# STUDY OF VARIOUS CATEGORIES OF DRUGS MAINLY THE RECENT B-BLOCKERS, KETOTIFEN (ZADITEN, SANDOZ) AND CORTICOSTEROIDS IN EXPERIMENTAL ANIMALS (GUINEA PIGS) AND ON ISOLATED ORGAN PREPARATIONS

Thesis

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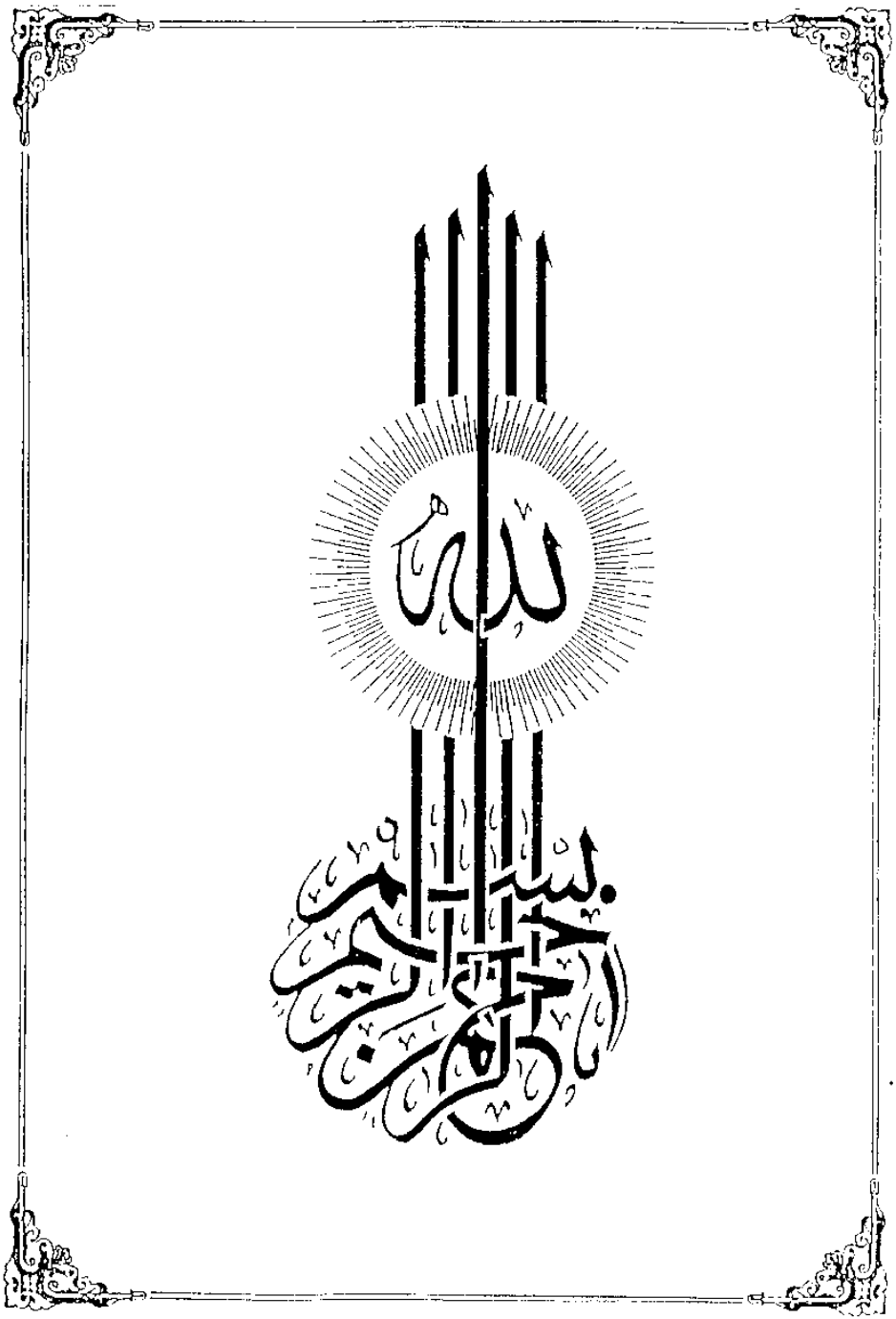

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# INTRODUCTION

# I N T R O D U C T I O N

Asthma is a common and important disorder with a long history of clinical recognition going back to ancient times (Pepys, 1978).

The circadian rhythm is an important cause of aggravation of asthmatic symptoms during the night and in the early morning. Air-way resistance reaches its maximum at about 5 a.m. and its minimum between noon and 6 p.m. This may be related to plasma cortisol level. (De Millas, 1971 and Gaultier et al.,1977 ).

The risk factors associated with the development and aggravation of asthma include age, sex, heredity, allergy, weather and air pollution, occupational exposure and infection (Speizer, 1976).

There are clinically relevant distinctions between the "widespread airway obstruction which are reversible spontaneously or by treatment", by which asthma can be defined, and the chronic productive cough which may be accompanied by wheezing and a low order of reversible airway obstruction, by which chronic bronchitis, may be defined (Pepys, 1978).

Abdel Tawab (1976) cited that the bronchial muscles constitute about half the total weight of the lungs. They are arranged as a network over the bronchi. With each inspiration, the bronchi become longer and wider and with each expiration, they become shorter and narrower. Contraction of the bronchial muscles narrows the lumen of all parts of the bronchial tree , but it is most effective in constricting the terminal bronchioles. In the guinea pig, full contraction of the terminal bronchioles obliterates their lumen and kills the animal by asphyxia.

There are 300 million alveoli in man (Ganong, 1977). The total area of the alveolar walls in contact with the capillaries in both lungs is about 70 Sq.m .

The alveoli are lined by two types of epithelial cells, type I cells are flat cells, with large cytoplasmic extensions and are the primary lining cells. Type II cells or granular pneumocytes are thicker and contain numerous lamellar inclusion bodies. These cells secrete surfactant ( Ganong, 1977).

Concerning innervation, it would seem that bronchial tone is regulated mainly via parasympathetic (Vagal) pathways (Widdicombe, 1964). On the one hand , vagal stimulation, or the direct stimulation of

vagal receptors with acetyl choline or histamine, produces bronchoconstriction , and on the other hand mild bronchodilation can be induced or the acetyl choline or histamine effect blocked by means of vagal blockade (Widdicombe, 1977).

As regards sympathetic innervation, the effect may conceivably operate directly on the B-receptors of the smooth muscles or indirectly on the $\alpha$ - receptors of the smooth muscles or indirectly on the $\alpha$ - receptors of the vagal ganglia (Richardson, 1977).

Szentivanyi (1968) explained the occurrence of bronchial hyperactivity in asthmatics in terms of a partial blockage of the B- receptors. This conclusion was based on animal models and on the fact that B- Blocking substances can elicit bronchoconstriction in asthmatics. However, it is impossible to tell whether the effect of the B-Blockers is due to direct impingement of the nervous structure or induced via circulating transmitter substances of the autonomic nervous system.

As regards non-adrenergic innervation, recently it has been possible to demonstrate in the bronchial system of the guinea pig and man , non adrenergic fibres

which belong neither to the vagus nor to the sympathetic nervous system (Burnstock et al., 1972).

There are grounds for believing that the innervation of the bronchial system is comparable to that of the gastro-intestinal tract. There are similar nerve plexuses in both systems and the pulmonary and gastro-intestinal ganglia exhibit similar structures. Non adrenergic innervation would exert mainly a relaxing effect; its mediator is possibly ATP(Burnstock et al., 1972).

From the point of view of mediator substances, mast cells are currently believed to derive from mastoblasts, primitive mesenchymal cells which become differentiated under neuroectodermal influences. An affinity with T-lymphocytes cannot be ruled out (Cutz and Orange, 1977). The mediator substances stored or synthetized in the mast cells , such as histamine, bradykinin, Kallikrein , SRS-A (slow reacting substances of anaphylaxis), ECF-A (eosinophil chemotactic factor of anaphylaxis) and NCF-A (neutrophil chemotactic factor of anaphylaxis) may have a direct influence on the tone of the bronchial muscles. In addition, in the case of histamine , an indirect broncho-constrictor effect may be exerted through stimulation of the vagus nerve (Austen, 1977).

Further indirect effects are produced by the chemotactic action of the factors specified on neutrophilic and eosinophilic granulocytes and on blood platelets (PAF; platelet activating factor) (Austen, 1977).

Very recently researchers become aware of the importance of the argyrophil cell elements which occur in the bronchial epithelium and also elsewhere in the organism and presumably produce polypeptide hormones , the so- called APUD cells (amine precursor uptake and decarboxylation cells ) (Frohlich,1949).
They are found in the mucosa of the bronchial system, concentrated at the bifurcations (Cutz and Orange. 1977). In the intrapulmonary airways they occur in groups with an organ- like structure,the" neuroepithelial bodies" (Lauweryns et al.,1979). The cells contain granules (dense core vesicles) which are generally recognized to have a neuro-secretory function and contain amines and polypeptide hormones. The neuroepithelial bodies have a cholinergic innervation and possibly afferent and efferent fibres. The normal function of these cells is obscure. It is possible that they produce amines which influence the pulmonary circulation and

the bronchial tone. They may also possibly be hypoxia receptors (Lauweryns et al.,1973).

The guinea pig isolated trachea is generally considered to resemble human airway smooth muscle in its responses to drugs (Foster, 1974).
Since broncho-constrictor prostaglandins may contribute to the pathogenesis of asthma, and bronchodilator prostaglandins may be of value in its treatment (Mathé et al.,1977), the action of these compounds on guinea pig trachea is of interest.
Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) which is a bronchoconstrictor in experimental animals and in man (Rosenthale,1975) has been shown to relax guinea pig isolated trachea (Puglisi, 1973). However, E series prostaglandins also have contractile action on this preparation. It is to be remarked that guinea pig isolated trachea has spontaneous tone and whilst $PGE_1$ and prostaglandin $E_2$ cause relaxation when tone is present, they cause contraction when it is absent (Puglisi, 1973; Lambley and Smith, 1975).

As regards receptors in the tracheobronchial tree, a pharmacologic receptor can be defined as a tissue macromolecule probably protein in nature, which specifically interacts with agonists (receptor-stimulant drugs)

and antagonists (receptor- blocking drugs). Beta receptor stimulation stimulates adenyl cyclase which in turn, raises intracellular levels of cyclic AMP (Robison and Sutherland, 1971). On the other hand, $\alpha$-receptor stimulation decreases cyclic AMP levels (Murtle and Kipnis, 1967). Sutherland et al, (1968) suggested that cyclic AMP might function as a "Second messenger", since its intracellular levels are influenced by a number of hormones.

Using isolated strips of human bronchi, Mathe et al., 1971) and Svedmyr (1971) concluded that these tissues contain $\alpha$-receptors in addition to the well known B- receptors.

The ability of the B- adrenoceptor blocking drugs to cause bronchospasm has been widely reported in man (e.g. Mc Neill, 1964; Macdoland et al. 1967 and Stone et al., 1973). It has always been assumed that the broncho constriction was due to blockade of B -adrenoceptors in the airway smooth muscle and therefore it was expected that the cardioselective drugs, which cause relatively less blockade in the lungs would be less likely to cause bronchospasm. However, there have been several clinical reports of bronchoconstriction induced by cardioselective B-adrenoceptor blocking drugs (Powles et al., 1969 and Marlin et al., 1975).

The presence of ∝-adrenergic receptors in the normal human bronchus and in the bronchi of asthmatic patients has been described(Bianco et al.,1972; Gaddie et al.,1972; Griffen et al.,1972; and Prime et al.,1972). They have reported the synergistic bronchodilator action of the ∝-adrenergic blocking drug thymoxamine with sympathomimetic bronchodilators in asthmatic patients. Likewise, Bianco et al.(1974) have shown the value of the ∝-adrenergic blocking drug indoramin in the management of exercise induced asthma. A model explaining this type of drug interaction has been developed by Coffey et al.,(1972), who showed that adrenergic stimulant drug potentiated the plasma membrane ATPase in leucocytes from asthmatics who had raised levels of membrane ATPase.

In further work, Logsdon et al.(1973) used leucocytes from asthmatic subjects and showed that isoprenaline increased the level of cyclic 3`,5`-AMP and inhibited histamine release. Alpha adrenergic blockade plus isoprenaline inhibited an even greater rise in cyclic 3`, 5`-AMP. On the basis of these studies Logsdon et al.(1973) postulated that ATPase and adenyl cyclase enzymes, compete for the same substrate namely ATP. Thus while ∝-adrenergic blockage inhibited ATPase and isoprenaline stimulated

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deleterious effects of ... adrenergic blocking agents, such as propranolol, in asthmatic patients (... Neill,1974). Lands et al. (1967) have postulated that B - adrenoceptors can be divided into two groups, $B_1$ adrenoceptors which mediate the cardiac inotropic and chrono-tropic effects, relaxation of intestinal smooth muscle, whereas, $B_2$-receptors mediate effects on bronchial smooth muscle without cardiac acceleration.

Introduction of specific $B_2$ stimulating drugs was an important advent in the treatment of asthma. Isoetharine, an $\alpha$ - alkyl- substituted derivative of isoprenalol was found to produce more than ... on bronchial ...