



Leucotrienes and Its Biological Activities: A Review

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Abstract

Leucotrienes have attracted the attention of physician, medicinal chemist and pharmacist for its versatile biological activities. The present review highlights physiological and pathophysiological aspects of Leucotrienes. Leukotrienes, together with the prostaglandins and other related compounds, are derived from 20 carbon (eicosa) fatty acids that contain double bonds (enoic). They are formed from the breakdown of arachidonic acid, a polyunsaturated 20 carbon fatty acid. In its esterified form, arachidonic acid is bound to the phospholipids of the cell membranes. Both immunological and non-immunological stimuli can release arachidonic acid from membrane phospholipids by activating phospholipase A₂. There is wide scope of Leukotrienes in therapeutic efficacy against many diseases, hence in this regard the review is outlined to collect the data of history of Leukotrienes related to its molecular study, structure, pathophysiology and application. It is very interesting and note worthy to develop Leukotrienes for its medicinal values.

Key words: Arachidonic acid, Asthama, Leucotrienes, Phospholipids.

Introduction

Leukotrienes, together with the prostaglandins and other related compounds, are derived from 20 carbon (eicosa) fatty acids that contain double bonds (enoic). Hence this group of substances is

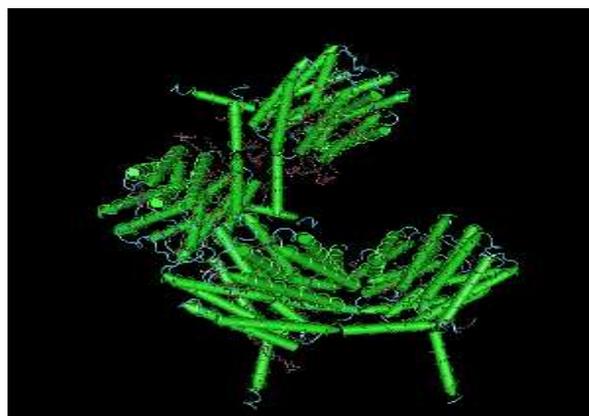
called the eicosanoids. The name leukotriene derives from the original discovery of these substances in white blood cells (polymorphonuclear leucocytes) and the fact that they all have in common 4 double bonds (hence the 4 subscript), 3 of which are in a conjugated triene structure. Leukotrienes do not exist preformed in cells. They are formed from the breakdown of arachidonic acid, a polyunsaturated 20 carbon fatty acid. In its esterified form, arachidonic acid is bound to the phospholipids of the cell membranes. Both immunological and non-immunological stimuli can release arachidonic acid from membrane phospholipids by activating phospholipase A₂. The glucocorticosteroid drugs can inhibit phospholipase A₂ and thereby decrease the production of all the leukotrienes and hence leukotriene-mediated responses. [1]

History [2, 3, 4]

1979	The name <i>leukotriene</i> , introduced by Swedish biochemist Bengt Samuelsson, comes from the words <i>leukocyte</i> and <i>triene</i> (indicating the compound's three conjugated double bonds).
1938 and 1940	What would be later named leukotriene C, "slow reaction smooth muscle-stimulating substance" (SRS) was originally described. The researchers isolated SRS from lung tissue after a prolonged period following exposure to snake venom and histamine

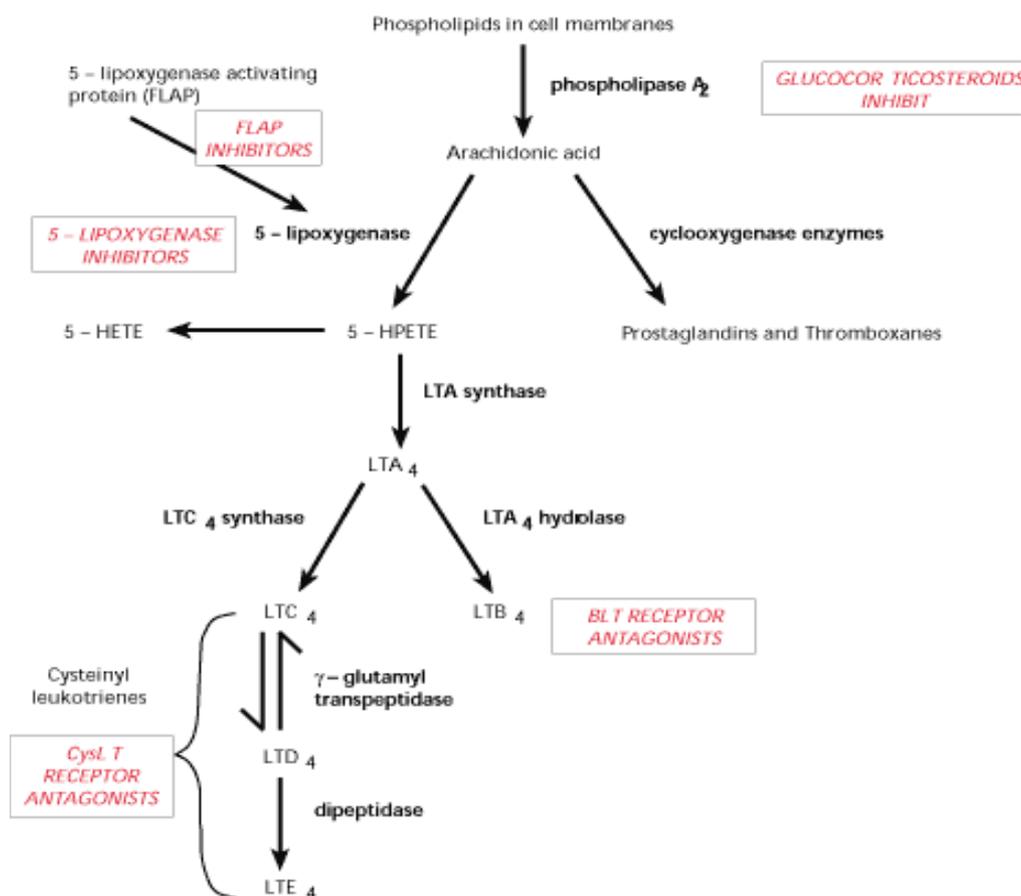
Crystal structure of a human membrane protein involved, in cysteinyl leukotriene biosynthesis. [5]

The cysteinyl leukotrienes, namely leukotriene (LT) C₄ and its metabolites LTD₄ and LTE₄, the components of slow-reacting substance of anaphylaxis, are lipid mediators of smooth muscle constriction and inflammation, particularly implicated in bronchial asthma. LTC₄ synthase (LTC₄S), the pivotal enzyme for the biosynthesis of LTC₄, is an 18-kDa integral nuclear membrane protein that belongs to a superfamily of membrane-associated proteins in eicosanoid and glutathione metabolism that includes 5-lipoxygenase-activating protein, microsomal glutathione S-transferases (MGSTs), and microsomal prostaglandin E synthase 1. LTC₄S conjugates glutathione to LTA₄, the endogenous substrate derived from arachidonic acid through the 5-lipoxygenase pathway. In contrast with MGST2 and MGST3, LTC₄S does not conjugate glutathione to xenobiotics. Here we show the atomic structure of human LTC₄S in a complex with glutathione at 3.3 Å resolution by X-ray crystallography and provide insights into the high substrate specificity for glutathione and LTA₄ that distinguishes LTC₄S from other MGSTs. The LTC₄S monomer has four transmembrane alpha-helices and forms a threefold symmetric trimer as a unit with functional domains across each interface. Glutathione resides in a U-shaped conformation within an interface between adjacent monomers, and this binding is stabilized by a loop structure at the top of the interface. LTA₄ would fit into the interface so that Arg 104 of one monomer activates glutathione to provide the thiolate anion that attacks C6 of LTA₄ to form a thioether bond, and Arg 31 in the neighbouring monomer donates a proton to form a hydroxyl group at C5, resulting in 5(S)-hydroxy-6(R)-S-glutathionyl-7,9-trans-11,14-cis-eicosatetraenoic acid (LTC₄). These findings provide a structural basis for the development of LTC₄S inhibitors for a proinflammatory pathway mediated by three cysteinyl leukotriene ligands whose stability and potency are different and by multiple cysteinyl leukotriene receptors whose functions may be non-redundant.



Biosynthesis of leukotrienes from arachidonic acid [1]

The first steps in the generation of leukotrienes are catalysed by the calcium and ATP-dependent enzyme 5-lipoxygenase. This is one of a family of lipoxygenase enzymes that metabolise arachidonic acid to hydroperoxyeicosatetraenoic acids (HPETEs).



Normal font - main pathways; Bold – enzymes; Boxed italics - drug groups (in red)

Fig. 1 The main pathways to the formation of the leukotrienes and the sites of action of the current drug groups (in boxes) that can attenuate leukotriene responses.

Each enzyme catalyses the insertion of an oxygen moiety at a specific position in the arachidonic acid backbone. 5-lipoxygenase forms 5-HPETE, the precursor of the leukotrienes. When cells are activated, cytosolic 5-lipoxygenase is translocated to the nuclear membrane. A nuclear membrane protein, 5-lipoxygenase activating protein (FLAP), is required before 5-lipoxygenase can synthesise 5-HPETE from arachidonic acid. Compounds are now available that block the biosynthesis of the leukotrienes through specific inhibition of 5-lipoxygenase e.g. zileuton (approved for asthma treatment in the U.S.A.). Experimental drugs are also available that inhibit leukotriene synthesis by inhibition of FLAP. The rearrangement of 5-HPETE to form the unstable LTA₄ is the rate-limiting step in the synthesis of the leukotrienes. This step is catalysed by LTA synthase. LTA₄ is then converted to either LTB₄ or LTC₄. LTC₄ is actively transported out of cells and rapidly metabolised to LTD₄ and then to LTE₄ (see Fig. 1 for enzymes involved in these steps). LTC₄, LTD₄ and LTE₄ are referred to as the cysteinyl (Cys) leukotrienes because of their chemical structure. LTE₄ is either excreted in the urine or metabolised to a variety of biologically less active, or inactive, metabolites, including LTF₄. In summary, the ability of cells to synthesise leukotrienes depends on – their enzymic capacity to cleave arachidonic acid from its phosphorylated store – the 5-lipoxygenase system to synthesise LTA₄. The lungs contain cells that have the full capacity to synthesise all the leukotrienes *de novo*. Hence, there has been significant interest in their effects on the lung.

Leukotriene receptors [6]

Early studies of the leukotrienes focused on their functional responses and their rank order of potency as agonists for various responses. These studies revealed that responses to LTB₄, and hence possibly its receptor, were distinguishable from those of the CysLTs. There was also an indication that there may be subtypes of receptors for the CysLTs. Since then, attempts have been made to classify and satisfactorily name the leukotriene receptors. An IUPHAR (International Union of Pharmacology) committee on drug classification and nomenclature developed recommendations for the leukotriene receptors. The current (1998) nomenclature is summarised in Table 1, together with the order of potency of the leukotrienes and the names of some selective antagonist drugs. The classification, based mainly on functional data, recognizes a distinct receptor for LTB₄ (now called the BLT receptor) and subtypes of receptors for the CysLTs (now called the CysLT₁ and CysLT₂ receptors). At present, there are no useful selective *agonist* compounds for any of the leukotriene receptor types. Numerous compounds have been shown to be selective *antagonists* of BLT or CysLT₁ receptors in animal studies. Some of the CysLT₁ receptor antagonists are now being used in the treatment of asthma. There is no selective antagonist for the CysLT₂ receptors. The compound, BAY u9773, appears to be a non-selective blocker of both CysLT₁ and CysLT₂ receptors. Hence, at present, those responses that are not blocked by one of the selective CysLT₁ receptor antagonists are assumed to be mediated by CysLT₂ receptors. The classification of the type(s) of receptor mediating the different responses to the leukotrienes is still evolving because of the lack of a complete range of selective agonists and antagonists and a lack of success in cloning and sequencing the CysLT receptors.

BLT Receptors [7]

LTB₄ is a potent chemo tactic agent for neutrophils, eosinophils and monocytes. It promotes the adhesion of neutrophils to the vascular endothelium and enhances their migration across the

endothelial wall into the surrounding tissue. LTB₄ also increases the release of toxic oxygen products, lysosomal enzymes and cytokines from pro-inflammatory cells.

CysLT Receptors [8]

It was shown in the 1930s that, if the lungs from sensitized guinea-pigs were perfused with sensitizing antigen, a substance was released that could cause a slow contraction of isolated smooth muscle preparations. In addition to the contractile responses in the lung, CysLTs have been shown to contract human coronary artery and distal and mesenteric pulmonary artery. They have no effect on most systemic large arteries or on the renal vasculature.

Table 1: Current nomenclature for the leukotriene receptors, based on that published by the IUPHAR nomenclature subcommittee. Also shows relative potency of agonists and some key selective antagonists.

	Leukotriene receptor type		
	BLT receptor	CysLT ₁ receptor	CysLT ₂ receptor
Previously known as	LTB ₄ receptor	LTD ₄ receptor	LTC ₄ receptor
Order of potency of agonists	LTB ₄ >12(R)-HETE (LTC ₄ and LTD ₄ are mainly inactive)	LTD ₄ =LTC ₄ >LTE ₄ (LTE ₄ is a partial agonist in some tissues)	LTC ₄ >LTD ₄ >LTE ₄ (LTE ₄ is a partial agonist in some tissues)
Selective antagonists	LY 293111	montelukast	BAY u9773 is a
	SC 53228	iralukast	non-selective
	SB209247	pobilukast	antagonist at
	CP 105696	zafirlukast	CysLT ₁ and
	CGS 25019C	pranlukast	CysLT ₂ receptors

Table no: 2: Physiological roles of LTB₄

1.Leukocytes	a)Activation of granulocytes, macrophages, monocytes, eosinophils and T-cells b)Chemotaxis c)Adhesion of leucocytes to endothelial cells d)CD11b upregulation e)Release of lysosomal enzymes f)Generation of reactive oxygen species g)Activation of natural killer cells h)Induction of IL-2 receptor
2.Endothelium	Adhesion of Neutrophils
3.Respiratory system	Constriction of lung parenchyma
4.Brain and Nervous system	Modulation of ryanodine receptor Activation of capsaicin receptors
5.Skin	Melanocyte pigmentation

Data from these studies, together with that from ligand binding studies and from experiments with FPL 55712, the first drug shown to block responses to the leukotrienes, indicated that there might be distinct receptors for LTD₄ and LTC₄. Subsequently, the effects of the newer, more selective, CysLT₁ receptor antagonists and BAY u9773 on responses to LTD₄, LTE₄ and/or LTC₄ have allowed us to predict the receptor type(s) likely to be involved in some tissues. Human bronchi may have a homogeneous population of CysLT₁ receptors, whereas guinea-pig trachea and ileum probably have both CysLT₁ and CysLT₂ receptors. Some tissues, e.g. guinea-pig and human lung, may have an additional receptor, but this is controversial. The current classification may be an oversimplification and it is likely to be modified as more data accumulate, appropriate tools are found and the molecular features of the receptors are unravelled.

Leukotriene Modifiers

Leukotrienes are very powerful chemicals released by mast cells in the airways, and they are an important cause of asthma. [9] Medications called leukotriene modifiers (e.g. Accolate and Singulair either interfere with the sequence of chemical reactions that leads to symptoms, or interfere with the binding of leukotrienes with their corresponding receptors and thus limit their ability to cause asthmatic symptoms. Leukotrienes can be released in sites of allergic inflammation in the nose, sinus mucosa, eyes, lungs and skin. After exposure to allergens or irritants, leukotrienes are released from the mucous membranes of the nose, sinuses and/or chest causing symptoms of swelling and obstruction. This can lead to osteomeatal complex blockage, reduced mucociliary clearance and increased risk for sinusitis.

Brand Name	Generic Name	Dose	Other Instructions
Accolate®	zafirlukast	20mg tablet twice a day	use 1 hour before, or 2 hours after meals
		10mg tablet twice a day (5 - 11 years)	
Singulair®	montelukast	10mg tablet once a day, (ages 15 years and older)	not affected by meals
		5mg tablet once a day, (6 - 14 yrs)	
		4mg chewable tablet once a day (2 - 5 years)	
		4mg granules once a day (12 - 24 months)	

Use

Treatment with leukotriene modifiers can improve lung function, decrease the need for sympathomimetic inhalers (e.g. albuterol), and reduce symptoms. Although these medications are effective, they do not appear to be quite as effective as oral or inhaled corticosteroids in controlling asthma. Further, there is no clear evidence that leukotriene modifiers prevent remodeling of the airways as does corticosteroids treatment. In contrast, corticosteroids are effective in the vast majority of individuals. That being said, The Asthma Center specialists have found the combination of corticosteroids and leukotriene modifiers to be beneficial. Use of both leukotriene modifiers and corticosteroids can better control asthmatic symptoms than either medication alone in some individuals; while also reducing the dose of corticosteroids needed to achieve good control of asthmatic symptoms.[10] Leukotriene modifiers have been available since 1997 for the treatment of asthma. By modifying leukotriene effects, these medications reduce the symptoms of allergies, asthma and possibly

sinusitis and nasal polyps. Although leukotriene modifiers are used for the treatment of sinusitis and nasal polyps, especially for those with aspirin intolerance, it is an “off-label” use and not yet in alignment with FDA recommendations. [11]

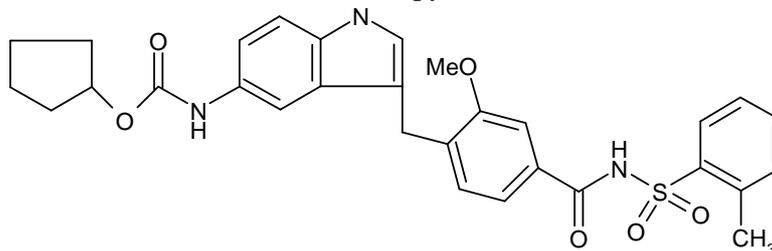
Risks and Precautions

These medications are usually well tolerated. Side effects are uncommon but include: headache, nausea, stomach upset, pain, fever, muscle ache, fatigue, sore throat, laryngitis and liver enzyme elevation.[12] Churg Strauss syndrome, a form of vascular inflammation, rarely is noted with these medications and can include vague symptoms of fever, fatigue, weight loss, vasculitis leading to kidney disease, hypotension, abdominal pain, bowel damage, heart disease, muscle aches and wasting, nervous system damage and arthritis. Liver function abnormalities have been reported with all of these agents and should be periodically monitored.[13]

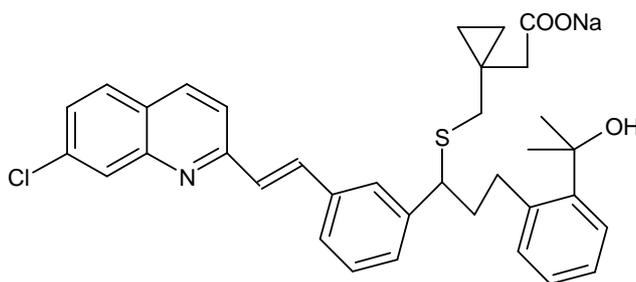
Role of leukotriene

A) In Asthama

Zileuton and zafirlukast, two oral leukotriene modifiers, have been approved for prophylaxis and chronic treatment of asthma in adults and children 12 yr of age and older. Current experience with zileuton and zafirlukast suggests that these drugs may be first-line therapy in the following patients with persistent asthma. [14] Patients with mild to moderate disease who fail to respond adequately to inhaled corticosteroid therapy. [15] Patients with moderate to severe asthma who have systemic side-effects from high doses of inhaled corticosteroids or who are at risk for these adverse effects. These patients should be considered for a trial of leukotriene modifiers to determine whether these agents will allow a reduction in the corticosteroid dose.[16] Patients with poor adherence to a regimen of inhaled corticosteroids because of improper technique or physical limitations.[17] There does appear to be a group of patients who respond early (within 2 wk of the beginning of treatment) to leukotriene modifiers with improved peak expiratory flow rates and FEV₁ values. If the drug appears beneficial after 6 to 8 wk of therapy, a longer treatment period may be indicated, especially for patients receiving oral corticosteroids or high doses of inhaled corticosteroids. Peak expiratory flows monitored at home, along with symptom diaries, are helpful in documenting the efficacy of these agents and indicating the patients who would most benefit from leukotriene modifier therapy.



Zafirlukast

**Montelukast****B) Rheumatoid arthritis (RA)**

It is an autoimmune inflammatory disease that affects 1% of the world population. Despite lack of consensus on what initiates RA in humans, many recent developments point to a role for the innate immune system in the pathogenesis of RA [18,19] Many concepts developed in experimental animal models have begun yielding effective therapeutics for arthritis such as anti TNF- α and anti IL-1 β based therapies that are currently leading the way [20] These therapies have been effective, but subgroups of RA patients do not respond to them. Another treatment regimen that showed great promise was the use of cyclooxygenase-2 (COX-2) inhibitors [21] However, these had to be withdrawn due to increased risk of cardiovascular complications in patients taking the drug.[22] A clear understanding of the pathogenic mechanisms in mouse models will likely provide additional therapeutic targets for the treatment of RA. One of these potential leads involves leukotriene B₄ (LTB₄), a potent lipid inflammatory mediator and a strong chemoattractant for neutrophils. LTB₄ mediates its effects through two G-protein coupled receptors (GPCRs), BLT1 (high affinity) and BLT2 (low affinity).[23,24] Recent data from animal models and arthritis patients demonstrate a critical role for LTB₄ and its receptors in the progression of RA and suggests potential new targets for treatment. Here, we discuss briefly the available mouse models of RA and their use in the demonstration of an important role for LTB₄ and its receptors in the development of RA.

C) Collagen-induced arthritis [25, 26]

Treatment with anti-TNF biological-response modifiers significantly reduced paw swelling and histological evidence of the severity of inflammation in collagen-induced arthritic mice and. These results showed that TNF- α also plays an important role in the pathogenesis of collagen-induced arthritis in mice. Our previous studies showed that mast cells accumulate in inflamed paws of collagen-induced arthritic mice, and treatment with a mast cell-stabilizing compound, cromoglycate lisetil, decreased the number of mast cells and effectively suppressed the development of collagen-induced arthritis. Based on the above evidence, we thought that collagen-induced arthritis in mice is a useful experimental model to explore the role of TNF- α derived from synovial mast cells. A recent *in vitro* study revealed that mast cells express cysteinyl leukotriene type 1 receptor, that TNF- α production by mast cells is increased by incubation with cysteinyl leukotrienes and that this increase is significantly suppressed by treatment with a selective cysteinyl leukotriene type 1 receptor antagonist, MK571 .Therefore, we hypothesized that cysteinyl leukotriene type 1 receptor antagonists will inhibit TNF- α production by mast cells in synovium, thereby attenuate the development of collagen-induced

arthritis in mice. To test this hypothesis, and to further elucidate the role of mast cells in the pathogenesis of arthritis, we evaluated the therapeutic effects of a selective cysteinyl leukotriene type 1 receptor antagonist, montelukast, on the development of collagen-induced arthritis in mice.

Biological activity of leucotrienes

Leukotriene B₄	It has an important function in the inflammatory process by its effect on leukocytes mediated via two G-protein-coupled receptors. It causes neutrophils to adhere to vascular endothelial cells and enhances the rate of migration of neutrophils into extra-vascular tissues, and it triggers several functional responses important for host defense, including the secretion of lysosomal enzymes, the activation of NADPH oxidase activity, nitric oxide formation, and phagocytosis. Also, it activates such intracellular signalling events as the mobilization of calcium, activation of phospholipases, the production of diacylglycerols and phosphoinositides, and the release of either anti- or pro-inflammatory agents, depending on circumstances. 5-Lipoxygenase and LTB ₄ especially have been implicated in the chronic inflammation that is a part of the pathophysiology of atherosclerosis. [27]
Leukotriene C₄	together with LTD ₄ and LTE ₄ (the cysteinyl-leukotrienes, which jointly comprise the slow-acting substance of anaphylaxis), are known to exert a range of pro-inflammatory effects, including constriction of the airways and vascular smooth muscle, increasing plasma exudation and oedema, and enhanced mucus secretion. There is a general impression is that leukotrienes produce harmful effects, especially in relation to the immune system and allergic diseases, such as asthma. However, there are suggestions that they may also be beneficial in that they stimulate the body's innate immunity against pathogens, including bacterial, fungal and viral infections, by promote the expression of mediators and receptors that are important for immune defense. For example, leukotriene B ₄ can trigger the release of antimicrobial agents. [27]
Eoxin	have been implicated in inflammation of the airways in asthma patients, and in those with Hodgkin lymphoma, a malignant disorder with many characteristics of an inflammatory illness. [28]
Lipoxins	were the first eicosanoids to be discovered with a role in the resolution of inflammation, i.e. they are 'switched on' to limit the effects of inflammation. Indeed, they control the inflammatory response in such pathogenic conditions as asthma, arthritis, cardiovascular disorders, and gastrointestinal, periodontal, kidney and pulmonary diseases. Thus, they have opposing effect to LTC ₄ and inhibit bronchial spasms. Like lipoxins, the aspirin-triggered. [29]
Epilipoxins	Also have potent anti-inflammatory actions, and this may provide further explanation for the efficacy of aspirin as a drug. It not only inhibits the synthesis of pro-inflammatory mediators but also induces the synthesis of anti-inflammatory ones. The signals that lead to the synthesis of such molecules in turn stimulate the transcription of enzymes required for the generation of lipoxins from arachidonate and the resolvins from fatty acids of the <i>omega</i> -3 family of fatty acids, which also have anti-inflammatory properties. The lipoxins are believed to function in promoting resolution by controlling the entry of neutrophils to sites of inflammation and the affected organs. They are also chemo-attractants for monocytes, i.e. cells that are required for wound healing. In effect, it appears that leukocytes are programmed to progress from pro- to anti-inflammatory responses, utilizing metabolites derived from both <i>omega</i> -6 and <i>omega</i> -3 fatty acids in the process. The possibilities for therapeutic intervention with such lipids to reduce the adverse effects of inflammation in various disease states are being actively explored.[30]
Hepolipoxins	Have pro-inflammatory properties in the skin, but anti-inflammatory in neutrophils. Most of the observed activities are associated with mobilization of calcium and potassium within cells or across membranes. In addition, hepoxilin A ₃ is now known to be an important regulator of mucosal inflammation in response to infection by bacterial pathogens.[31]

Conclusion

LTRAs are one of the first asthma drugs to be developed as an attempt to antagonize the effects of a specific inflammatory pathway. They not only provide a further therapeutic tool in which to control inflammation, bronchial hyper-responsiveness and symptoms, Rheumatoid arthritis and Collagen-induced arthritis it facilitate an orally active means by which to reduce the burden of disorders in both primary and secondary care settings.

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