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Review

Treatment of asthma with antileukotrienes: First line or last resort therapy?

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Abstract

Twenty five years after the structure elucidation of slow reacting substance of anaphylaxis, antileukotrienes are established as a new therapeutic modality in asthma. The chapter reviews the biochemistry and pharmacology of leukotrienes and antileukotrienes with particular focus on the different usage of antileukotrienes for treatment of asthma and rhinitis in Europe and the US. Further research needs and new areas for leukotriene involvement in respiratory diseases are also discussed.

Keywords: Asthma; Allergic rhinitis; Leukotriene; Glucocorticosteroid; Bronchoprovocation

Contents

1. Introduction

In the years immediately before the Second World War, a cosmopolitan group of pharmacologists including principally Kellaway, Feldberg and Trethewie discovered slow reacting substance of anaphylaxis (SRS-A). Using perfused guinea-pig lungs, they found that challenge with cobra venom or antigen caused the appearance of a substance that could be distinguished from histamine due to the slow in onset but long-lived contractions of the guinea-pig ileum bioassay tissue (Feldberg et al., 1938; Kellaway and Trethewie, 1940). The structure of SRS-A however remained at large for about forty years. After the war, studies of SRS-A continued (Vogt, 1957; Chakravarty et al., 1959; Brocklehurst, 1960), and it was established that SRS-A was not a prostaglandin (Strandberg and Uvnäs, 1971). Further work by several investigators in Europe and the US nevertheless provided compelling indications that SRS-A was associated with arachidonic acid metabolism (Orange et al., 1973; Bach et al., 1977; Jakschick et al., 1977; Morris et al., 1978), but the pieces in the puzzle could only be put together once the 5-lipoxygenase pathway in leukocytes (Borgeat et al., 1976)

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had been found to generate a new groups of metabolites (Borgeat and Samuelsson, 1979).

Thus, in 1979, Samuelsson and coworkers published the identification of SRS-A from a mouse mastocytoma cell line as leukotriene (LT) C_4 (Murphy et al., 1979), a compound formed in reactions initiated by 5-lipoxygenation of arachidonic acid and completed by conjugation of the arachidonic acid backbone with glutathione (Fig. 1). The structure of SRS-A was immediately confirmed in different preparations of SRS-A from several laboratories (Bach et al., 1980; Lewis et al., 1980; Morris et al., 1980; Parker et al., 1980). The studies also showed that the biological principle SRS-A in fact was made up of LTC_4 and its two immediated metabolites LTD_4 and LTE_4, formed by metabolism of the glutathione side chain in LTC_4. Moreover, the biological activities of LTC_4, LTD_4 and LTE_4 were closely similar, if not always identical (Hedqvist et al., 1980; Drazen et al., 1980). In vitro studies soon indicated that LTC_4, LTD_4 and LTE_4 were major mediators of antigen-induced contractions of bronchi obtained from subjects with asthma (Dahlén et al., 1983a). However, it took ten years from the discovery of leukotrienes until sufficiently potent and bioavailable modifiers of the leukotriene pathway provided conclusive proof of concept in subjects with asthma by demonstration of significant inhibition of exercise and allergen-induced bronchoconstriction (Manning et al., 1990; Dahlén et al., 1990; Taylor et al., 1991). After further clinical drug development, the first approval of antileukotrienes as a new class of drugs for the treatment of asthma came in 1995 in Japan, followed in the next few years by USA and Europe. During the first few years of this millennium, antileukotrienes have also been registered in many countries for treatment of allergic rhinitis. Antileukotrienes represent the first successful registration of a mediator antagonist for the treatment of asthma.

This chapter will first outline the pathways for biosynthesis of leukotrienes and describe their biological activities with focus on the respiratory system, followed by an overview providing perspective on the use of antileukotrienes for the treatment of asthma. There is recent experimental evidence, reviewed elsewhere, that leukotrienes have important functions in innate immunity (Peters-Golden et al., 2005), immunological responses including lung fibrosis (Charbeneau and Peters-Golden, 2005) and artherosclerosis (Funk, 2005).

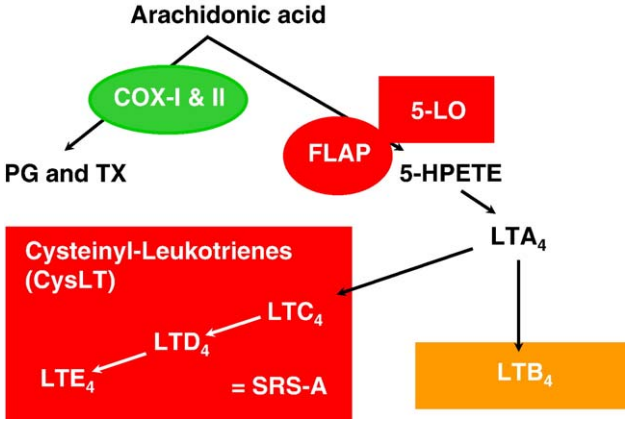

Fig. 1. Pathways for transformations of arachidonic acid. Cyclooxygenase (COX, two isoenzymes COX-1 and COX-2) catalyze the formation of prostaglandins (PG) and thromboxane (TX). The biosynthesis of leukotrienes (LT) is catalyzed by the 5-lipoxygenase (5-LO) in co-operation with FLAP (Five Lipoxygenase Activating Protein). The primary leukotriene intermediate LTA_4 is metabolized to LTB_4 or the cysteinyl-leukotrienes LTC_4, LTD_4 and LTE_4, that made up the biological activity previously known as slow reacting substance of anaphylaxis (SRS-A).

2. Biosynthesis, receptors and metabolism of leukotrienes

Leukotrienes thus constitute a class of potent biological lipid mediators derived from arachidonic acid (Funk, 2001). Leukotrienes are however not to be found in a resting cell. Biosynthesis of leukotrienes requires a cellular activation, such as cross-binding of the IgE receptor on the mast cell surface, to stimulate cellular conversion of the substrate arachidonic acid into biologically active messenger products. Arachidonic acid is normally esterified to membrane phospholipids. The release of arachidonic acid is predominantly controlled by the action of different phospholipase A_2 enzymes, all of which cleave arachidonic acid from membrane phospholipids. The liberated arachidonic acid can be metabolized to prostaglandins (PG), thromboxane A_2 (TXA_2) or leukotrienes, as well as a great number of other molecules collectively named eicosanoids (Fig. 1). The name eicosanoids is derived from the Greek prefix eicosa (=twenty) and refers to the number of carbon atoms in the substrate arachidonic acid.

The iniating enzyme in leukotriene synthesis is the 5-lipoxygenase (5-LO). The enzyme has two catalytic activities, the conversion of arachidonic acid to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) and the subsequent formation of leukotriene A_4 (LTA_4) (Fig. 1). Leukotriene A_4 is a short-lived compound that can be further metabolized to LTB_4 or LTC_4, in reactions catalyzed by LTA_4 hydrolase and LTC_4 synthase, respectively. Leukotriene C_4 and its metabolites, LTD_4 and LTE_4, are collectively designated cysteinyl-leukotrienes (CysLT) because of the common constituent cysteine in the side-chain.

For comparison, the prostaglandin H synthase (PGHS) initiates the metabolism of arachidonic acid to prostaglandins and thromboxane (TX) A_2 (Fig. 1). The PGHS is, as the 5-LO, a dual enzyme catalyzing two coupled reactions, an initial cyclo-oxygenation and a subsequent hydroperoxidase reaction. However, as drugs that inhibit prostaglandin formation usually inhibit the first cyclo-oxygenase reaction, the prostaglandin H synthase is functionally and pharmacologically usually described as the prostaglandin cyclo-oxygenase (COX). Two forms of the enzyme exist: COX-1 which is constitutively expressed in many cells and believed to be mainly involved in the production of prostanoids in physiological reactions, and COX-2 which often is induced in cells during inflammation and therefore considered primarily involved in pathological states (FitzGerald, 2003). As illustrated by the recently documented cardiovascular side effects of selective COX-2 inhibitors (Fitzgerald, 2004), there are several important exceptions to the general dogma of COX-2 as an inducible and exclusively pro-inflammatory enzyme.