

Leukotrienes and Prostaglandins in Asthma

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In the attempt to comprehend the pathophysiological events in asthma, research in the allergic-inflammatory mediators is important. Prostaglandins and leukotrienes represent newly discovered mediators of possible relevance to asthmatic disease.

Biochemistry

The leukotriene and prostaglandin families are not found preformed in cells but are synthesized after adequate stimulation. The initial steps consist of membrane phospholipid methylation involving conversion of phosphatidyl ethanolamine to phosphatidylcholine. This perturbation of the cell membrane brings about an influx of Ca^{++} into the cell, and the increased Ca^{++} level activates a membrane-bound phospholipase (23) to cleave arachidonic acid away from the formed phosphatidylcholine (21) (see Fig. 1). Arachidonic acid then becomes the substrate for two enzymes: cyclooxygenase, which transforms arachidonic acid into prostanoids, i.e., prostaglandins (PG), thromboxanes and prostacycline, and lipoxygenase which is involved in the formation of the leukotrienes (see Fig. 2). The generic name for arachidonic acid is eicosatetraenoic acid, and therefore the leukotrienes and prostaglandins are often grouped together under the heading eicosanoids.

The antigen antibody reaction as well as a number of non-specific stimuli, such as col-

lagen, thrombin, bacterial peptide and trauma, will stimulate the synthesis of eicosanoids. Furthermore, cholinergic, adrenergic and histaminergic substances are able to modulate or initiate their synthesis. The mechanisms are still unclear but it is thought that changes in the intracellular levels of cyclic nucleotides (31) and Ca^{++} are involved (23).

Regulation of the synthesis of arachidonic acid's cascade is thought to be closely related to phospholipase activity (9). In the guinea pig, a negative feedback mechanism between the synthesis of PG and leukotrienes has been found.

Cyclooxygenase is a microsomal enzyme that, in the presence of oxygen, attacks the disengaged arachidonic acid, transforming this 20-carbon fatty acid into a cyclopentane structure with two aliphatic side chains. This structure is characteristic of the prostanoids. The so-called "classic prostaglandins" are classified into groups A to H according to the nature of their side chains. The most thoroughly investigated prostaglandins include the hydroxyketone PGE_2 , its isomer PGD_2 and the diol structure PGF_{20} . The numerical subscript represents the number of double bonds while the symbol α/β specifies the orientation of the cyclopentane ring's hydroxyl group.

The soluble enzyme lipoxygenase introduces a hydroperoxide group into arachidonic acid, resulting in the formation of hydroperoxyeicosatetraenoate (HPETE) (see Fig. 2). This product can either be decomposed to the hydroxy-

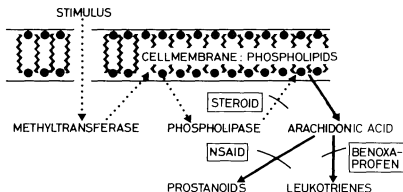


Fig. 1. Arachidonic acid is the precursor for leukotrienes and prostanooids. Arachidonic acid is liberated from the phospholipids in the cell membrane through the action of a phospholipase, which is activated by an influx of Ca^{++} . The Ca^{++} influx is brought about by an initial methylation of the membrane phospholipid after adequate stimulation of the cell. The enzymes are targets for pharmacological interventions.

analogue (HETE) or to the unstable intermediate oxidoeicosatetraenoate, called leukotriene A_4 (LTA_4). Hydrolysis of LTA_4 leads to the formation of leukotriene B_4 (LTB_4). Alternatively, LTA_4 can be conjugated with glutathione to yield the formation of leukotriene C_4 (LTC_4). Successive decomposition of the amino acids leads to the metabolic products leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4). Further steps in the metabolism of leukotrienes are as yet unknown.

The prefix leuco in leukotriene results from the fact that these compounds were originally isolated from leukocytes, and the suffix triene indicates that the compounds all contain a triene structure. The capital letters A–E represent the chronological division of the discovered structures. Since leukotriene can also be formed from eicosatrienoate and eicosapentaenoate, they are systematically arranged according to the number of double bonds present in the structure (34).

The type of eicosanoid that is synthesized within an individual cell depends on the type of enzymes that are present within the cell; these enzymes are usually membrane-bound and located mainly on ribosomes (22). The synthesizing capacity of these enzymes is presumably specific for the different cell types, but it can be altered by external stimuli, such as catecholamines, kinins, trauma and hypoxia.

SRS-A

Since 1938 when Feldberg & Kellaway (13) first described Slow Reacting Substance (SRS), obtained from the eluate from guinea pig lungs perfused with cobra venom, investigation vainly sought to identify the chemical structure of the substance. Only in the middle of the 1970s did the search become more circumscribed. The reason for the difficulty in identification of SRS is that it is not located intracellularly and that it is formed in such small amounts by stimulation. Only by utilization of high pressure chromatographic techniques could larger amounts be recovered. An intense research effort was directed toward identification of SRS, while at the same time Samuelsson's group at Karolinska Institute discovered the products of lipoxygenase activity. By fortunate symbiosis, the two lines of investigation determined that the identity of SRS was a mixture of LTC_4 , LTD_4 and LTE_4 (35).

SRS-A (SRS formed by anaphylactic reaction) from human lungs *in vitro* was subsequently identified as a mixture of LTC_4 , LTD_4 and LTE_4 (27).

Originally, SRS-A was isolated from mast cells. Now, SRS-A leukotrienes – as well as prostaglandins – are isolated from a large number of cell types and it is expected that they can also be synthesized in most of the cells

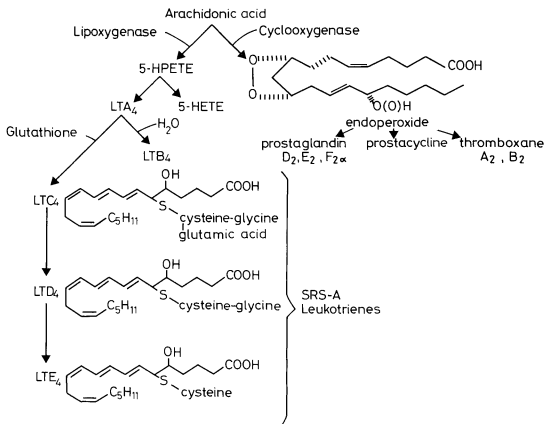


Fig. 2. *Eicosanoids*: arachidonic acid is the substrate for a cyclooxygenase, which transforms it into prostanoids, i.e., prostaglandins, thromboxanes and prostacyclin. Through a lipoxygenase, arachidonic acid can be metabolized into 5-HPETE, 5-HETE and leukotrienes.

in the body, since their precursor, arachidonic acid, is a component in most cell membranes.

Pharmacology

Clarification of the biochemistry of arachidonic acid's cascade contributed to a rational pharmacology, as the effects of many of the therapeutic drugs used nowadays can be explained by their action on leukotriene or prostaglandin synthesis.

Acetylsalicylate, indomethacin and similar Non-Steroid Anti-Inflammatory Drugs (NSAID) inhibit cyclooxygenase and thereby block the formation of prostanoids. Since Vane (41) in the beginning of the 1970s published these findings, the anti-inflammatory and anti-

pyretic effects of these compounds were explained by their inhibition of prostanoid synthesis.

The powerful anti-inflammatory and anti-allergic effects of steroids can also be explained by their interference in arachidonic acid metabolism. Steroids influence a receptor in the cytosol to liberate a peptide, macrocortin, which inhibits phospholipase and, consequently, the formation of both prostanoids and leukotrienes (8). In addition, steroids also inhibit exocytosis of preformed mediators, such as histamine. Interesting studies have linked these two conditions, as they have shown that the presence of HPETE, the precursor to leukotrienes, is obligatory for the exocytosis of histamine. This is illustrated by the finding that abundance of leukotriene's precursor, HPETE, increases the

allergen-induced histamine liberation, whereas inhibition of phospholipase or lipoxygenase blocks histamine exocytosis (33).

Lipoxygenase is thought to be inhibited by benoxaprophen (42) which, however, has been withdrawn from general use due to its side effects. For experimental use, some presumed leukotriene receptor antagonists are known, e.g., the chromone FPL 55712 (2), which has been recognized for more than 10 years but which cannot be employed effectively clinically because of its short half-life.

It can be expected that preparations will become available in the future that specifically inhibit lipoxygenase and/or cyclooxygenase. Optimistic projections suggest that a preparation will be made which has the potent anti-inflammatory and anti-allergic effects of steroids without their well-known side effects.

Physiological effects

Kock outlined in 1881 the prerequisites for an acceptance of a causality between an agent and a disease (25). Accordingly, the possible involvement of eicosanoids in the asthmatic pathophysiology should be inferred from their proved ability to reproduce some of the pathophysiological features of asthma when administered to man. The mediators should be identified in body fluids during asthmatic attacks, and finally, pharmacological antagonism of the eicosanoids should ameliorate the disease process.

The possible involvement of eicosanoids in the asthmatic pathophysiology should be inferred accordingly.

In general, inhalation of PGE_2 relaxes the bronchial muscles in asthmatic individuals, but bronchoconstriction is observed now and then, possibly provoked by a stimulation of irritant receptors to inhalation of the compound.

Inhalation of $\text{PGF}_{2\alpha}$ induces bronchoconstriction in the small and large airways in non-atopic persons with a potency considerably larger than histamine. Asthmatic persons have been found to be extremely hyperreactive to $\text{PGF}_{2\alpha}$. This hyperreactivity is quantitatively, and possibly qualitatively, different from the

hyperreactivity toward histamine and acetylcholine, as the relationship between the amount of histamine and $\text{PGF}_{2\alpha}$ that induces a standardized increase in airway resistance is about 3:1 in non-atopics and about 2000:1 in asthmatics (29).

Prostanoids were found in the eluate after specific allergen provocation *in vitro* of human asthma lung tissue. Moreover, in guinea pigs thromboxan A_2 and endoperoxides were detected, and these compounds were quantitatively dominant. To what extent these metabolites are also dominant in humans is as yet unclear.

After an asthma attack the plasma levels of a $\text{PGF}_{2\alpha}$ metabolite was found to be increased and the degree of increase correlated with the severity of the attack (16). $\text{PGF}_{2\alpha}$ metabolites in urine have been found to be increased in asthmatics compared with normal persons (37). On the basis of these investigations, PG has been suspected of being involved in asthma pathogenesis, possibly due to an imbalance between PGE_2 and $\text{PGF}_{2\alpha}$. However, cyclooxygenase blockers like aspirin, which inhibit the PG formation, have no favourable effect on asthma attacks and do not change the airway resistance, which raises doubts about the importance of $\text{PGF}_{2\alpha}$ in asthma. The apparent contradiction of this finding may, however, be explained by the fact that total inhibition of cyclooxygenase is not possible, and even a very small trace of the potent $\text{PGF}_{2\alpha}$ will be able to provoke bronchospasms.

Ten to fifteen percent of asthmatic persons undergo an attack after consumption of the cyclooxygenase inhibitors (39). This represents a potentially practical problem, as this includes not only NSAID preparations, such as indomethacin, acetylsalicylate, ibuprofen, naproxen and similar cyclooxygenase inhibitors, but also food-colouring agents, such as tartrazin, as well as benzoate which is used extensively as a conservation substance and which occurs naturally in fruit. This reaction is thought not to be caused by allergy toward these different substances but to their capacity to block cyclooxygenase, as their potency in this respect is correlated with their capacity to provoke an asthma attack (38). The relationship between

cyclooxygenase inhibition and asthmatic attack may be explained by a reduced synthesis of the bronchodilatory PGE_2 and/or an enhancement of the release of histamine and SRS-A, which contribute to bronchoconstriction. The enhanced mediator release is thought to be the result of arachidonic acid accumulation caused by blockade of PG synthesis, as this accumulation leads to increased formation of SRS-A (12) and other lipoxygenase products which potentiate the release of histamine (33).

For many years, SRS-A was suspected of being an important mediator in asthma, originally because it possesses a high physiological activity in extremely low concentrations, provoking a slow contraction of a human bronchial muscle preparation and being liberated from asthmatic lung tissue after incubation with a specific allergen *in vitro*. *In vivo* human investigations of SRS-A's effect on the lungs were first reported in 1963 by Herxheimer & Stresemann (19). They found that inhalation of biologically pure SRS-A obtained from guinea pigs brought about a reduction in the vital capacity of four asthmatics but no change in normal persons. Recent studies of the effect of synthesized leukotrienes have confirmed the extremely potent bronchoconstrictor ability of leukotrienes (6, 20, 43). In a double blind design we found the expected increase in airway resistance but no accompanying symptoms were experienced by the individuals tested. A pronounced bronchospasm without accompanying subjective symptoms is an interesting picture which resembles the one observed in asthmatic persons between attacks (30). Other authors have compared the reactivity to LTD_4 in asthmatics and non-atopic individuals and found no difference (17), which is remarkable as the asthmatics are specifically characterized by their hyperreactivity to almost anything.

However, there still remains the need to investigate whether leukotrienes *per se* induce hyperreactivity toward other mediators and stimuli. Animal experiments have shown a hyperreactivity toward histamine after treatment with leukotriene (11).

Using a newly developed radioimmunoassay (18) the occurrence of the SRS-A leukotrienes

in venous and arterial blood following an asthma attack has been sought thus far with a negative result. However, we did find significantly increased amounts of LTC_4 immunoreactivity in the tears of nine persons with allergic conjunctivitis after a specific type I allergic reaction *in vivo* (3). These findings confirm the *in vivo* synthesis of SRS-A leukotrienes in allergic reactions in man.

In addition to bronchospasms, asthma attacks are characterized by a reduced mucociliary clearance. This decrease can be blocked *in vivo* by the leukotriene antagonist FPL 55712 (1). Thus, these indirect studies suggest a role for leukotrienes in the reduced mucociliary clearance in asthmatics. In direct studies of human ciliary activity, we have shown *in vitro* that perfusion with LTC_4 reduces the beat frequency of cilia (5). Others have shown *in vitro* studies that LT stimulates mucus production in human airway explants (28).

Although the clinical picture in asthmatic attacks is marked by increased mucus production and wheezing respiration with reduced air flow, traditionally measured by the parameters reflecting the flow in the large airways, such as Peak Flow and Forced Expiratory Flow in the first second, it is important to emphasize the inflammatory process which underlies the acute asthma attack and which persists long after the subjective and clinically observable symptoms have disappeared. It has been shown that the parameters which are assumed to reflect the functional condition of the peripheral section of the lung, e.g., Volume of Trapped Gas (VTG), end respiratory flow and Residual Volume (RV), are abnormal long after flow in the large airways has returned to normal. It seems as if both the large and small airways are involved in the beginning of an asthma attack, where first the flow in the large and thereafter in the small airways is improved after remission (30). In order to understand the basis for this, it is necessary to examine the pathology of the asthmatic lung. In addition to an increased amount of smooth muscle tissue and mucus plugs in bronchial and bronchiolar lumina, the most outstanding features are edema in the mucosa and submucosa, exfoliation of the epithelium,

dilatation of the capillaries in the submucosa, eosinophilia and thickening of the basal membrane (26). It is clear from this picture that asthma cannot only be considered a reversible bronchospasm, but rather it must be judged by its underlying inflammation. Such an inflammatory swelling of mucous membranes plays a very large role in airways of small diameter, and since edema abates slower than the bronchospasm, the small airways will remain obstructed long after the symptoms in the large airways have disappeared. The asymptomatic airway obstruction can be recorded in asthmatic patients long after the attack, e.g. by an increased RV (30). This knowledge is important both for a choice of therapy and for an understanding of the pathophysiological components in asthmatic disease.

Prostanoids, especially PGE_2 , are recovered from a large number of inflammation types *in vivo* (14). As yet, leukotrienes have only been demonstrated *in vivo* in immediate allergic reaction. Both prostanoids and leukotrienes possess properties that orient them centrally in both the allergic inflammation and the general inflammation processes.

The first pathophysiological changes that take place during the development of inflammation are an increase in blood flow and permeability in the microcirculation, resulting in edema. PGE_2 , LTC_4 and LTD_4 are potent vasodilators (7). The effects of PGE_2 are prolonged, whereas the duration of the effects of LTC_4 and LTD_4 are similar to histamine. Besides a direct effect on blood vessels, the PGE_2 acts by blocking the liberation of noradrenalin from the sympathetic nerve endings, contrary to what is found for leukotrienes (4).

PGE_2 potentiate mediators that increase capillary permeability by its vasodilatory effect, even though PGE_2 itself does not cause important edema formation (44). On the other hand, LTC_4 and LTD_4 are potent mediators in edema formation (36) and are potentiated by PGE_2 . Consequently, there is an obvious synergism between the two different lines of the arachidonic acid cascade.

Invasion of activated inflammatory cells is the next step in the allergic-inflammatory re-

action. A large number of chemotactically active factors are known. Arachidonic acid derivatives are thought to be essential components in the extremely complex system of chemotactic mediators. 5-HETE and particularly LTB_4 are potent chemotactic factors. LTB_4 is thus equipotent with C5a and fMLA. In addition to the chemotactic activity, LTB_4 induces leukocyte adherence to the endothelium, which is a necessary precondition to chemotaxis (32). Finally, LTB_4 produces exocytosis of lysosomes (15). Recent studies have highlighted LTB_4 's role in the inflammatory process. For example, LTB_4 has been found to be elevated in the synovial fluid of rheumatoid arthritis. This concentration was normalized after injection of steroid (24). In psoriasis plaques, where intraepidermal abscesses are pathognomonic, the concentration of LTB_4 is also elevated (10).

Cyclooxygenase products have no chemotactic potency. On the contrary, PGE_2 can inhibit the chemotactic activity in leukocytes, presumably by increasing the cAMP level, which additionally inhibits liberation of lysozymes, histamine, leukotriene and lymphokines. After the initial pro-inflammatory effects of vasodilation and increased permeability have occurred, PGE_2 exercises an anti-inflammatory effect. Furthermore, PGE_2 inhibits leukocyte metabolism, phagocytosis and cytotoxicity, and it suppresses certain lymphocyte functions (40).

Summary

Leukotrienes and prostaglandins possess properties which are central in the asthmatic reaction. They are bronchoconstrictors, they inhibit the mucociliary clearance, increase blood flow and permeability and thereby induce edema formation, and they attract and activate leukocytes. They are formed partly by allergic reactions and partly by a large number of other more non-specific reactions. Finally, the concentration of prostanoids has been found increased in the asthmatic reaction *in vivo*. The leukotrienes have not been traced *in vivo* in asthmatic attacks so far, but have been found *in vivo* in man in a specific type I allergic conjunctival reaction. Much evidence suggests that these

mediators are relevant in asthmatic diseases, even though prostaglandin inhibitors have no effect in asthma. There still remains the need to investigate the influence on asthmatic diseases by as yet unavailable leukotriene blocking agents. Even though leukotrienes are judged today to be important mediators in asthma, it does not seem reasonable to expect that a single mediator is responsible for asthmatic diseases. Rather, it seems quite likely that asthma is caused by a complex interplay of a large number of mediators, circulating hormones, nervous mechanisms, receptor abnormalities, intracellular metabolic defects, etc. Despite this complexity, investigations in recent years have increased the knowledge of the biochemistry and human physiological effects of leukotrienes and prostaglandins which has created an improved understanding of the asthmatic reaction's pathophysiology, contributed a pharmacological rationale for previously used therapy, and stimulated new perspectives for specific pharmacological research.

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