CONTINUING MEDICAL EDUCATION

LEUKOTRIENES

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Leukotrienes are a group of newly discovered, pharmacologically active derivatives of arachidonic acid—a 20-carbon polyunsaturated fatty acid present in the phospholipid layers of all cell membranes. These have chemotactic and spasmogenic properties and act as mediators of immediate hypersensitivity reactions and inflammation. Recently, these have been suggested in the aetiopathogenesis of certain dermatological conditions such as psoriasis and atopic dermatitis.

History

The term slow reacting substance (SRS) was introduced by Feldberg and Kellaway[1] in 1938, for a substance isolated from the perfusion of guinea pig lung with cobra venom. Later, Brocklehurst (1960)[2] used the term slow-reacting-substance of anaphylaxis (SRS-A) to describe the material produced by the lungs on immunological challenge by antigens. Brocklehurst[2] also demonstrated that H_1 antihistaminics failed to antagonize the spasmogenic activity of SRS-A. Both these chemical substances, SRS and SRS-A, whether produced by immunological or non-immunological challenge were later on shown to be physico-chemically and pharmacologically identical, and the acronyms SRS and SRS-A are now used interchangably. SRS-A was shown to be an acidic, highly polar lipid[3] of molecular weight <700[4] and containing a sulphur atom[5] in its structure. Jakschik et al 1977[6] and Bach et al 1977[7] demonstrated that arachidonic acid (AA) stimulated the release of SRS-A and that radio-labelled AA could be incorporated into SRS-A. A structural relationship between SRS and leukotrienes was indicated by studying their UV absorption spectra.[8] Rat SRS-A was subsequently shown to contain three leukotrienes LTC_4, LTD_4 and LTE_4.[9] Specific structures of LTB_4, LTC_4 and LTD_4 were described later on.[10,11] These compounds are formed by the action of 5-lipoxygenase on arachidonate and are structurally related as shown by similar UV absorption spectra. Recently, leukotrienes formed through 15-lipoxygenase enzyme have also been described.[12]

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Cellular origin and chemistry

The term leukotrienes (LT) originated as these substances were first described in leukocytes (L) and possess 3 double bonds or trienes (T). The suffix A (LTA) depicts the epoxide : compound having two adjacent carbon atoms conjugated by oxygen, while the number (LTA_4) denotes the number of double bonds in the molecule.[13]

Inflammatory or immunologic injuries to the cell membrane, such as due to immediate hypersensitivity,[14] platelet activating factor,[15] calcium ionophore[6,7] or UV light induced,[4] result into the liberation of a lytic enzyme phospholipase A_2 (PLA_2). The PLA_2, a calcium dependant enzyme, releases unsaturated fatty acids, especially arachidonic acid, from cell membrane phospholipids, from polymorphonuclear leukocytes, basophils, macrophages and mainly the mast cells.[16] The arachidonic acid thus formed undergoes metabolic degrada-

tion by one of the two enzymes: cyclo-oxygenase or lipoxygenase. Although cyclo-oxygenase activity is detected in microsomal fraction, a recent study has demonstrated that the lipoxygenase activity is associated with cytosol and microsomal fractions in human platelets.[17,18]

Cyclo-oxygenase, present in all cells except mature RBCs,[19] converts AA to a generation of prostaglandins, prostacycline and thromboxanes.

The synthesis of lipoxygenase products has been shown in a number of tissues including leucocytes such as polymorphs (PMNs),[8] macrophages,[20] basophilic leukemia cells,[21] platelets[22] lungs[23,24] and uterus.[25] The formation of 5-hydroperoxyeicosatetraenoic acid (5-HPETE) from AA is the initial step in this pathway which gives rise to a series of compounds containing a triene structure. The next step is the formation of an unstable nine membered oxacyclononatriene, the 5, 6-epoxide leukotriene A_4 (LTA_4).[13,26] The LTA_4 can undergo a non-enzymic chemical hydrolysis to diastereomers of 5, 6-dihydroxyeicosatetraenoic acid (5, 6-diHETE), and 6, 8, 10-trans-14-cis-diastereomers of 5, 12-diHETE, or can be enzymatically converted to (5S, 12R)-dihydroxy-6, 14-cis-8, 10-trans-eicosatetraenoic acid, Leukotriene B_4 (LTB_4).[8] The products of chemical hydrolysis have little biological activity as compared to enzymatically formed LTB_4.[26] Alternatively, the enzymatic addition of glutathione to LTA_4 results in the formation of leukotriene C_4 (LTC_4), which can then be converted to the cysteinylglycyl adduct named leukotriene D_4 (LTD_4) by removal of the terminal glutamine by gamma-glutamyl-transpeptidase. LTD_4 can be further metabolized to the cysteinyl adduct leukotriene E_4 (LTE_4).[10]

LTB_4 has been further shown to undergo omega-oxidation in human PMNs.[27] These oxidation products are 20-hydroxy-leukotriene B_4, which can be further metabolized to the 20-carboxy-leukotriene B_4.

The formation of another series of compounds via a 14, 15-epoxide intermediate, with a conjugated triene structure analogous to LTA_4 has also been reported in human PMNs.[12] These have been named 8, 15-leukotriene B_4 and 14, 15-leukotriene B_4.

These derivatives of cyclo-oxygenase and lipoxygenase enzyme pathways are shown in Fig. 1

Pharmacological activity

5-monohydroxyeicosatetraenoic acid (5-HETE) modulates the motility[28] and possibly the glucose transport[29] of neutrophils. LTB_4 is a potent chemotactic factor,[30] causes a dose-dependant increase in the number of leukocytes adhering to the endothelium of post-capillary and larger venules, diapedesis, and migration of leukocytes, almost exclusively of neutrophils, in the extravascular space.[31] LTC_4, LTD_4 and LTE_4 have more potent vasoactive and spasmogenic activities than those of histamine.[32] LTD_4 and LTE_4 are about 100 times more potent than histamine in initiating an increase in vasopermeability in guinea pig skin.[32] Leukotriene B_4, C_4, D_4 and E_4 activate a phospholipase and stimulate the release of cyclo-oxygenase products, mainly the thromboxane A_2, in guinea pig lungs.[33] LTC_4, LTD_4 and LTE_4 may have a role as primary mediators of inflammatory plasma exudation due to their oedema producing properties.[34] Intradermal injection of LTC_4 or LTD_4 has been shown to cause significant extravasation of Evans blue in guinea pigs.[35] Furthermore, a dose dependant and reversible plasma exudation, specifically located to post-capillary venules is seen with LTC_4 and LTD_4 in the hamster cheek pouch preparation.[31] In this respect, LTC_4, LTD_4 and LTE_4 were each found to be atleast 1000 times as potent as histamine.[34] The effects of LTC_4 and LTD_4 on vascular permeability were found to be unrelated to the release of histamine or cyclo-oxygenase products.[31,36]

Fig. 1. THE ARACHIDONATE CASCADE

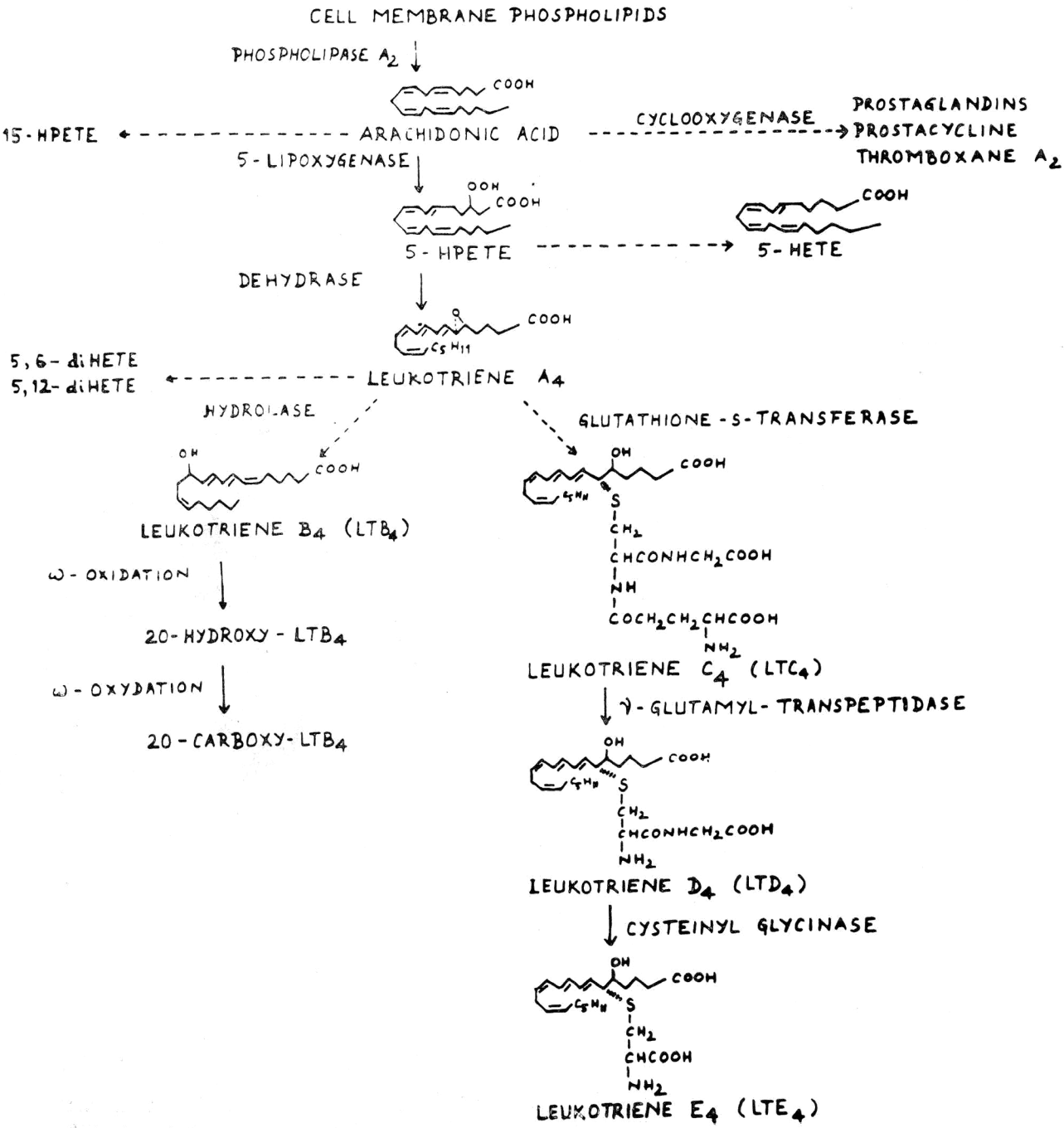

Table I. Major biological effects of leukotrienes.

Leukotriene	Action
LTB_4	Adhesion of PMNs to endothelium Chemotaxis of PMNs Diapedesis of PMNs Exudation of plasma Keratinocyte proliferation
LTC_4, LTD_4, LTE_4	Contraction of smooth muscles Increased mucus production Constriction of peripheral pulmonary airways Exudation of plasma from post-capillary venules Coronary artery constriction

LTB_4 also causes tissue oedema but it is slower in onset, derives from both post capillary and larger venules, and is preceded by a marked adhesion of leukocytes to the vessel wall.[34]

Synthesis of leukotrienes in various tissues

Leukocytes metabolize AA by the 5-lipoxygenase pathway to mono and dihydroxy products, of which LTB_4 is the most active biologically. A 15-lipoxigenase pathway has also been described in rabbit and human PMNs. Other tissues able to form mono and dihydroxy metabolites of AA include normal and psoriatic skin,[37] bone marrow derived mast cells,[38] platelets,[22] lungs,[23,24] kidneys,[39] and ocular[40] and gastro-intestinal tissues.[41]

LTB_4 has been identified in the inflammatory exudates including tear fluid,[42] synovial fluid from patients with arthritis and spondyloarthritis,[43,44] gout,[45] and in blister fluid from human psoriatic skin.[46] The gammaglutamyl-transpeptidase activity in synovial fluid is higher than that of plasma. At 16-fold dilution still 50% activity of this enzyme is present in synovial fluid as against nil in plasma.[44]

Catabolism

The major pathways for bio-inactivation and excretion of leukotrienes are still not clear. LTB_4 is known to undergo omega-oxidation and LTC_4 is rapidly converted into LTD_4 and LTE_4 in reactions analogous to the glutathione pathway. The activated leukocytes have also been shown to generate hypochlorous acid through a myeloperoxidase reaction which converts LTC_4, LTD_4 and LTE_4 into comparatively inactive sulfoxides and dihydroxy acids.[47]

Effects of leukotrienes on various tissues

Lungs : LTC_4 and LTD_4 have been suggested to be important mediators of the reversible loss of pulmonary elasticity and the ventilation-perfusion inequalities as seen in asthmatics even when the central airways are sufficiently patent.[48] LTC_4 and LTD_4 are more than 1000 times as potent as histamine and 500 times more potent than PGF_2 alpha in contracting the smooth muscles of human bronchi.[49] This effect is about 20,000 times more potent than that of histamine in certain other species.[50] LTB_4 also has a bronchoconstricting effect on guinea pig parenchyma although it is 100 times less potent than LTC_4.[51] The leukotrienes mainly affect the peripheral airways whereas more central airways show only little changes.[52-54] Leukotrienes also increase the mucus secretion[55] as well as decrease the airway mucus clearance rate.[56]

Leukocyte function and vascular permeability: Leukotrienes have a potent chemotactic and chemokinetic activity on human neutrophils, and cause aggregation and increased adherence of neutrophils to the vascular endothelium.[57] LTB_4 is about 100 times more potent a chemokinetic agent than any of the mono-HETE or HPETEs. The HPETEs are generally more potent chemokinetic agents than their corresponding HETEs.[57]

An intradermal injection of LTB_4, LTC_4 and LTD_4 produces a wheal and flare at the local site with vasodilatation of both superficial and deep venules.[58] This is associated with a

pronounced infiltration of neutrophils when LTB_4 is injected but not with LTC_4 and LTD_4. A peak of neutrophils at 24 hours with subsequent lymphocytic predominance in perivascular cell population has been observed in human skin after topical application of LTB_4.[59] LTB_4 stimulates release of enzymes and certain other factors from leukocytes.[60] A similar leukocyte dependance is seen in most types of inflammatory oedemas.[60] But, how these activated leukocytes increase vascular permeability is not clear.

Cardio-vascular system : LTC_4 causes a dose dependant and short-lived constriction of terminal arterioles while LTB_4 and LTD_4 result in their dilatation.[62] LTD_4 also shows a hypotensive effect in the intact guinea pig with 500 ng/kg dose producing a 50% fall in the mean arterial pressure.[32] LTC_4 and LTD_4 result in systemic anaphylaxis characterized by hypotension, reduced coronary blood flow and impaired left ventricular performance after an intravenous injection in guinea pigs.[63]

Immune system : Leukotriene B_4 affects T-cell function.[64] A decreased production of LTB_4 may impair the defence system. The synthesis of LTB_4 by neutrophils obtained from the peripheral blood of patients with diabetes is impaired.[65] Diabetic patients are prone to bacterial infections and their neutrophil functions are impaired.[66] Synthesis of LTB_4 by alveolar macrophages obtained from smokers is also reduced as compared with those of non-smokers[67] and cigarette smoking is associated with an increased incidence of infectious diseases in the lungs.[68] Further, LTB_4 stimulates production of interleukin-2 and gamma-interferon. The impaired production of LTB_4 by neutrophils may play a significant pathophysiological role in the recurrent infections in vitamin-D deficient rickets. Thus, LTB_4 may contribute to the various immune reactions by affecting several cell types and the production of various cytokinins.

Uterus : Both the cyclo-oxygenase and lipoxygenase pathways are operative in the rabbit and rat uterus during the preimplantation period.[70,71] The one of the earliest discernible pre-requisite events in blastocyst implantation is the increased uterine stromal capillary permeability at the site of blastocyst.[72] As the increases in uterine vascular permeability preceding the decidual cell reaction are of the post-inflammatory type, it is suggested that an interaction exists between the prostaglandins and leukotrienes in the generation of the decidual cell reactions.[73]

Skin : A widespread scaly dermatosis with psoriasiform epidermal hyperplasia but without associated parakeratosis is seen in animals on a diet deficient in AA and linoleic acid.[74] An increase in 5,8,11-eicosatrienoic acid level has also been demonstrated in them which besides inhibiting cyclo-oxygenase, could also be converted into leukotrienes thus possibly contributing in their pathogenesis.[75] Abnormally high 5-lipoxygenase levels are present in psoriatic skin.[76] There is no enhanced activity of 5-lipoxygenase in circulating PMNs in psoriatic patients.[77] Large amounts of LTB_4 in scale extracts from pustular psoriasis and psoriasis, but not in uninvolved psoriatic skin, has been detected.[78] Further, the topical application of 2% lonapalene (RS-43179) has shown significant clinical improvement in psoriasis alongwith significant reduction in LTB_4 levels in psoriatic lesions as compared to normal skin.[79] Patients with atopic dermatitis,[80-82] allergic contact dermatitis[83] and incontinentia pigmenti[84] have also been shown to have high levels of LTB_4. It has been proposed that neutrophil accumulation as seen in the very early stages of psoriasis, and accumulation of eosinophils within the epidermis in incontinentia pigmenti result from high levels of LTB_4 at these sites. LTB_4, LTC_4 and LTD_4 have been shown to increase DNA synthesis in epidermal keratinocytes but not of dermal

fibroblasts, thus, possibly mediating the aberrant epidermal growth in psoriasis.[85] Further, oral benoxaprofen has been shown to be effective in psoriasis probably by inhibiting the epidermal 5-lipoxygenase.[86,87]

Leukotriene inhibitors

Only a few leukotriene inhibitors and antagonists are available for clinical use. Topical corticosteroid treatment has been shown to be causing a significant reduction in the AA and LTB_4 levels associated with clinical improvement in psoriasis.[88] Corticosteroids do not directly effect the arachidonate metabolizing enzymes but rather interfere with the release of fatty acids from cell membrane phospholipids by inducing the synthesis of an antiphospholipase A_2 protein[89,90] termed macrocortin or lipomodulin. Other compounds known to be interfering with both the pathways of AA metabolism are eicosatetraenoic acid, phenidone (1-phenyl-3-pyrazolidin), lonapalene, ichthyols, QA 208-199, anthralin and benoxaprofen. Methotrexate also inhibits the LTB_4 induced intra-epidermal accumulation of PMNs.[91] Recently, FPL 55712 has been found to be selectively inhibiting the 5-lipoxygenase pathway in rat basophilic leukemia cell homogenates.[92] A diet rich in linoleic acid has also been shown to improve psoriasis and atopic dermatitis probably by limiting the production of leukotrienes.[93]

Conclusion

The leukotrienes are the mediators or modulators of acute inflammatory reactions. Their role in respiratory allergies is supported by a number of experimental evidences. Leukotrienes are not much studied in connection with dermatological conditions and their role in the pathogenesis of certain diseases such as psoriasis, atopic dermatitis and incontinentia pigmenti needs exploration. Developments in the specific lipoxygenase pathway inhibitors and antagonists can produce a better understanding of this subject.

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