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# Leukotrienes deficiency

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ABSTRACT

There are many diseases connected with deficiency of leukotrienes, but all people suffering from this are also exposed to infection. This is a result of low amounts of cysLTs and $LTB_4$, which are potent inflammatory mediators, resulting in the host defenses of people with decreased levels of leukotrienes being impaired. Bacteria exploit this condition and many patients with conditions such as HIV or diabetes mellitus die due to complications. It is important for doctors to know in which cases they should monitor such other parameters as lung functions.



## Introduction

Leukotrienes (LTs) are products of 5-lipoxygenase (5-LO) action. They are known as potent mediators of inflammation in the upper and lower airways. Leukotrienes are divided into two groups: $LTB_4$ and cysteinyl-LTs ($LTC_4$, $LTD_4$, $LTE_4$) [1]. They were first described in the period 1938 and 1940 when Feldberg and Kellaway identified a ''slow reaction smooth muscle-stimulating substance'' (SRS), which was later named $LTC_4$ [2].

SRS was first identified as a result of cobra venom administration to guinea-pig lungs. The main problem was isolating the effects of the venom from those of histamine, which was made possible only after anti-histamine drugs were invented. Blocklehurst, using anti-histamine drugs, described the formation of SRS-A in anaphylaxis in 1960 [3], Drazen and Nicosia emphasized the important role of SRS-A in asthma in the 1980s, while Samuelsson discovered that SRS-A is a mixture of cysteinyl-LTs [4–6]. In 1981 Dahlen et al. confirmed that leukotrienes induce microcirculatory alterations similar to those seen in the early phases of acute inflammatory response [7]. Leukotriene B4 has been known as a chemoattractant for phagocytes since 1983 [4].

## 5-LO and LTs

5-LO, after activation by FLAP, synthesizes 5-HPETE from arachidonic acid (AA) in response to inflammatory and immune stimulation. 5-HPETE is then quickly transformed to leukotriene $A_4$ ($LTA_4$). $LTA_4$ is the first of the generated leukotrienes and acts as a substrate for $LTA_4$ hydrolase or $LTC_4$ synthase. The molecular mechanism of transferring $LTA_4$ to $LTC_4$ involves glutathione, while $H_2O$ is needed for its conversion to $LTB_4$. $LTC_4$ is converted to $LTD_4$ and $LTE_4$ (Fig. 1) [8].

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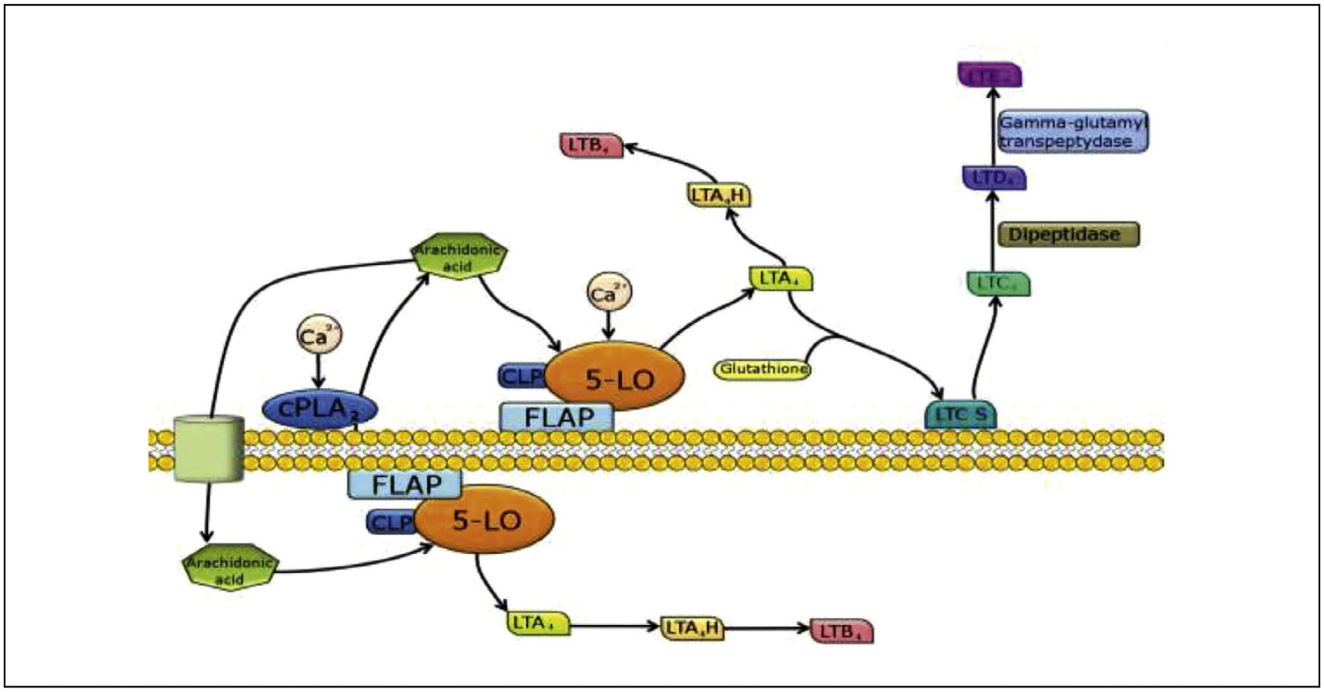


**Fig. 1 – Biosynthesis of leukotrienes**

According to Mandal et al. FLAP is essential for $LTC_4$ synthesis. There are two different FLAP populations: one (heterodimer/heterotrimer) assists with $LTC_4$ synthase $LTC_4$ synthase while the second (homodimer/homotrimer) is involved with $LTB_4$ production [8]. All leukotrienes have G-protein-coupled receptors [9, 10]. Nowadays they are well characterized: cysLT type I receptor, cysLT type II receptor, GPR17, $CYST_ER$, and $BLT_1/BLT_2$ [9, 11–14].

Macrophages, basophils, eosinophils, dendritic cells, neutrophils and mast cells are all known to produce leukotrienes [15, 16], a large number of which are produced during inflammatory response. Nevertheless, conditions exist, which are associated with LT deficiency and represent a growing area of research which is described in this review. Table I shows a list of such illnesses and dysfunctions.

**Table I – Diseases related with dysfunctions resulting in a lack of LTs.**

| Condition | Dysfunction |
|---|---|
| HIV | FLAP metabolism, 5-LO metabolism |
| Malnutrition | Glutathione synthetase deficiency, $LTC_4$ synthase deficiency, protein-calorie malnutrition |
| Vitamin $D_3$ deficiency | 5-LO activity |
| Cigarette smoking | Defects at 5-LO and phospholipase levels |
| Cirrhosis | Inhibition of 5-LO by substrate or by 15-HETEs |
| Parasites | Inhibition of 5-LO |
| Postsepsis | Inhibition of 5-LO |
| Newborn period | Lower expression of 5-LO and FLAP |

## HIV

Patients with HIV infection have abnormally low levels of leukotrienes generated by monocytes (PBMs), peripheral blood neutrophils (PBNs) and alveolar macrophages (AMs). LTs as inflammatory mediators play an important role in host-defense and their deficiency could have an influence on increased susceptibility to infection. The lung is an organ that is exposed to many environmental influences and, hence, is one of the most popular sites of infection in HIV patients.

Coffrey et al. investigated dysfunctions in the LT synthesis pathway of AMs, PBMs and PBNs. AMs play an important role in host defense mechanism of the lung. Together with PMNs, they have the potential to produce LTs, although this capability is impaired during HIV infection. This impaired capability is related to the reduced 5-LO metabolism and lower FLAP expression which can be seen to progress during the course of the HIV infection. Coffrey et al. report no difference between HIV infected and control subjects in a study which investigates whether reduction of LTs could be related to the release of AA by $cPLA_2$. Decreased levels of $LTB_4$ and 5-HETE indicate a dysfunction in the 5-LO pathway [17]. Moreover expression of 5-LO was seen to be a limiting factor for the conversion of exogenous AA whereas FLAP expression is a limiting factor for endogenous AA. CD4 counts were also found to be related to the amount of 5-LO and FLAP [17].

A similar effect connected with FLAP and 5-LO expression disorder, can be seen in PMNs and these dysfunctions in the LT pathway result in impaired *in vitro* PMN antifungal