

Bronchial asthma: pathophysiological mechanisms and corticosteroids

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The clinical effects in asthma of corticosteroids can be ascribed to their strong anti-inflammatory action. The pathophysiology of asthma is complex. A diversity of mediators and interactions between mediators and between mediators and various cell types enhances and maintains the inflammatory process in the airways resulting in severe asthma. This is a vicious circle. Penetration through the airway epithelium of allergens and other insulting particles trigger release of inflammatory mediators and neurotransmitters, which, by chemotaxis and activation of inflammatory cells, results in enhanced and prolonged mediator release. Several of these mediators possess tissue-toxic properties enhancing the airway inflammation. The glucocorticoids have several points of action affecting both mediator release and accumulation and activation of inflammatory cells, which explains their favourable effect in asthma.

Key words: allergen; bacteria; bronchoconstriction; cells; corticosteroids; epithelium; inflammation; mediators; neurotransmitters.

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It is well known that corticosteroids are effective in the treatment of bronchial asthma and that this is due to their anti-inflammatory action. It is today possible to form a more exact picture of these effects. Here it is important to bear in mind that inflammatory processes are an essential feature in the pathophysiology of asthma. There is a diversity of mediators and interactions, both between the mediators and between mediators and various cell types which enhance and maintain the inflammation resulting in severe asthma. It can therefore not be expected that specific antagonists directed towards a single mediator can have clinical effect. Here the corticosteroids excel, having several points of action affecting both mediator release and accumulation and activation of inflammatory cells.

A more profound understanding of the pathogenesis of asthma and the effect of corticosteroids has been achieved through intensive study of inflammatory cells and mediators. An attractive model of the pathogenesis of asthma

is the different steps of mediator release and accumulation of inflammatory cells seen after bronchial provocation with the responsible allergen (24, 26, 27). The initial steps after exposure to allergen or other environmental insults seem to take place on the luminal surface of the airway epithelium (Fig. 1). Hogg and associates (10, 23) have shown that in animals both antigen and histamine challenge can increase the airways' mucosal permeability by disruption of the epithelial tight junctions. In asthmatic subjects it is therefore possible that inhaled particles as allergens, bacteria and virus can increase the epithelial permeability by stimulating cells lying on the surface of the airways to release histamine and other mediators. In fact, patients with extrinsic asthma, but not normal individuals, show increased number and sensitivity of the superficially lying mast cells (15, 33), which would allow a sufficient release of histamine by allergens for the opening of tight junctions. This might also be the case with bacteria, since our preliminary results with

Staph. aureus demonstrate histamine release from bronchoalveolar lavage cells (unpublished results). Opening of the tight junctions now allow entrance of mediators and inhaled particles which stimulate submucosal mast cells and other cells to release histamine and other mediators and activate afferent nerve endings in the airway mucosa. This leads to reflex bronchoconstriction via cholinergic pathways and possibly also axon (local) reflexes with release of sensory neuropeptides such as substance P, neurokinin A and calcitonin gene-related peptide, causing bronchoconstriction, oedema and mucous secretion (3).

The release of histamine and other mediators from the mast cell can thus be the initial step in the inflammatory process. These mediators also increase the microvascular permeability and some of them possess chemotactic activity as eosinophil chemotactic factor, neutrophil chemotactic factor and platelet activating factor (PAF = Paf-acether). The chemotactic factors promote an accumulation of migrating cells from the vascular beds and the tissue into submucosa and the airway wall. Like the mast cells, these cell types, comprising eosinophils, neutrophils and mononuclear cells, will release various mediators as leukotrienes, prostaglandins and PAF (2, 4, 6, 7, 8, 19, 24). Like histamine, several of these mediators cause bronchoconstriction, oedema and inflammation as well as mucous secretion (Table 1), but the effect can be more potent and of a longer duration. Another important property is their chemotactic capacity and capability of activating different cell types, in particular eosinophils, but also neutrophils and mononuclear cells, which renders them responsible for the development of asthma.

The activated cells thus release cytotoxic proteins including major basic protein (MBP) and eosinophil cationic protein and peroxidase derived from the eosinophil granulocyte granules and neutral proteases from the granules of neutrophils (12, 17, 34). Furthermore, toxic oxygen radicals are produced by different cell types including neutrophils and eosinophils (34). These cytotoxic compounds are suspected of breaking down the epithelium, and the epi-

thelium-damaging effect is regarded to be of significance for the development of the bronchial hyperreactivity. Toxic concentrations of MBP are thus present in the sputum of patients with asthma, and MBP can be localized to sites of damage in tissues of patients who died of bronchial asthma (17). Moreover, the sputum contains a component that inhibits ciliary beating, and both MBP and neutral proteases show ciliotoxic activity (13). Damage of the epithelium will further the entrance of inhaled particles, and the toxic influence of the epithelial cells might stimulate the cells to release arachidonic acid. This would lead to generation of chemotactic leukotrienes including 8,15-diHETE (dihydroxyeicosatetraenoic acid) and other 15-lipoxygenase metabolites of arachidonic acid, since these mediators are synthesized by epithelial cells from human trachea in the presence of arachidonic acid (25).

These events constitute a vicious circle which will enhance and maintain the inflammatory processes in the airways. But the epithelial cells also seem to have a direct moderating effect on the smooth muscle of the bronchi. Thus, intact epithelium might release broncho-dilating substances and the broncho-dilating effect will be lost during damage of the epithelium, thereby rendering the bronchial muscle more sensitive to released bronchoconstrictory mediators and neurotransmitters (14).

The anti-inflammatory effect of corticosteroids in asthma is due to a decrease or elim-

Table 1
Effects of mediators

	BC	BD	VD	VP	CT	MS
Histamine	+		+	+	+	+
LTB ₄					+	
LTC ₄	+			+		+
LTD ₄	+			+		+
PGD ₂	+		+		+	+
PGE ₂		+	+			
PGF ₂	+					+
PAF	+			+	+	+

LT (leukotriene), PG (prostaglandin), PAF (platelet-activating factor), BC (bronchoconstriction), BD (bronchodilatation), VD (vasodilatation), VP (increased vascular permeability), CT (chemotaxis), MS (increased mucous secretion).

ination of the inflammatory processes caused by reduced mediator release (1, 11) and inhibition of both accumulation and activation of inflammatory cells (34). The airway epithelium is healed and the bronchial hyperreactivity diminishes. Inhibition of mucous secretion contributes to their clinical effect (28, 29).

The subcellular mechanisms of the anti-inflammatory effect of corticosteroids in asthma has been the subject of intensive study (16). A more profound understanding might form a basis for new and more selective drugs. A central problem is whether corticosteroids are effective via one or several mechanisms. This question cannot be answered, but there is strong evidence that the formation of specific protein could be responsible for at least part of their effect. The glucocorticoids enter the cell by passive diffusion and interact with a specific receptor in the cytoplasm (22, 32). The steroid-receptor complex then reaches the nucleus of the cell (18). The transcription apparatus of the cell is activated and a specific messenger-RNA is synthesized, which initiates the production of specific proteins (5, 20). Of certain interest is the production of lipocortin, also called lipomodulin, macrocortin or renocortin, since this protein inhibits the phospholipase A_2 activity in the cell membrane (9, 20, 21). Fig. 2 shows how, via formation of lipocortin, corticosteroids can reduce the release of PAF, leukotrienes and prostaglandins from the cell membrane (1, 9, 11, 30, 31). These mediators are released by different stimuli as toxic stimuli, allergens, microorganisms, mediators and neurotransmitters, which activate the phospholipase A_2 enzyme in the cell membrane. The different membrane phospholipids are split, and the split products, lyso-PAF and arachidonic acid, form the basis of mediator synthesis. Lipocortin inhibits phospholipase A_2 , thus reducing the ability of the cells to synthesize and release PAF, leukotrienes and prostaglandins. Their biological effects in asthma have already been mentioned, and in the light of this it is understandable that a blocking of the synthesis of these potent mediators can explain the strong anti-inflammatory effect of the corticosteroids.

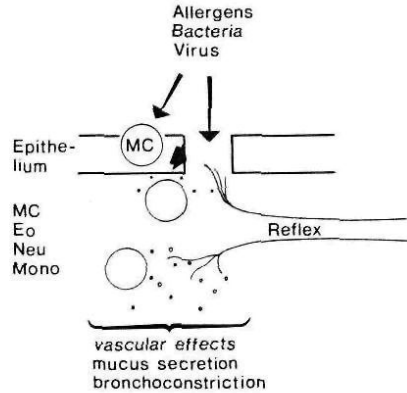


Fig. 1. Possible initiating steps in the pathogenesis of asthma. The tight junctions are opened by mediator release from mast cells (MC) in the airway epithelium. Entrance of insulting particles triggers release of mediators & neurotransmitters.

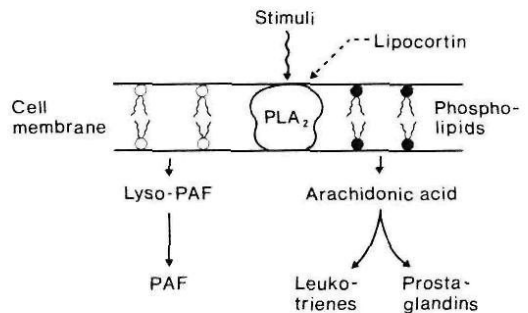


Fig. 2. Corticosteroids decrease mediator release of the cells via lipocortin, which inhibits phospholipase A_2 (PLA₂) in the cell membrane.

However, it must be emphasized that the inhibitory effect of corticosteroids on the interaction of various mediators is of significance. Thus oedema is enhanced if vasodilating drugs, facilitating the blood flow (prostaglandins D_2 and E_2), are present together with factors increasing the permeability (leukotrienes C_4 and D_4), and the inflammation is enhanced in the presence of chemotactic factors (PAF and leukotriene B_4). Corticosteroids inhibit all steps: the increase in permeability, the vasodilatation and the synthesis of chemotactic factors. This is not

only a consequence of the reduced mediator release, but is also caused by a direct effect of corticosteroids on the endothelial cells and the vascular smooth muscles. Moreover, corticosteroids cause a decrease in circulating eosinophils, mononuclear cells and T-lymphocytes by redistribution of cells to the bone marrow or the lymph glands.

It is unclear whether corticosteroids have a direct effect on the smooth muscle of the bronchi. Animal experiments suggest that treatment with corticosteroids can increase the number of β_2 -receptors and stimulate the subsequent coupling reactions. In the doses used the corticosteroids hardly affect the formation of antibodies or the antigen-antibody reaction. But the subsequent reactions are affected - inflammatory reactions which are caused both by allergic and non-allergic stimuli as bacteria, virus and other inhaled insulting particles. Therefore, corticosteroids are effective in both exogenous and endogenous asthma.

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