Perspectives

The Biologically Active Leukotrienes

Biosynthesis, Metabolism, Receptors, Functions, and Pharmacology

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The biological activity of one major class of leukotrienes, originally described as slow reacting substance of anaphylaxis (SRS-A)[1] (1, 2) and now known to be composed of the sulfidopeptide leukotrienes, 5*S*-hydroxy-6*R*-*S*-glutathionyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid (leukotriene C_4, LTC_4), 5*S*-hydroxy-6*R*-*S*-cysteinylglycyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid (leukotriene D_4, LTD_4), and 5*S*-hydroxy-6*R*-*S*-cysteinyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid (leukotriene E_4, LTE_4) (3–7), has been known for over 40 years. The biological activity and structure of the second major class of leukotrienes, represented solely by 5*S*-12*R*-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid (leukotriene B_4, LTB_4), was recognized only 5 years ago (8–11). On the basis of the earlier definition of SRS-A in terms of chromatographic, functional, and chemical characteristics (12–15), it was possible to generate a similar material with radiolabeled constituents by ionophore activation of mouse mastocytoma cells and to achieve a chemical characterization of LTC_4 (3). The stereospecific synthesis of both LTC_4 (16) and LTB_4 (17) has now permitted the delineation of the common and separate enzymes in the pathways for biosynthesis of LTC_4 and LTB_4 from arachidonic acid (reviewed in 18), the identification of cellular mechanisms for inactivation of these products (19–23), the appreciation of structure-function relationships for agonist function (11, 24–26), the identification of receptor heterogeneity (27–30), and the demonstration of remarkably potent proinflammatory pharmacologic actions in animals and humans (11, 31–43).

This review will not consider the oxidative metabolism of arachidonic acid by the cyclooxygenase pathway to prostaglandins and thromboxane (reviewed in 44), the lipoxygenation of arachidonic acid by pathways that do not lead to biologically active leukotrienes (45, 46), or the putative biologic functions of the intermediates (47–51) in the 5-lipoxygenase pathway leading to the formation of LTB_4, LTC_4, LTD_4, and LTE_4. As each cell type responds to membrane perturbation, physiologic or pathobiologic, by elaborating a characteristic profile of oxidative products of arachidonic acid, the consequences of arachidonate release reside in the biochemical machinery of each cell type and in the receptor class of the surrounding target cells in the microenvironment.

Biosynthesis, metabolism, and catabolism. After an appropriate physiologic transmembrane signal or, under experimental circumstances, activation with a calcium ionophore, cellular phospholipases and lipases of distinct pathways cleave arachidonic acid from membrane phospholipids, which serve as substrates for a particular oxidative pathway (52, 53). Whereas the oxidative metabolism of arachidonic acid to cyclooxygenase pathway products via five or more terminal synthetases with differential cellular prominence is characteristic of most cell types, 5-lipoxygenation appears to be less widely distributed. Further, among the human cell types relevant to a host inflammatory response, the generation of leukotrienes, quantitatively and qualitatively, exhibits remarkable cellular specificity (Table I). Peripheral blood polymorphonuclear neutrophilic leukocytes (PMN) generate ~50 ng $LTB_4/10^6$ cells and only one-tenth as much LTC_4 in response to activation with calcium ionophore A23187, whereas the quantities and ratios are reversed with normal eosinophils (54). With eosinophils from patients with hypereosinophilic states, the preferential generation of LTC_4 relative to LTB_4 is even more dramatic, and the quantities of the LTC_4 per 10^6 eosinophils can reach 150 ng (54). Both pe-

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1. *Abbreviations used in this paper:* 5-HPETE, 5*S*-hydroperoxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid; LTA_4, 5,6-*trans*-oxido-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid; LTB_4, 5*S*-12*R*-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid; LTC_4, 5*S*-hydroxy-6*R*-*S*-glutathionyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid; LTD_4, 5*S*-hydroxy-6*R*-*S*-cysteinylglycyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid; LTE_4, 5*S*-hydroxy-6*R*-*S*-cysteinyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid; LTB_5, 5,12-dihydroxy-6,8,10,14,17-eicosapentaenoic acid; LTC_5, 5-hydroxy-6-*S*-glutathionyl-7,9-*trans*-11,14,17-*cis*-eicosapentaenoic acid; PMN, peripheral blood polymorphonuclear neutrophilic leukocytes; RP-HPLC, reverse phase-high performance liquid chromatography; SRS-A, slow reacting substance of anaphylaxis.

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Table I. Average Quantitative Generation of Leukotrienes from Human Cells

Cell type	Stimulus	LTB_4	LTC_4	Reference
		ng/10^6 cells	*ng/10^6 cells*	
Neutrophil	A23187	50	7	54
Eosinophil	A23187			
Normal donors		6	40	54
Hypereosinophilic donors		2	70	54
Monocyte	A23187	70	30	55
	Zymosan	10	2	
Macrophage	A23187	200	10	56, 57
(alveolar)	Zymosan	50	ND	57
	Opsonized zymosan	80	ND	57
Mast cell	IgE/antigen	<4	25	*

ND, not determined.
* S. P. Peters and L. M. Lichtenstein, personal communication.

ripheral blood monocytes in monolayers (55) and adherent or suspended alveolar macrophages (56, 57) respond to the ionophore with a substantial generation of LTB_4 and, for the former, of LTC_4; alveolar macrophages generate LTB_4 in amounts ranging from 100 to 400 ng/10^6 cells and in an average 20-fold excess, relative to LTC_4. Thus, depending upon the cell type in an inflammatory focus, the potential leukotriene production can be predominantly LTB_4, with implications for endothelial cell adherence and chemotaxis of additional cells (9, 10, 32), or LTC_4, with marked arteriolar constrictive and venular permeability-augmenting effects (7, 31, 32, 36, 43).

Implications about the role of a cell, which are drawn from profiles of products obtained with ionophore activation, must be tempered by the limited data available for cells in response to transmembrane physiologic stimuli. In the case of monocyte monolayers responding to unopsonized zymosan (55), the quantities of leukotriene products are reduced to one-third or less of those elaborated by the calcium ionophore. Similarly, murine bone marrow-derived mast cells, differentiated in vitro and presumed to be mucosal-type mast cells, elaborate 20–50 ng LTC_4 and 4–8 ng LTB_4/10^6 cells after IgE-dependent activation, or less than one-half of the leukotrienes obtained from the same cells activated with calcium ionophore (58–60). These murine mast cells generate almost no prostaglandin D_2, whereas that is the predominant product of oxidative metabolism of arachidonic acid by rat and human connective tissue mast cells activated by an immunologic mechanism (61).

The definitions of the various enzymes in the 5-lipoxygenase cascade (Fig. 1) are mainly based upon the knowledge of their respective substrates and products, and to a much lesser degree upon biochemical parameters. No mammalian enzyme in the 5-lipoxygenase pathway has been purified to homogeneity in a functional state. The 5-lipoxygenase converts arachidonic acid (5,8,11,14-eicosatetraenoic acid) to 5*S*-hydroperoxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid (5-HPETE) (62). 5-lipoxygenase is a calcium-dependent cytosolic enzyme in cell-free preparations from RBL-1 rat basophilic leukemia cells, guinea pig PMN, and human PMN (63–65), and in the RBL-1 preparations it is considered to manifest catalytic activity only as a calcium-dependent dimer (63). After extraction from guinea pig PMN, its preferential substrates are arachidonic acid and (5,8,11,14,17-*cis*)-eicosapentaenoic acid, which is preferentially present in fish fatty acid-enriched diets, but not such common fatty acids as linoleic (9,12-*cis*-octadecadienoic acid) and linolenic (9,12,15-*cis*-octadecatrienoic acid), which lack a 5,6-olefinic bond (64). The 5-lipoxygenase of human PMN has the same preferential substrate profile, with the Michaelis constant for arachidonic acid $\cong$ 12 μM and maximum velocity $\cong$ 0.5 nmol/min per 10^7 cells (65).

5-HPETE is converted by a dehydrase to 5,6-*trans*-oxido-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid, (leukotriene A_4, LTA_4) (66) or is hydrolyzed to its alcohol, 5*S*-hydroxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid. Nonenzymatic hydrolysis of LTA_4 generates the biologically inactive isomers of LTB_4, 5*S*,12*R*- and 5*S*,12*S*-dihydroxy-6,8,10-*trans*-14-*cis*-eicosatetraenoic acid (6-*trans*-LTB_4 diastereoisomers) along with small quantities of 5,6-dihydroxy-eicosatetraenoic acids (66). From LTA_4, an epoxide hydrolyase generates LTB_4, and a glutathione-*S*-transferase adducts glutathione to form LTC_4. The cytosolic epoxide hydrolase of the RBL-1, a cell that generates the biologically active leukotrienes, is biochemically uncharacterized (67). Rat liver has both cytosolic and microsomal epoxide hydrolases, which differ in antigenic determinants, pH optima, and substrate specificity (68, 69). One of these converts various *cis*-epoxides of arachidonic acid to diols (70) but has not been assessed for activity on *trans*-epoxides such as LTA_4. The LTA_4-glutathione-*S*-transferase of the RBL-1, which generates LTC_4, is associated with a 10,000 *g* particulate fraction after cell disruption (71). Rat liver cytosolic and microsomal glutathione-*S*-transferases have been shown to be both biochemically and antigenically distinct from each other, and the microsomal enzyme requires preincubation with *N*-ethylmaleimide to achieve maximal catalytic activity (72). Of the purified glutathione-*S*-transferases, only the E and μ-type cytosolic isoenzymes from rat and human liver, respectively, demonstrate the capacity to utilize a non-leukotriene epoxide substrate (72, 73) to form a glutathione adduct.

The biosynthetic events leading to the generation of LTC_4 and LTB_4 are generally entirely intracellular. An LTA_4 epoxide hydrolase has been demonstrated as an extracellular enzyme in blood plasma (74) but the physiological significance is undetermined and would depend upon the extracellular generation or release of LTA_4. In contrast, γ-glutamyl transpeptidases and dipeptidases, which convert LTC_4 to LTD_4 (75, 76) and LTE_4

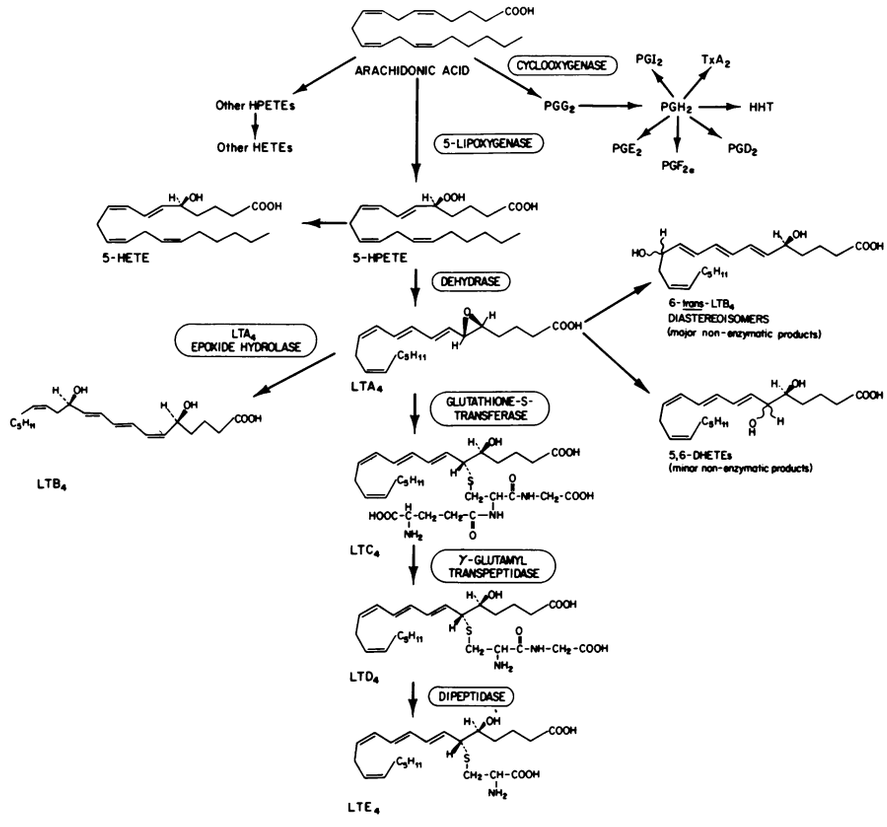

Figure 1. Biosynthetic pathways of leukotriene generation: enzymatic cascade for the oxidative metabolism of arachidonic acid. The enzymes of the 5-lipoxygenase pathway are specifically indicated. 5,6-DHETE, 5,6-dihydroxy-eicosatetraenoic acid; 5-HETE, 5*S*-hydroxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid; HHT, 12-hydroxy-heptadecatrienoic acid; PGD_2, PGE_2, $PGF_{2\alpha}$, PGG_2, PGH_2, PGI_2, prostaglandins D_2, E_2, $F_{2\alpha}$, G_2, H_2, I_2, respectively; TXA_2, thromboxane A_2.

(77–79), respectively, largely include enzymes associated with cell membranes (75), secreted cellular granules (78), and plasma (79).

The processing of LTC_4 to LTD_4 and LTE_4 by peptide cleavage represents bioconversion from one active mediator to another and not a catabolic inactivation process. The rapid inactivation of each of the sulfidopeptide leukotrienes by human PMN stimulated with phorbol myristate acetate occurs extracellularly by the interaction of released myeloperoxidase, generated H_2O_2, and chloride ion to form hypochlorous acid (HOCl) (20, 21). The latter compound generates a chlorosulfonium ion intermediate from each sulfidopeptide leukotriene, and subsequently, the biologically inactive 6-*trans*-LTB_4 diastereoisomers and the substrate-specific S-diastereoisomeric sulfoxides of LTC_4, LTD_4, and LTE_4 (Fig. 2). In view of the spasmogenic activity of the synthetic sulfones (80), these compounds have been sought but not found during the oxidative inactivation of the sulfidopeptide leukotrienes (21). The initial observations that eosinophils from hypereosinophilic donors spontaneously inactivated SRS-A, whereas peripheral blood neutrophils and monocytes from normal donors did not (81), is now explicable by the finding that such "activated" eosinophils spontaneously convert LTC_4 to the 6-*trans*-LTB_4 diastereoisomers and the *S*-diastereoisomeric LTC_4 sulfoxides through the generation of HOCl (54). The inactivation of SRS-A by eosinophil arylsulfatase B (82), and arylsulfatase A and B of other cell types (15, 83) is now attributed to their contamination with dipeptidases, which converted LTD_4 to the less spasmogenic LTE_4, as assessed on the guinea pig ileum. Whereas the catabolism of the sulfidopeptide leukotrienes by endogenously or experimentally activated neutrophils and eosinophils is extracellular and completely curtailed in the presence of a scavenger of HOCl, such as L-serine (20, 21, 54), the inactivation of LTB_4 is intracellular in neutrophils (19) and is not observed with eosinophils or peripheral blood monocytes in adherent monolayers (54, 55). The neutrophil-dependent intracellular inactivation of LTB_4 occurs by ω-oxidation (19) and is not augmented by activation with the calcium ionophore.

Receptors and secondary factors in the integrated response to leukotrienes. The evidence for cellular receptors for LTB_4 and for the sulfidopeptide leukotrienes is derived from studies of structure-function correlations and radioligand binding. For LTB_4, the specificity of its interaction with human PMN was first suggested by its 30- to 300-fold greater chemotactic potency as compared with naturally occurring isomers (10, 11), 12-epi-6-*trans*-8-*cis*-LTB_4, derived by sequential 5- and 12-lipoxygenation of arachidonic acid (84), and 5*S*,12*S*- and 5*S*,12*R*-6-*trans*-LTB_4. Saturation binding of [^{3}H]LTB_4 to human PMN has been presented as additional evidence for the existence of specific receptors (85, 86). In one study, the dissociation constant (K_d) for the ligand was 11–14 nM and the number of specific binding

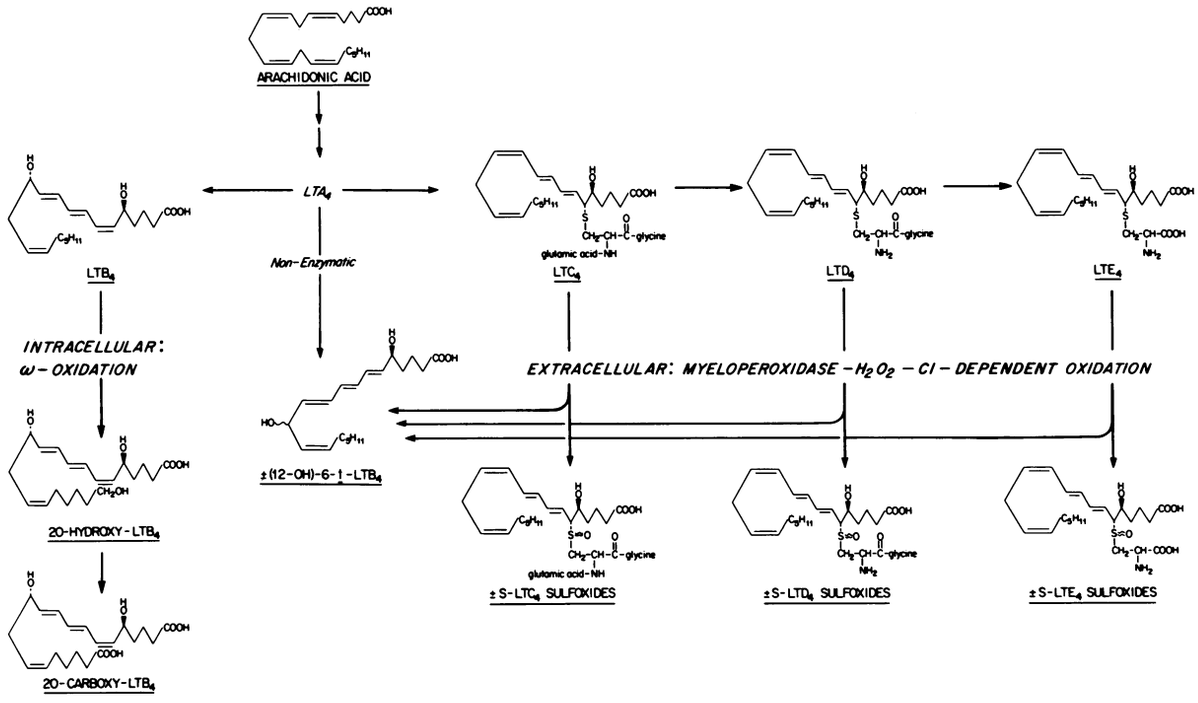

Figure 2. Oxidative metabolism of the leukotrienes by human PMN. Sequence for the further metabolism of the leukotriene products of the 5-lipoxygenase pathway.

sites per cell was 26,000–40,000 (85). In the other study, the K_d was 270 nM with 386,000 specific binding sites per cell and the binding at 4°C was irreversible (86). The criteria for a stereospecific receptor for LTB_4 on human PMN are not yet adequately delineated.

The structural determinants of LTC_4 and LTD_4 spasmogenic functions on nonvascular smooth muscle have been shown to exist in the presence of the hydrophobic omega region and in the spatial relationships of the polar region. Although the precise stereochemistry of the omega region is not essential for modest nonvascular smooth muscle contractile activity, as indicated by potencies of the 14,15-dihydro and 9,10,11,12,14,15-hexahydro analogues of both LTC_4 and LTD_4 (24), the region cannot be deleted. C-9, C-12, and C-14-apo-LTD_4, respectively lacking 9, 12, and 14 carbons, are completely inactive as spasmogens, indicating a possible binding function for the hydrophobic omega region (26) as a requisite for receptor activation by the stereochemically appropriate polar region. Stereochemical requirements for spasmogenic activity on the guinea pig ileum and guinea pig pulmonary parenchymal strip have been identified by use of synthetic chiral isomers at the three optically active centers in the natural sulfidopeptide leukotrienes: carbon 5 (C-5) of the eicosanoid backbone, which bears the hydroxyl; C-6, to which is conjugated the sulfidopeptide; and the asymmetric carbon of cysteine in the sulfidopeptide adduct. Diastereoisomers at C-5 and C-6 of LTD_4 and that at C-6 of LTC_4 each exhibit <0.5% of the nonvascular smooth muscle spasmogenic activity of the corresponding naturally occurring leukotriene (25, 26). Substitution of D-cysteine for L-cysteine in LTD_4 causes only a modest decrement in potency, and replacement of the glycine of LTD_4 by D- or L-alanine is relatively inconsequential in effect (25, 26). Thus, the rigorous relationships of function to the stereochemistry of the C-5 and C-6 polar adducts to the eicosanoid backbone are not expressed more distally in the sulfidopeptide chain, indicating that the critical spatial arrangements exist between the eicosanoid carboxyl and the polar adducts, as would be the case for true receptors.

Initial functional evidence for heterogeneity of sulfidopeptide leukotriene receptors is provided by the markedly different molar ratios of the concentrations of $LTC_4/LTD_4/LTE_4$ required for elicitation of identical biologic effects in different tissues (7, 87), by the biphasic dose-response isometric contraction of guinea pig lung parenchymal strips to LTD_4 but not LTC_4, and by the capacity of FPL55712 to competitively inhibit only the low-dose phase of the LTD_4-mediated contraction (31). The putative high affinity receptor mediating a LTD_4 response that is competitively inhibited by FPL55712 is tentatively designated LT-R_1, whereas the lesser affinity receptor, apparently responding to LTC_4 and high concentrations of LTD_4, has been designated LT-R_2. This interpretation is supported by the finding that a calcium channel blocker (diltiazem) inhibits the high-dose LTD_4 contraction presumably via LT-R_2 and allows FPL55712 to

give dose-related inhibition of a full LTD_4 dose-response via LT-R_1 (88).

Specific [^{3}H]LTC_4 binding at 4°C to cells of the DDT_1 MF-2 smooth muscle line, derived from Syrian hamster ductus deferens, was rapid, reversible at equilibrium upon addition of excess unlabeled homoligand, and demonstrated a single high affinity site with a K_d of 5 nM and a receptor density of 250,000 sites per cell (27). Whereas myotonically active structural analogues of LTC_4 competed effectively for binding of [^{3}H]LTC_4, an inactive analogue, lacking only the free amino group of the natural leukotriene, did not. The finding that the other natural biologically active sulfidopeptide leukotrienes, LTD_4 and LTE_4, did not compete within 2–3 logs of the homoligand, indicated that the LTC_4 receptor on this nonvascular smooth muscle cell line is specific for LTC_4 and is not a class receptor for the sulfidopeptide leukotrienes (27). [^{3}H]LTC_4 binding to a 15,000 *g* sediment of homogenized rat lung at 4°C has also demonstrated a specific LTC_4 receptor, with a K_d of 4 nM for LTC_4 and low affinity for LTD_4 and LTE_4 (28).

A radioligand binding study, which utilizes intact segments of guinea pig ileum smooth muscle, disrupted ileal smooth muscle cells, and subcellular fractions of these cells (enriched for mitochondrial membranes and for plasma membranes, respectively), has provided additional evidence for separate primary receptors for LTC_4 and LTD_4 (30) in a tissue known to respond to each natural sulfidopeptide leukotriene (7). Saturation binding of [^{3}H]LTC_4 at 4°C to each of the four preparations was rapid, reversible with excess unlabeled homoligand after reaching equilibrium, and revealed a single high affinity receptor site with an average K_d of 8 nM and low affinity for LTD_4 or LTE_4. Plasma membrane fractions of the disrupted guinea pig ileum smooth muscle also bound incremental inputs of [^{3}H]LTD_4, with specific binding approaching a plateau, indicative of saturable binding sites and a single receptor, with a K_d of 2.2 nM (30). Since the ratio of K_d values for LTC_4 to LTD_4 on guinea pig ileal membrane preparations of ~4:1 is comparable with the molar ratios affecting equal contractile responses on the intact tissue, it is likely that each agonist is regulating the response mainly via its unique receptor.

A full understanding of the integrated basis of a tissue response to the sulfidopeptide leukotrienes, even in vitro, requires consideration of at least three variables in addition to the plasma membrane distributions and nature of specific receptors. These include: the recruitment of intracellular stored receptors, the bioconversion of the initial agonist to another subclass, and the release of arachidonic acid from the responding tissue, so as to form local agonists or antagonists. The number of LTC_4 receptors on intact ileal segments or the plasma membrane fraction obtained from disrupted ileal cells represents no more than one-third of the total receptors recognized after subcellular fractionation, on the basis of specific [^{3}H]LTC_4 binding (30). Thus, as has been shown for certain prostaglandin receptors (89), the majority of LTC_4 receptors may reside in an intracellular pool and be recruited to the plasma membrane during activation.

The effect of ongoing bioconversion of [^{3}H]LTC_4 and [^{3}H]LTD_4 on the magnitude and time course of the contractile response of the guinea pig ileum to each has been determined by recording the pattern of the contraction and serially quantitating the initial agonist and its metabolic products by their retention times on reverse phase-high performance liquid chromatography (RP-HPLC) (90). LTC_4 and LTD_4 were each shown to have potent inherent spasmogenic activities, and the activity of LTC_4 was independent of its conversion to LTD_4. The spasmogenic response to LTD_4 was immediate, suggesting an adequate distribution of receptors to the plasma membrane. In contrast, there was a latent period of 1 min before any response was evident to LTC_4 (90), which could reflect the time required for recruitment of intracellular receptors to the plasma membrane or for a postreceptor biochemical event.

Pretreatment of guinea pig lung parenchymal strips with indomethacin (91) or acetylsalicylic acid (92) has been reported to attenuate their response to limited, but defined, concentrations of LTC_4 or LTD_4. However, a very detailed concentration-effect curve analysis of the contractile response of guinea pig pulmonary parenchymal strips to synthetic LTB_4, LTC_4, LTD_4, and LTE_4, in the presence and absence of different concentrations of indomethacin and the thromboxane synthetase inhibitor, clotrimazole, revealed cyclooxygenase products to mediate the LTB_4 effect, while being of minor importance to the contractions induced by the sulfidopeptide leukotrienes (93).

Pharmacologic actions. The sulfidopeptide leukotrienes LTC_4 and LTD_4 evoke preferential bronchospastic responses by peripheral airways vs. central airways after intravenous infusion in guinea pigs and after administration as aerosols to both guinea pigs and humans (31, 34, 40, 41, 94). It is not presently possible to ascribe the preference of a sulfidopeptide leukotriene for compromise of small as compared with large airways to a specific biologic effect on smooth muscle, microvasculature, and/or mucus-secreting cells (95, 96), and more than one target tissue may be involved.

It is particularly intriguing to speculate that the sulfidopeptide leukotrienes may be critical to the clinical problem of bronchial asthma, a condition marked by "hyperirritability" of the airways as defined by impaired pulmonary function in response to inhalation of pharmacologic agonists and irritants at concentrations that are inactive in normal individuals (97, 98). When asymptomatic asthmatic subjects with a demonstrated hyperreactivity to inhaled histamine received LTD_4 by aerosol, the average concentration evoking a 30% decrement in maximal midexpiratory airflow, measured at 30% of vital capacity ($\dot{V}_{30}$), was similar to that having a comparable action in normal subjects (41, 42). The molar potency of LTD_4 relative to histamine was 2 logs greater in asthmatic subjects and 3.5 logs greater in normal persons (41, 42). Because hyperresponsiveness to LTD_4 inhalation was not observed in the asthmatic subjects, LTD_4 may act at a site distinct from that of other agonists and irritants to compromise air flow, and may, in addition, effect the nonspecific airway hyperresponsiveness. In view of the recent delineation of at least two distinct sulfidopeptide leukotriene receptors (27, 28, 30), it is possible that one receptor accounts for the airway

"hyperirritability" and another for the direct leukotriene-mediated component of bronchoconstriction.

In addition to their actions on nonvascular smooth muscle, LTC_4 and LTD_4 effect arteriolar constriction. This action was originally observed by injecting guinea pigs intradermally with 10–100 pmol of LTC_4 and LTD_4 and infusing sufficient Coomassie Blue dye to pigment all areas of the skin except for those pretreated with the leukotrienes (31). Subsequently, direct visualization of blood flow in the hamster cheek pouch, using intravascular fluorescein, allowed photomicrographic documentation of the vasoconstrictor response to LTC_4 and LTD_4 after each had been separately applied topically to the buccal mucosa (32).

A separate vascular effect mediated by the sulfidopeptide leukotrienes, that of augmented vasopermeability in response to LTC_4, LTD_4, or LTE_4, was also observed in guinea pig skin (7, 31), hamster buccal mucosa (32), and human skin (43). Human subjects injected intradermally with 1 nmol of LTC_4, LTD_4, and LTE_4 developed a local wheal at each site, which lasted >2 h, and an erythematous flare persisting 6–8 h (43). The combined vascular effects of the sulfidopeptide leukotrienes have been recognized in rats subjected to a 5-min intravenous infusion of LTC_4. Increased total peripheral resistance, coronary resistance, and renovascular resistance occurred during the infusion as immediate and direct responses, and augmented venopermeability with depletion of plasma volume appeared as a subsequent response. The combined effects decreased cardiac output, renal blood flow, and glomerular filtration rate, long after the LTC_4 infusion had been completed (36).

The in vivo actions of LTB_4, after intradermal injection in the rhesus monkey (11) and humans (43), promote neutrophil infiltration of the local tissue sites as assessed by biopsies. In the human subjects, this response was also recognized by induration and tenderness at the site, most prominent 4–6 h after injection (43). That the movement of neutrophils into tissues in response to LTB_4 follows their margination was demonstrated by topical application of the agonist to the hamster cheek pouch (32). The mechanism of the LTB_4-stimulated neutrophil adherence to endothelial cell monolayers in vitro is a selective effect on the endothelial cells to increase their adherence capacity for neutrophils (99). This finding is consistent with the selective adherence of neutrophils in vivo to venules within the area of tissue injury (100).

Pharmacotherapeutic intervention. The rationale for seeking pharmacotherapeutic agents to limit leukotriene biosynthesis and/or end-organ effects is based upon the potent proinflammatory actions of these compounds in pharmacologic studies of normal humans, the demonstrated in vitro capacities of certain human cells and tissues to generate leukotrienes in response to selected agonists (Table I), the recovery and measurement of leukotrienes in complex biological fluids associated with certain disease states, and the knowledge that nonsteroidal antiinflammatory drugs have substantial efficacy, but modify only one of the two major routes of the oxidative metabolism of arachidonic acid (101). Sulfidopeptide leukotrienes, characterized only as SRS-A, were identified in the sputum of allergic asthmatics by bioassay (102), in the sputum of cystic fibrosis patients by bioassay after RP-HPLC (103), and in bronchial lavage fluids obtained from infants with primary pulmonary hypertension by retention time after resolution by RP-HPLC (104). LTB_4 was first tentatively identified in inflammatory synovial fluids of patients with rheumatoid arthritis by ultraviolet absorbance after RP-HPLC (105) and was later quantitated in rheumatoid and gouty synovial fluids by bioassay after RP-HPLC (106, 107).

Three approaches to pharmacotherapy have already been initiated: pharmacologic inhibition of specific synthetic enzymes, dietary provision of alternative substrates, and chemical receptor antagonists.

Inhibitors for several of the biosynthetic enzymes in the 5-lipoxygenase pathway (Fig. 1) have been synthesized and tested in both cell-free and cellular systems. Historically, the first recognized inhibitor of this cascade was diethylcarbamazine, which prevented the generation of SRS-A in rat peritoneal cavities prepared with hyperimmune serum and challenged with specific antigen (108, 109), and in monkey and human lung fragments activated by IgE-dependent mechanisms (110, 111). More recently, diethylcarbamazine was shown to act as an inhibitor of the conversion of 5-HPETE to LTA_4 by ionophore-activated murine mastocytoma cells (112) and by IgE-sensitized bone marrow-derived murine mast cells activated by specific antigens (113). The 5,8,11,14-tetraethylenic derivative of arachidonic acid and a variety of antioxidants (e.g., BW755c and nordihydroguaiaretic acid) have been shown to have inhibitory activities for the 5-lipoxygenase as well as other monolipoxygenases and cyclooxygenase, and are not specific (101). In contrast, 5,6-dehydro-arachidonic acid has been shown to be a specific inhibitor of cell-free 5-lipoxygenase prepared from RBL-1 cells (114, 115) and to prevent, in a dose-related manner, the antigen-induced generation of 5*S*-hydroxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid (5-HETE), LTC_4, and LTB_4 from murine bone marrow-derived mast cells under conditions that do not influence secretion of granule constituents (113). That secretion is not necessarily linked to 5-lipoxygenase pathway function, suggests that their apparent dependence in other studies (116) may have been due to the use of nonspecific inhibitors. The conversion of LTA_4 to LTC_4 by glutathione-*S*-transferase is inhibited by a prostacycline analogue, 6,9-deepoxy-6,9-phenylimino-$\Delta^{6,8}$-prostaglandin I_1 (U-60,257), in ionophore-activated rat mononuclear cells (117), and this effect is selective in murine bone marrow-derived mast cells activated by an IgE-dependent mechanism (113).

A second mechanism for exerting control over the 5-lipoxygenase pathway products is by providing alternative substrates in the membrane phospholipids, thereby yielding products with less total proinflammatory activity. Eicosapentaenoic acid, incorporated into membrane lipids of human platelets and rat synovial cells, is a poor substrate for the cyclooxygenase pathway and may, in addition, inhibit the generation of cyclooxygenase products from arachidonic acid (118, 119). Murine mastocytoma cells, grown in the peritoneal cavities of mice fed an eicosa-

pentaenoic acid-enriched diet and then stimulated in vitro with calcium ionophore, generated LTB_4 and LTB_5 (5,12-dihydroxy-6,8,10,14,17-eicosapentaenoic acid), in preference to LTC_4 and LTC_5 (5-hydroxy-6-*S*-glutathionyl-7,9-*trans*-11,14,17-*cis*-eicosapentaenoic acid) (120). The 5-lipoxygenase products generated by immune complexes in peritoneal cavities of rats fed an eicosapentaenoic acid (fish fatty acid)-enriched diet also preferentially included LTB_5/LTB_4 relative to LTC_5/LTC_4 (121). Additionally, although LTC_5 has comparable spasmogenic activity to LTC_4 in contracting the guinea pig ileum and pulmonary parenchymal strips (121), LTB_5 is one-tenth as potent and is a partial agonist relative to LTB_4 as a chemotactic or aggregating agent for human PMN (122).

A third approach involves antagonism of leukotrienes at the receptor level. The capacity of FPL55712 to inhibit antigen-induced anaphylaxis in monkeys (123) and to abrogate the cardiovascular and renal abnormalities resulting from intravenous administration of LTC_4 to rats (36) exemplifies this approach. The agent is generally active only at relatively high concentrations and presumably acts only at LT-R_1; it can thus be considered as a feasibility prototype for design of new compounds.

Concluding comments. The oxidative metabolism of arachidonic acid in response to cell perturbation, physiologic or pathobiologic, provides the microenvironment with a unique array of membrane-derived lipid mediators of remarkable potency. The only points of regulation that are well recognized at present relate to the selective biochemical machinery of each cell type and the distribution of class- and subclass-specific leukotriene receptors among and within target cells. It is likely, however, that another major control point will be recognized when receptor-specific stimuli are used to activate cells for leukotriene biosynthesis. For example, in adherent human monocytes, phagocytosis of unopsonized zymosan releases both LTC_4 and LTB_4, whereas comparable numbers of monocytes that are ingesting particles via an Fc-IgG receptor generate one-tenth the quantity of each leukotriene (55). Whether receptor-mediated regulation of oxidative metabolism of arachidonic acid relates to the distribution and action of membrane phospholipases and lipases or to presentation of phospholipid substrate(s) or both is not known. It is necessary to restudy each responding cell type, using discrete stimuli for transmembrane activation, rather than the nonspecific agonist, calcium ionophore A23187, and additionally to carry out simultaneous assessment of product bioconversion and catabolism. Additionally, the specificities of sulfidopeptide leukotriene receptors on vascular endothelium and smooth muscle, as well as nonvascular smooth muscle, need to be delineated since it seems logical that the blood vessels, rather than the circulating leukocytes, are the critical targets early in inflammation (99, 100). Further characterization of the class- and subclass-selective leukotriene receptors and their cellular and subcellular distribution (27, 30) should lead to clarification of the differences in functions mediated by each and to biochemical assessment of the mechanisms that mediate postreceptor functional responses. Finally, it will be crucial to develop new pharmacological agents, both to assess putative relationships between the 5-lipoxygenase pathway and cellular functions, such as secretion, and to provide clinical probes that may clarify the true roles of the leukotrienes in health and disease.

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