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ACTIVITY OF LEUKOTRIENES IN INFLAMMATION

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ABSTRACT

Leukotrienes (LTs), both LTB4 and Cysteinyl LTs (CysLTs) LTC4, LTD4 and LTE4 are produce a wide variety of inflammation diseases. These are lipid mediators generated from Arachidonic acid via multistep enzymatic process through which Arachidonic is produced from membrane phospholipids through the action of phopholipase A2. LTB4 is known as a potent chemokinetic and chemotactic agent whereas CysLTs are potent contracting agents of smooth muscle in airways and blood vessels. Leukotrienes plat a major role in the pathogenesis of asthma and inflammatory disorder. The affinity of lipid bioeffectors are synthesized during the course of inflammatory reactions and their pharmacological modulation is able to significantly attenuate the clinical manifestations associated with different inflammatory disorder. Selective leukotriene (LTs) inhibitors and receptor antagonists are currently under evaluation in the treatment of various inflammatory diseases.

KEYWORDS: Leukotriene, CysLTs, Inflammation, LTB_4.

INTRODUCTION

Inflammation is the response of living tissue to damage. The inflammatory process is the reaction of blood vessel, which brings about an accumulation of fluid and white blood cell in the extravascular tissue. The acute inflammatory response has functions of destroying and eliminating the components of exudates.[1] The damaged tissue can be broken down and partially liquefied and the debris removed from the site of damage.[1] Leukotrienes (LTs) are a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of arachidonic acid enzyme arachidonate 5-lipoxygenase (5-LO).[2, 3] As their name implies, leukotrienes were first discovered in leukocytes, but have since been found in other immune cells.[3] Leukotriene used in lipid signaling to transmit information to either cell producing the or neighboring cell in order to regulate a immune response. LTs are divided into two classes, LTB_4 mainly by neutrophils and cysteinyl LTs (LTC_4, LTD_4 and LTE_4) mainly by macrophages.[4, 5] LTs exert biological effect by binding G-protein coupled receptor (GPCRs).[6] Leukotrienes are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury, notably asthma, rheumatoid arthritis, Psoriasis, inflammatory bowel disease, Chronic obstructive pulmonary disease, allergic rhinitis, atopic dermatitis, Obliterative broncholitis after lung transplantation and intestinal lung disease.[7,8] This review provides an overview of synthesis of leukotrienes (LTs) and discusses both current and future therapeutic potential.

Leukotriene

Leukotrienes (LTs), together with prostaglandins (PGs), thromboxanes and lipoxins, are the major constituents of a group of biologicallyactive oxygenated fatty acids known as eicosanoids18 and constituent family of lipid mediators with potent biological activities.[6, 9] Because myeloid cells contain substantial amounts of esterified arachidonic acid (AA) and constitutively express all of the enzymes necessary to hydrolyze it and metabolize it via the 5- lipoxygenase (5-LO) pathway, they are capable of generating large quantities of products termed leukotrienes (LTs) within seconds to minutes after encountering an activating stimulus.[10] LTs are not stored but synthesized de novo in response to inflammatory stimuli.[11] The leukotrienes can be divided into two distinct classes, based upon their biological activity and chemical structures: a) the cysteinyl leukotrienes (Cys-LTs), namely leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4), containing different amino acid residues and b) the dihydroxy derivative leukotriene B_4 (LTB_4). Both classes arise from the oxidative metabolism of arachidonic acid (AA) through the action of the 5-lipoxygenase enzyme. Leukocytes are the major sources of leukotrienes (LTs). The name “leukotriene” is indeed referring to the cellular source as well as the conjugated triene that characterizes their structure.[12, 13]

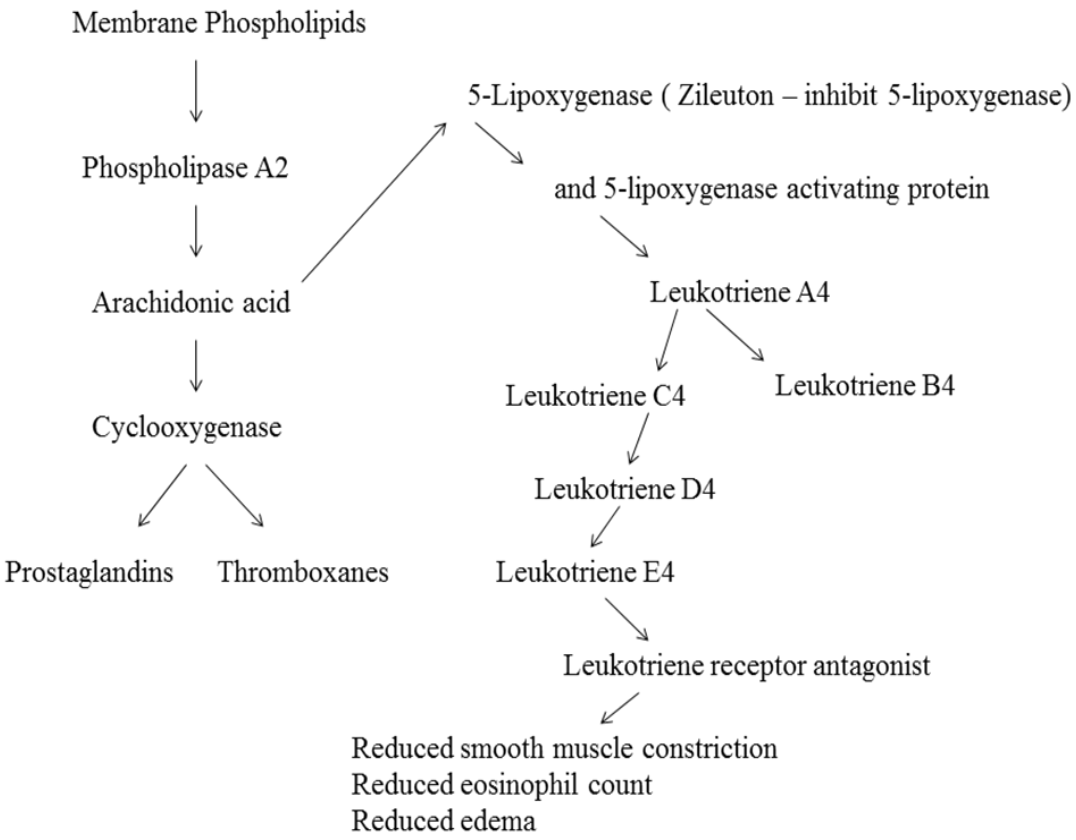

Figure: Leukotriene pathway.

Biosynthesis of leukotriene

1. Mobilization of Arachidonic acid

Arachidonic acid (AA) is a type of omega-6 fatty acid that is involved in inflammation. Arachidonic acid is a polyunsaturated fatty acid present in the phospholipids and the first step toward leukotriene generation is represented by the activation of specific phospholipases. Together with AA mobilization, 5-lipoxygenase (5-LO) activity requires cell activation and influx of extracellular calcium levels to produce leukotrienes.[14, 15, 16] The first step is biosynthesis of eicosanoidsis a receptor mediated influx of Ca2+ ions that causes translocation of a phospholipase enzyme, cytosolic phospholipase A_2, to the cell membran.[17] This enzyme then catalyzes the hydrolysis of the esterified form of arachidonic acid. Several phospholipase A_2 enzymes of varying molecular weight have been identified in cells such as macrophages, neutrophils, platelets, and mast cells, all of which are involved in eicosanoid biosynthesis.[18] The activity of phospholipase A_2 is increased by a phospholipaseA_2 activating protein that, when activated by cytokines suchas tumor necrosis factor and interleukin-1, can lead to arachidonicacid release and leukotriene formation in leukocytes.[19]

2. Role of 5-Lipooxygenase in the Formation of Leukotriene A_4

Synthesis of leukotriene from arachidonic acid by arachidonate 5-lipoxygenase. The catalytic mechanism involves the insertion of an oxygen moiety at a specific in the arachidonic acid backbone.[11] The lipoxygenase pathway is active in leukocyte and other including mast cell, neutrophils, eosinophils, monocytes and basophils. Which such cell are activated, Arachidonic acid is liberated from cell membrane phospholipids by phospholipase A_2 and donated by the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase (5-LO).[20, 21] 5-LO uses FLAP to convert Arachidonic acid (AA) into 5-hydroperoxyeicosatetraenoic (5-HPETE), which spontaneously reduces to 5-hydroxyeicosatetraenoic (5-HETE). The enzyme 5-liopxygenase (5-LO) acts again on 5-HETE to convert it into Leukotriene A_4 (LTA_4) which is unstable product.[20]

Biosynthesis of leukotriene B_4 (LTB_4) and the Cysteinyl leukotriene

The formation of LTA_4 is the last common step in the synthesis of LTB_4 on the one hand and cysteinyl Leukotrienes (LTC_4, LTD_4, and LTE_4) on the other.[12] LTB_4 is dihydroxy formed from LTA_4 through the action of LTA_4 hydrolase, a cytosolic protein.[22] Leukotriene B_4 can undergo further oxidation at the 20 carbon atom to less active metabolites.[9] The string of cysteinyl leukotrienes is inaugurated when LTC_4 synthase, a glutathione-S-transferase enzyme, converts LTA_4 to the glutathione-containing sulfidopeptide LTC_4. Leukotriene C_4 may then be converted to LTD_4 by glutamyltranspeptidase by removing glutamic acid from LTC_4 and LTD_4 may be subsequently metabolized to

LTE_4 by cysteinylglycine dipeptidase by removing of glycine from LTD_4.[13,23]

Leukotriene Receptor

The classification and nomenclature of leukotriene receptors (LTRs) have been proposed by an ad hoc committee appointed by the International Union Pharmacology (IUPHAR).[24] Leukotriene Receptors is activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid.[25] Leukotrienes act by binding to specific heptahelical receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells. Once ligated by the leukotriene, these receptors interact with G proteinsin the cytoplasm, thereby eliciting increases in intracellularcalcium and reductions in intracellular cyclic AMP. These proximal signals activate downstream kinase cascades in ways that alter various cellular activities, ranging from motility to transcriptional activation.[26, 27, 28]

Receptors for Leukotriene B_4

Two receptors for leukotriene B_4 (LTB_4) have been molecularly identified: BLT_1 and BLT_2. Both receptors are G protein-coupled seven transmembrane domain receptors, are member of the rhodopsin-like receptor superfamily,[29] whose genes are located in very close proximity to each other in the human and mouse genomes. The two receptors differ in their affinity and specificity for LTB_4: BLT_1 is a high-affinity receptor specific for LTB_4 (Kd 0.15-1 nM), whereas BLT_2 is a lowaffinity receptor for LTB_4 (Kd 23 nM) that also binds other eicosanoids. The two receptors also differ in their pattern of expression with BLT_1 being expressed primarily in leukocytes and on neutrophils therebyinduces their chemotaxis and adhesion in response to LTB_4,[30] whereas BLT_2 is expressed more ubiquitously. By mediating the activities of LTB_4, these receptors participate both in host immune responses and in the pathogenesis of inflammatory diseases. Reduced disease severity in animal inflammatory models seen with LTB_4 receptor antagonists and in mice with targeted deletion of BLT_1 have revealed important roles for LTB_4 and its receptors in regulating pathologic inflammation.[31]

Receptor of cysteinyl leukotriene

CysLTs mainly classified into two major subtypes: $CysLTs_1$ and $CysLTs_2$. Both are G-protein coupled receptor (GPCRs).[32] $CysLTs_1$ Contributes to mediating various allergic and hypersensitivity reactions in humans as well as models of the reactions in other animals.[33] The CYSLTR1 mRNA is expressed in lung smooth muscle, lung macrophages, monocytes, eosinophils, basophils, platelets, neutrophils, T cells, B lymphocytes, pluripotent hematopoietic stem cells (CD34+), pnacrease, mast cells, small intestine, interstitial cells of the nasal mucosa, prostate, airway smooth muscle cells, bronchial fibroblasts and vascular endothelial cells.[34, 35, 36] $CysLTs_2$ receptor is expressed on alveolar macrophages, cardiac purkinje cell, airwaysmooth muscle, adrenal medulla cell, peripheral blood leukocytes and brain cell.[35] $CysLT_2$, similar to $CysLT_1$, is a G-protein coupled receptor that links to and when bound to its CysLT ligands activates the Gq alpha subunit and/or Ga subunit of its coupled G-protein, depending on the cell type acting through these G proteins and their subunits, ligand-bound $CysLT_1$ activates a series of pathways that lead to cell function.[34, 37]

The order of affinities of the CysLTs in stimulating $CysLTR_1$ is LTD_4>LTC_4>LTE_4 LTB_4 and $CysLTR_2$ is LTD_4=LTC_4 LTE_4 LTB_4 respectively.[38] The potency of LTD_4 for the receptor is about 350 fold higher than that of LTC_4 and 200 fold higher than that of LTE_4. LTD_4 is about 10 fold more potent than LTC_4 in activating the receptor while LTE_4 is a weak agonist. The $CysLT_2$ receptor has been suggested to dampen $CysLT_1$ receptor activities.[39]

Leukotriene B4

LTB4 was introduced by Ford-Hutchinson and colleagues and LTB_4 produced from leukocytes in response to mediators of inflammation and is able to generate the adhesion and activation of leukocytes on the endothelium, allowing them to bind and cross it into the tissue.[40] In neutrophils, it is also a potent chemoattractant, and is able to generate the formation of reactive oxygen species and the release of lysosomal enzymes by these cells.[41, 42, 43]

At nanomolar concentrations, LTB_4 causes the release of substantial quantities of glucuronidase and lysozyme from neutrophils, although less effectively than the chemotactic fragment of the complement component C. Leukotriene B_4 induced enzyme secretion is mediated by LTB_4 recognition of a surface receptor of substantially lower affinity than that which mediates neutrophil aggregation, adherence to endothelium and chemotaxis. Microvascular microscopy showed rapid adhesion of leukocytes upon superfusion with LTB_4, followed by progressive diapedesis into extravascular tissues.[11] In addition to effects on leukocyte adhesion and migration, leukotriene B_4 ($LTB_{4)}$ stimulates the secretion of superoxide anion and release of different granular constituents from leukocytes. Adhesion and migration of leukocytes was accompanied by increased microvascular permeability that was totally leukocyte dependent.[44, 45]

In vitro, LTB_4 stimulates myelopoiesis, a phenomenon that maybe linked to the secretion of significant quantities of LTB_4 by human bone marrow cells.[11] LTB_4 and to a lesser extent other lipoxygenase products, is able to induce neutrophil aggregation and degranulation,[44] and it has been demonstrated that the secretion of azurophilic granules in human polymorphonuclear leukocytes is largely generated through an autocrine effect of LTB_4.[45]

Leukotriene C_4, D_4, and E_4

Controversy exists regarding the number and specificity of receptors for the sulfidopeptide leukotrienes and whether the pattern and specificity of the sulfidopeptide leukotriene receptors vary between animal and human models of inflammation.[46] Although highly selective receptors for LTC_4 have been identified in the lungs of rats and guinea pigs similar LTC_4-specific receptors have not been identified in human lung tissue. Instead, the demonstrated ability of LTC_4 to contract bronchial smooth muscle may be explained by its byconversion to LTD_4. In human lung parenchyma, LTD_4 interacts with highand low-affinity receptors of the rhodopsin-like superfamily. Selective LTD_4 receptor antagonists inhibit both LTC_4 and LTD_4 contractile activity in human lung tissue, suggesting that LTC_4 interacts with a common LTD_4 binding site. Because LTE_4 competes for the LTD_4 receptor, LTD_4 and LTE_4 probably interact with the same molecule on the cell surface.[47, 48]

Biological Consequences of Leukotriene B_4

Leukotriene B4 secretion by myeloid cells as well as by nonmyeloid cells caused by transcellular metabolism induces a range of cellular and molecular responses that coordinate and amplify the inflammatory response.[49] Although the chemotactic, chemokinetic and vasoactive properties of LTB_4 are perhaps the best elucidated, this molecule may also possess other biological activities, ranging from mediation of pain to modulation of diverse immune responses. LTB_4 is most potent neutrophil chemotactic agent produced by the Arachidonic acid cascade. They exert substantially stronger chemokinetic effect on human cell. Intratracheal instillation of LTB_4 induces the selective recruitment of functionally active neutrophils into bronchoalveolar lavage fluid in humans.[50,51] Subcutaneous injection of LTB_4 into humans causes neutrophils to accumulate rapidly in the affected tissue. Leukotriene B4-induced endothelial cell hyperadhesiveness for neutrophils depends on increased CD11/CD18 expression on the neutrophil surface and possibly a specific domain of the adhesion molecule CD54 found on endothelial cells.[52, 53] LTB_4 also depend on T-lymhocyte proliferation in response to mitogen through the stimulation of interlukin-2 secretion.[54] Leukotriene B_4 may be an important mediator of inflammatory pain. Injecting LTB_4 into a rat paw results in a prolonged, neutrophil-dependent hyperalgesic reaction,[55] which is associated with a sustained reduction in the nociceptive pressure threshold under these circumstances, LTB_4 appears to be roughly equipotent with bradykinin.[56]

Biological consequence of Leukotriene C_4, D_4, and E_4

The sulfidopeptide leukotrienes were first identified as the constituents of the slow-reacting substance of anaphylaxis. The sulfidopeptide leukotrienes play a complicated role within the inflammatory process, inducing vasoconstriction, increasing vasopermeability, enhancing mucous secretion and acting as immunomodulatory agents.[57] LTC_4 and LTD_4 are among the most potent bronchoconstricting agents. LTC_4 and LTD_4 may relaxed pulmonary arteries in guinea pig. LTE_4 is relatively less potent than LTC_4 and LTD_4 in this respect, but substantial hyper reactivity toward LTE_4 has been observed in asthmatic patients. In addition CysLTs are able to induce mucous secretion from human bronchial mucosa that may contribute to the obstruction of airway lumen in asthma.[9, 58] Leukotrienes C_4 and D_4 are potent mucous secretagoguesin human bronchial explants in vitro and in the trachea of dogs and cats in vivo. The sulfidopeptide leukotrienes are also intimately involved in changes within the vasculature.[59, 60] The increase in the permeability of the venular endothelium that allows proinflammatory cells to migrate to the site of inflammation is thought to be driven by the sulfidopeptide leukotrienes. The sulfidopeptide leukotrienes may also modulate the activity of several components of the immune system.[61, 62]

Leukotriene Release In Inflammation

Leukotrienes are potent lipid bioeffectors and their synthesis is tightly controlled in 5-lipoxygenase (5-LO) bearing cells. Since their structural characterization,[6] their biological activities suggested a potential involvement of both CysLTs and LTB_4 in inflammatory responses. Urinary excretion of LTE_4 has been widely used as an index of systemic production of CysLTs and increased urinary LTE_4 has been reported after antigen challenge of atopic asthmatics and either oral or inhaled aspirin challenge of aspirin-sensitive subjects.[63, 64] LTC_4 and LTD_4 have been detected in pulmonary lavages from children showing essential pulmonary hypertension.[65] Elevated levels of LTB_4 and sulfidopeptide leukotrienes have been recovered in the bronchoalveolar lavage fluid of patients with the adult respiratory distress syndrome (ARDS).[66] Thus, release of LTB_4 may promote the influx of large numbers of neutrophils into the airways and sulfidopeptide leukotrienes may be important mediators of the hypoxemia, permeability pulmonary edema, and reduced pulmonary compliance observed in patients with ARDS.[65] Much less information is available concerning the involvement of LTB_4 in inflammatory reactions. LTB_4 is generated and released in vitro from colonic mucosa obtained from patients with ulcerative colitis or Crohn's disease and in vivo.[65]

LTB_4 has also been found to be present in high concentrations in psoriatic scales. An important inflammatory feature of psoriasis is neutrophil infiltration of the epidermal skin lesions. Higher levels ofLTB_4 are found in both acute and chronic psoriatic skin lesions than in normal skin.[67]

Elevated levels of LTB_4 and sulfidopeptide leukotrienes are found in the bronchoalveolar lavage fluid,[11] sputum and urine 80 of patients with cystic fibrosis disease. Thus, LTB_4 may be important in mediating the neutrophil infiltration of the airways observed in cystic fibrotic patients.[68]

Patients with allergic rhinitis experience both early and late phase periods of mucosal inflammation after nasal instillation of a specific allergen such as ragweed pollen; LTC_4 is recovered in their nasal lavage fluids during both the early and late phases of inflammation after allergen challenge.[69] LTB_4 release promoting leukocyte infiltration and degranulation in the glomeruli, which are characteristic features of glomerular immune injury. High basal synthesis of LTB_4 by isolated glomeruli has been observed in rats with cationic bovine gamma globulin induced glomerulonephritis.[70] The renal plasma flow and glomerular filtrate rates decrease and the number of glomerular neutrophils increases after the in vivo intrarenal infusion of LTB_4 in rats with nephrotoxic serum induced glomerulonephritis.[71] Sulfidopeptide leukotrienes may reduce the glomerular filtration rate in glomerular immune injury by stimulating contraction of mesangial smooth muscle cells. Urinary LTE_4 levels directly correlate with disease activity in patients with and with a marked increase in LTE_4 levels observed during periods of active disease.[72]

The blood and synovial fluids of patients with rheumatoid arthritis contain higher levels of LTB_4 than those of normal persons. Synovial fluid levels of LTB_4 and sulfidopeptide leukotrienes are substantially higher in patients with rheumatoid arthritis than in patients with osteoarthritis; Synovial fluid levels of leukocytes, immune complexes and rheumatoid factor directly correlate with LTB_4 levels in patients with rheumatoid arthritis.[73] In inflamed joints, infiltrating neutrophils are the probable source of LTB_4 because the synovial lining cells from patients with rheumatoid arthritis generate little LTB_4.[72]

Role of Leukotriene in Diseases[74,75]

Allergic diseases: Asthma, Allergic rhinitis, Rhino sinusitis, Atopic dermatitis, Urticaria, Allergic fungal sinusitis.

Fibrotic diseases: Airway remodeling in asthma, Bronchiolitis obliterans after lung transplantation, Idiopathic pulmonary fibrosis, Scleroderma, Asbestosis.

Other pulmonary syndromes: Acute lung injury or adult respiratory distress syndrome, Viral bronchiolitis, Obstructive sleep apnea, Chronic obstructive pulmonary disease, Cystic fibrosis and other forms of bronchiectasis, Bronchopulmonary dysplasia.

Other local inflammatory diseases: Arthritis (including osteoarthritis and gout), Glomerulonephritis, Interstitial cystitis, Psoriasis, Inflammatory bowel disease.

Systemic inflammatory diseases: Rheumatoid arthritis, Vasculitides (systemic lupus erythematosus, Churg–Strauss syndrome, Henoch–Schonlein purpura), Transplant rejection.

Cancer: Solid tumors (including melanoma, mesothelioma and pancreatic, lung, esophageal, prostate and colon cancers), Leukemias, Lymphomas, etc.

Cardiovascular disease: Atherosclerosis, Aortic aneurysm, Sickle cell crisis, Ischemia–reperfusion injury, Pulmonary arterial hypertension, Sepsis.

Use of Leukotriene Inhibitors and Antagonists in Inflammatory Diseases

Mainly two modes of action are available for inhibition of leukotriene effects: 1) inhibition of synthesis; and 2) antagonism of leukotriene receptors. Many different approaches are available for inhibiting leukotriene synthesis, including antagonism of FLAP, iron chelation, redox-activity, and inhibition of 5-LO active site. Inhibitors of 5-LO have the added advantage of also preventing the synthesis of LTB_4 in addition to that of cysteinyl leukotrienes. Antagonism of leukotriene receptors is mainly achieved by using specific cysteinyl leukotriene receptor antagonists and blocking the actions of cysteinyl leukotrienes.[76]

Leukotriene Synthesis Inhibitors

One design hypothesis was to devise a pharmacophore that would bind the Fe^{+3} atom in the active site of 5-LO and thus block oxidative catalysis. Corey and coworkers first reported hydroxamate containing lipophilic compounds which effectively inhibited 5-LO in vitro. Zileuton became the first 5-LO inhibitor to demonstrate anti-LT activity in man and efficacy in the treatment of asthmatics.[77, 78] Inhibitors of 5-lipoxygenase reactions can act through a number of mechanisms, which include trapping of radical intermediates, chelation or reduction of iron, reversible binding at an active or a regulatory site, as well as combinations of these mechanisms.[76] Direct inhibition of 5-LO, partly through an iron-catalysed redox mechanism, has been achieved with compounds such as benzofurans (L-670,630 and L-650,224), hydroxamates (BWA4C), N-hydroxyurea derivatives (A-64077 or zileuton) and indazolinones (ICI 207,968), with good selectivity and potency. Zileuton had similar in vitro potency and selectivity to acetohydroxamates and inhibited leukotriene synthesis *ex vivo*.[79] Zileuton inhibit airway microvascular leakage and bronchoconstriction induced by inhaled allergen in the sensitized guinea pig model, in addition to inhibiting leucocyte accumulation. A new series of non redox 5-lipoxygenase inhibitors, devoid of iron-chelating properties, the methoxyalkylthiazoles, such as ICI D2138, are most potent and selective inhibitors of 5-lipoxygenase.[76]

FLAP Inhibitors

Inhibitors of FLAP such as MK-886 and MK-591 which is a structural analogue of MK-886, have no direct activity on 5-LO but antagonizes FLAP thus preventing the translocation of the enzyme to the membrane.[80] MK886 is ahighly selective compound with no effects of prostaglandin synthesis. MK886 inhibits antigen induced

bronchoconstriction in Ascaris-sensitive squirrel monkeys. MK-591 inhibits LTB_4 synthesis ex-vivo by up to 90% and urinary LTE4 by >80% at 24 hour. Although FLAP antagonists REV5091 and WY50295 were shown to be active in vitro and in animals, they were inactive in inhibiting leukotriene synthesis in volunteers. BAY-X-1005 inhibits anti-immunoglobulin E (IgE) challenge in human airways in vitro.[76]

Estimation of the potency of 5-LO inhibitors and FLAP antagonists has been based on inhibition of ex vivo LTB4 production from whole blood leukocytes. Following administration of therapeuticdoses, zileuton, BAY x1005 and MK886 each produced approximately 90% inhibition of ex vivo LTB_4 production. Basedupon the clinical activity of these agents, this degree of LT inhibition appears sufficient for meaningful efficacy.[80, 81]

Leukotriene Receptor Antagonists

There are two classes of receptors for leukotrienes, those for the dihydroxy-leukotrienes, LTB_4, termed BLT receptors, and those for cysteinyl leukotrienes, CysLT receptors. Although few synthetic agonists for CysLT receptors now exist, many antagonists have been produced. Two broad subgroups of Cys LT-receptors have been recognized, those blocked by known antagonists ($CysLT_1$- receptors) and those that are resistant to blockade ($CysLT_2$- receptors). One recent antagonist appears to have activity both for $CysLT_1$-receptors and $CysLT_2$-receptors.[75] In human airway smooth muscle, LTC_4, LTD_4 and LTE_4 all activate a $CysLT_1$-receptor, although a subclass of $CysLT_1$-receptor may be activated specifically by LTE_4 alone. In human pulmonary vasculature, a $CysLT_2$-receptor has been identified. $CysLT_1$-receptor is likely to be G-protein coupled, leading to calcium mobilization on activation.[76, 81]

Early compounds in the development of receptor antagonists were relatively weak in activity. The first leukotriene receptor antagonist of the hydroxyacetophenone class described was FPL-55712, which exhibited poor bioavailability and a short half-life. Other compounds within the same class, e.g. LY 171883 (tomelukast), L-649,923, and YM-16638, were synthesized, but did not possess sufficient potency to act effectively as an LTD4 receptor antagonist. In addition to having no effect on allergen induced responses, L-649,923 was poorly-tolerated, with a high incidence of gastrointestinal effects.[76, 80] The newer generation of leukotriene antagonists, such as ICI 204,219 (or Accollate), the quinolones MK-571 and RG-12,525, ONO-1078 (pranlukast) and SK&F 104,353 are more promising. The efficacy and safety of potent leukotriene receptor antagonists against leukotriene-induced bronchoconstriction in normal and asthmatics has been shown in several studies. Although a great number of leukotriene $CysLT_1$ receptor antagonists have been developed, only three have reached the market, montelukast, pranlukast and zafirlukast. With regard to $CysLT_2$ antagonists, there are only early preclinical candidate substances and it is unknown if the $CysLT_2$ receptor is a relevant target for treatment of asthma.[76]

CONCLUSION

In conclusion the leukotrienes appear to fulfill the "major criteria as mediators of inflammation. The accumulating evidence that the secretion of leukotrienes may initiate a chain of biochemical events that amplify inflammatory responses possess a challenge for those attempting to devise appropriate pharmacologic interventions because the complex of reactions may have both pathologic and homeostatic consequences. The more specific our knowledge of the biochemical changes, the more likely it is that specific interventions producing more benefit than harm in reducing leukotriene-induced inflammation, vasodilation, and edema will be found.

The development of new leukotriene receptor antagonists or synthesis inhibitors possessing higher potencies and good safety profiles, as well as novel therapeutic approaches to different targets, such as the leukotriene C_4 synthase or nuclear transcription factors of corresponding enzymes, represent an important task that might help to provide a better understanding of the role of these lipids in physiology and pathology.

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