Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 7626–7630, December 1983
Immunology

Generation and metabolism of 5-lipoxygenase pathway leukotrienes by human eosinophils: Predominant production of leukotriene C_4

(neutrophils/oxidative metabolism/polymorphonuclear leukocytes/inflammatory mediators/arachidonic acid)

PETER F. WELLER*†, CHONG W. LEE†‡, DONALD W. FOSTER*†, E. J. COREY§, K. FRANK AUSTEN†‡, AND ROBERT A. LEWIS†‡

*Charles A. Dana Research Institute and Harvard–Thorndike Laboratory, Department of Medicine, Beth Israel Hospital, Boston, MA 02215; ‡Department of Rheumatology and Immunology, Brigham and Women's Hospital, Boston, MA 02115; †Department of Medicine, Harvard Medical School, Boston, MA 02115; and §Department of Chemistry, Harvard University, Cambridge, MA 02138

Contributed by K. Frank Austen, September 12, 1983

ABSTRACT **5-Lipoxygenase pathway-derived products of arachidonic acid released by human eosinophils activated *in vitro* have been measured by using radioimmunoassays specific for leukotriene B_4 (LTB_4) and for sulfidopeptide leukotrienes including leukotriene C_4 (LTC_4). Eosinophil-enriched leukocytes (mean, 85% eosinophils) from five hypereosinophilic donors activated with 5.0 μM ionophore A23187 for 15 min at 37°C in the presence of 50 mM L-serine released 69 ± 28 and 1.5 ± 0.8 (mean ± SEM) ng of LTC_4 and LTB_4, respectively, per 10^6 cells; ratios of LTC_4 to LTB_4 ranged from 16 to 149. Eosinophils stimulated with ionophore (2.5 μM) or phorbol myristate acetate (1 μg per ml) metabolized exogenously added LTC_4 to products that coeluted on reverse-phase high-performance liquid chromatography with synthetic S-diastereoisomeric LTC_4 sulfoxides and 6-*trans*-LTB_4 diastereoisomers, and this metabolic inactivation was inhibited by L-serine or catalase. Ionophore-activated eosinophils purified from three normal donors also preferentially generated LTC_4 (38 ± 3 ng per 10^6 cells) relative to LTB_4 (6.0 ± 3.1 ng per 10^6 cells), whereas neutrophils from the same donors released LTB_4 (48 ± 21 ng per 10^6 cells) in a >7-fold excess to LTC_4. The predominant production by human eosinophils of LTC_4 with its potent smooth muscle spasmogenic and vasoactive properties may contribute to the pathobiology of allergic and other diseases associated with eosinophilia.**

Human polymorphonuclear leukocytes, activated with diverse stimuli, oxidatively metabolize arachidonic acid by the 5-lipoxygenase-dependent pathway to 5,6-*trans*-oxido-7,9-*trans*-11,14-*cis*-icosatetraenoic acid (leukotriene A_4, LTA_4) (1), which in turn is converted enzymatically to (5*S*,6*R*)-5,6-dihydroxy-6,14-*cis*-8,10-*trans*-icosatetraenoic acid (leukotriene B_4, LTB_4) or to (5*S*,6*R*)-5-hydroxy-6-*S*-glutathionyl-7,9-*trans*-11,14-*cis*-icosatetraenoic acid (leukotriene C_4, LTC_4) (2–4). LTB_4 is a potent chemoattractant and aggregating stimulus for both neutrophilic and eosinophilic polymorphonuclear leukocytes (5, 6), and LTC_4 is exquisitely active as a spasmogenic and vasoactive substance when administered locally to human airways and skin, respectively (7, 8).

Human polymorphonuclear leukocytes, predominantly neutrophils, when stimulated with the calcium ionophore A23187 produce LTB_4 in marked preference to the sulfidopeptide leukotrienes, LTC_4 and its peptide cleavage products (5*S*,6*R*)-5-hydroxy-6-*S*-cysteinylglycyl-7,9-*trans*-11,14-*cis*-icosatetraenoic acid (leukotriene D_4, LTD_4) and (5*S*,6*R*)-5-hydroxy-6-*S*-cysteinyl-7,9-*trans*-11,14-*cis*-icosatetraenoic acid (leukotriene E_4, LTE_4) (2, 4, 9, 10). We now report that human eosinophils, stimulated with calcium ionophore A23187, produce LTC_4 as their predominant 5-lipoxygenase product, a finding with substantial implications for understanding the pathobiology of human disease states associated with tissue and blood eosinophilia.

MATERIALS AND METHODS

Materials. Hanks' balanced salt solution (HBSS) (Microbiological Associates); Ficoll/Hypaque, Percoll, and 6% dextran 70 (Macrodex) (Pharmacia); phorbol myristate acetate (PMA), catalase (thymol-free bovine liver, 11,000 units/mg), and L-serine (Sigma); calcium ionophore A23187 (Calbiochem); HPLC grade methanol (Burdick and Jackson Laboratories, Muskegon, MI); Aquasol scintillation fluid, [14,15-^{3}H]LTC_4 (40 Ci per mmol, 1 Ci = 3.7 × 10^{10} becquerels), and [14,15-^{3}H]LTB_4 (40 Ci per mmol) (New England Nuclear); and hydroxyethyl starch (Hetastarch 6% in 0.9% saline) (American Hospital Supply, McGraw Park, IL) were obtained as indicated. LTB_4, LTC_4, LTD_4, LTE_4, 6-*trans*-LTB_4 diastereoisomers, and the *S*-diastereoisomeric sulfoxides of LTC_4 were prepared as described (11–14).

Cell Purification. Human neutrophils were prepared from citrate-anticoagulated blood of normal volunteer donors by dextran sedimentation of erythrocytes, centrifugation on cushions of Ficoll/Hypaque, and hypotonic lysis of erythrocytes (15). Human eosinophils were obtained from the citrate-anticoagulated blood of five donors with eosinophilia associated with rheumatoid arthritis (78% eosinophils), mastocytosis (32%), bronchial asthma (40%), a cephalosporin drug reaction (46%), and an idiopathic hypereosinophilic syndrome (85%) by erythrocyte sedimentation. In order to purify eosinophils from donors with blood eosinophilia of <78% and to obtain both neutrophil-enriched and eosinophil-enriched leukocytes from normal donors, leukocytes obtained after sedimentation of erythrocytes in dextran or hydroxyethyl starch were centrifuged on gradients of isotonic Percoll (16) at 1,600 × *g* (average) at 10°C for 22 min in a fixed-angle SM-24 rotor on an RC-5B superspeed centrifuge with a slow-start mechanism (Sorvall).

Leukotriene Generation and Catabolism. Leukocytes (1–7 × 10^6) were preincubated in 1 ml of HBSS with or without L-serine (50 mM, pH 7.4) for 5 min at 37°C and stimulated with calcium ionophore A23187 for various durations. After incubations were terminated by quenching on ice, supernatants were collected by centrifugation at 8,000 × *g* for 1 min. Selected cell pellets and supernatants were assayed for eosinophil peroxidase

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: LTA_4, leukotriene A_4; LTB_4, leukotriene B_4; LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4; PMA, phorbol myristate acetate; RIA, radioimmunoassay; RP-HPLC, reverse-phase high-performance liquid chromatography.

activity at pH 6.0 in 0.1 M *N*-(2-acetamido)iminodiacetic acid buffer by using *p*-phenylenediamine as the hydrogen donor (17). LTB_4 and LTC_4 were measured in the supernatants at several dilutions by radioimmunoassays (RIAs). The LTB_4 RIA detects synthetic LTB_4 on the linear portion of the radioligand binding inhibition curve over dose ranges of 0.1–5.0 ng, with 50% inhibition of the radioligand binding—ID_{50}—occurring at 0.3 ng, and does not recognize 6-*trans*-LTB_4 diastereoisomers (9). The LTC_4 RIA, specific for sulfidopeptide-class leukotrienes, detects LTC_4, LTD_4, and LTE_4 over dose ranges of 0.1–5.0 ng with ID_{50}s at 1.4, 0.7, and 0.6 ng, respectively (18, 19). L-Serine had no effect on the RIAs.

For studies of catabolism, eosinophils (10^6 in 1 ml of HBSS) and neutrophils (10^7 in 1 ml) were incubated alone or with PMA (1 μg per ml) or calcium ionophore A23187 (2.5 μM), with and without L-serine (50 mM, pH 7.4) for 5 min at 37°C. Synthetic LTB_4 or LTC_4 (1–2 μg) mixed with 0.08–0.16 ng of [^{3}H]LTB_4 or 0.14–0.28 ng of [^{3}H]LTC_4 (10,000–20,000 ^{3}H cpm) were incubated with cell suspensions for 5, 15, or 60 min. The reactions were quenched on ice, and the supernatants were collected.

Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC). Aliquots (0.4–0.8 ml) of the supernatants from generation or catabolism experiments were analyzed by RP-HPLC with an isocratic solvent of methanol/water/acetic acid, 65:34.9:0.1 (vol/vol), pH 5.6, at a flow rate of 1 ml per min with a 10-μm C_{18} Ultrasphere ODS column (4.6 × 250 mm) and an Altex HPLC column (Rainin, Woburn, MA). Column eluates were continuously monitored for absorbance at 280 nm (model 100-40 spectrophotometer, Hitachi, Tokyo). Radioactivity was determined in 1.0-ml fractions. Synthetic LTB_4, LTC_4, LTD_4, and LTE_4 were eluted with average retention times of 20.8, 13.2, 20.8, and 26.3 min, respectively. Synthetic *S*-diastereoisomeric LTC_4 sulfoxides and 6-*trans*-LTB_4 diastereoisomers each were eluted as doublets with average retention times of 10.6 and 11.7 min and of 16.2 and 18.0 min, respectively (19, 20). Recovery of [^{3}H]LTC_4 and [^{3}H]LTB_4 from RP-HPLC averaged 86% and 85%, respectively.

RESULTS

Generation of Leukotrienes by Eosinophils. The extracellular release of LTC_4 and LTB_4 by ionophore-stimulated (0–20 μM) eosinophils (mean ± SEM, 85 ± 3%) from five hypereosinophilic donors was dose-related with maximal generation of both products occurring at 2.5–5 μM ionophore. In a representative experiment with eosinophils from the donor with 78% eosinophilia, maximum generation of LTC_4 with and without L-serine was 155 and 80 ng per 10^6 leukocytes and of LTB_4 with and without L-serine was 2.3 and 2.2 ng per 10^6 cells (Fig. 1). In a kinetic experiment with eosinophils from the same donor, LTC_4 generation was near maximal at 15 min with and without L-serine at values of 130 and 65 ng per 10^6 cells, whereas LTB_4 at 15 min was 1.4 and 0.9 ng per 10^6 cells with and without L-serine, respectively (Fig. 2). The preferential generation of LTC_4 relative to LTB_4 for each donor at 15 min in the presence of L-serine yielded LTC_4/LTB_4 ratios from 16 to 149 (Table 1).

The addition of L-serine to 5 μM ionophore-stimulated eosinophils from the five hypereosinophilic donors increased LTC_4 concentrations by 160–290% (mean ± SEM, 211 ± 40%) at 15 min. In contrast, LTB_4 concentrations were not altered, with means ± SEM of 1.7 ± 0.8 and 1.6 ± 0.8 ng per 10^6 cells with and without L-serine, respectively. The supernatants of eosinophils stimulated in the absence of L-serine (Fig. 3 *Left*) resolved a peak with the retention time of LTC_4 and a less polar doublet with the retention times of the 6-*trans*-LTB_4 diastereoisomers. In the presence of 50 mM L-serine (Fig. 3 *Right*), the LTC_4 peak increased in magnitude and the 6-*trans*-LTB_4 doublet was markedly diminished. The other sulfidopeptide

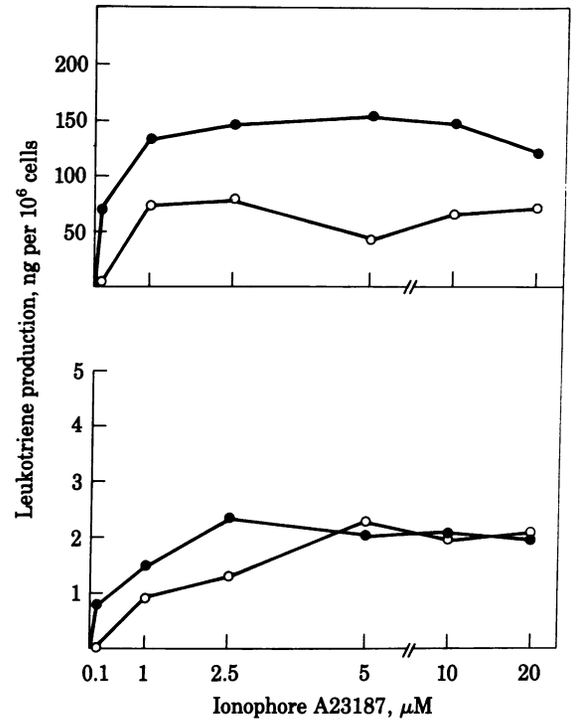

FIG. 1. LTC_4 (*Upper*) and LTB_4 (*Lower*) production (measured by RIAs) by 10^6 leukocytes (78% eosinophils) stimulated for 15 min with doses of calcium ionophore A23187 in the presence (●) or absence (○) of 50 mM L-serine.

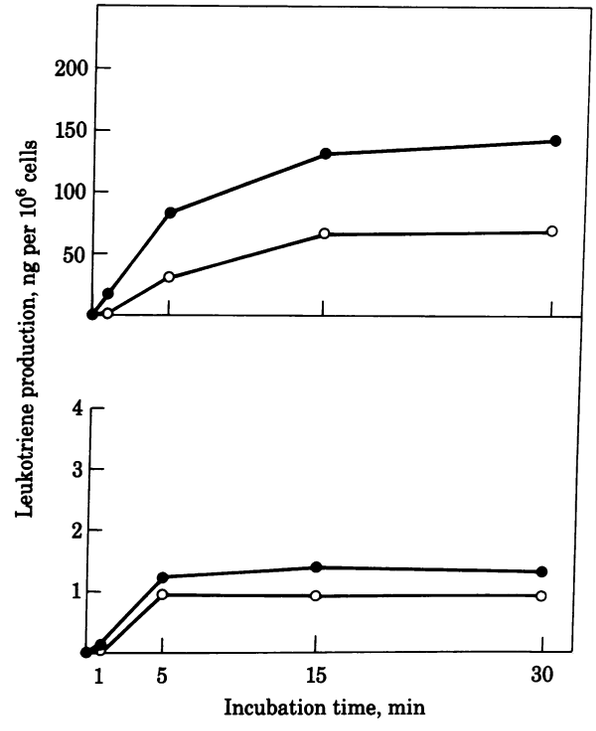

FIG. 2. Time course of production of LTC_4 (*Upper*) and LTB_4 (*Lower*) by 10^6 leukocytes (78% eosinophils) stimulated with 1 μM calcium ionophore A23187 in the presence (●) or absence (○) of 50 mM L-serine.

Table 1. Leukotriene production by eosinophil-enriched leukocytes from hypereosinophilic donors

	Donor					
	1	2	3	4	5	Mean ± SEM
Eosinophils, %	93	81	87	85	78	85 ± 3
Neutrophils, %	7	17	13	7	13	11 ± 5
LTC_4, ng/10^6 cells	9.8	104	6	70	155	69 ± 28
LTB_4, ng/10^6 cells	0.3	0.7	0.3	4.4	2.0	1.5 ± 0.8
LTC_4:LTB_4	33	149	20	16	77	59 ± 25

Eosinophil-enriched leukocytes (1–7 × 10^6 in 1 ml) were stimulated with 5 μM calcium ionophore A23187 for 15 min at 37°C in the presence of 50 mM L-serine; leukotriene production was measured by RIAs.

leukotriene-derived products that were eluted as doublets at 8 and 9 min and at 10 and 11 min were also less apparent in the presence of L-serine. The integrated area under the LTC_4 A_{280} peak increased 144% in the presence of L-serine, corresponding to the 160% increase in LTC_4 measured by RIA in the supernatant.

For 10^7 normal neutrophils (>97% purity) stimulated in 1 ml with an optimal dose of 1 μM ionophore, peak LTC_4 production occurred at 15 min in three experiments and was increased 76% to a mean ± SEM of 3.7 ± 0.6 ng per 10^6 cells in the presence of 50 mM L-serine. RP-HPLC analysis of the supernatants from the stimulated neutrophils confirmed the quantitative production of LTC_4 and the protective effect of L-serine. The major leukotriene products from neutrophils resolved by RP-HPLC were LTB_4, the 6-*trans*-LTB_4 diastereoisomers, and a polar peak with a retention time of 6 min, compatible with the ω-oxidation products of LTB_4. When neutrophil activation was reduced to 5 min to increase LTB_4 relative to the ω-oxidation products, LTB_4 release was 32.1 ± 11.1 ng per 10^6 cells (mean ± SEM, $n = 4$).

Eosinophil- and neutrophil-enriched cells, from the same three normal donors, when stimulated with ionophore in the presence of L-serine, yielded a predominance of LTC_4 from normal eosinophils and LTB_4 from normal neutrophils. Eosinophil-enriched leukocytes (mean, 87% eosinophils) elaborated an average of 38 ng of LTC_4 per 10^6 cells and 6 ng of LTB_4 per 10^6 cells, whereas the neutrophil-enriched preparations (mean, 96% neutrophils and 3% eosinophils) yielded 7.5 ng of LTC_4 per 10^6 cells and 48 ng of LTB_4 per 10^6 cells (Table 2).

Catabolism of Exogenous Leukotrienes. The catabolism of exogenous LTC_4 and [^{3}H]LTC_4 by 10^6 eosinophil-enriched leukocytes from two donors (87% and 78% eosinophils), activated for 15 min with PMA (1 μg per ml), which did not elicit measurable leukotriene production, or with calcium ionophore (2.5 μM), was analyzed by resolution of the products on RP-HPLC monitored at A_{280} and quantitated by assay of radiolabel. The LTC_4 metabolites were resolved by RP-HPLC into three products, which were eluted as three doublets with mean retention times of 7.2 and 7.6, 8.8 and 9.3, and 15.7 and 16.8 min, respectively, in response to either PMA or ionophore stimuli. In a representative experiment (Fig. 4) in which the response to PMA was analyzed at 15 min, 77% of the radioactivity was recovered: 11% from the front, 7% from the most polar doublet, 7% from the doublet coeluted with synthetic *S*-diastereoisomeric LTC_4 sulfoxides, 33% with LTC_4, and 17% with the doublet coeluted with synthetic diastereoisomeric 6-*trans*-LTB_4.

In the presence of L-serine, catabolism at 15 min of [^{3}H]LTC_4 into tritiated products corresponding to the three doublets was decreased an average of 89% and 94% in experiments with PMA and ionophore, respectively. The addition of 1,000 units of catalase completely prevented the formation of tritiated metabolites. Eosinophil peroxidase activity was present in the stimulated supernatants and ranged from 0.7% to 2% of total cellular peroxidase activity.

Catabolism of exogenous LTB_4 and [^{3}H]LTB_4 was assessed with 10^6 eosinophils, from the same two donors utilized above,

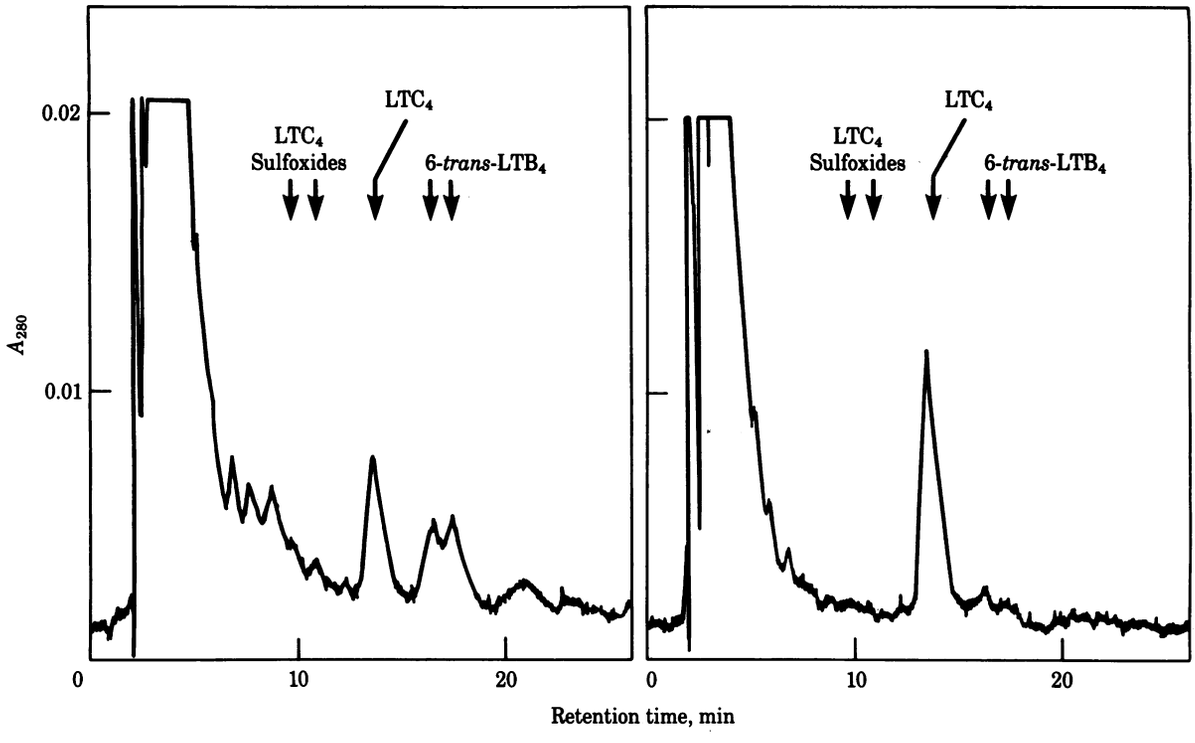

FIG. 3. RP-HPLC of supernatant from 10^6 leukocytes (81% eosinophils) stimulated with 5 μM calcium ionophore A23187 for 15 min in the absence (*Left*) or presence (*Right*) of 50 mM L-serine. Products were detected by absorbance at 280 nm. Retention times of synthetic *S*-diastereoisomeric LTC_4 sulfoxides, LTC_4, and diastereoisomeric 6-*trans*-LTB_4 are indicated.

Table 2. Leukotriene production by eosinophil- and neutrophil-enriched leukocytes from normal donors

	Donor			
	1	2	3	Mean ± SEM
Eosinophil-enriched leukocytes				
Eosinophils, %	88	88	85	87 ± 1
Neutrophils, %	12	12	15	13 ± 1
LTC_4, ng/10^6 cells	40	32	42	38 ± 3
LTB_4, ng/10^6 cells	0.5	6.1	11	6 ± 3
Neutrophil-enriched leukocytes				
Eosinophils, %	4	1	5	3 ± 1
Neutrophils, %	96	99	94	96 ± 1
LTC_4, ng/10^6 cells	4.4	3.2	15	7.5 ± 4
LTB_4, ng/10^6 cells	5.5	70	68	48 ± 21

Eosinophil- and neutrophil-enriched leukocytes (10^6 in 1 ml) from the same normal donors were stimulated with 5 μM calcium ionophore A23187 for 15 min in the presence of 50 mM L-serine. Leukotrienes were quantitated by RIAs.

stimulated with PMA (1 μg per ml) or ionophore (2.5 μM) for 15 and 60 min. RP-HPLC of the supernatants from the eosinophils showed no catabolism in that >99% of the recovered tritium radioactivity was eluted as a single peak coincident with the single LTB_4 A_{280} peak; 87% of the tritium applied was recovered. In contrast, incubation of LTB_4 with 10^7 neutrophils from one normal donor, with or without PMA activation, resulted in conversion at 15 min of one-third of the unlabeled and ^3H-labeled LTB_4 to a more polar peak that was eluted at 6 min.

DISCUSSION

Although the eosinophil and neutrophil are both polymorphonuclear leukocytes, stimulation of these two cell types with calcium ionophore A23187 causes them to preferentially elaborate different subclasses of leukotrienes from the 5-lipoxygenase pathway of arachidonic acid metabolism. With eosinophils derived from hypereosinophilic donors and enriched to a mean of 85% purity, 2.5–5 μM ionophore elicited maximal detected release of both LTC_4 and LTB_4 by these cells at 15 min. The inclusion of 50 mM L-serine during cell stimulation increased recoveries of immunoreactive LTC_4 in the supernatant fluids by a mean of 211% and had no significant effect on the concentrations of immunoreactive LTB_4. Eosinophils from hypereosinophilic donors released a mean of 69 ng of LTC_4 per 10^6 cells but only a mean of 1.5 ng of LTB_4 per 10^6 cells (in the presence of 11% neutrophils) (Table 1). Although the range of LTC_4 production for the five donors was 25-fold, for each there was an excess of LTC_4 to LTB_4, with the lowest ratio being 16. RP-HPLC of the supernatants confirmed the results of the RIAs (Fig. 3) in documenting a marked preponderance of LTC_4 relative to LTB_4. The preferential generation of LTC_4 to LTB_4 found with hypereosinophilic donor-derived eosinophils was not solely a consequence of the "activated" state manifested by these cells (21) but was also observed with eosinophils from normal donors (Table 2).

A role for L-serine in protecting sulfidopeptide leukotrienes from oxidative metabolism is consistent with the findings with activated neutrophils that a myeloperoxidase-dependent reaction, involving H_2O_2 and chloride ion, generated hypochlorous acid, which interacted with the sulfur moiety of LTC_4 to generate three products: an unidentified, nonsulfone polar metabolite that was eluted with retention times of 7.4 and 8.4 min; the *S*-diastereoisomeric LTC_4 sulfoxides that were eluted at 10.6 and 11.7 min; and the 6-*trans*-LTB_4 diastereoisomers that were eluted at 16.2 and 18.0 min (19, 20). The metabolites resolved from endogenously generated LTC_4 by eosinophils were similar (Fig. 3 *Left*), and the increased immunoreactive LTC_4 in cell supernatants stimulated in the presence of L-serine, a scavenger of hypochlorous ions (22), was shown by RP-HPLC analysis (Fig. 3 *Right*) to be a consequence of the inhibition of me-

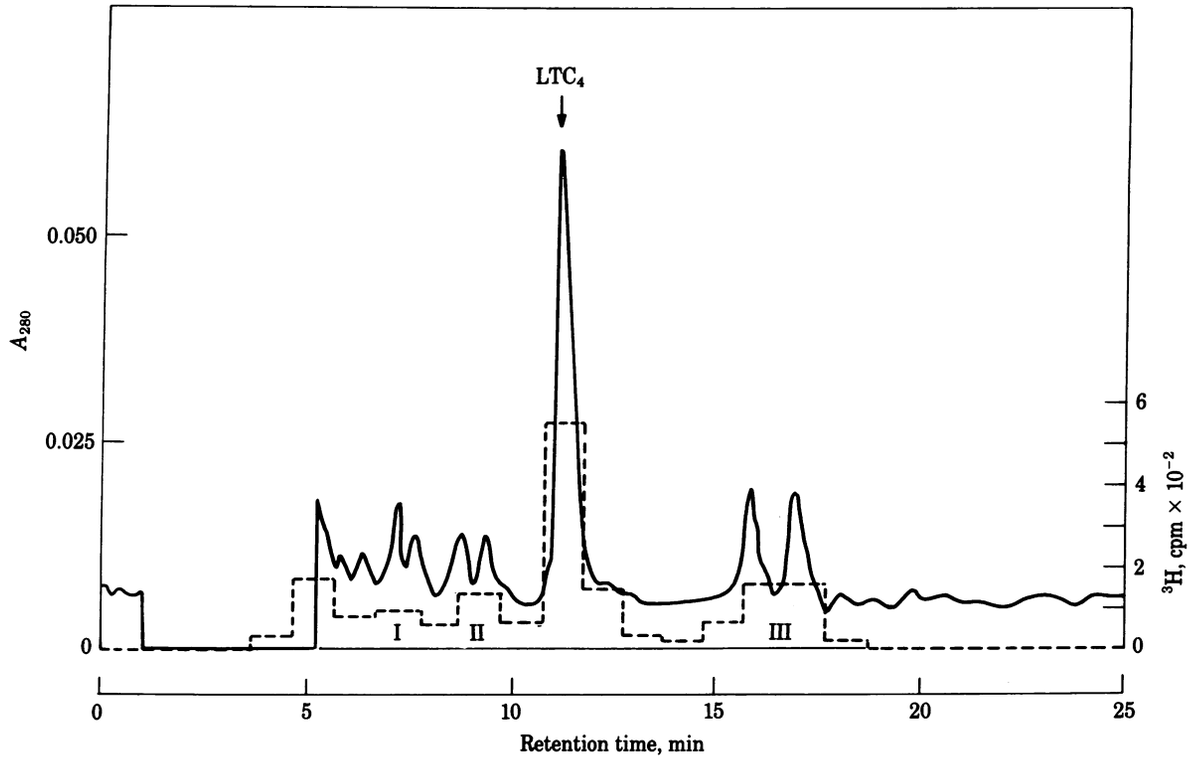

FIG. 4. RP-HPLC of supernatant from 10^6 leukocytes (78% eosinophils) incubated with 1 μg of LTC_4 and 0.11 ng of [^3H]LTC_4 and stimulated with PMA (1 μg per ml). Products, detected by absorbance at 280 nm (——) and by tritium radioactivity (– – –), include three doublets.

tabolism of endogenously generated LTC_4. Catabolism of exogenous LTC_4/[^{3}H]LTC_4 by eosinophil-enriched leukocytes stimulated with ionophore (2.5 μM) or PMA (1 μg per ml) (Fig. 4) yielded the same products as assessed by the A_{280} and the tritium radioactivity of eluates from RP-HPLC. Eosinophil peroxidase, which may inactivate leukotrienes (23), was released into the supernatants of the ionophore-activated eosinophils. The protection of LTC_4 degradation by L-serine and catalase and the resolution of metabolites from endogenous and exogenous LTC_4 with retention times of those fully characterized in studies with activated neutrophils (19, 20) suggest that eosinophil peroxidase may cause sulfidopeptide leukotriene inactivation by means of hypochlorous acid reactivity with the sulfur atom.

In contrast to the neutrophil, which metabolizes LTB_4 to 20-hydroxyl and 20-carboxyl LTB_4 by ω-oxidation (24, 25), eosinophils from hypereosinophilic donors stimulated with PMA or ionophore failed to metabolize exogenously added LTB_4. Although the ratios of LTC_4/LTB_4 generated from the hypereosinophilic donor-derived leukocytes in the presence of L-serine are not affected by catabolic degradation of either LTC_4 or LTB_4, it is likely that contaminating neutrophils in the eosinophil preparations contributed to the measured LTB_4. Conversely, in neutrophil preparations the elaboration of LTC_4 by contaminating eosinophils, together with the ongoing degradation of LTB_4 to ω-oxidation products, would yield overestimated LTC_4/LTB_4 ratios. Five-minute incubations for neutrophils increased the amounts of undegraded LTB_4 and, with 15-min periods for LTC_4, yielded an increased LTC_4/LTB_4 ratio of 1:9, as compared to 55:1 for eosinophils from the hypereosinophilic donors.

The almost complete suppression of 6-*trans*-LTB_4 production by L-serine indicates that, in the eosinophil, precursor LTA_4 is efficiently utilized to form LTC_4 and that little LTA_4 is available for nonenzymatic hydrolysis to 6-*trans*-LTB_4. Leukotriene generation by ionophore-stimulated horse eosinophils (98% purity) has been noted, with LTC_4 and LTD_4 production exceeding that of LTB_4 (26). Human eosinophils, relative to neutrophils, produce more 15-lipoxygenase products from arachidonic acid (27) in addition to their demonstrated preferential elaboration of LTC_4 from the 5-lipoxygenase pathway. This predominant production by the eosinophil of LTC_4 with its capacity to impair normal airflow in human airways (7) and to elicit vasoactive changes in human skin (8) suggests that the eosinophil may contribute to the manifestations of the allergic diseases with which it is frequently associated (28). In bronchial asthma eosinophilia of respiratory tissues and secretions is common, and increases in blood eosinophilia have been correlated with symptomatic exacerbations, including those associated with idiosyncratic reactions to nonsteroidal anti-inflammatory agents (29, 30). The effects of LTC_4 generation by human eosinophils may contribute to the pathobiology of allergic, metazoan parasitic, and other diseases characterized by blood or tissue eosinophilia.

This work was supported in part by Grants AI-20241, AI-07722, AI-10356, AI-20081, HL-17382, and RR-05669 from the National Institutes of Health and in part by a grant from the Lillia Babbitt Hyde Foundation. The research in the Department of Chemistry was supported by grants from the National Science Foundation and the National Institutes of Health. Dr. Lewis is a recipient of an Allergic Diseases Academic Award (AI-00399) from the National Institutes of Health.

1. Radmårk, O., Malmsten, C., Samuelsson, B., Clark, D. A., Goto, G., Marfat, A. & Corey, E. J. (1980) *Biochem. Biophys. Res. Commun.* **92**, 954–961.
2. Borgeat, P. & Samuelsson, B. (1979) *Proc. Natl. Acad. Sci. USA* **76**, 2148–2152.
3. Radmårk, O., Malmsten, C. & Samuelsson, B. (1980) *Biochem. Biophys. Res. Commun.* **96**, 1679–1687.
4. Hansson, G. & Radmårk, O. (1980) *FEBS Lett.* **122**, 87–90.
5. Lewis, R. A., Goetzl, E. J., Drazen, J. M., Soter, N. A., Austen, K. F. & Corey, E. J. (1981) *J. Exp. Med.* **154**, 1243–1248.
6. Nagy, L., Lee, T. H., Goetzl, E. J., Pickett, W. C. & Kay, A. B. (1982) *Clin. Exp. Immunol.* **47**, 541–547.
7. Weiss, W., Drazen, J. M., Coles, N., McFadden, E. R., Jr., Lewis, R. A., Weller, P., Corey, E. J. & Austen, K. F. (1982) *Science* **216**, 196–198.
8. Soter, N. A., Lewis, R. A., Corey, E. J. & Austen, K. F. (1983) *J. Invest. Dermatol.* **80**, 115–119.
9. Lewis, R. A., Mencia-Huerta, J.-M., Soberman, R. J., Hoover, D., Marfat, A., Corey, E. J. & Austen, K. F. (1982) *Proc. Natl. Acad. Sci. USA* **79**, 7904–7908.
10. Lindgren, J. Å., Hammarström, S. & Goetzl, E. J. (1983) *FEBS Lett.* **152**, 83–88.
11. Corey, E. J., Clark, D. A., Goto, G., Marfat, A., Mioskowski, C., Samuelsson, B. & Hammarström, S. (1980) *J. Am. Chem. Soc.* **108**, 1436–1439, and correction (1980) **108**, 3663.
12. Lewis, R. A., Drazen, J. M., Austen, K. F., Clark, D. A. & Corey, E. J. (1980) *Biochem. Biophys. Res. Commun.* **96**, 271–277.
13. Lewis, R. A., Drazen, J. M., Austen, K. F., Toda, M., Brion, F. & Corey, E. J. (1981) *Proc. Natl. Acad. Sci. USA* **78**, 4579–4582.
14. Corey, E. J., Marfat, A., Munroe, J., Kim, K. S., Hopkins, P. B. & Brion, F. (1981) *Tetrahedron Lett.* **22**, 1070–1080.
15. Boyüm, A. (1968) *Scand. J. Clin. Lab. Invest.* **21**, Suppl. 97, 77–89.
16. Gartner, I. (1980) *Immunology* **40**, 133–136.
17. Migler, R. & DeChatelet, L. R. (1978) *Biochem. Med.* **19**, 16–26.
18. Levine, L., Morgan, R. A., Lewis, R. A., Austen, K. F., Clark, D. A., Marfat, A. & Corey, E. J. (1981) *Proc. Natl. Acad. Sci. USA* **78**, 7692–7696.
19. Lee, C. W., Lewis, R. A., Tauber, A. I., Mehrota, M., Corey, E. J. & Austen, K. F. (1983) *J. Biol. Chem.*, in press.
20. Lee, C. W., Lewis, R. A., Corey, E. J., Barton, A., Oh, H., Tauber, A. I. & Austen, K. F. (1982) *Proc. Natl. Acad. Sci. USA* **79**, 4166–4170.
21. Bass, D. A., Grover, W. H., Lewis, J. C., Szejda, P., DeChatelet, L. R. & McCall, C. E. (1980) *J. Clin. Invest.* **66**, 1265–1273.
22. Slivka, A., LoBuglio, A. F. & Weiss, S. J. (1980) *Blood* **55**, 347–350.
23. Henderson, W. R., Jorg, A. & Klebanoff, S. J. (1982) *J. Immunol.* **128**, 2609–2613.
24. Lindgren, J. Å., Hansson, G. & Samuelsson, B. (1981) *FEBS Lett.* **128**, 329–335.
25. Hansson, G., Lindgren, J. Å., Dahlén, S.-E., Hedqvist, P. & Samuelsson, B. (1981) *FEBS Lett.* **130**, 107–112.
26. Jorg, A., Henderson, W. R., Murphy, R. C. & Klebanoff, S. J. (1982) *J. Exp. Med.* **155**, 390–402.
27. Turk, J., Maas, R. L., Brash, A. R., Roberts, L. J., II, & Oates, J. A. (1982) *J. Biol. Chem.* **257**, 7068–7076.
28. Cohen, S. G. & Ottesen, E. A. (1983) in *Allergy Principles and Practice*, eds. Middleton, E., Jr., Reed, C. E. & Ellis, E. F. (Mosby, St. Louis, MO), pp. 701–769.
29. Samter, M. & Beers, R. F., Jr. (1968) *Ann. Int. Med.* **68**, 975–980.
30. Horn, B. R., Robin, E. D., Theodore, J. & Van Kessel, A. (1975) *N. Engl. J. Med.* **292**, 1152–1155.