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Leukotrienes: Biosynthesis, Metabolism, and Pathophysiologic Significance

ERTAN MAYATEPEK AND GEORG F. HOFFMANN

Department of General Pediatrics, University Children's Hospital, Heidelberg, Germany

Leukotrienes (LT) comprise a group of biologically highly potent lipid mediators synthesized by 5-lipoxygenase from 20-carbon polyunsaturated fatty acids, predominantly arachidonate (1–3). They include the cysteinyl LT, LTC_4, LTD_4, LTE_4, representing biologically active constituents of the long-known "slow-reacting substance of anaphylaxis" and the dihydroxyeicosatetraenoate, LTB_4. LT act at nanomolar concentrations in intercellular communication, signal transduction and on host defense. Extensive studies during the last years have demonstrated that LT are not only locally acting mediators but also systemically acting substances.

Recent progress in LT research has led to a more detailed understanding of their biosynthesis, degradation, and inactivation. Moreover, the pathogenetic role of LT in various human diseases has become recognized, and inhibitors of biosynthesis as well as receptor antagonists interfering with signal transduction were developed.

The aims of the review are *1*) to update the current knowledge of the synthesis, metabolism, and principal role of LT as mediators under physiologic and pathologic conditions; *2*) to give a brief overview about the development, state of the art, and limitations of analytical techniques; *3*) to discuss clinical conditions with particular emphasis on pediatric diseases in which LT are assumed to play a pathobiologic role; *4*) to illustrate how present knowledge has influenced current pathophysiologic concepts; and *5*) to briefly present future aspects of biochemical and clinical research on LT.

BIOSYNTHESIS, METABOLISM, AND INACTIVATION

Ca^{2+}-dependent activation of 5-lipoxygenase induces conversion of arachidonate via 5-HPETE (5*S*-hydroperoxy-6,8, 11,14-eicosatetraenoate) to the labile 5,6-epoxide LTA_4 (4) (Fig. 1).

By enzymatic action of LTA_4 hydrolase, LTB_4 (5*S*, 12*R*-dihydroxy-6,8,10,14-eicosatetraenoate) is formed (5). Alternatively, enzymatic conjugation of LTA_4 with glutathione at carbon 6 catalyzed by LTC_4 synthase results in the formation of LTC_4, the primary cysteinyl LT (6). Stepwise cleavage of glutamate and glycine from LTC_4 by γ-glutamyltransferase and dipeptidase followed by enzymatic action of N-acetyltransferase yields LTD_4, LTE_4, and N-acetyl-LTE_4, respectively (2). LTD_4 represents the biologically most potent cysteinyl LT.

LT are predominantly produced by macrophages, monocytes, neutrophils, eosinophils, mast cells, and basophils (7–9). Additionally, transcellular synthesis of LTB_4 and LTC_4 from the 5,6-epoxide LTA_4 occurs in endothelial cells, platelets, mast cells, lymphocytes, and erythrocytes (10–13). Table 1 summarizes the biologic effects and functions of the cysteinyl LT and LTB_4.

Enzyme-catalyzed chemical modification of the cysteinylglycine moiety of LTD_4 followed by stepwise ω-oxidation and β-oxidation of the degradation products of LTE_4 and LTB_4 result in complete inactivation (Fig. 1). LTC_4 and LTD_4 are rapidly metabolized in the blood circulation to LTE_4 with an half-life of 30 s up to 4 min (14–16). Therefore, the estimation of the biologically active LT in plasma is without real significance.

The liver represents the main organ for the uptake, metabolic inactivation, and biliary elimination of LT and their metabolites (17–20). However, renal uptake also contributes to the disappearance of cysteinyl LT from the circulation (17, 21–23). Changes in the urinary excretion of LTE_4 are assumed to reflect short-term changes in the rate of formation of LTC_4 (24).

Unlike the prostaglandins that are degraded from the carbon-1-carboxyl-group, LTE_4 and LTB_4 are further degraded from the ω-end by β-oxidation of their respective ω-carboxy-metabolites. ω-Oxidation of LTB_4 to ω-hydroxy-LTB_4, ω-aldehyde-LTB_4, and ω-carboxy-LTB_4 has been shown to occur in leukocytes and hepatocytes (25–27). Hepatocytes were also shown to β-oxidize ω-carboxy-LTB_4 to ω-carboxy-dinor-LTB_4 and ω-carboxy-tetranor-LTB_3 (26–28). Furthermore, the liver converts LTE_4 to the respective ω-hydroxy and ω-carboxy metabolites (29, 30). These substances are further degraded by β-oxidation yielding ω-carboxy-dinor-LTE_4 and ω-carboxy-tetranor-LTE_3 (31, 32) (Fig. 1). Measurement of urinary ω- and β-oxidation products of LTE_4 may reflect long-term changes in cysteinyl LT biosynthesis and metabolism (24).

Peroxisomes have been recently identified as the site of β-oxidation of the LT from the ω-end (33). Whereas the cysteinyl LT ω-carboxy-N-acetyl-LTE_4 has been found to be exclusively β-oxidized in peroxisomes, ω-carboxy-LTB_4 was degraded both in isolated peroxisomes and mitochondria. Further evidence for the essential role of peroxisomes in the

Correspondence: Dr. Ertan Mayatepek, University Children's Hospital, Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany.

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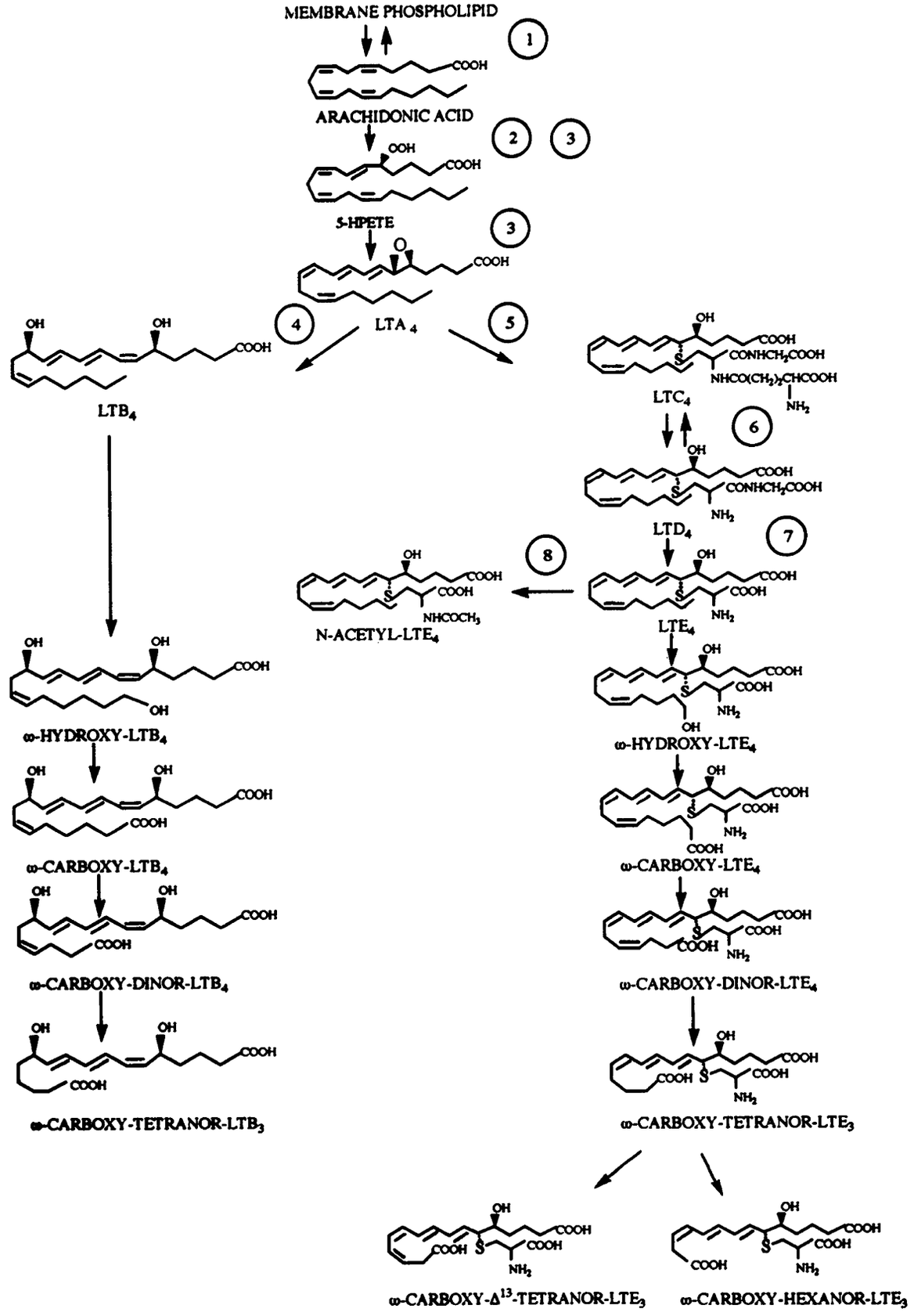

Figure 1. Metabolic pathway of LT biosynthesis and metabolism. The numbers refer to the enzymes most active in the pathways, as follows: *1*, phosholipases; *2*, 5-lipoxygenase-activating protein; *3*, 5-lipoxygenase; *4*, LTA_4 hydrolase; *5*, LTC_4 synthase; *6*, γ-glutamyl transpeptidase; *7*, γ-glutamyl dipeptidase; *8*, N-acetyltransferase.

Table 1. *Biologic effects of LT*

Cysteinyl LT	LTB_4
Vasoconstriction	Aggregation; chemokinesis
Increase of vascular permeability in postcapillary venules	Chemotaxis; release of lysosomal enzymes; stimulation of superoxide anion production
Bronchoconstriction	Adhesion and transendothelial migration of neutrophils
Stimulation of mucus secretion	Increase of vascular permeability (in the presence of PGE_2)
Intestinal contraction (ileum)	Enhancement of C3b receptor expression and complement-dependent cytotoxicity
Plasma extravasation	Modulation of lymphocyte function
Decrease of blood pressure	Affector of the production and action of cytokines
Reduction of myocardial contractility and coronary blood flow	Release of intracellular calcium
Decrease of renal blood flow and GFR	Increase of cAMP and cGMP synthesis
Proliferation of glomerular endothelial cells	
Release of LH-releasing hormone	
Stimulation of prostacyclin synthesis (endothelium)	

catabolism of LT has been obtained by studying endogenous LT excretion in the urine of patients with peroxisome deficiency disorders (34). In these patients the defect of peroxisomal LT degradation results in increased levels of LTE_4 and LTB_4. In addition, the concentrations of urinary ω-carboxy-LTE_4 and ω-carboxy-LTB_4, which are the immediate substrates for peroxisomal β-oxidation, are markedly increased.

ANALYTICAL METHODS FOR DETERMINATION IN BIOLOGIC FLUIDS

The low nanomolar and picomolar concentrations of these mediators in biologic fluids make analysis difficult. Additionally, LT have an extremely short half-life *in vivo*. LT are susceptible to oxidative degradation during sample preparation. They are easily artificially generated and released *in vitro* from blood leukocytes during blood sampling (22). Therefore, LT analysis in plasma is of little meaning and not a reliable way to evaluate the role of LT under pathologic conditions. The generation of LT, especially LTB_4, in isolated and stimulated white blood cells can be used to obtain information about the role of LT in various disease states (7, 35–37). Activation is carried out with different stimuli such as calcium ionophore A23187, zymosan, antigen, or aggregated immunoglobulins. This approach appears to be the most reliable *in vitro* method to estimate LTB_4 generation.

For the investigation of systemic cysteinyl LT production, species-characteristic index metabolites could be defined by tracer studies. After administration of radiolabeled LTC_4 to humans, [^{3}H]LTE_4 is the main urinary metabolite (32, 38, 39). In contrast, [^{3}H]LTB_4 is not detectable in urine after i.v. [^{3}H]LTB_4 infusion (40). In addition, i.v. administration of [^{3}H]LTE_4 leads to the detection of ω-and β-oxidation products that are excreted into bile and urine (31, 32, 38). In humans, urinary LTE_4 has been proposed as an index metabolite for the systemic generation of cysteinyl LT *in vivo* (36, 41–44). To get reliable information on the role of cysteinyl LT in pathologic states or after pharmacologic intervention, cysteinyl LT metabolites have to be analyzed in urine.

Quantitative determinations of LT can be performed by bioassays, HPLC, RIA or enzyme immunoassays, or gas chromatography-mass spectrometry. Extraction, purification, and separation of LT metabolites by HPLC serve as an initial analytical step (45). The use of immunoassays for LT measurements requires that identification be verified by HPLC or mass spectrometry. The method of choice for unequivocal identification is gas chromatography-mass spectrometry (46–48). Because no specific antibodies for ω- and β-oxidation products of LTE_4 are available, a recently described procedure for determination of ω-carboxy-LTE_4 in human urine using ^{18}O-labeled standards provides a promising technique (34).

PATHOPHYSIOLOGIC ROLE OF LT IN HUMAN DISEASES

In recent years, research on LT and their significance in human diseases focused on the determination of the different LT in biologic fluids and tissues. The amounts of these biologically highly active mediators were found to be sufficient to elicit pathophysiologic responses in humans and experimental animals in a variety of conditions. A selection of diseases in which increased or impaired LT synthesis or metabolism is implicated is presented in Table 2.

Lung diseases. In acute asthma, allergic rhinitis, and aspirin-sensitive and exercise-induced asthma, elevated concentrations of LT have been recovered from biologic fluids, including bronchoalveolar lavage, sputum, blood, and urine, spontaneously as well as after antigen challenge (43, 49–53) (Table 2). Clinical studies with LT receptor antagonists (see below) resulted in clinical improvement. Because LT are up to 1000 times more potent constrictors of bronchial smooth muscle than histamine and because of their capacity to stimulate mucus secretion, their mediator role in the pathogenesis of asthma is evident.

Sputum, lung lavage, or lung edema fluid obtained from patients with cystic fibrosis, adult respiratory distress syndrome, and neonatal hypoxemia with pulmonary hypertension contained elevated concentrations of cysteinyl LT (54–56). Recently, it was suggested that the aspiration of tracheal secretions can be used to monitor airway LT biosynthesis in patients with lung injury (57). Elevated airway LT levels may reflect airway epithelial damage but may not predict the development of adult respiratory distress syndrome (57). Recent studies also suggested an involvement of amniotic fluid surfactant in LT production (58) and demonstrated a stimulatory effect of arachidonic acid on surfactant phospholipid secretion in type II pneumocytes mediated at least in part by cysteinyl LT (59).

Cysteinyl LT appear to be important mediators of group B β-hemolytic streptococcus–induced pulmonary hypertension in newborn lambs (60). It has been shown that LT inhibition prevents and reverses hypoxic pulmonary vasoconstriction in newborn lambs (61). Therefore, specific LT synthesis inhibitors may be useful in the management of infants with persistent pulmonary hypertension. Severe bronchiolitis due to respiratory syncytial virus infection results from IgE-mediated hypersensitivity reactions to viral antigens with subsequent release

Table 2. *Elevated concentrations of leukotrienes in human diseases*

Disease	Source	LT*	Ref.
Lung diseases			
Asthma	Sputum, urine, leukocytes	LTC_4, LTD_4, LTE_4	43, 49–53
Cystic fibrosis	Sputum, urine, leukocytes	LTB_4, LTD_4, LTE_4	54, 131
Viral bronchiolitis	Nasopharyngeal secretion, urine	LTB_4, LTC_4, LTD_4, LTE_4	60, 61
Adult respiratory distress syndrome	Lung edema fluid, urine	LTB_4, LTD_4, LTE_4	56, 132
Neonatal hypoxemia with pulmonary hypertension	Lung lavage fluid	LTC_4, LTD_4	55
Allergic disorders			
Allergic rhinitis/conjunctivitis	Tears, nasal secretion, urine	LTC_4, LTD_4, LTE_4	43, 133
Connective tissue disorders			
(Juvenile) rheumatoid arthritis/spondyloarthritis	Synovial fluid, urine	LTB_4, LTE_4	78–80, 82
Lupus erythematosus/scleroderma	Urine	LTE_4	81
Gout	Synovial fluid	LTB_4	77
Lyme arthritis	Synovial fluid	LTB_4	35
Skin diseases			
Psoriasis	Epidermis, urine, skin chamber fluid	LTB_4, LTC_4, LTD_4, LTE_4	95–97
Urticaria	Skin chamber fluid, plasma	LTE_4	98
Kawasaki disease	Leukocytes	LTB_4	99
Gastrointestinal diseases			
Inflammatory bowel disease	Mucosa, dialysate	LTB_4	83–85, 87
Acute pancreatitis	Bile	LTE_4	134
Liver cirrhosis/hepatorenal syndrome/hepatitis/cholestasis	Urine	LTE_4, N-acetyl-LTE_4	44, 90–92
Hematogic diseases			
Chronic myeloid leukemia	Leukocytes	LTC_4	101
Sickle cell disease	Urine, plasma	LTB_4, LTC_4, LTD_4	103
Inherited metabolic diseases			
Peroxisome deficiency disorders	Urine	LTB_4, LTE_4, ω-carboxy-LTE_4/LTB_4	34
Mevalonate kinase deficiency	Urine	LTE_4	93
Glutathione synthetase deficiency	Urine, leukocytes	LTB_4, LTC_4 ($\Downarrow$), LTE_4 ($\Downarrow$)	37
Cystinosis	Leukocytes	LTC_4, LTB_4 ($\Downarrow$)	130
Nutritional diseases			
Kwashiorkor	Urine, whole blood	LTC_4, LTE_4, LTB_4 ($\Downarrow$)	36
CNS disorders			
Astrocytoma	Urine	LTE_4	121
MS	Cerebrospinal fluid, leukocytes	LTB_4, LTC_4	122, 123
Other clinical conditions			
Myocardial ischemia	Urine	LTE_4	42, 137
Chronic smoking	Leukocytes	LTB_4	138
Multiple trauma/severe burns	Urine, leukocytes	LTE_4, LTB_4 ($\Downarrow$)	131, 135, 136
Capillary leak syndrome	Urine	LTE_4	94
Cytokine therapy	Urine	LTE_4, N-acetyl-LTE_4	107, 108

* Concentrations of the LT listed were found to be elevated unless decreased concentrations are specifically indicated by ($\Downarrow$).

of LT leading to airway obstruction (62). The positive correlation between elevated LT levels and symptoms and the decrease in LT levels in parallel with clinical improvement after ribavirin treatment support an involvement of LT in the pathophysiology of acute viral bronchiolitis in infants (63).

Host defense. The high levels of LTB_4 measured in bronchoalveolar lavages and pulmonary tissues from nonimmune animals infected with live bacteria implicate LTB_4 as an important amplifier of the inflammatory response during acute pulmonary infections with mucoid *Pseudomonas aeruginosa* in unimmunized hosts (64). LTB_4 also exerts stimulatory effects on macrophage association and intracellular destruction, *e.g.* in *Trypanosoma cruzi* infection (65). In contrast, LT production by macrophages ingesting *Toxoplasma gondii* was found to be absent (69), possibly explaining the relative lack of a neutrophil inflammatory response in diseases due to obligate intracellular organisms. In general, LT formation in human leukocytes induced by various microorganisms under different conditions is probably important in host defense (66–68).

The nonimmune response to a single stimulus induces complement activation, phagocytosis, and LT generation. LT are generated by monocytes upon stimulation of their β-glucan receptor during phagocytosis (70). The release of LTB_4 by monocytes during nonimmune phagocytosis is believed to potentiate recruitment and margination of leukocytes onto the interior surface of blood vessels and to create a gradient for the entry of leukocytes into the tissue space (70). In the newborn polymorphonuclear leukocytes (PMNL), chemotaxis to LTB_4 *in vitro* is lower than in adults (71). This may protect the neonate against excessive inflammation as in bronchopulmonary dysplasia, but may also increase susceptibility to infection in the newborn.

ω-Oxidation of LTB_4 by PMNL is inhibited by pyocyanin, a phenazine derivative produced by *P. aeruginosa*, having im-

portant implications for PMNL chemotaxis *in vivo* (72). ω-Oxidation of LT was further shown to be inhibited by bifonazole (73), isoniazid (74), ethanol (75), or trifluoro-analogs of LT (76). Inhibition of ω-oxidation by these substances *in vivo* may thus be reflected in an altered pattern of LT metabolites.

Connective tissue disorders. Elevated levels of LTB_4 have been reported in synovial fluid from patients with acute flares of gout (77), spondyloarthritis (78–80), Lyme arthritis (35), and severe seropositive rheumatoid arthritis (78–80), relative to patients with degenerative or traumatic joint diseases. The concentrations of LTB_4 in synovial fluid in these disorders most likely contribute to the inflammatory reactions. Additionally, increased LTB_4 production by stimulated PMNL has been reported from patients with rheumatoid arthritis, while elevated urinary LTE_4 levels were found in patients with active systemic lupus erythematosus, scleroderma (81), and juvenile rheumatoid arthritis (82).

Gastrointestinal diseases. The concentration of LTB_4 was significantly elevated in inflamed mucosal extracts from patients with inflammatory bowel disease (IBD) (83–85). It was suggested that LTB_4 ω-hydroxylase activity plays an important role in the pathogenesis of IBD because the apparent V_{max} values of this enzyme in PMNL were significantly higher in patients with Crohn's disease and ulcerative colitis than in healthy control subjects (86). Furthermore, enhanced formation of cysteinyl LT was inhibited by 5-aminosalicylic acid (84), and increased generation of LTB_4 in rectal dialysis fluid from patients with ulcerative colitis could be reduced under treatment with a 5-lipoxygenase inhibitior (87). These results together with the effect of accelerated healing after application of a specific 5-lipoxygenase inhibitor in an animal model of IBD (88) should encourage further clinical trials of inhibiting LT synthesis in IBD. So far, elevated levels of cysteinyl LT have not been reported to occur in IBD. However, cysteinyl LT have been shown to mediate staphylococcal enterotoxin-induced enteric intoxication in the monkey (89).

In nonalcoholic liver cirrhosis, synthesis of LTB_4 by PMNL is altered in association with an impaired O_2^- production (90). In hepatorenal syndrome, renal clearance of LTE_4 is reduced, whereas excretion rate of LTE_4 is increased as result of an increased production of cysteinyl LT (44, 91). Urinary cysteinyl LT concentrations are only slightly enhanced in patients with hepatic diseases associated with primary renal failure (44). In humans, hepatobiliary elimination of cysteinyl LT predominates over renal excretion. However, extrahepatic cholestasis leads to a compensatory diversion of cysteinyl LT elimination to the kidney with subsequent increased excretion of endogenous LTE_4 into urine (92).

Capillary leak syndrome/kwashiorkor. Cysteinyl LT may induce increased vascular permeability by contracting endothelial cells (3, 7, 9), resulting in edema and hemoconcentration. High urinary LTE_4 levels were found in the edematous malnutrition syndrome kwashiorkor, suggesting that LT are involved in the pathophysiology of the syndrome, particularly in edema formation (36). During acute crisis conditions, patients with mevalonate kinase deficiency, a rare genetic defect of cholesterol biosynthesis, show features similar to those seen in capillary leak syndrome (93), a condition that is also associated with an increased urinary LTE_4 excretion (94). A positive linear relationship between increased urinary excretion of mevalonate and LTE_4 suggests that increased cysteinyl LT synthesis is involved in the pathogenesis of mevalonate kinase deficiency.

Skin diseases. LTB_4 was found to be elevated in psoriatic skin and implicated in neutrophil infiltration leading to the formation of microabscesses in psoriasis (95). LTC_4 and LTD_4 obtained from skin chambers applied to lesional skin in patients with psoriasis suggest that cysteinyl LT contribute to pathology by increasing blood flow (96). Furthermore, *in vivo* cysteinyl LT synthesis is enhanced in psoriatic patients as measured by increased urinary LTE_4 (97). The *in vitro* results of elevated LT levels obtained in patients with urticaria (98) and Kawasaki disease (99) still have to be confirmed by measuring their urinary LTE_4 excretion as an indicator of an increased cysteinyl LT generation *in vivo*.

Hematologic diseases. The possible role of LT in regulating the proliferation of hemopoietic cells has been the object of several studies (100). The proliferation of both normal and malignant hemopoietic cells is stimulated by exogenous LT. However, up to now there was no evidence that hemopoesis is modulated by LT generation and that the autocrine secretion of LT is important for the continuous proliferation of leukemic cells. Abnormal formation of lipoxygenase products has been observed in chronic myeloid leukemia (101). Inasmuch as neutrophil chemotaxis to LTB_4 is significantly impaired in patients with chronic granulocytic leukemia, specific defects in LTB_4-mediated responses may contribute to neutrophil dysfunction in this disease (102). Results of an altered LT metabolism in sickle cell disease (103) have to be verified with additional analytical techniques. *In vitro* studies demonstrated an increase in eosinophil LTC_4 generation in hypereosinophilic states (104). The significance of these findings with regard to the pathogenesis of hematologic disorders is still highly speculative.

Cytokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor, prime cells *in vitro* for an enhanced biosynthesis of LT (105, 106) and can lead to *in vivo* symptoms compatible with an increased generation of LT. Clinical studies established an enhanced endogenous LT production after exogenous granulocyte-macrophage colony-stimulating factor or IL-3 treatment (107, 108). Furthermore, infusion studies with tumor necrosis factor lead to an increased production of cysteinyl LT in humans (109).

CNS. Human brain tissue has the capacity to synthesize large amounts of cysteinyl LT (110). LT occur in a number of regions in the normal brain, including the median eminence and other parts of the hypothalamus (111–113). Cysteinyl LT are normal constituents of the cerebrospinal fluid (114). LTC_4 is concentrated in the choroid plexus by an active transport system (113). LT are viewed as potential messengers or modulators of central nervous activity and neuroendocrine events (110, 112, 115–117). Antibody reacting with bound LTC_4 suggests that LTC_4-immunoreactive nerve endings exist in mammalian brain (112). Additionally, LTB_4 may contribute to neuronal dysfunction during inflammatory diseases by affecting neuronal membrane currents (118).

LT increase blood-brain permeability and enhance the formation of vasogenic edema surrounding tumors (119). The *in vitro* formation of LTC_4 is stimulated by intracranial tumors (120). A pathophysiologic significance of cysteinyl LT is especially suggested in human astrocytomas. Their *in vivo* production, as measured by urinary LTE_4 excretion, correlates with the grade of malignancy and perifocal edema (121).

LTB_4 and LTC_4 levels in cerebrospinal fluid of patients with multiple sclerosis (MS) were significantly increased (122). Lipoxygenase products were implicated in the early encephalitic phase of MS. LTB_4 and LTC_4 stimulate the adherence of leukocytes in MS patients treated with high doses of prednisone, possibly reflecting alterations of membrane processes in MS leukocytes associated with calcium homeostasis and the arachidonic acid metabolic cascade (123). Finally, LT might participate in the cerebrovascular reactions in migraine (124, 125).

Renal disorders. LT have been implicated in the pathogenesis of renal disorders, including nephrotoxic serum nephritis in the rat, murine lupus nephritis, and hepatorenal syndrome in humans (126, 127). Studies on the normal and hydronephrotic kidney demonstrate a preferential preglomerular vasoconstriction under LTD_4 and LTE_4 causing a marked decrease in renal and glomerular blood flow, GFR, and filtration fraction (128). Furthermore, studies on the role of 5-lipoxygenase products in obstructive nephropathy indicated an increased synthesis of LT in the hemodynamic changes seen after unilateral release of bilateral urethral obstruction (129). It is uncertain whether plasma levels of LT are high enough to have direct effects on the kidney even under pathologic conditions (91). However, there is evidence that LT influence renal hemodynamics within the kidney inasmuch as synthesis of cysteinyl LT occurs in the kidney itself (23). It was shown that the isolated pig kidney can metabolize LTE_4 by an extensive oxidative metabolism via β-oxidation from the ω-end (23). The role of the kidney regarding synthesis, inactivation, and degradation of LT in man still has to be established.

Inherited metabolic diseases. The generation of LTC_4 in calcium ionophore–stimulated PMNL of untreated cystinotic children was significantly increased compared with that in controls (130). LTB_4 production, however, was found to be decreased. PMNL from cysteamine-treated cystinotic children generated lower amounts of LTC_4 that increased after removal of cysteamine. These findings indicate an abnormal synthesis of LTC_4 in PMNL in infantile cystinosis. Patients with peroxisome deficiency disorders such as the Zellweger syndrome show an impaired catabolism of LT and an altered pattern of urinary metabolites (34). Defective peroxisomal β-oxidation results in an unique pronounced urinary excretion of ω-carboxy-LTE_4, ω-carboxy-LTB_4, LTB_4, and massive decrease of urinary ω-carboxy-tetranor-LTE_3. In glutathione synthetase deficiency, an inborn error of glutathione biosynthesis leading to generalized intracellular glutathione deficiency, LTC_4 synthesis is significantly decreased in ionophore-stimulated neutrophils and monocytes, whereas LTB_4 synthesis is increased and other lipoxygenase products are not affected (37). Neutrophils and monocytes from those patients show a markedly reduced capacity to form $[^3H]LTC_4$ from $[^3H]LTA_4$. Inasmuch as urinary LTE_4 is found to be greatly decreased in this disorder, glutathione synthetase deficiency may serve as a model for the linkage between LT synthesis and glutathione metabolism *in vivo*.

PHARMACOLOGIC REGULATION OF THE GENERATION AND EFFECTS OF LT

The current understanding of the LT biosynthetic pathway and the importance of LT in the pathogenesis of human diseases have led to the development of LT antagonists and inhibitors. Initial pharmacologic strategies for inhibition of arachidonic acid metabolism involved use of corticosteroids that were believed to inhibit LT synthesis, *e.g.* in IBD (83), or dietary manipulation with n-3 fatty acids such as eicosapentenoic acid, which is highly enriched in fish oil (139–141). A preliminary study also suggests that endogenous LT production can be reduced effectively by high doses of vitamin E (142). The inhibition of 5-lipoxygenase by vitamin E *in vivo* is probably not entirely due to its antioxidant function and deserves further investigation. Today, potential strategies to block LT synthesis include inhibiting the release of arachidonic acid, preventing the conversion of arachidonic acid to LTA_4 via 5-lipoxygenase enzyme inhibitors, blocking the synthesis of LTB_4, LTC_4, and LTD_4, inhibiting the release of LTA_4, or blocking the uptake of LTA_4. In addition to inhibitors of LTA_4 hydrolase, antagonists of the receptor binding of LTB_4, and inhibitors of phospholipase A_2, LT antagonists of clinical relevance include inhibitors of 5-lipoxygenase and LTC_4 or LTD_4 receptor antagonists. Several 5-lipoxygenase inhibitors are currently undergoing phase II trials. These agents either block the biologic activity of 5-lipoxygenase or its activating protein. In this group, zileuton (compound A-64077) seems promising for clinical use in the form of an oral agent (143–145). Other promising agents acting as LT receptor antagonists include LY 171883 (146), ICI 204,219 (147), SK&F 104353 (148), and MK-571 (149). Clinical trials suggest that these agents are efficacious in the management of different forms of asthma.

FUTURE ASPECTS OF BIOCHEMICAL AND CLINICAL RESEARCH

In addition to clinical and pharmacologic trials that are needed to clarify the role of LT in human disease states, future aspects of research on LT will include the development of improved analytical methods ultimately allowing quantification of ω- and β-oxidation products of LTE_4 and LTB_4. Further studies will concentrate on the role of the human kidney in synthesis, metabolism, and degradation of LT; the relative importance of cell compartmentation (mitochondria *versus* peroxisomes) to degradation and inactivation; the interaction of antioxidants (*e.g.* vitamin E or glutathione) and 5-lipoxygenase; and the pathophysiologic significance of LT in the CNS. Of particular interest will be the pathobiologic role of LT in the neonate, especially with respect to chronic lung disease of prematurity, sepsis, complement activation, and persistent pulmonary hypertension.

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