

Leukotrienes in gynaecology: the hypothetical value of anti-leukotriene therapy in dysmenorrhoea and endometriosis

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The lipoxygenase products (leukotrienes) have been demonstrated in many mammalian tissues including humans. They are widely distributed in the lungs, gut, uterus, kidneys, skin, heart and the liver. Their roles as mediators of inflammation have made them therapeutic targets. Significant amounts of leukotrienes have been demonstrated in the endometrium of women with primary dysmenorrhoea who do not respond to treatment with anti-prostaglandins. Also, in endometriosis, cytokines, which can initiate the cascade for the biosynthesis of leukotrienes, have been shown to be elevated. It is estimated that 10–30% of patients with painful periods fail to respond to prostaglandin (PG) synthetase inhibitors. Of adult females ~40% have painful menstruation and 10% of these are incapacitated for 1–3 days per month, and ~10% of women aged between 15–45 years suffer from endometriosis, which is a significant cause of infertility. Leukotriene receptor antagonists have recently been licensed for the treatment of asthma in the UK. In this review, we present the case for the potential use of these products in the management of primary dysmenorrhoea (especially in patients who are not responding to the traditional treatment using PG synthetase inhibitors) and possibly also in cases of endometriosis.

Key word: anti-leukotrienes/dysmenorrhoea/endometriosis/leukotrienes/prostaglandins

TABLE OF CONTENTS

Introduction	200
Biosynthesis of leukotrienes	201
Distribution of leukotrienes	202
Leukotriene receptors	202
Leukotrienes in the lungs	202
Leukotrienes in the uterus	203
Potential clinical application of anti-leukotrienes in gynaecology	203
Conclusions	204
References	204

Introduction

In 1938, Feldberg and Kellaway performed an experiment to examine the effects of cobra venom on guinea pig lungs and discovered an activity in the lung perfusate that caused slow-onset, sustained contraction of smooth muscle (Feldberg and Kellaway, 1938). Two years later, Kellaway and Trethewie (1940) observed that the time course of this contraction was different from that produced by histamine, and they named the mediator slow-reacting substance of anaphylaxis (SRS-A). In contrast to histamine-induced contractions, which were rapid in onset and short-lived, the

perfusate-induced contractions developed slowly and reversed slowly. It was not until 20 years after this initial experiment that Brocklehurst (1960) reported that lung fragments obtained from a person with asthma released SRS-A when they were exposed to an allergen. It took another 20 years for the chemical characteristics of SRS-A to be identified when it was found that SRS-A consisted of the cysteinyl leukotrienes: leukotriene C (LTC) sub 4, leukotriene D (LTD) sub 4 and leukotriene E (LTE) sub 4 (Murphy *et al.*, 1979; Lewis *et al.*, 1980; Morris *et al.*, 1980). The leukotrienes were then found to provide a new system of biological regulators that are important in many diseases involving inflammatory or immediate hypersensitivity reactions.

Leukotrienes, together with prostaglandins and thromboxanes are the major constituents of a group of biologically active oxygenated fatty acids known as eicosanoids (Henderson, 1991). They are involved in the mediation of various inflammatory disorders and have been implicated in inflammatory diseases, such as asthma, psoriasis, rheumatoid arthritis and inflammatory bowel disease. Such inflammatory role involves modulation of vascular permeability and vasoconstriction, enhancement of mucus secretion as well as immune modulation. Leukotrienes also cause neutrophil chemotaxis and aggregation, induction of neutrophil–endothelial cell adhesion and degranulation, lysosomal enzyme release and mediation of pain.

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Apart from their inflammatory property, leukotrienes have also been demonstrated to stimulate smooth muscle contraction both in the lungs (Davis *et al.*, 1982; Jones *et al.*, 1982) and in the uterus (Weichman and Tucker, 1982; Ritchie *et al.*, 1984). There is also evidence for prominent systemic effects initiated by leukotrienes following in-vitro infusion of LTC₄ or LTD₄ into sheep and rat where systemic venous, coronary and renal vasoconstrictive effects were variously demonstrated (Michellasi *et al.*, 1982; Badr *et al.*, 1984).

Their role as mediators of inflammation has therefore made them therapeutic targets. Inhibiting the production of leukotrienes or blocking their receptor sites may decrease the inflammatory response and thereby provide a useful therapeutic modality. Three approaches have been employed in attempts to affect the action of leukotrienes: firstly, inhibition of 5-lipoxygenase (5-LO); secondly, inhibition of 5-lipoxygenase-activating protein (FLAP) and thirdly, leukotriene receptor antagonism. Several anti-leukotriene agents have been developed. Clinical trials with these agents began in the mid-1980s. Subsequently, leukotriene receptor antagonists with greater potency have been extensively evaluated after initial disappointing results with agents inhibiting the production of leukotrienes. Recently, some leukotriene receptor antagonists (e.g. Montelukast; Merck, Sharp and Dohme Ltd, Hoddesdon, UK; Zafirlukast; Astra-Zeneca, Wilmslow, Cheshire, UK and Zeileuton; Abbott Laboratories, Maidenhead, Berks, UK) have been licensed for use in the treatment of asthma in the UK. Zeileuton inhibits leukotriene synthesis by 70–90% (Isreal *et al.*, 1990).

In this review, we discuss the biosynthesis and distribution of leukotrienes, and the in-vitro and in-vivo evidence, which has culminated in the clinical applications of anti-leukotrienes in pulmonology. We also examine the evidence for the distribution and the role of leukotrienes in gynaecology and thereafter speculate on the potential application of anti-leukotrienes in gynaecology.

Biosynthesis of leukotrienes

Unlike many other biologically active molecules, the eicosanoids are not stored preformed but are synthesized *de novo* from membrane phospholipids (arachidonic acid) through a cascade of enzymes. Arachidonic acid (5,8,11,14-*cis*-eicosatetraenoic acid) is found esterified in the sn-2 position, to cell membrane phospholipids in a wide variety of mammalian cells (Dennis, 1990). The trigger for eicosanoid biosynthesis begins after trauma, infection and inflammation (Henderson, 1994). The initial step in the biosynthesis is a receptor-mediated influx of calcium ions that causes translocation of a phospholipase enzyme, cytosolic phospholipase A₂ (phospholipase A₂), to the cell membrane (Clark *et al.*, 1991a; Sharp *et al.*, 1991; Drazen *et al.*, 1999). The enzyme then catalyses the hydrolysis of the esterified form of arachidonic acid at its sn-2 position (Glaser *et al.*, 1993). This selectively cleaves arachidonic acid from cell membranes.

There are three major pathways of metabolism from arachidonic acid as the substrate – the cyclo-oxygenase, lipoxygenase and epoxygenase pathways (Fraser, 1992; see Figure 1). The cyclo-oxygenase pathway leads to the formation of prostaglandins and thromboxanes while the lipoxygenase pathway is responsible for initiating the synthesis of leukotrienes. The third pathway (the epoxygenase pathway) is probably least important and also poorly understood, although it leads to the formation of prostaglandin

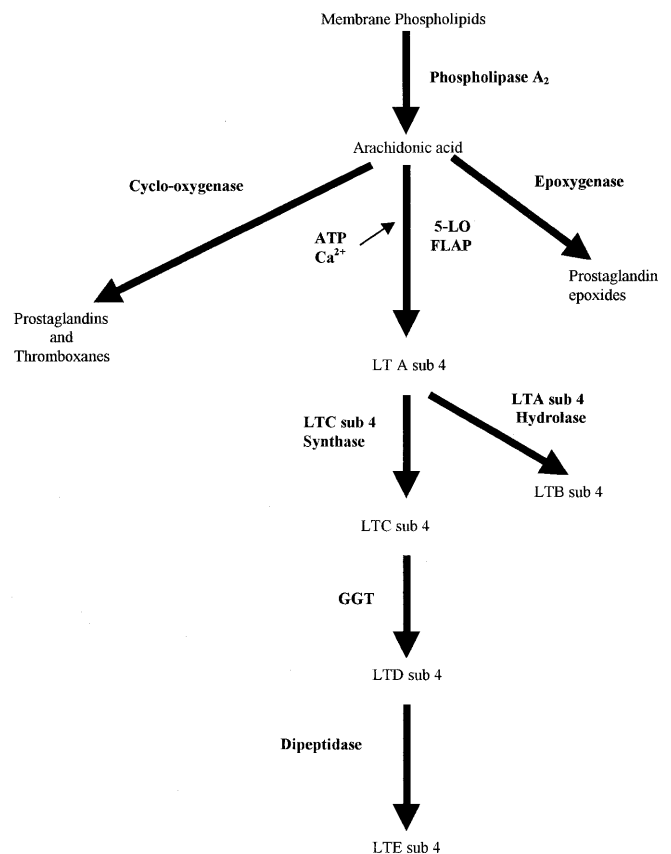


Figure 1. The biosynthetic pathway for leukotrienes. LO = lipoxygenase; FLAP = 5-lipoxygenase-activating protein; GGT = γ -glutamyl transpeptidase.

epoxides which are thought to play a role in bleeding disorders (Fraser, 1992). Only the second pathway (the lipoxygenase pathway) will be discussed in detail here.

The activity of phospholipase A₂ is increased by a phospholipase A₂-activating protein. This protein, when activated by cytokines e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1), can lead to arachidonic acid release and subsequent leukotriene formation (Clark *et al.*, 1991a). Arachidonic acid is then converted sequentially to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and then to LTA₄ by a catalytic complex consisting of 5-LO and FLAP in the presence of adenosine triphosphate (ATP) and calcium ions (Ca²⁺) (Dixon *et al.*, 1990; Reid *et al.*, 1990). LTA₄ is unstable and is either metabolized by LTA₄ hydrolase to leukotriene B (LTB) sub 4 or conjugated to the tripeptide glutathione (γ -glutamylcysteinylglycine) by LTC₄ synthase (a unique glutathione S-transferase) to form LTC₄. In many biological systems, LTC₄ is then rapidly converted to LTD₄ via γ -glutamyl transpeptidase, which removes the amino acid glutamic acid from the glutathione moiety. LTD₄ may then be converted to LTE₄ by the actions of a dipeptidase, which removes the glycine residue. This leaves cysteine as the only amino acid conjugated to the lipid portion of LTE₄. Because LTC₄, LTD₄ and LTE₄ contain cysteine, they have been designated cysteinyl leukotrienes. LTB₄ can undergo further oxidation at the 20-carbon atom to the less active metabolites.

Distribution of leukotrienes

The term leukotriene is derived from leukocytes because they were initially identified as products of leukocytes and the chemical structure contains three conjugated double bonds (triene). Apart from leukocytes, other myeloid derived cells can produce leukotrienes. The sites at which the leukotrienes are synthesized are determined by the cellular distribution of the enzymes controlling each stage of the biosynthetic pathway. The synthesis of LTA₄ is limited to cells of the myeloid lineage, which are the primary sites of 5-LO (Jones *et al.*, 1982). However, the enzymes determining the next step in the biosynthetic pathway (conversion to either LTB₄ or the cysteinyl leukotrienes) are more widely distributed. This enables a much broader range of cells to act as leukotriene producers.

The distribution of 5-LO is limited to neutrophils, eosinophils, monocytes, macrophages, mast cells, basophils and B-lymphocytes (Jones *et al.*, 1982; Jakobsson, 1991). Considerable variation exists in both the type and the quantity of leukotrienes secreted in these cells. Apart from human monocytes and macrophages which produce both LTB₄ and LTC₄ all the other cells produce appreciable quantities of either LTB₄ or LTC₄ but not both (Henderson, 1994). LTC₄ is the principal 5-LO product released from activated eosinophils (Jorg *et al.*, 1982; Weller *et al.*, 1983; Henderson *et al.*, 1984) as well as purified pulmonary mast cells (MacGlashan *et al.*, 1982) while activated neutrophils secrete LTB₄ as a product of 5-LO activity (Henderson and Klebanoff, 1983).

The main sites of leukotriene production in the body by the myeloid derived cells that have been demonstrated are the lungs (MacGlashan *et al.*, 1982; Martin *et al.*, 1984; Ritchie *et al.*, 1984; Levi-Schaffer *et al.*, 1987; Martin *et al.*, 1987) and the uterus (Ritchie *et al.*, 1984; Rees *et al.*, 1987; Chegini and Rao, 1988; Benedetto, 1989; Nigam *et al.*, 1991; Bieglmayer *et al.*, 1995). The other potential sites of production are the kidneys (Ardailou *et al.*, 1986); the skin of patients with urticaria, atopic dermatitis and psoriasis (Bischoff *et al.*, 1996); the coronary circulation in patients with cardiac ischaemia and in the biliary system following human bile duct obstruction (Richter *et al.*, 1996). Increased concentrations of LTB₄ and the cysteinyl leukotrienes are found in the sputum, bronchoalveolar lavage fluid, and urine of patients with cystic fibrosis (Cromwell *et al.*, 1981; Zakrzewski *et al.*, 1987; Sampson *et al.*, 1990; Spencer *et al.*, 1992). Some other conditions in which leukotriene production is increased are inflammatory bowel disease (Dias *et al.*, 1992), sickle cell disease (Richter *et al.*, 1996) and rheumatoid arthritis (Nagai *et al.*, 1992). In the gut, LTB₄ is found in colonic epithelial cells where synthesis is thought to take place (Dias *et al.*, 1992), and it is believed to promote infiltration by neutrophils of injured colonic mucosa in patients with inflammatory bowel disease. In patients with ulcerative colitis and Crohn's disease, the colonic mucosa contains significantly elevated concentrations of LTB₄ compared with normal controls (Sharon and Stenson, 1984; Harthorne *et al.*, 1992). LTB₄ concentrations are also substantially elevated in the rectal dialysate fluid of this group of patients (Lauritsen *et al.*, 1986, 1988).

Leukotriene receptors

Leukotrienes produce their biological effects by binding to and activating specific receptors. Two types of receptors for the cysteinyl leukotrienes (CysLT₁ and CysLT₂) have been demonstrated

(Coleman *et al.*, 1995). Recently, the molecular and pharmacological characteristics of cloned human CysLT₁ receptor have been reported (Lynch *et al.*, 1999). The CysLT₁ receptor (designated HG55) is a glycosylated G-protein-coupled receptor (GPCR) (Meters and Zamboni, 1993) and it encodes a protein of 337 amino acids with a molecular mass of 38 549. All the three marketed cysteinyl leukotriene antagonists [Montelukast (Merck, Sharpe and Dohme Ltd); Zafirlukast (Astra-Zeneca) and Zileuton (Abbott)] were demonstrated to be potent competitors with the CysLT₁ receptor for binding of radiolabelled LTD₄. Such characterization has so far not been elucidated for CysLT₂ receptor. The receptor for the non-cysteinyl leukotriene (LTB₄), is a seven-transmembrane-spanning protein known as the B leukotriene receptors (BLT) (Yokomizo *et al.*, 1997). These G-coupled receptors are members of the rhodopsin-like receptor superfamily (Goldman and Goetzl, 1982; Hoover *et al.*, 1984).

The leukotriene receptors are located in the plasma membranes of smooth muscle cells and in other types of cells (Cristol *et al.*, 1989; Crooke *et al.*, 1990; Krell *et al.*, 1990). Most of the biological effects of the leukotrienes are mediated by the CysLT₁ receptor (Piper, 1983; Henderson, 1994). These effects include the contraction of human airway smooth muscle, chemotaxis, and increased vascular permeability (Drazen *et al.*, 1980). LTC₄ and LTD₄ have equal capacity to stimulate smooth muscle contraction in the human lung *in vitro* by acting on CysLT₁ receptors and the potency of LTE₄ is lower by a factor of 10 (Davis *et al.*, 1982; Jones *et al.*, 1982). In the uterus, cysteinyl leukotrienes have also been demonstrated to stimulate myometrial smooth muscles (both circular and elongated myometrial smooth muscle) where specific binding sites have been demonstrated (Chegini and Rao, 1988). Similar binding sites have also been demonstrated in the endometrial cells (Chegini and Rao, 1988). The action of the CysLT₂ receptor is less well defined although in humans, they have been shown to mediate contraction of pulmonary vascular smooth muscle (Coleman *et al.*, 1995).

Two distinct sites of high and low affinity for LTB₄ exist on the surface of neutrophils (Goldman and Goetzl, 1982; Lin *et al.*, 1984). LTB₄ is a very potent neutrophil chemotactic agent and may play a pivotal role in the induction of neutrophil-endothelial cell adherence as well as a mediator of inflammatory pain (Yokomizo *et al.*, 1997).

Leukotrienes in the lungs

Leukotrienes have been shown to cause spontaneous bronchoconstriction leading to the narrowing of airways in asthmatic patients (Crocker *et al.*, 1997) via a major inflammatory role (Henderson, 1994). This bronchoconstriction effect is reversed by CysLT₁ receptor antagonist in patients with moderately severe asthma (Hui and Barnes, 1991). Leukotrienes also cause airway hyper-responsiveness in patients with asthma compared with non-asthmatic patients and the more responsive the airways, the more severe the asthma (Ryan *et al.*, 1982; Woolcock *et al.*, 1984).

The inflammation of the airway is central to the pathogenesis of symptoms, bronchoconstriction, and airway hyper-responsiveness in patients with asthma. Many studies have demonstrated the presence of inflammatory cells (mast cells, activated eosinophils, macrophages and lymphocytes) in the airway lumen of many asth-

matic patients (Kirby *et al.*, 1987; Beasley *et al.*, 1989). Mast cells and activated eosinophils release the cysteinyl leukotrienes persistently in asthmatic patients causing persisting airway inflammation (Sampson *et al.*, 1995). These have been the major reasons for the interest in leukotrienes among respiratory physicians and scientists. Leukotrienes have also been shown to cause tissue oedema (Wasserman *et al.*, 1995), migration of neutrophils and stimulation of airway secretions (Laitinen *et al.*, 1993). All these responses prompted research programmes in respiratory medicine to identify agents that could inhibit the action or synthesis of leukotrienes. Following these, a wide range of leukotriene receptor antagonists and leukotriene synthesis inhibitors have been identified, characterized, and tested in clinical trials. By the first half of 1998, some of these became available on prescription for certain categories of asthmatic patients mainly as an add-on therapy, either to maintain control or reduce corticosteroid use. The leukotriene modifiers therefore became the first new drugs for the treatment of asthma to be introduced in more than two decades (Drazen *et al.*, 1999).

Leukotrienes in the uterus

The ability of uterine tissues to elaborate leukotrienes was first suggested in the guinea pig using the leukotriene receptor antagonist FPL 55712, which inhibited antigen-induced uterine contractions (Carragher *et al.*, 1983). Although several other studies were conducted after this initial experiment to demonstrate increased amounts of leukotrienes in the endometrium and myometrial smooth muscles of patients with primary dysmenorrhoea (Demers *et al.*, 1984; Rees *et al.*, 1987; Chegini and Rao, 1988; Nigam *et al.*, 1991) little has been done on the potential therapeutic role of anti-leukotrienes in the management of this condition.

Leukotriene receptors were shown to be present in uterine tissues in the 1980s (Levinson, 1984). The number of these receptor sites for the cysteinyl leukotrienes has been demonstrated to be as high as that in lung (Chegini and Rao, 1988). Incubation studies using light microscopic autoradiographs of non-pregnant human uterine and bovine lung tissues demonstrated the presence of specific LTC₄ receptor sites in endometrial and myometrial smooth muscle cells (Chegini and Rao, 1988). Experimental studies carried out by Demers *et al.* (1984) using human endometrium and myometrium demonstrated the capacity of these tissues to synthesize leukotrienes. In the menstrual blood from women with primary dysmenorrhoea compared with that in women without, significantly higher concentrations of LTC₄ and LTD₄ have been demonstrated (Nigam *et al.*, 1991). The presence of specific LTC₄ binding sites in the myometrial cells have also been localized (Mitchell and Grzybowski, 1987).

Potential clinical application of anti-leukotrienes in gynaecology

Primary dysmenorrhoea is an extremely common condition in gynaecology. It usually begins within the first few months or years after the menarche, when ovulatory cycles first begin. It has its maximum incidence in the late teens and 20s (Fraser, 1992). Of adult females, ~40% have painful menstruation and ~10% of these are incapacitated for 1–3 days per month (Dawood, 1990). It is estimated that 10–30% of patients with painful periods fail to respond

to prostaglandin (PG) synthetase inhibitors (Benedetto, 1989; Nigam *et al.*, 1991), and that the concentrations of PGF_{2α} and PGE₂ in the menstrual blood from these non-responders are very similar to those found in normal controls (Rees *et al.*, 1987). This implies that prostaglandins may not be the pathway for their dysmenorrhoea. Experimental data exist to suggest that leukotrienes might be the alternative pathogenic pathway for primary dysmenorrhoea (Nigam *et al.*, 1991) especially where there is an abnormally high value of polymorph neutrophils (amongst other cells such as eosinophils) in the menstruum (Robertson, 1981). In fact, this high neutrophil concentration may account for the increased synthesis of leukotrienes in this group of women.

Evidence from in-vitro studies have shown that the production of leukotrienes by the endometrium from women with dysmenorrhoea is significantly higher compared with that from women without dysmenorrhoea (Sundell *et al.*, 1990; Nigam *et al.*, 1991; Hofer *et al.*, 1993; Bieglmayer *et al.*, 1995). If the primary dysmenorrhoea is modulated by this alternative pathway, then it is conceivable that suitable antagonists to lipoxygenase products may prove useful in the management of patients with primary dysmenorrhoea refractory to cyclo-oxygenase inhibitors. The distribution of specific receptors for leukotrienes in myometrial and endometrial cells (Carragher *et al.*, 1983; Levinson, 1984; Chegini and Rao, 1988) and the increased concentration of LTC₄ and LTD₄ in menstrual blood from women with primary dysmenorrhoea (Rees *et al.*, 1987; Chegini and Rao, 1988; Bieglmayer *et al.*, 1995) suggest a possible role for these inflammatory mediators in the reproductive system. Therefore, the two clinical conditions in gynaecology where these mediators might be involved in their pathogenesis are primary dysmenorrhoea and endometriosis. In endometriosis, the concentration of cytokines has been shown to be elevated (Odukoya *et al.*, 1995, 1996). Some of these cytokines activate phospholipase A₂ activating protein, which initiates the cascade for the biosynthesis of leukotrienes (Clark *et al.*, 1991b). Of women aged 15–45 years, ~10% have been estimated to have endometriosis (Barbieri, 1990). Its prevalence in infertile couple is 20–40% (Mahmood and Templeton, 1991). The symptoms are varied but include dysmenorrhoea, menorrhagia and pelvic pain. In this condition, there is significant increase in inflammatory cells. These inflammatory cells are known to be rich sources of leukotriene synthesis. Therefore, it is postulated (although there is no evidence for this yet) that the concentration of leukotrienes in the peritoneal fluid and the menstrual loss from women with endometriosis will be significantly elevated. Indeed, the reportedly high cytokine concentrations in the peritoneal fluid from women with endometriosis may also be another possible mechanism of the elevated concentration of leukotrienes. It is recognized that in the symptomatic treatment of women with endometriosis, there is a group that will not respond to anti-inflammatory agents or prostaglandin synthetase inhibitors. On the basis of the alternate pathological process involving leukotriene synthesis, in this group we speculate that treatment with anti-leukotrienes might be beneficial in the relief of dysmenorrhoea and pelvic pain.

Conclusions

Leukotrienes are widely distributed in the body. Their involvement in inflammatory processes in the lungs has resulted in the successful

application of their receptor blockers in the treatment of asthma. In reproductive biology, leukotrienes have been demonstrated to be high in the menstrual loss of women with primary dysmenorrhoea. We speculate that a similar observation will be made in women with endometriosis. In fact, in women with primary dysmenorrhoea who are unresponsive to prostaglandin synthesis inhibition, the lipoxygenase products (leukotrienes) have been implicated as an alternative pathway to the cyclo-oxygenase products (prostaglandins) in the pathogenesis of the primary dysmenorrhoea. We have provided evidence that has led us to conclude that anti-leukotrienes may be used to treat this group of women. In addition, we have postulated that higher leukotriene concentrations will be found in endometriosis and that such women may benefit from anti-leukotrienes.

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