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THE LEUKOTRIENES: A NEW GROUP OF BIOLOGICALLY ACTIVE COMPOUNDS

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Abstract. - The leukotrienes (LT), originally discovered in leukocytes, are formed from polyunsaturated fatty acids as arachidonic acid. The unstable intermediate LTA_4 (5(S)-oxido-trans-7,9-trans,11,14-cis-eicosatetraenoic acid), is converted enzymatically by hydrolysis into LTB_4 (5(S),12(R)-dihydroxy-6,8,10,14-eicosatetraenoic acid), and by addition of glutathione into LTC_4 (5(S)-hydroxy,6(R)-S-glutathionyl-7,9-trans,11,14-cis-eicosatetraenoic acid. LTC_4 is metabolized to corresponding cysteinylglycine derivative (LTD_4) and cystein derivative (LTE_4). Corresponding leukotrienes can be formed from 5,8,11-cis-eicosatrienoic acid and 5,8,11,14,17-cis-eicosapentaenoic acid. LTC_4 and LTD_4 which are identical with slow reacting substance of anaphylaxis, are bronchoconstrictors and increase the permeability of microvasculature. LTB_4 is a potent chemotactic agent. The leukotrienes might therefore be important mediators both in immediate hypersensitivity reactions and in inflammation.

INTRODUCTION

Our knowledge about the oxygenation and further transformation of polyunsaturated fatty acids into biologically active derivatives has increased considerably during recent years. The products consist of prostaglandins (including prostacyclin), thromboxanes, and various hydroxylated fatty acids formed in lipoxygenase catalyzed reactions. These oxygenated derivatives constitute important regulators and mediators of various cell functions (1). In 1979 an additional group of arachidonic acid derived products, the leukotrienes, was discovered. These compounds are of particular interest since two of the leukotrienes are responsible for the biological activity earlier referred to as slow reacting substance of anaphylaxis (SRS-A). Furthermore, there is evidence that both these compounds and a leukotriene with pronounced chemotactic properties might function as mediators in inflammation. The present review summarizes the development of this area of research.

METABOLISM OF ARACHIDONIC ACID IN POLYMORPHONUCLEAR LEUKOCYTES

The major metabolites of arachidonic acid and 8,11,14-eicosatrienoic acid in rabbit polymorphonuclear leukocytes (PMNL) were identified as 5(S)-hydroxy-6,8,11,14-eicosatetraenoic acid and 8(S)-hydroxy-8,11,14-eicosatrienoic acid, respectively (2). However, more recently several new metabolites were detected (3,4).

PMNL, obtained from the peritoneal cavity of rabbits, were incubated with arachidonic acid. The products were purified using silicic acid chromatography and high-pressure liquid chromatography (HPLC). Metabolites were identified by spectrophotometric and gas chromatographic - mass spectrometric techniques. Fig. 1 shows a high pressure liquid chromatogram of five polar products in a typical experiment (4). The mass spectra of several derivatives of compounds I, II and III were practically identical, indicating that the three compounds were isomers, and demonstrating the presence of hydroxyl groups at C-5 and C-12. The ultraviolet spectra of compounds I-V (cf. Fig. 2) showed the characteristic absorption bands of three conjugated double bonds (4,5). Infrared spectrometric analysis demonstrated that the conjugated triene in compounds I and II had the trans geometry whereas similar analysis indicated the presence of two trans and one cis ethylenic bonds in the conjugated triene of compound III. Steric analysis of the alcohol groups indicated that compounds I, II and III had the (S) configuration at C-5 and that compounds I and III had the (R) configuration at C-12, whereas compound II had the (S) configuration at C-12 (Fig. 3). Compounds I, II, and III were thus stereoisomeric 5,12-dihydroxy-6,8,10,14-eicosatetraenoic acids.

Mass spectrometric analyses of compounds IV and V indicated that they were 5,6-dihydroxy derivatives of arachidonic acid (4). The ultraviolet spectra of compounds IV and V were identical (Fig. 2) and showed the presence of three conjugated double bonds in the molecules (4). Infrared spectrometry and steric analyses of the alcohols were not performed because of the limited amount of material available. The gas chromatographic, mass spectrometric, and ultraviolet spectrometric data indicated that compounds IV and V were diastereoisomeric 5,6-dihydroxy-7,9,11,14-eicosatetraenoic acid (4). The proposed mechanism of formation of compound IV and V (see below) requires that the compounds are epimers at C-6 (Fig. 3).

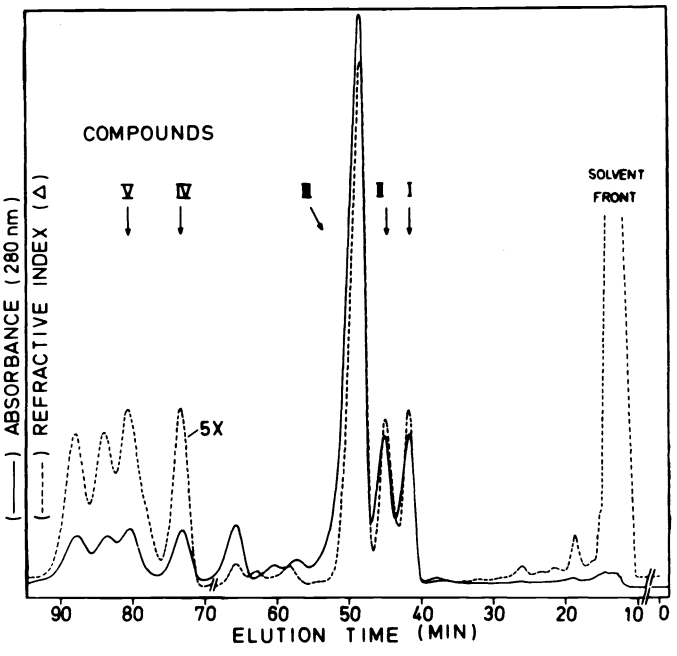

Fig. 1. Dihydroxylated metabolites of arachidonic acid formed by rabbit PMNL. An ether extract was purified by silicic acid column chromatography and the ethyl acetate fraction was subjected to RP-HPLC. The traces show ultraviolet absorbance at 280 nm (solid line) and the change in refractive indes (broken line). Column: μC_{18} Bondapack; solvent: methanol/water, 70/30, v/v plus 0.01% acetic acid at 3 ml/min.

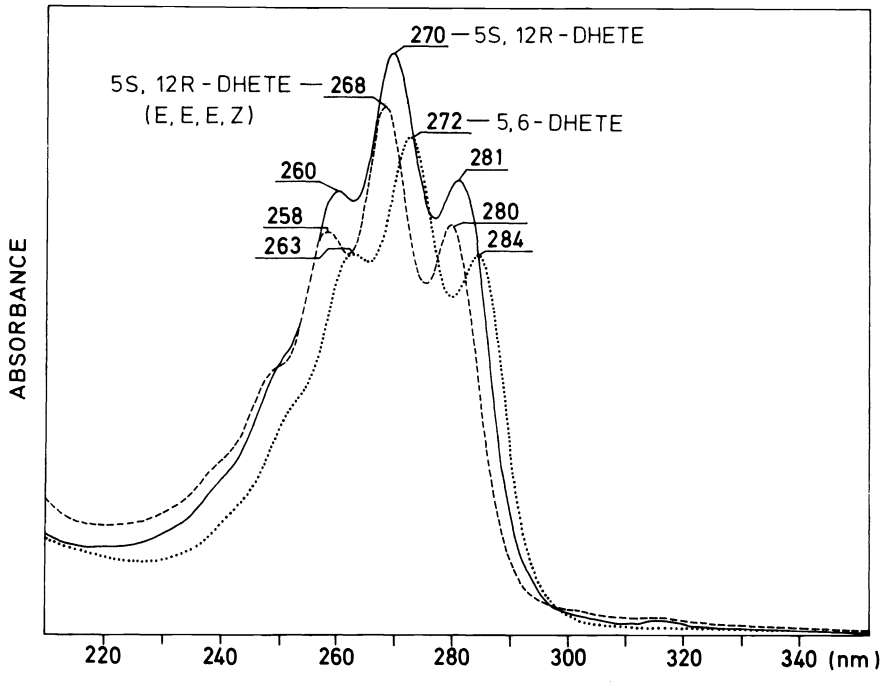

Fig. 2. Ultraviolet spectra of the methyl esters (Me) of some metabolites of arachidonic acid in rabbit PMNL. The spectra of compounds II and V were identical to those of compounds I and III, respectively. Spectra were recorded in methanol. 5S,12R-DHETE (E.E.E.Z) = compound I, 5S,12R-DHETE = compound III and 5,6-DHETE = compound IV.

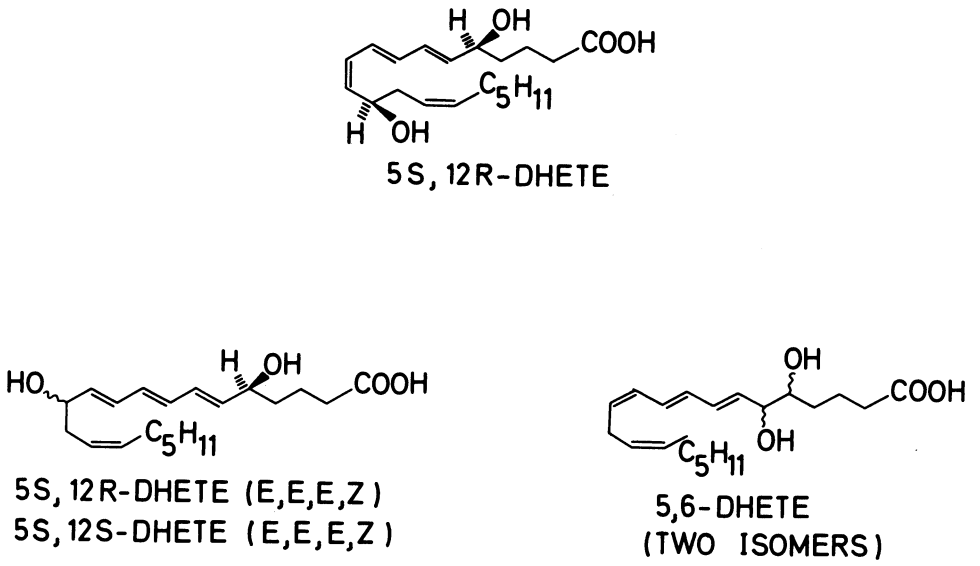

Fig. 3. Structures of dihydroxylated metabolites of arachiodnic acid in rabbit PMNL.

EVIDENCE FOR AN UNSTABLE INTERMEDIATE IN THE FORMATION OF DIHYDROXYEICOSATETRAENOIC ACIDS

Rabbit PMNL were incubated with arachidonic acid under an atmosphere of $^{18}O_2$ (6). The products, purified by reversed phase (RP)-HPLC, were esterified with diazomethane and hydrogenated over PtO_2. The presence and position of ^{18}O in the molecules were determined by mass spectrometry. Compounds I-V each contained a single atom of ^{18}O located at C-5. The 5S-hydroxy-eicosatetraenoic acid was also labeled at C-5. These data show that the hydroxyl groups at C-5 in the metabolites of arachidonic acid in Fig. 3 are derived from molecular oxygen. Incubation of rabbit peritoneal PMNL in H_2 ^{18}O-enriched buffer confirmed that the hydroxyl groups at C-12 in compounds I, II and III originated in water. Based on these observations, it was postulated that an unstable intermediate was generated from arachidonic acid by the leukocytes which would undergo nucleopholic attack by water, alcohols, and other nucleophiles.

Rabbit peritoneal PMNL were therefore incubated for 30 sec with arachidonic acid before addition of 10 volumes of methanol (A), 10 volumes of ethanol (B) or 0.2 volumes of N HCl (C). After extraction and silicic acid column chromatography, the products were analyzed by RP-HPLC. The chromatogram in Fig. 4 shows the pattern of products obtained (polar metabolites only). The material formed upon trapping with methanol (or ethanol) consisted of two additional compounds present in equal amounts. Their ultraviolet spectra were identical to those of compounds I and II (Fig. 2), indicating the presence of three conjugated double bonds. Infrared spectrometry further indicated that the conjugated double bonds had trans geometry. Gas chromatographic - mass spectrometric analyses of several derivatives of the two compounds showed that they were isomeric and carried hydroxyl groups at C-5 and methoxy groups at C-12. Steric analyses showed that the alcohol groups had (S) configuration. Although the configurations at C-12 were not determined it is clear that the compounds are the C-12 epimers of 5(S)-hydroxy,12-methoxy-6,8,10,14(E.E.E.Z)-eicosatetraenoic acid (c.f. Fig. 3).

Analoguous derivatives were identified when ethanol or ethylene glycol were used for trapping. These data show that a metabolite of arachidonic acid in leukocytes can undergo a facile nucleophilic reaction with alcohols.Interestingly, RP-HPLC analysis of samples obtained from trapping experiments performed under various conditions always indicated inverse relationships between the amount of compounds I and II formed and their 12-O-alkyl derivatives. This suggested that compounds I and II are formed nonenzymatically from the same intermediate that gives rise to the 12-O-alkyl derivatives.

To determine the stability of the intermediate, rabbit PMNL were incubated with arachidonic acid for 45 sec before addition of 1 volume of acetone (to stop enzymatic activity). At different time intervals, aliquots of the mixture were transferred to flasks containing 15 volumes of methanol. The relative amounts of metabolites were estimated by RP-HPLC. Fig. 5 shows the decay of the intermediate, measured as the 12-O-methyl derivative, at pH 7.4 and 37°C ($t_{1/2}$ = 3-4 min). Simultaneously, the concentrations of compounds I, II, IV and V increased with time.

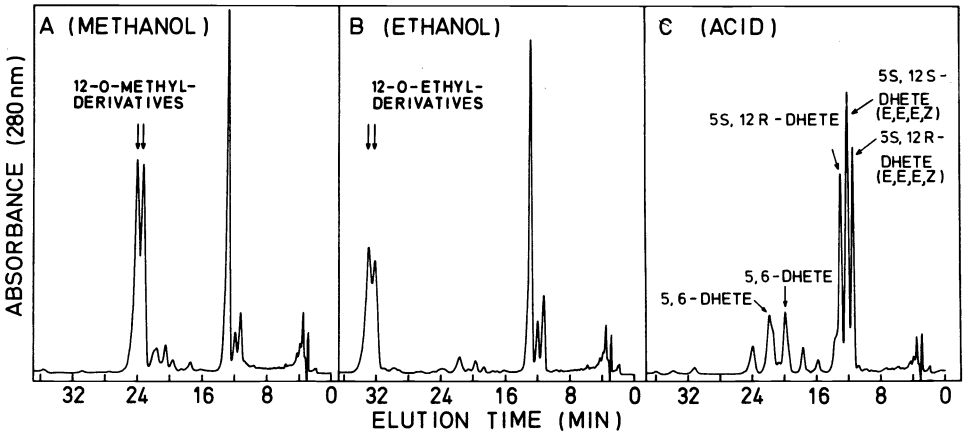

Fig. 4. RP-HPLC chromatograms of the products obtained upon addition of (A) 10 volumes methanol; (B) 10 volumes of ethanol; and (C) 0.2 volumes of N HCl to suspensions of PMNL incubated for 30 sec with arachidonic acid. The samples were fractionated by silicic acid column chromatography and the ethyl acetate fractions were analyzed by RP-HPLC. (Nucleosil C_{18}); solvent, methanol/H_2O, 75/25, v/v + 0.01% acetic acid at 1 ml/min.

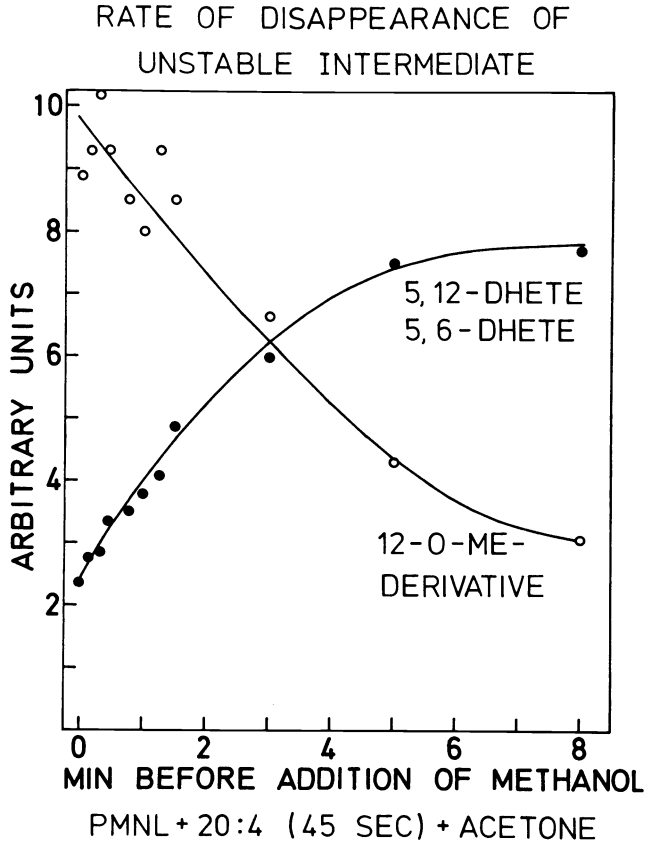

Fig. 5. Time course of the formation of compounds I, II, IV or V (o——o) and of the disappearance of the unstable intermediate measured as 12-O-methyl compounds I-II (o——o) in a mixture of water/acetone, 1/1, v/v at pH 7.4 and 37°C. Prostaglandin B_2 was added as an internal standard for quantitation by RP-HPLC.

The concentrations of compounds III and 5-hydroxy-6,8,11,14-eicosatetraenoic acid remained constant (not shown). This suggests that compounds I, II, IV and V are formed nonenzymatically by hydrolysis of a common unstable intermediate, whereas compound III arises by enzymatic hydrolysis of the same intermediate. Similar experiments performed at acid and alkaline pH indicated that the intermediate was acid-labile and somewhat stabilized at alkaline pH.

Based on the experimental data described above, the structure 5(S)-oxido-7,9,11,14-eicosatetraenoic acid (Fig. 6) was proposed for the intermediate. Hydrolysis of epoxides is acid catalyzed and opening of allylic epoxides is favored at allylic positions (C-6 in this case).

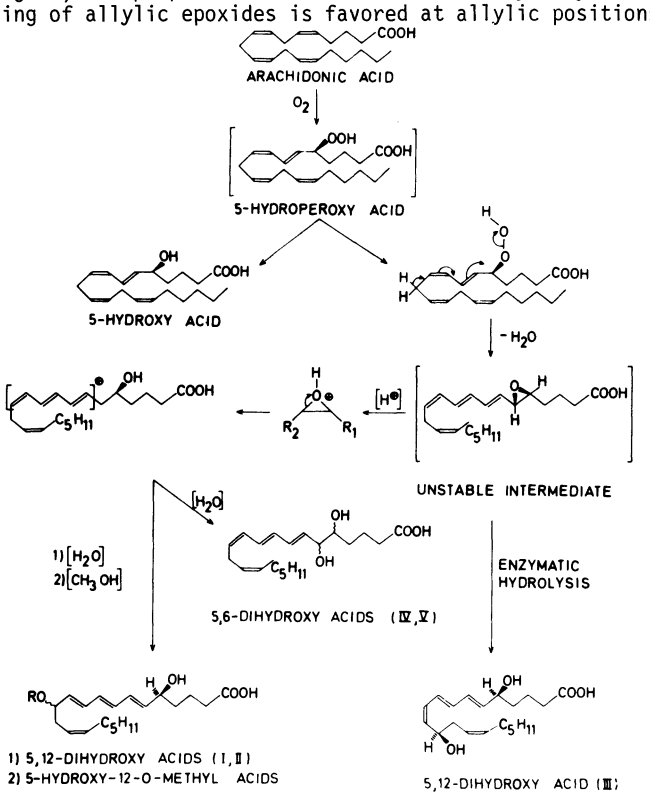

Fig. 6. Scheme of transformations of arachidonic acid in PMNL.

This agrees with the retention of ^{18}O at C-5 in compounds IV and V. A mechanism for the formation of compounds I-V from the epoxide intermediate is proposed in Fig. 6. Except for compound III these are formed by chemical hydrolysis of the epoxide through a mechanism involving a carbonium ion. The latter added hydroxyl anion preferentially at C-6 and C-12 to yield four isomeric products which contain the stable conjugated triene structure. Compound III is formed enzymatically from the intermediate since it is not racemic at C-12 and because it is only formed by nondenatured cell preparations.

A proposed pathway for the formation of the epoxide from arachidonic acid is shown in Fig. 6. It involves initial formation of 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) which is the precursor of the 5-hydroxy acid. The epoxide is formed from 5-HPETE by abstraction of a proton at C-10, and elimination of hydroxyl anion from the hydroperoxy group. The proposed structure (fig. 6), 5,6-oxido-7,9,11,14-eicosatetraenoic acid (6) (leukotriene A_4, c.f. below) of the intermediate has been confirmed by chemical synthesis and the stereochemistry has been elucidated (7). The allylic epoxide intermediate has recently been isolated from human polymorphonuclear leukocytes (8). Like the endoperoxides, it can thus exist in free form in cells and tissues. As will be apparent from the following discussion the concept that the unstable epoxide plays an important role in the transformation of arachidonic acid in leukocytes was a prerequisite for the work leading to elucidation of the structure and biogenesis of slow reacting substance of anaphylaxis (SRS-A).

SLOW REACTING SUBSTANCE OF ANAPHYLAXIS (SRS-A)

Structures and biosynthesis

Feldberg and Kellaway introduced the term SRS (Slow Reacting Substance) for a smooth muscle contracting factor appearing in the perfusate of guinea pig lung following treatment with cobra venom (9). Subsequent studies have suggested that SRS is an important mediator in asthma and other types of immediate hypersentitivity reactions (10,11,12,13). Immunologically released SRS is usually referred to as SRS-A (Slow Reacting Substance of Anaphylaxis). It is considered to be released together with other mediators (e.g. histamine and chemotactic factors) after interaction between IgE molecules, bound to membrane receptors, and antigens as pollen etc.

Earlier work on the structure of SRS was severely limited by the difficulty in obtaining sufficient quantities of pure preparations of SRS. However, it had been characterized as a polar lipid (14,15) possibly containing sulfur and having ultraviolet absorption (15,16,17). Studies with labelled arachidonic acid indicated that is was incorporated into SRS (18,19).

In a survey of methods for production of SRS, we found that murine mastocytoma cells treated with ionophore A23187 and L-cysteine generated SRS. This method proved superior to previously described systems with respect to formation of spasmogenic material antagonized by SRS antagonist FPL55712 and incorporation of isotopically labeled precursors (see below) (20).

To purify SRS, incubation mixtures were centrifuged supernatants mixed with ethanol to 80%, filtered, and evaporated to dryness. The residue was hydrolyzed with base, purified by Amberlite XAD-8 and silicic acid chromatography followed by two steps of RP-HPLC. This afforded essentially pure SRS.

Purifications were monitored by bioassay on isolated guinea pig ileum in the presence of atropine and pyrilamine maleate. Reversal of contractions by the SRS antagonist FPL55712 was used as a criterion for biological activity. A preparation of SRS prepared by ionophore challenge of human luekocytes was used to standardize the contractile response.

Purified preparations of mast cell tumor SRS gave a characteristic ultraviolet spectrum (Fig. 7). Inset A of this figure shows the biologic effect of a small aliquot of this fraction. The absorbance at 280 nm and the SRS response of ten fractions collected during a final HPLC purification were highly correlated (inset B, Fig. 7). This suggested that the UV-

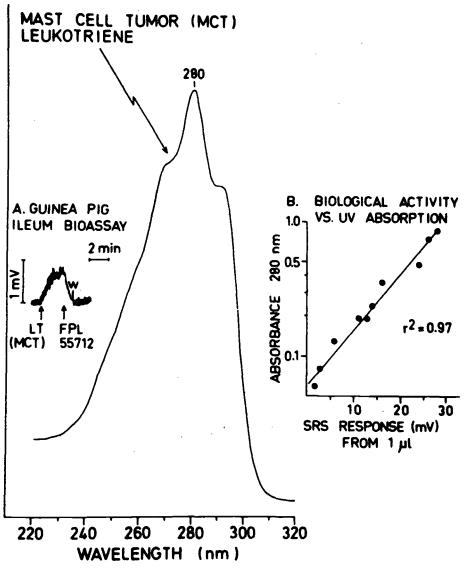

Fig. 7. Ultraviolet spectrum of a slow-reacting substance. SRS (leukotriene C), from mast cell tumor. Inset A. Contraction of guinea pig ileum after addition of UV-absorbing material. Note the addition of FPL55712 at the second arrow. Inset B. Correlation between the log absorbance at 280 nm from a purification of the mast cell tumor leukotriene C and the biologic response on isolated guinea pig ileum (least square linear regression).

absorbing material and SRS are identical. The spectrum is similar to those of dihydroxylated arachidonic acid metabolites in rabbit PMNLs (Fig. 2) but shifted 8 to 12 nm bathochromically, indicating that the SRS contained a conjugated triene with an α-auxochrome (vide infra). Experiments with labeled precursors showed that arachidonic acid and cystein (both sulfur and the three carbon atoms) were incorporated into the products (20).

Purified SRS from [$^3H_3$]-arachidonic acid was degraded by Raney nickel desulfurization. The desulfurized product was esterified and purified by silicic acid chromatography. The mass spectrum of the major radioactive component was practically identical to that of similarly derivatized 5-hydroxyarachidic acid (Fig. 8). This indicated that the arachidonic acid derivative and cystein were linked by a thioether bond (Fig. 9). The alcohol group at C-5 in the fatty acid reinforced the hypothesis of a biogenetic relationship between the arachidonic acid metabolites we had found in leukocytes and SRS (20,21).

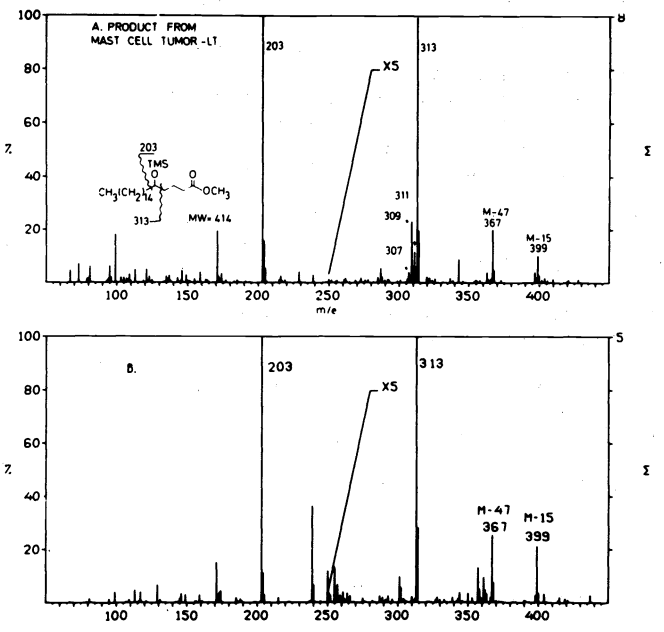

Fig. 8. (A) Mass spectrum of the radioactive product with an equivalent carbon number of 21.6. (B) Mass spectrum of the methyl ester, TMS derivative of 5-hydroxyarachidic acid.

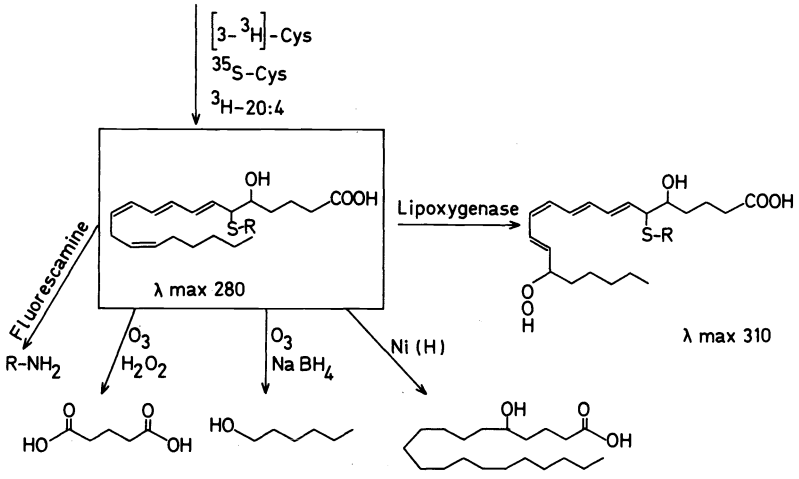

Fig. 9. Some transformations in structural studies on SRS.

The locations of the double bonds in SRS biosynthesized from tritium labeled arachidonic acid acid were determined by reductive ozonolysis. This yielded |^{3}H|-1-hexanol demonstrating retention of the Δ^{14}-double bond of arachidonic acid. A unique method was used for locating the conjugated triene (20). Previous studies in our laboratory had shown that arachidonic acid and related fatty acids containing two methylene interrupted cis double bonds at the ω-6 and ω-9 positions are oxygenated by soybean lipoxygenase to form ω-6 oxygenated derivatives with isomerization of the ω-6 double bond to ω-7 (22). Incubation of SRS with the lipoxygenase resulted in isomerization of the Δ^{14} double bond into conjugation with the conjugated triene (forming a tetraene) since there was a bathochromic shift of 30 nm. This finding indicated the presence of a Δ^{11}-cis-double bond and additional double bonds at Δ^7 and Δ^9 in SRS. The structural work at this stage showed that the SRS was a derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid with a cystein containing substituent in thioether linkage at C-6. Derivatization of cystein was suggested by failure to isolate alanine after dedulfurization (20,21, 23).

Additional studies involving amino acid analyses of acid hydrolyzed SRS demonstrated that in addition to cystein, one mol of glycine and one mol of glutamic acid were present per mol of SRS. The structure of the peptide as determined by end group (dansyl method and hydrazinolysis) and sequence analyses (dansyl-Edman procedure) was γ-glutamylcysteinylglycine (glutathione) (24). The experiments described above thus showed that the SRS from murine mastocytoma cells is 5-hydroxy-6-S-glutathionyl-7,9,11,14-eicosatetraenoic acid (Fig. 10), leukotriene (LT) C_4 (c.f. below) (20,23,24). The structure was confirmed by comparison with synthetic material (24). This represented the first structure determination of an SRS-A. The preparation and some properties of corresponding cysteinylglycine derivative (LTD_4) and

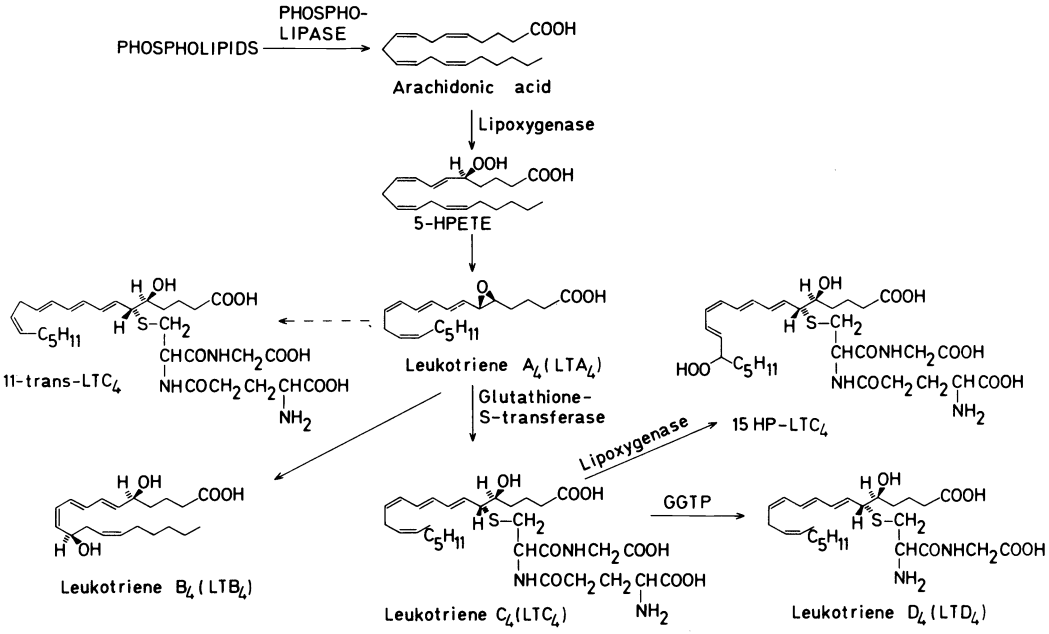

Fig. 10. Formation and transformation of leukotrienes. GGTP=γ-glutamyl transpeptidase. 5-HPETE = 5-hydroperoxyeicosatetraenoic acid.

cysteinyl derivative (LTE_4) were also reported at the same time (24). These compounds have later been isolated from natural sources (see below). The stereochemistry of LTC_4 was unambiguously assigned by total synthesis including preparation of stereoisomers of LTC_4 (25, 26). The synthetic work was carried out by E.J. Corey et al. LTC_4 is thus 5(S)-hydroxy,6(R)-S-glutathionyl-7,9-trans-11,14-cis-eicosatetraenoic acid.

A minor component of SRS from murine mastocytoma cells, which was provisionally referred to as LTC-2 was found to be 5(S)-hydroxy,6(R)-S-glutathionyl-7,9,11-trans-14-cis-eicosatetraenoic acid (11-trans-LTC_4, c.f. below) i.e. the conjugated triene has all trans geometry (Fig. 10) (27).

The previously proposed (20,24) biogenetic relationship between LTA_4 and LTC_4 has recently been confirmed by the actual conversion of synthetic LTA_4 into LTC_4 in human polymorphonuclear leukocytes (28) (Fig. 11). The HPLC chromatogram of the product is shown in Fig. 11. Compound I was identical with LTC_4 and compound II was 11-trans-LTC_4. It is not known whether the isomerization to the all trans compound occurs at the LTA_4 stage. About 10 per cent of LTA_4 was converted into LTC_4 and 11-trans-LTC_4 and 8 per cent into LTB_4.

Subsequent studies with a different cell type, the RBL-1 cells, demonstrated that the major slow reacting substance was less polar than LTC_4 (29). That the fatty acid part of this compound and LTC_4 were identical was indicated by their ultraviolet spectra, the product obtained after Raney nickel desulfurization and the spectral change observed after treatment with soybean lipoxygenase. Amino acid analysis, however, showed that the less polar product lacked glutamic acid. Edman-degradation indicated that glycine was C-terminal. Incubation of LTC_4 with γ-glutamyl transpeptidase yielded additional proof for the structure. The product, 5(S)-hydroxy,6(R)-S-cysteinylglycine-7,9-trans-11,14-cis-eicosatetraenoic acid (LTD_4) was identical with the less polar product from RBL-1 cells (Fig. 10) (29). LTD_4 is more potent than LTC in the guinea pig ileum bioassay and the contraction is faster (29).

Rat peritoneal mononuclear cells, when stimulated with ionophore A23187 and L-cysteine, produce a slow reacting substance (SRS^{ri}). This SRS has been fractionated into two components (peaks I and II) by HPLC. Peak I corresponded chromatographically and by the nature of the contractile response to immunologically released SRS-A from human lung (30). In collaboration with Bach et al. we have recently identified their SRS from rat peritoneal mononuclear cells as LTC_4 and 11-trans-LTC_4 (peak II) and LTD_4 (peak I) (31, 32). Immunologically released

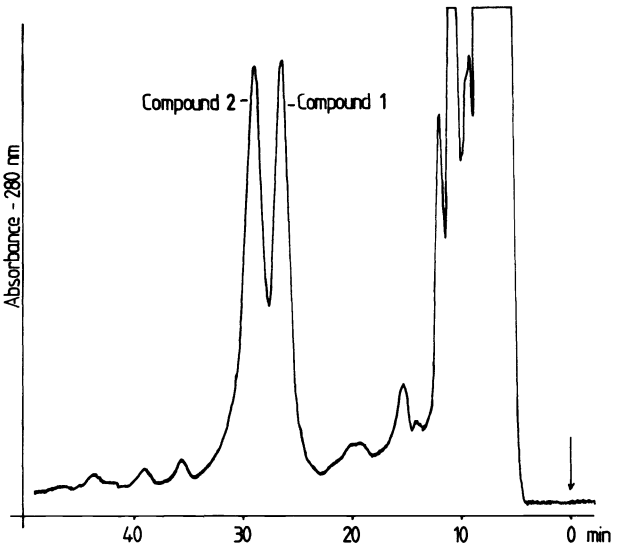

Fig. 11. Reverse phase HPLC chromatogram of products obtained from incubation of LTA_4 with human PMNL.

SRS-A from rat peritoneal mononuclear cells has been found by Lewis et al. to consist of LTC_4 and LTD_4 (33). Their identification was based on comparison with synthetic material. Some experimental evidence for the formation of LTD_4 in RBL cells has also been reported by Morris et al. (34). This partial characterization by mass spectrometry gave mainly information about the amino acid portion of the molecule and the identification was based on the previously described structures for LTC_4, LTD_4 and LTE_4 (20,24). SRS-A from human lung has been shown to contain both LTC_4 and LTD_4 (33) whereas only LTD_4 was found in SRS-A from guinea-pig lung (35).

As described above SRS-A from different sources consists of LTC_4 and LTD_4 in varying proportions. LTD_4 is a metabolite of LTC_4 and the composition of SRS-A will depend on the conditions used for its generation. Another metabolite, LTE_4, has also been isolated from natural sources. The relative amounts of the leukotrienes formed under *in vivo* conditions remains to be determined.

Nomenclature

The studies described have indicated that the lipoxygenase pathway with initial formation of 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid and leading to the 5,6-oxido-intermediate,5, 13-dihydroxy-eicosatetraenoic acid and SRS-A is of considerable biological significance. The name leukotriene has therefore been introduced to designate compounds of the pathway containing a conjugated triene (23). Another reason for using this nomenclature is the finding that SRS from different sources contains varying amounts of several leukotrienes with SRS activity. The different leukotrienes have been designated alphabetically: leukotriene A is the unstable epoxide intermediate; leukotriene B, the enzymatically formed 5(S),12(R)-dihydroxy acid; leukotriene C the γ-glutamylcysteinylglycine (glutathione) containing SRS, leukotriene D, a cysteinylglycine containing SRS and leukotriene E, corresponding derivative with cystein as substituent at C-6. Leukotriene C with all *trans* geometry of the triene is referred to as 11-*trans*-LTC (Fig. 10).

Analoguous structures can be derived from 5,8,11-eicosatrienoic acid, and 5,8,11,14,17-eicosapentaenoic acid. A subscript (e.g. LTC_3, LTC_4 and LTC_5) has therefore been added to indicate the number of double bonds in the molecules (36). Thus the compounds derived from arachidonic acid and earlier referred to as LTA, LTB, LTC and LTD become LTA_4, LTB_4, LTC_4 and LTD_4 (Fig. 12) (36).

Biological effects

Leukotrienes C_4 and D_4 are potent constrictors of air ways in the guinea pig assayed either *in vivo* or *in vitro* using tracheal rings or parenchymal strips (37,33). Furthermore, human bronchial muscle is extremely sensitive to LTC_4 and LTD_4. Both compounds are about 1000 times more active than histamine on human muscle preparations (38). The same compounds also increase vascular permeability and it is therefore likely that LTC_4 and LTD_4 act as mediators of both the bronchospasm and the mucosal oedema of bronchial asthma.

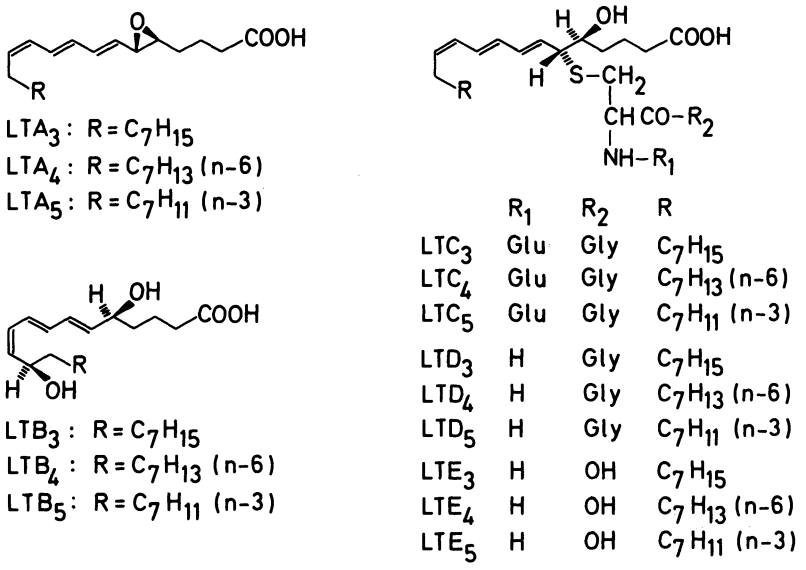

Fig. 12. Nomenclature for leukotrienes.

Leukotriene B_4 has recently been found to have pronounced chemotactic and chemokinetic effects on human polymorphonuclear leukocytes (39,40,41). Both LTB_4 and LTC_4 are formed by human neutrophils (42,43). These findings are of considerable interest in relation to inflammatory reactions since the effects of these leukotrienes on chemotaxis and permeability of microvasculature might be of pathophysiological significance in inflammation. Further work is needed to explore this possibility.

A synergism between the leukotrienes with bronchoconstrictor effects and thromboxane A_2 is also conceivable. LTC_4 and LTD_4 cause release of TXA_2 in guinea-pig lung. Since TXA_2 is a potent constrictor of air ways, its release might contribute to the bronchospasm in asthma. In a similar way the vasodilators PGE_2 and PGI_2 (prostacyclin) might contribute to the effects of LTC_4 and LTD_4 (increase permeability of microvasculature) in the formation of oedema.

The biochemical interrelationship between the cyclo-oxygenase pathway (yielding prostaglandins and thromboxanes) and the leukotriene pathway is illustrated in Fig. 13. The increased knowledge about arachidonic acid derived mediators as described in this review seems to offer many new possibilities of exploring the role of this system in physiological and pathophysiological processes.

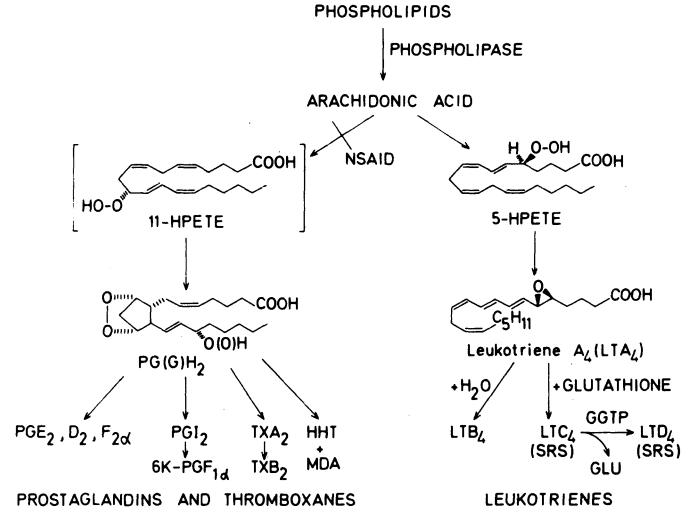

Fig. 13. Formation of prostaglandins, thromboxanes and leukotrienes from arachidonic acid.

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