# STUDY ON BRONCHIAL HYPERREACTIVITY AND COLD AIR CHALLANGE TEST

**THESIS**

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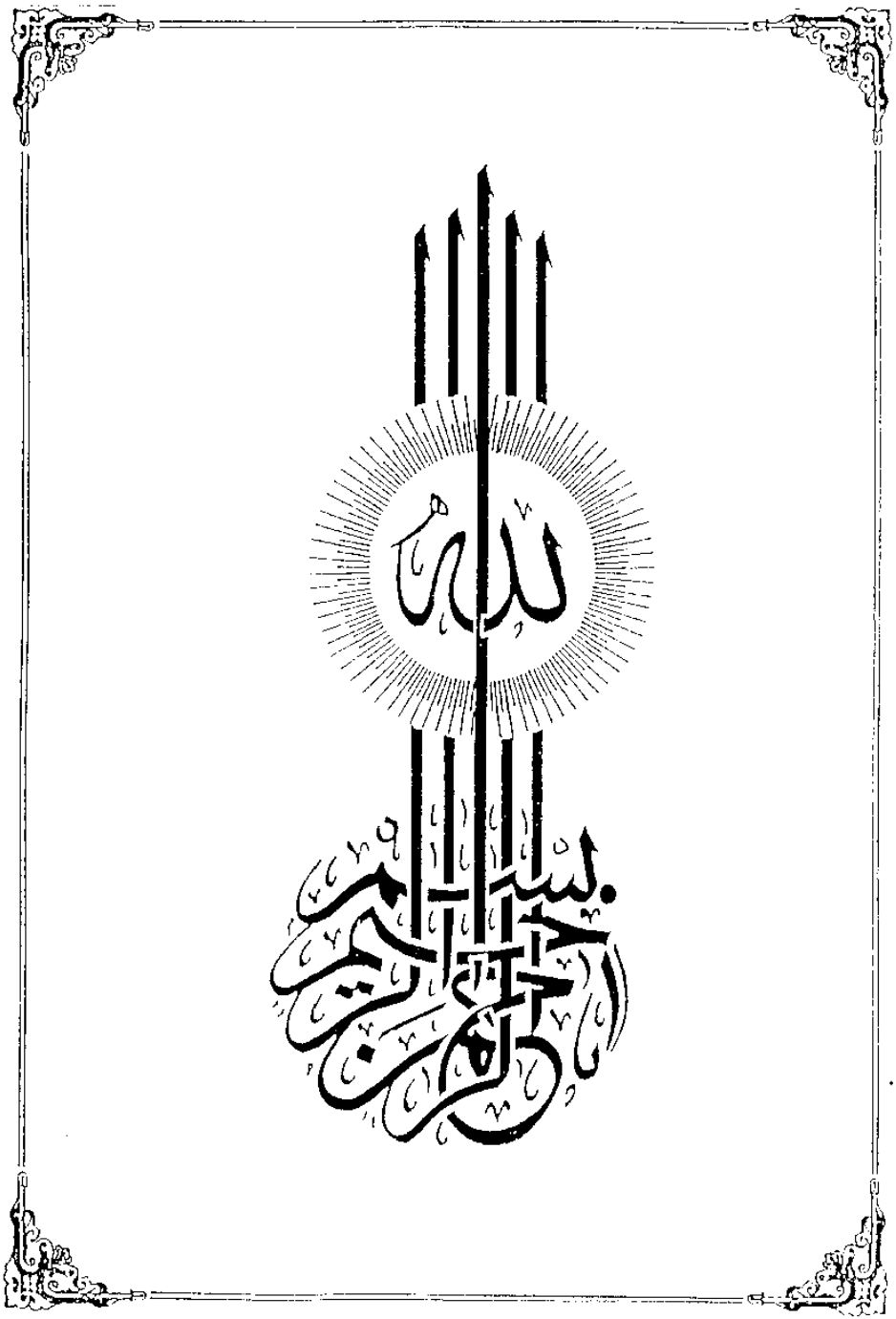
**1983**

TO MY WIFE AND MY SON KARIM



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# C O N T E N T S

# A REVIEW ON BRONCHIAL HYPERREACTIVITY

# I- Introduction

Recently it has become fashionable to think of asthma in terms of airways reactivity, but this concept is not a new one, it was introduced by John Baptista Van Helmot in the 17th. Century, who described asthma-like symptoms in a monk exposed to dust and to Fried Fish. We now know that many other kinds of stimuli can induce broncho constriction, these stimuli will be listed below.

The subject of bronchial hyperreactivity to various stimuli occupies nowadays a central position in the pathogenesis of bronchospasm whether the later is a part of bronchial asthma or an asthmatoid response. Increased bronchial reactivity is considered an essential prerequisite for the diagnosis of bronchial asthma. Non - specific bronchial hyperreactivity is a feature of asthmatic patients both allergic and non-allergic.

Definition :

Bronchial hyperreactivity is an altered responsiveness of the airways due to imbalance in the system regulating bronchial diameter.
or, it is a condition in which the airways show a much greater bronchoconstriction than normal in response to

provocative stimuli.

The provocative stimuli may be specific as house-dust and mite allergens, or non-specific as exercise, cold air inhalation, pharmacological agents and many other irritants. The provocative stimuli can be divided into Four Categories as follows :

Pharmacological and immunological aerosols; such as Methacholine, histamine, propranolol, prostaglandin $F_2$ , leukotrienes and antigens.

Physico chemical agents; such as ozone, sulphur dioxide, nitrogen dioxide, distilled water and hypertonic solutions.

Thermal Factors; such as exercise, hyperventilation and cold air.

Infections; such as common cold, influenza and others.

Asthmatics tend to be hyperreactive to more than one of these stimuli and the increased reactivity usually correlates with increased disease severity.

## Glossary of frequently used terms

| | |
|---|---|
| FVC | Vital capacity during full forced expiration. |
| $FEF_{25-75\%}$ | Forced mid-expiratory flow (between 25-75% of FVC). |
| $FEV_1$ | Forced expiratory volume in one second. |
| $PC_{20}$ | Provocation concentration producing 20% reduction in $FEV_1$. |
| $PD_{20}$ | Provocation dose producing 20% reduction in $FEV_1$. |
| PEF | Peak expiratory flow in litres per minute. |
| $SG_{aw}$ | Specific airways conductance. |
| $SR_{aw}$ | Specific airways resistance. |
| $\dot{V}$ | Volume of gas Flow per minute. |
| $\dot{V}E$ | Expired volume of ventilation per minute. |
| $\dot{V}T$ | Tidal volume. |
| VTP | Vaso active intestinal peptide. |
| EIA | Exercise-induced asthma. |
| $ED_{50}$ | Is the dose producing a 50% change in $SR_{aw}$. |

## II - ANATOMY OF NERVE SUPPLY OF AIRWAYS SMOOTH MUSCLE .

The Control of normal airways smooth muscle is complex and incompletely understood, but knowledge of what is known about the normal condition is necessary prerequisite to any discussion of abnormal hyperreactive airways.

There are three types of innervation of airways smooth muscle :

- Parasympathetic cholinergic nerves pass down the vagus and stimulation leads to broncho constriction. This is the pathway which is best-established experimentally.

- Parasympathetic non-adrenergic nerves may be also present. Stimulation of which lead to bronchodilation. The importance of this supply has not been demonstrated convincingly for human airways. This mechanism have not been shown to be controlled from C. N. S.

- Also, sympathetic adrenergic nerves have a dilator effect, there is some controversy but the evidence tends to suggest that these are not the major source of dilator control.

Fine structure of nerves and muscles in the bronchi:

Smooth muscle cells in the airways are connected by gap junctions which could lead to direct electrical communication between the cells.

Several different types of nerve may be identified from electron-micrographs, clear vesicles contain acetyl choline, dense-cored vesicles contain catecholamines, and large dense vesicles associated with the non-adrenergic system. These data are still of limited value due to the lack of confirmatory biochemical and physiological data.

There are two types of vertebrate smooth muscle:

- Single-unit smooth muscle, this acts as a continum. There are many gap junctions between the muscle cells, but few nerves. It shows inherent activity and tone.
- Multi-unit smooth muscle, these fibres tend to act independently one from another. They are poorly electrically coupled but well-supplied with nerves. They show no myogenic tone.

A feature of the smooth muscle in normal human airways is that it does not fit neatly into either category.

It has been suggested that in bronchial hyperreactivity there is a shift such that the airways smooth

muscle becomes much more like single-unit muscle in its properties.

Evidence for non-adrenergic nervous control of airways Calibre :

Experiments with an in vitro preparation of human trachealis muscle showed that a burst of vagal stimulation leads to contraction followed by a relaxation. The cholinergic vagal pathway was blocked by atropine and under these conditions no contraction was seen following vagal stimulation, but the relaxation was still present. If tetrodotoxin (which specifically blocks the fast sodium channels in nerves and there-by prevents transmission along nerve fibres) was added to the preparation the relaxation was also blocked. These experiments showed that while vagal Ach-mediated smooth muscle contraction was blocked by atropine, there was a nerve-mediated smooth muscle relaxation not affected by atropine. This relaxation was still occured after addition of propranolol to the preparation, and was only blocked by tetrodotoxin .

This favours the conclusion that this relaxation is due to non-adrenergic mechanism. The transmitter substance which may be involved in such mechanism were

investigated to be one of three likely candidates : ATP, substance P or VIP.

The purine ATP is the non-adrenergic relaxant transmitter found in the gut which is derived embriologically from the same origins as the lungs. Burnstock, has identified $P_1$ and $P_2$ purinergic receptors in the gut smooth muscle but attempts to demonstrate their importance as transmitters in the lungs have so far been unsuccessful. Substance P and VIP are found extensively throughout the respiratory tract. They have been more studied in the nose than in the bronchi where it may will be important.

(Richardson J, Béland J 1976; 41:764-71. J Appl physiol)(1)

Airways smooth muscle is in a constant state of tone which can be increased or decreased by appropriate nervous input. This is influenced by the possible efferent motor pathways from the C.N.S. described above. Activity in the motor pathways is affected both by the psychological state of the individual and indirectly by afferent sensory input from the airways. Excitation of nervous receptors in the airways could therefore lead to bronchoconstriction mediated via a C.N.S. arc.

Receptors in the lungs :

Electron-microscopical evidence shows the presence of nerves in the epithelial lining of the trachea and bronchi. These nerves could act as receptors for antigens or irritants, being separated from the lumen of the airways by less than 1 um. In normal aiways, however , tight junctions between the epithelial cells limit penetration of materials from the lumen to the nerves or to the deeper regions of the tissue. In abnormal airways the integrity of the barrier may be reduced, exposing the receptors to supranormal stimuli. This possibility will be the subject of later contributions but could be one mechanism which leads to hyperreactive airways.

Extensive electrophysiological evidence suggests that more than one type of receptor may be present and that stimulation can lead to reflex Broncho constrictriction both via a C.N.S. pathway, and possibly via local connection in the walls of the airways. In addition to bronchoconstriction, cough, changes in ventilation , laryngeal constriction and mucous production may also be induced.