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Pharmacotherapy of diseases mediated by 5-lipoxygenase pathway eicosanoids

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Abstract

Inflammatory eicosanoids generated by the 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism are now known to have at least 6 receptors: OXE, which recognizes 5-HETE and 5-oxo-ETE; a putative receptor recognizing a potent 5-oxo-ETE metabolite, FOG_7; the LTB_4 receptors, BLT1 and BLT2; the cysteinyl leukotriene receptors, $CysLT_1$ and $CysLT_2$, which recognize leukotrienes LTC_4, LTD_4, LTE_4 and LTF_4. The 5-LO pathway is activated in many diseases and invokes inflammatory responses not affected by glucocorticoids, but therapy with selective BLT1 or $CysLT_1$ antagonists in asthma has met with variable success. Studies show that 5-LO pathway eicosanoids are not primary mediators in all cases of asthma, but may be especially important in severe persistent asthma, aspirin- and exercise-induced asthma, allergic rhinitis, COPD, idiopathic pulmonary fibrosis, atherosclerosis, atopic dermatitis, acne and ischemia-related organ injury. These disorders appear to involve multiple 5-LO pathway eicosanoids and receptor subtypes, suggesting that inhibition of the pathway at the level of 5-LO may be necessary for maximal efficacy.

Keywords: 5-Lipoxygenase; Leukotrienes; 5-Oxo-ETE; FOG_7; OXE; BLT1; BLT2; $CysLT_1$; $CysLT_2$; Asthma; Allergic rhinitis; COPD; Idiopathic pulmonary fibrosis; Atherosclerosis; Atopic dermatitis; Acne; Ischemia-reperfusion; Montelukast; Pranlukast; Zafirlukast; Zileuton

1. Introduction

The 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism generates leukotrienes (LTs) and other eicosanoids with diverse biologic effects that are involved in asthma and other inflammatory diseases [1]. Recent studies have found LT receptor subtypes that have unique functions. This review will provide a pharmacological perspective, in light of recent findings, of the roles of 5-LO pathway eicosanoids in disease pathology, and an analysis of how the differing modes of action of available inhibitors contribute to their established utility and future therapeutic prospects.

2. 5-LO pathway eicosanoids and inhibitors

The 5-LO pathway is shown schematically in Fig. 1. Arachidonic acid liberated from the nuclear membrane by cell activation is sequentially metabolized in two steps by the 5-LO enzyme, in concert with FLAP, the 5-lipoxygenase activating protein. Recent studies have identified new branches in the 5-LO pathway leading to production of 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) which has a nanomolar biologic potency and shares the OXE receptor with 5-HETE [2]. The 5-oxo-ETE molecule can be transformed to 5-oxo-7-glutathionyl-8,11,14-eicosatetraenoic acid

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(FOG_7) which retains the potency of 5-oxo-ETE but likely has a distinct receptor that is not yet characterized [3]. More research is needed to explore the expression and functional roles of these mediators and their receptors in disease compared to leukotriene B_4 (LTB_4) and the cysteinyl leukotrienes (cys-LTs) LTC_4, LTD_4, LTE_4, and LTF_4. Also, only a few functions have been established for BLT2 and $CysLT_2$, the respective low-affinity receptors for LTB_4 and the cys-LTs.

Chemotaxis of neutrophils, eosinophils and macrophages is mediated by OXE [2], FOG_7 [3], and BLT1 [4] receptors. The latter are also responsible for T cell migration. BLT2 receptors have been observed mediating chemotaxis of neutrophils [5] and macrophages [6]. The $CysLT_1$ receptor also mediates eosinophil chemotaxis [7]. Mast cells primed with IL-4 and stimulated with cys-LTs secrete different sets of cytokines via either $CysLT_1$ or $CysLT_2$ receptors [8,9]. The $CysLT_1$ receptor is most associated with bronchoconstriction [50] but governs many other effects. Fibroblast collagen deposition is regulated by $CysLT_1$ [10] but both $CysLT_1$ and $CysLT_2$ have been implicated in vascular leakage [11] and fibrosis [5,12]. $CysLT_2$ receptor engagement induces airway smooth muscle proliferation [13]. Cys-LTs have potent effects on epithelial cell proliferation [14] and induce secretion via $CysLT_2$ receptors [15].

Inhibitors of FLAP have been explored, but the only agents approved for asthma have been zileuton, a competitive inhibitor of the 5-LO enzyme which blocks the entire pathway, and the three selective $CysLT_1$ receptor antagonists: zafirlukast, montelukast and pranlukast [16]. An antagonist of LTB_4 receptors (BLT1) reached the clinic but was not efficacious [17].

3. Role of 5-LO pathway eicosanoids in asthma subpopulations

The chronic inflammatory events and airway remodeling responsible for the pathology of asthma [18] are summarized in Table 1 along with receptors of the 5-LO pathway eicosanoids that could be involved in virtually every major pathologic change. The $CysLT_1$ antagonists have only modest efficacy in asthma [19] possibly due to their lack of activity on the $CysLT_2$ receptor subtype [20] and the fact that they target only one among at least six 5-LO pathway eicosanoid receptors (Fig. 1). Also, not all cases of asthma are leukotriene dependent [21] showing that asthma is heterogeneous. An important subpopulation with prominent involvement of leukotrienes is aspirin-induced asthma (AIA) which occurs in 21% of adults and 5% of children with asthma, higher than previously thought [22]. AIA is associated with increased basal leukotrienes compared to other asthmatics, with a further elevation following aspirin challenge [23]. Montelukast was only partially effective in altering lower airway reactions to aspirin challenge in a small AIA study and there was no apparent effect on nasal symptoms [24]. In a study of 40 AIA patients, zileuton inhibited aspirin-induced bronchoconstriction, significantly increasing forced expiratory volume in 1 s (FEV_1) as well as morning and evening peak expiratory flow rate compared to placebo. Nasal symptoms, a cardinal sign of AIA, were also improved, which included a remarkable return of sense of smell, less rhinorrhea and a trend for less stuffiness and restricted nasal inspiratory flow [25]. An even more common disorder is exercise-induced asthma (EIA), which can be demonstrated in 70–80% of asthmatic patients [26]. Urinary LTE_4 levels increase following exercise in EIA patients but not in normal subjects [27]. EIA has responded to montelukast [28] as well as zileuton [29]. Because inhibitors

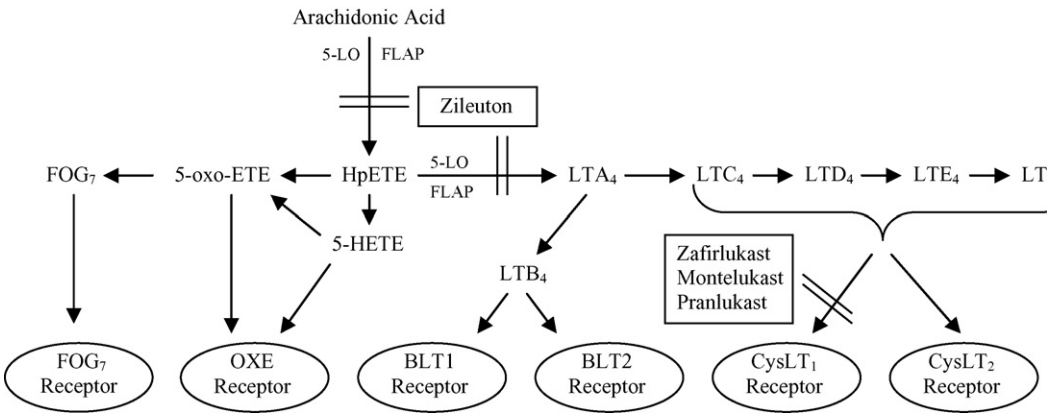

Fig. 1. The 5-LO pathway eicosanoids and inhibitors. Arachidonic acid metabolism initiated by 5-lipoxygenase leads to the bioactive eicosanoids shown here along with their receptors. Points of intervention are indicated for currently approved therapeutic agents.