New developments concerning leukotriene antagonists: a review

JOHN H. MUSSER, ANTHONY F. KREFT and ALAN J. LEWIS
Wyeth Laboratories, Inc., P.O. Box 8299, Philadelphia, PA 19101

Abstract

The numbers and subtypes of leukotriene (LT) receptors have only recently been investigated and more work is needed to evaluate the distribution of receptors on tissues and cells in both normal and pathological states. Classification of the heterogeneity of LT receptors may assist in the discovery of new antiallergy and antiinflammatory drugs much in the same way as the study of different adrenergic receptors has benefited cardiovascular drug discovery. The clinical evaluation of the currently available LT antagonists is awaited with interest; however, their therapeutic role in the treatment of asthma, a primary goal for the majority of these agents, will require painstaking clinical appraisal. They seem unlikely to supplant the currently used bronchodilators but may provide a valuable prophylactic adjunct that may suppress some of the inflammatory events that occur in obstructive lung disease. Whether the LT antagonists modify the hyperreactive state that prevails in asthma is also the subject of much speculation.

Introduction

Leukotrienes (LT), mediators derived from arachidonic acid via the 5-lipoxygenase pathway, may play an important role in the pathophysiology of such diseases as asthma, psoriasis, ulcerative colitis and rheumatoid arthritis [1, 2]. The sulfidopeptide LTs, LTC₄, LTD₄ and LTE₄, previously referred to as slow-reacting substance of anaphylaxis (SRS-A), are known to contract isolated airways and evoke bronchoconstriction in the guinea pig (GP) and man [3]. In humans, LTC₄ and LTD₄ may produce airway mucosal edema by enhancing post capillary permeability and may also stimulate the secretion of mucus from airways [4]. Administration of LTC₄, LTD₄ and LTB₄ intradermally to normal volunteers produces a wheal and flare response [5]. In asthmatic children plasma levels of LTC₄ correlate with severity of the disease [6]. The nonpeptidic LT, LTB₄, is a potent chemokinetic, chemotactic and aggregating agent for a variety of leukocytes in vitro; in vivo, it stimulates cell accumulation and affects vascular smooth muscle [7].

The multiple actions of LTs at low doses and the potential association of LTs in the pathophysiology of a number of diseases have prompted the development of agents that can inhibit their formation or action [8, 9]. In this article we intend to review those agents that primarily antagonize the action of LTs at their receptor sites.

A. Sulfidopeptide LT Receptors

Leukotriene receptors appear heterogenous since qualitative differences in LT responses exist between GP lung parenchyma and intestinal and uterine smooth muscle [10, 11]. Binding of [³H]LTC₄ and [³H]LTD₄ to GP and rat lung homogenates demonstrate the presence of specific, stereoselective, reversible, high affinity and saturable binding sites for both agonists [12–15]. [³H]LTC₄ binding sites seem ubiquitous [16, 17] and have been identified in numerous tissues including GP heart [18], ileum [19] and uterus [20], human fetal lung [21], rat glomeruli [22], human glomerular epithelial cells [23] and clonally derived smooth muscle cells [24]. The equilibrium dissociation constant (Kₐ) and maximum number of binding sites (B_max) for [³H]LTC₄ specific binding are 5 to 40 nM and 8.5 to 80 pmol/mg protein, respectively. It is noteworthy that LTC₄ specific binding sites occur in tissues that do not appear functionally sensitive to leukotrienes suggesting that these sites are not true receptors [17]. In contrast,
high affinity but low capacity LTD₄-specific binding sites have been described in a minority of tissues, including GP lung and trachea ($K_d = 0.2 - 1.8 \text{ nM}; B_{\text{max}} = 1.1 - 2.1 \text{ pmol/mg protein}$) [15, 16]. This suggests that $[^3\text{H}]\text{LTD}_4$ specific binding sites in GP lung represent the pharmacologically relevant receptors. Whether this is true of human lung is not yet established although human alveolar macrophages possess LTD₄ binding sites [25].

The end organ antagonist FPL 55,712 (1) inhibits smooth muscle contraction induced by LTD₄ and LTE₄ but not that induced by LTC₄ [26–30]. This was confirmed by binding studies suggesting FPL 55,712 more effectively competes with $[^3\text{H}]\text{LTD}_4$ for LTD₄ receptor sites than with $[^3\text{H}]\text{LTC}_4$ for LTC₄ receptor sites [16]. However, not all LTD₄-induced smooth muscle contractile responses are blocked by FPL 55,712 suggesting the existence of receptor subtypes [31].

$[^3\text{H}]\text{LTE}_4$ also binds to LTD₄ binding sites in GP lung membranes suggesting that both LTD₄ and LTE₄ contractile responses are mediated by similar receptors in GP lung [32, 33]. However, other studies indicate that the action of LTE₄ may be expressed at its own receptor since its action is blocked by cholinergic antagonists [34] and LTE₄ can induce GP tracheal hyperresponsiveness, unlike LTC₄ or LTD₄ [35].

Bioconversion of LTC₄ to LTD₄ (via $\gamma$-glutamyltranspeptidase) and LTD₄ to LTE₄ (via dipeptidase) by tissues responding to these sulfidopeptide leukotrienes can affect the magnitude and time course of response [36]. The metabolism of the LTs varies with species; for example, rapid conversion of LTC₄ to LTD₄ occurs in human and GP lung whereas in the rat lung, LTD₄ to LTE₄ conversion occurs rapidly [37].

**B. Sulfidopeptide LT Antagonists**

FPL-55,712 (1) (Table 1) was the first compound described as an antagonist of sulfidopeptide leukotrienes [38]. As a pharmacological tool, it has been extensively used to define the role sulfidopeptide LTs play in immediate hypersensitivity reactions in man and animals. Unfortunately, FPL-55,712 has a short biological half-life (0.6 min. when administered iv at 1 mg/kg in the GP) [39], and has not been developed as a drug. However, further clinical studies show that it does have aerosol activity [40]. The carboxylic acid homolog of FPL-55,712, FPL-59,257 (2), is a longer acting LTD₄ antagonist; however, it is still orally inactive [41]. While FPL-55,712 competitively antagonizes LTD₄ using GP ileum, FPL-59,257 is a non-competitive antagonist [42].

Numerous research groups have synthesized LT antagonists by substantial modification of the right hand portion of FPL-55,712 while retaining the left hand hydroxyacetophenone moiety [43–57]. Table 1 presents a summary of these compounds (3–17) along with their biological profiles. In comparison to FPL-55,712, Ro 23-3544 (14) is 300-fold, 80-fold and 16-fold more potent as an antagonist of LTC₄, LTD₄ and LTE₄ respectively, via aerosol in the GP. Ro 23-3544 is also a potent antagonist of antigen induced bronchoconstriction and surprisingly, it is active against LTB₄ induced bronchoconstriction in the GP [54].

We have extensively studied Wy-44,329 (8) and found that it not only competitively antagonizes LTD₄ on GP ilea but also inhibits the bronchoconstriction in GP induced by LTD₄, LTC₄ and ovalbumin (OA) [58]. While the in vivo potency of Wy-44,329 is comparable to FPL-55,712 upon LTC₄ or LTD₄ challenge, it is an order of magnitude more potent against OA. This may in part be due to its additional activity as a mediator release inhibitor. Wy-44,329 also possesses a much longer duration of action (> 40 min when administered iv) than FPL-55,712. Like FPL-55,712 which is reported to be a 5-lipoxygenase (LO) inhibitor in a cell free system [59], Wy-44,329 inhibits 5-LO in rat neutrophils [58]. Unfortunately, like the FPL compounds it is orally inactive.

In contrast to FPL-55,712 and Wy-44,329, LY-171,883 (10) is orally active against both LTD₄ and OA-induced increases in total pulmonary resistance in the GP [60]. LY-171,883 is a competitive antagonist of LTD₄ on GP ilea and parenchyma; however, it is a noncompetitive LTD₄ antagonist on GP trachea and is not effective against LTC₄ on GP ilea. In addition, LY-171,883 appears to be a bronchodilator which may be partially explained by its potent phosphodiesterase inhibitory activity. LY-171,883 is currently under clinical development as an antiasthma drug.

Another orally active LT antagonist in the GP is LY-163,443 (15) which antagonizes OA or LTD₄-induced increases in total pulmonary...