

ASTHMA:
Inhibition of Leukotrienes
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- I. Introduction
 - A. Asthma
 - 1. symptoms
 - 2. relief of _
 - B. Leukotrienes
 - 1. effects of _
- II. The Linear Pathway
 - A. The beginnings of leukotrienes
 - 1. Arachidonate to leukotrienes
 - a. Linear pathway
 - 2. Lipoxygenases
 - B A. The function of leukotrienes
 - 1. biological active lipids
 - 2. induce inflammation and swelling
 - 3. particular effects of respiratory system
- III. Inhibitory compounds of Leukotrienes
 - A. 5-Lipoxygenase inhibitors
 - 1. block production at step 1
 - B. Receptors of Leukotrienes
 - 1. blockage of receptor
- IV. Conclusion
 - A. Overview of Inhibitory methods
- V. References

Have you ever taken something precious for granted? Something so simple and effortless such as the air you inhale? Well, for those with asthma there are times when the breath they take cannot suffice, and a feeling of suffocation overwhelms them instantly. This phenomenon is of substantial importance to many of us, including our loved ones. What is not readily known about asthma is that there are alternatives to inhaled steroids and constant loss of breath. The typical asthma attack is brought about by an antigen, these substances (dust, pollen, etc.), living or non-living, are recognized as foreign material by the immune system when inhaled into the lungs. This antigen could be very harmless but to the asthmatic the vigorous action of their immune system closes access through their lungs by constricting arteries and veins to the normally resistance free blood flow. This constriction causes the oxygen depleted blood passing through the pulmonary arteries to continue without a new oxygen supply. Thereby depriving the rest of the body of needed oxygen. The normal blood pressure in the pulmonary arterial system is much lower than that of the systemic circulatory system. The decreased size of the arteries causes the body to try to increase pulmonary pressure and thus causes the asthmatic to feel chest pains as well as loss of breath.

One step into treatment of asthma is to understand the mechanism by which the constriction or inflammation occurs. This mechanism is partially due to the influence of the immune system and consists of a family of very potent biological signaling molecules called eicosanoids. The eicosanoids act as short range messengers affecting tissues near the cells that produce them. Some of the major signal molecules responsible for asthma attacks are the leukotrienes. Leukotrienes induce blood vessel constriction and allergic reactions. Knowing one source of the problem can point the direction for inhibiting it or taking it out of the picture all together. In today's world the technology exists to synthesize a leukotriene inhibitor which can inhibit these biological signal molecules. Inhibition of the leukotrienes can be accomplished by several methods, two of which this paper will cover: the lipoxygenase enzyme inhibition or receptor site inhibition. Both methods represent competitive mechanisms.

The pathway by which leukotrienes emerge is typically called the "Linear Pathway". Linear refers to the starting point of leukotrienes (LTs), arachidonate, a twenty carbon fatty acid abundant in membrane phospholipids. The cycle through which LTs are produced is relatively simple and proceeds as shown in Scheme 1.

Allergic reactions of the immune system cause a specific phospholipase, present in most human cells, to attack membrane phospholipids, releasing arachidonate. Two types of arachidonate are released, straight chain and the bent ring formation. It is the straight chain that is of interest to us and further mention of arachidonate will mean "straight" chain. Subsequent action of several lipoxygenases incorporate molecular oxygen onto the arachidonate forming several distinct leukotrienes. The leukotrienes formed from oxidative metabolism of the arachidonate are stepwise intermediates (metabolites) of each other with minor differences only in attached amino acids and oxygenation sites (figure 1). These metabolites are components of the reaction called anaphylaxis, a type of immediate hypersensitivity that is triggered when allergen molecules (antigens) cross-link to IgE antibodies causing the release of inflammatory substances. Allergens have direct access to the antibodies present in the lungs, hence the onset of pulmonary artery constriction and the asthma attack. The response of the immune system can be seen as an over reaction to a potential home invasion, to prevent bodily harm the windows and doors are shut as tight as can be. The primary concern of this paper is to address the inhibition of the fourth and fifth metabolites in the oxidation of arachidonate, leukotriene E-4, and LTD₄. Clinical investigation into the contribution of LTs to inflammation and

bronchoconstriction show high levels of cysteinyl-leukotriene (LTE₄) in urinary excretion following an asthma attack (2). Specificity of the LTs involved in bronchoconstriction can also provide beneficial information for the prevention of asthma attacks.

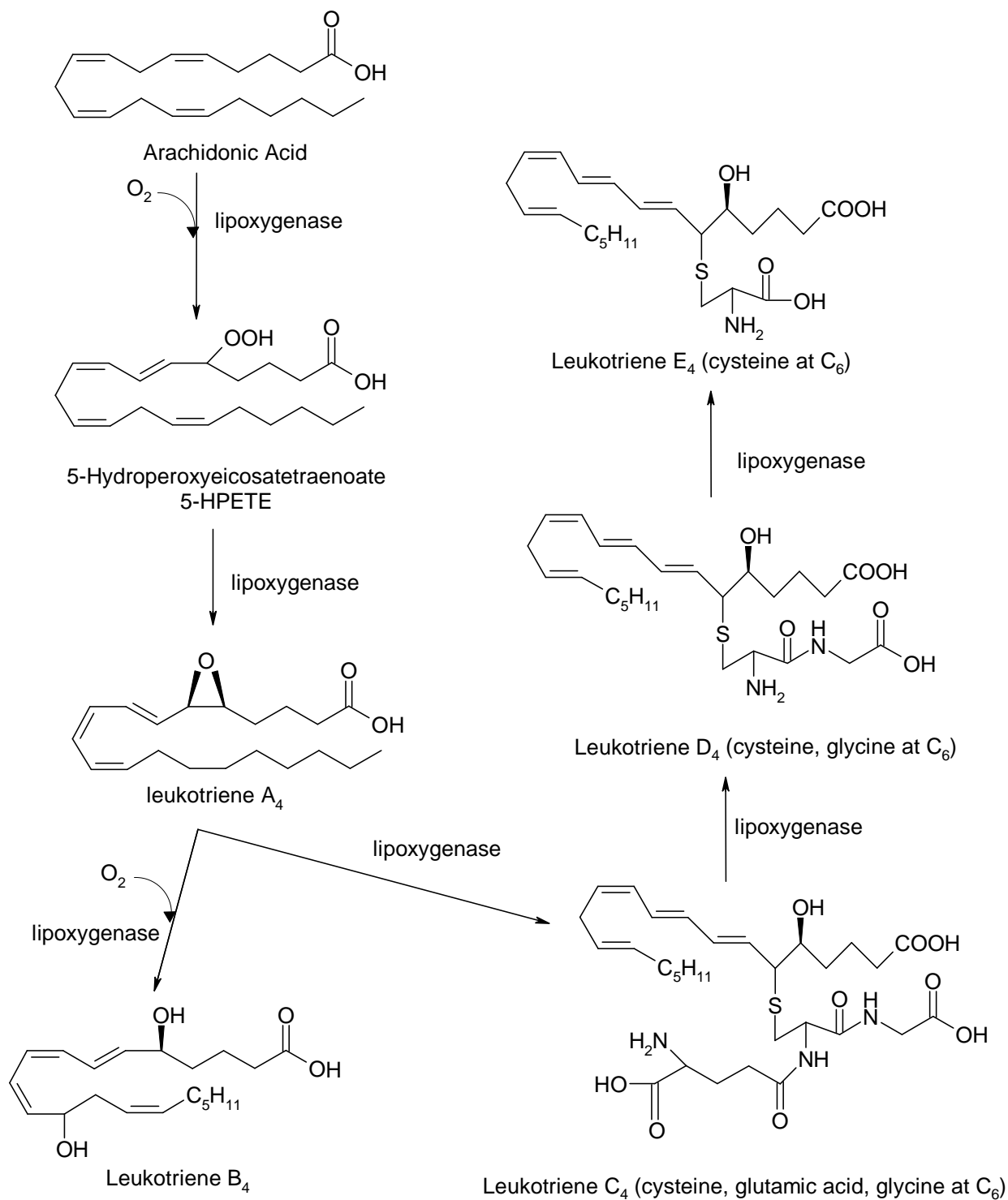
Scientists have discovered several ways to fight asthma but very few have meet with consistent success. Use of inhalants and anti-inflammatory drugs only pose temporary solutions to a constant problem. There is typically a 15-20% improvement in lung function with asthma inhalers. Unfortunately Ibuprofen and most anti-inflammatory / non-steroidal medications have no inhibitory effects on the linear pathway and production of LTs. However enzymatic inhibitors specific to lipoxygenases are of increasing interest. The first lipoxygenase to add molecular oxygen to arachidonate is the (5)-lipoxygenase, which adds to the fifth carbon of arachidonate. Competitive inhibition of this enzyme is of key importance in controlling the production of LTs. Zileuton® is a new chemical compound capable of inhibition of the 5-lipoxygenase (4). The inhibitor mimics the structure of the substrate and thereby decreases the number of arachidonate oxygenated to form LTs. The type of inhibition caused is competitive in nature.

A study involving 139 patients was conducted to asses the efficacy of Zileuton® 600mg 4 times daily or 800mg twice daily in the treatment of mild-to-moderate asthma over a 4 week period (Facts & Comparisons). Zileuton® 600mg significantly increased Forced Expectory Volume (FEV), compared with placebo beginning 1 hour after administration and continued to cause improvement throughout the study period. The group receiving 800mg twice daily also showed improvement in FEV, compared with placebo, but this difference failed to reach statistical significance. Patients who received 2.4g/day of Zileuton® also had significant improvement in forced vital capacity (FVC), airway function and reported asthma symptoms compared with placebo. In another study involving 8 aspirin-sensitive asthmatics, Zileuton® given in doses of 600 mg 4 times daily not only prevented the development of nasal, GI and dermal symptoms associated with aspirin ingestion, but it also curtailed the maximum rise in urinary LTE₄ and averted the fall in FEV.

A study involving rheumatoid arthritis patients was conducted to determine the effect of Zileuton® on leukotriene generation and clinical response. At the end of 1 week of study, patients receiving Zileuton® had a 70% decrease in leukotriene synthesis and an improvement in clinical response to Zileuton® therapy.

In contrast, higher doses of the inhibitor were needed to block blood LT production over a longer period of time as resistance to drug therapy increased. Like steroids Zileuton® reduces the inflammatory influx into the antigen-challenged site, which may yet have a long term effect of reversing some of the tissue alterations that occur as a result of the anaphylaxis. Specifically Zileuton® inhibited the urinary excretion of LTE₄ produced by antigen challenge in subject patients.

The receptor that mediates bronchoconstriction can be antagonized with an inhibitory cypocat that binds to the LTE₄ receptor. Zafirlukast® is one such antagonist of the cysteinyl leukotrienes-D₄ and -E₄ (CLTs). The CLT's, named for the cysteine amino acid linkage to the leukotriene at carbon six (figure 1), are potent bronchoconstrictors of small and large airways, which are approximately 100 to 5000 times more potent and have a longer duration action than histamine (a common inflammatory agent). Zafirlukast® was developed with the goal of attenuating the inflammatory effects of LTs in asthma. Zafirlukast® blocks the CLTs receptors that mediate bronchoconstriction, vascular permeability, and mucus secretion. This results in reduced asthma symptoms. When ingested orally the drug is rapidly absorbed into the blood.



Scheme 1: "Linear Pathway"

The mean terminal elimination half-life is approximately ten hours, 40% greater than that of Zileuton®. Once again competitive inhibition plays a key role in antagonism of LTs with

Zafirlukast®. A clinical study of Zafirlukast® involving 146 patients was done over a 13 week period in order to test the effectiveness of the anti-inflammatory drug. Each patient was 12 years or older, had not smoked cigarettes in the previous 6 months, had a smoking history of less than 10 pack-years, a FEV of at least 55% of normal, had demonstrated bronchial hyperresponsiveness, and were symptomatic during the first 7 evaluation days. In order to evaluate the drug effectively 103 patients were given Zafirlukast® (20mg twice daily), and 43 patients were given placebo (twice daily). Consequential data was obtained from medical examinations, patient questionnaires, and daily diaries. The clinical effectiveness was measured in days per month without asthma symptoms, limitation of activity, sleep disturbance, and episodes of asthma. The results of the 13 week period showed that the Zafirlukast® group had 89% more days without asthma symptoms, and 98% more days without episodes of asthma. They also had 55% fewer health care contacts and 55% fewer days of absence from work or school. Subjects used 17% less canisters of inhaled medication and 19% less non-asthma medication.

In conclusion the number one accepted cause of asthma symptoms and episodes are the leukotrienes. The LTs specified by this report, LTE4 and LTD4, are believed to be the most potent of the biological inflammatory signal molecules involved in asthma. Competitive inhibition of the metabolites in the linear pathway and LT receptor blockage can be of great importance to the asthmatic. Two drugs capable of accomplishing these individual tasks are Zileuton® and Zafirlukast®. Zileuton® inhibits the production of LTs by mimicking the arachidonate substrate of the (5)lipoxygenase and thereby competitively inhibiting the production of LTs. Zafirlukast® is an inhibitory copycat that binds to the LTE4 and D4 receptor ultimately blocking the inflammatory signal and asthma symptoms. Both drugs use different approaches to the same solution: asthma relief. Although scientists have not perfected the inhibition of LTs, they have managed to take two major steps in the treatment of asthma. Both drugs are capable of reducing asthma symptoms and providing hours of relief. As with all competitive reaction inhibitors a shift in the balance of one molecule over the other is of primary importance. Both drugs must be ingested on a daily basis for their full effects and long term usage results in loss of sensitivity to the specific drug.

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