).

The pre-formed, granule-associated mediators include amines (histamine), chemotactic factors (eosinophil chemotactic factor of anaphylaxis ECF-A), (Kay, 1970) and high molecular weight neutrophil chemotactic activity (NCA). (Kay & Lee, 1982).

Various enzymes (tryptase, arylsulphatase, etc.) and heparin proteoglycan.

The newly formed, membrane-derived mediators represent the various lipid products of arachidonic acid (Piper, 1983).

Arachidonic acid metabolism via the lipo-oxygenase pathway gives rise to leukotriene B4 and the sulphidopeptide leukotrienes LTC_4 and LTD_4 (previously referred to as slow-reacting substance of anaphylaxis (SRS-A)); metabolism via the cyclo-oxygenase pathway gives rise to the prostaglandins (PG) including PGD_2 and thromboxane. Platelet activating factor (PAF-acether) is a further membrane-derived lipid mediator. (Benveniste et al., 1981).

These substances have potent biological properties which may contribute, at least in part, to the observed pathological features of bronchial asthma.

These include smooth muscle contraction (histamine, LTC_4, LTD_4, PAF), mucosal oedema (histamine, LTC_4, LTD_4, PAF-acether), mucus secretion (histamine, LTC_4, LTD_4, LTE_4), inflammatory cell infiltration (NCA, ECF-A, LTB_4, PAF-acether), and desquamation of epithelium (tryptase, etc.)

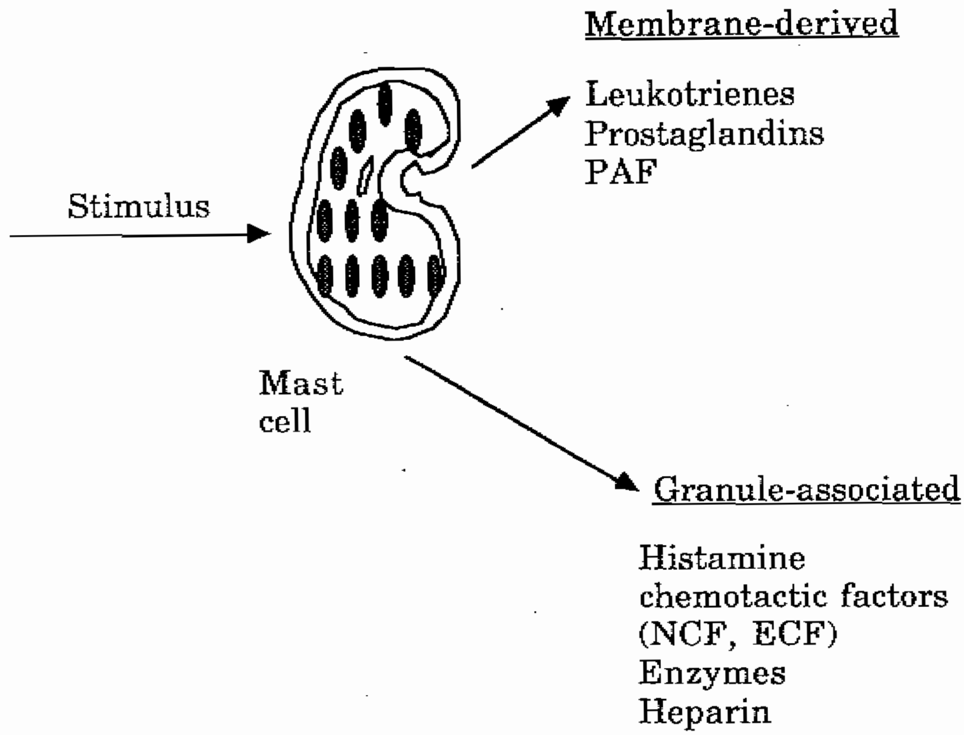

Fig. 1 The mast cell-associated mediators. PAF, neutrophil chemotactic factor (NCF) eosinophil chemotactic factor (ECF)

Table (A): Inflammatory mediators released from airway cells:-

Mediator	Cell of origin	Action
Histamine	Mast cells	Contraction of airway smooth muscle (direct and reflex), increased mucus secretion.
Leukotrienes (LTC4, LTD4)	Macrophages, eosinophils, polymorphs and mast cells	Contraction of airway smooth muscle, systemic vasocontriction, increased mucus secretion
Leukotriene B4 (LTB4)	Macrophages, polymorphs, eosinophils and mast cells	Neutrophil chemotactic factor
Prostaglandins (PGD2) Platelet activating factor (PAF-acether)	Mast cells Macrophages, eosinophils, neutrophils, platelets and airway mucosal cells.	Contraction of airway smooth muscle, vasodilatation. Mucus secretion, increased Bronchial hyperreactivity, increased microvascular protein leakage, chemotactic for eosinophil
High molecular weight neutrophil chemotactic factor (HMW-NCF) Adenosine Interleukin 5 Substance P	Eosinophils Mast cells CD4 lymphocytes sensory nerves	Chemotactic for polymorph Contraction of airway smooth muscle, eosinophil differentiation contraction of airway smooth muscle, vasodilatation of bronchial vessels, increased microvascular protein leakage

2. Cholinergic vagal fibres innervate human bronchial smooth muscle. Activation of these efferent fibres causes bronchoconstriction. Stimulation of vagal afferents, possibly by inflammatory mediators (e.g. histamine), may then reflexly activate such cholinergic efferent vagal bronchoconstrictor nerves.

However, inhaled anticholinergic drugs (e.g. ipratropium) are not particularly effective when used alone in the treatment of bronchial asthma, implying that this mechanism does not play a major role. (Jenne and Murphy, 1987).

3. Inflammation of the airways, with consequent release of inflammatory mediators, e.g. prostaglandins, leukotrienes, histamine, kinins, platelet activating factor (PAF), etc., many of which are recognized pharmacological broncho-constrictors, is widely regarded today as the common mechanism underlying asthma.

Furthermore, airway inflammation is also thought to cause bronchial hyperreactivity. (Weiss et al., 1985).

The airways of patients dying from asthma are undoubtedly inflammed, but this is also shown in bronchial biopsies from non-fatal cases of chronic asthma. However, the airways are also inflammed in chronic bronchitis, yet this condition lacks the spontaneous variability in airway calibre which is the characteristic feature of bronchial asthma,