

Lipid Mediators in Inflammatory Disorders

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Summary

During the past few decades, intensive collaborative research in the fields of chronic and acute inflammatory disorders has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. Modern therapeutic approaches are still not satisfactory and shock, sepsis and multiple organ failure remain the great challenge in intensive care medicine. However, the treatment of inflammatory diseases like rheumatoid arthritis, ulcerative colitis or psoriasis also represents an unresolved problem.

Many factors contribute to the complex course of inflammatory reactions. Microbiological, immunological and toxic agents can initiate the inflammatory response by activating a variety of humoral and cellular mediators. In the early phase of inflammation, excessive amounts of interleukins and lipid-mediators are released and play a crucial role in the pathogenesis of organ dysfunction. Arachidonic acid (AA), the mother substance of the pro-inflammatory eicosanoids, is released from membrane phospholipids in the course of inflammatory activation and is metabolised to prostaglandins and leukotrienes.

Various strategies have been evaluated to control the excessive production of lipid mediators on different levels of biochemical pathways, such as inhibition of phospholipase A₂, the trigger enzyme for release of AA, blockade of cyclooxygenase and lipoxygenase pathways and the development of receptor antagonists against platelet activating factor and leukotrienes. Some of these agents exert protective effects in different inflammatory disorders such as septic organ failure, rheumatoid arthritis or asthma, whereas others fail to do so. Encouraging results have been obtained by dietary supplementation with long chain ω -3 fatty acids like eicosapentaenoic acid (EPA). In states of inflammation, EPA is released to compete with AA for enzymatic metabolism inducing the production of less inflammatory and chemotactic derivatives.

Inflammatory processes are the physiological response of the organism to different stimuli such as trauma, infections or immunological mechanisms. The inflammatory reaction is characterised by the stimulation of humoral and cellular medi-

ator systems and the release of a great variety of inflammatory mediators which result in alterations in microvascular tone and permeability. The products of the classical cascade systems and various other mediators are capable of activating the lipid

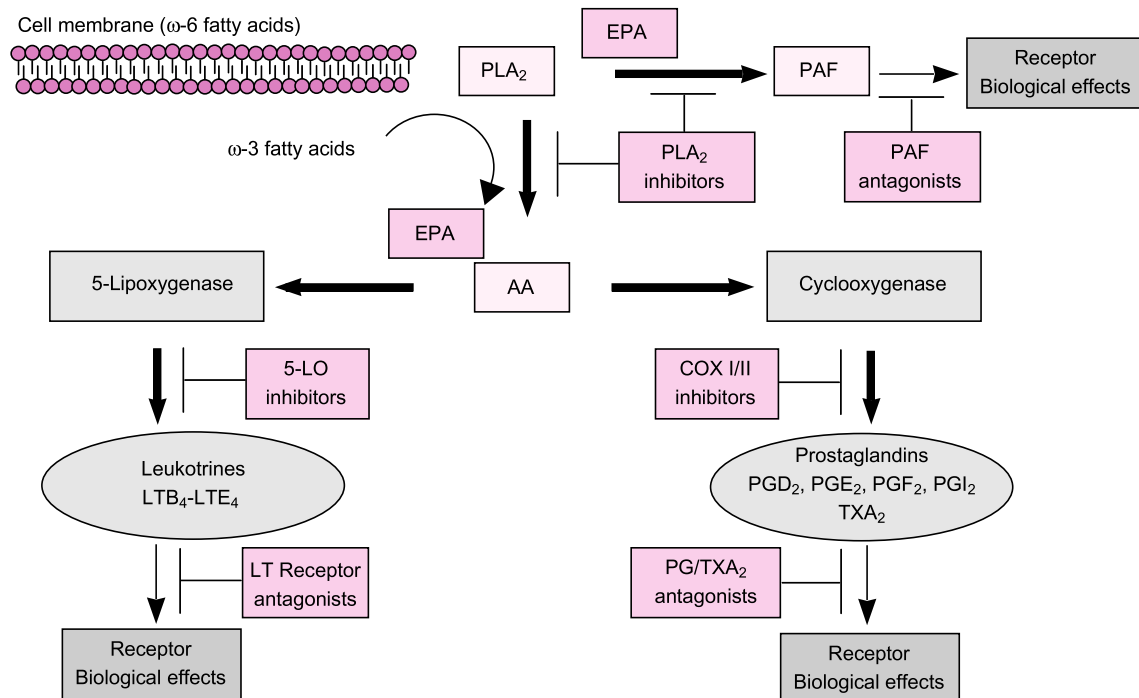


Fig. 1. Eicosanoid and platelet activating factor (PAF) pathways and possibilities for intervention in the sequence of lipid mediator generation. Depending on the fatty acid content of cellular membranes, lipid mediators are generated from ω -3- or ω -6 fatty acids via the cyclo- or lipoxygenase pathway. Arachidonic acid (AA) is metabolised to pro-inflammatory tetraene leukotrienes and diene prostanoids including thromboxane A₂. Eicosapentaenoic acid (EPA) derivatives (pentaene leukotrienes, triene prostaglandins and thromboxane A₃) exert reduced inflammatory properties. *Abbreviations:* COX = cyclooxygenase; LO = lipoxygenase; LT = leukotriene; PG = prostaglandins; PLA₂ = phospholipase A₂; TX = thromboxane.

mediator syntheses which are essentially involved in the regulation of the complex inflammatory reaction.^[1]

Prostaglandins such as prostaglandin (PG) E₂ and PGI₂ (prostacyclin) induce oedema formation (tumour) and vasodilation (rubor), and contribute to the development of hyperalgesia at the site of inflammation (dolor). Fatty acid peroxides and leukotrienes additionally increase local permeability and are potent chemoattractants for neutrophil granulocytes, resulting in a further accumulation of phagocytes in the microcirculation. The inflammatory activity is further maintained by platelet activating factor (PAF), which is another important lipid mediator stimulating neutrophils and partially influencing the vascular tone and permeability. Moreover, PAF is a chemotactic agent, which con-

tributes to leucocyte-mediated injury in inflammatory processes. The aim of this article is to give a brief update of the pathophysiological impact of lipid mediators in inflammatory disorders and to summarise the recent development of therapeutic approaches.

1. Origin and Metabolism of Biogenic Fatty Acids

The precursors of eicosanoids are lipid compounds of cellular membranes. The activation of the phospholipase A₂ (PLA₂) family induces the mobilisation of fatty acids, particularly arachidonic acid (AA), from the membrane lipid pool for the synthesis of lipid mediators at the site of cellular damage or inflammation. In individuals without relevant dietary intake of ω -3 polyunsaturated fatty

acids (ω -3-PUFAs, contained in fish oils), AA is predominantly released from the phospholipid pool of cellular membranes, which is metabolised by 2 major pathways to pro-inflammatory mediators^[2] (fig. 1). The vaso- and bronchoconstrictive metabolites thromboxane A₂ (TXA₂) and PGF_{2 α} are produced via the cyclooxygenase (COX) pathway. The TXA₂-induced vaso- and bronchospasm predominates over the relaxing effects of simultaneously generated PGI₂ and PGE₂ on smooth muscle cells of vessels and bronchioli. The pattern of eicosanoids formed depends on the enzyme content of the particular cells^[3] (fig. 2).

Alternatively, AA is metabolised by 5-lipoxygenase, thereby forming chemotactic leukotriene

(LT) B₄ and the slow reacting substance of anaphylaxis (SRS-A) identified in 1980 as LTC₄, LTD₄ and LTE₄^[4], which increase capillary permeability. In the case of increased membrane lipid content of ω -3 fatty acids, eicosapentaenoic acid (EPA) competes with AA for metabolism via the COX and lipoxygenase pathways.^[5] The EPA-derived metabolites have lower biological activity^[6] than the analogous AA derivatives. In comparison with the AA-derived TXA₂, the EPA-derived COX-product of the 3-series TXA₃ has considerably reduced pro-aggregatory and vasoconstrictive properties, while PGI₃ possesses similar antiaggregatory and vasodilative effects to those of PGI₂.

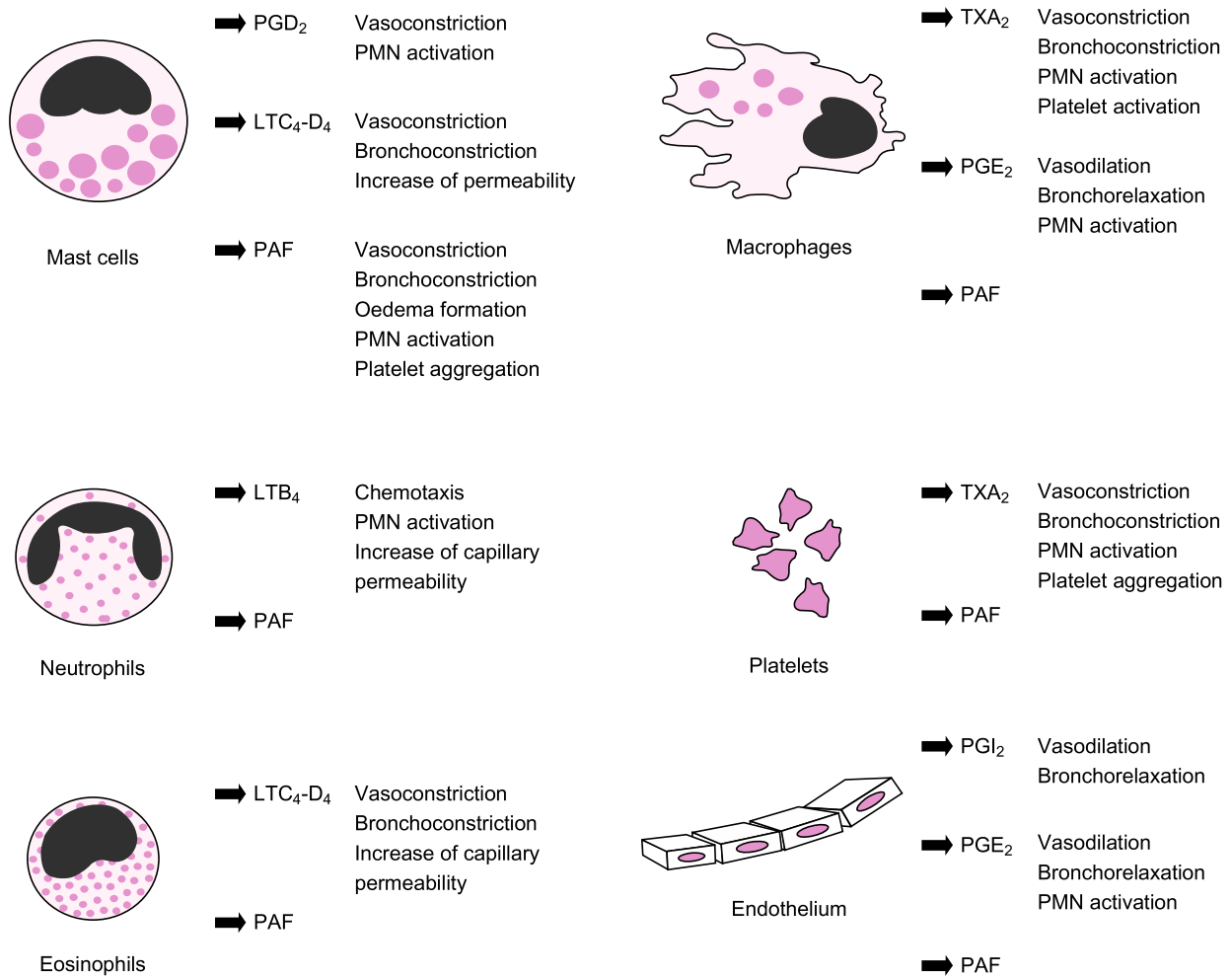


Fig. 2. Sites of synthesis and profiles of action of the most important arachidonic acid derivatives. *Abbreviations:* LT = leukotriene; PAF = platelet activating factor; PG = prostaglandin; PMN = polymorphonucleocytes; TX = thromboxane.

Enzymatic conversion of EPA generates the 5-series leukotrienes (LTB₅, C₅, D₅, E₅) which have partially antagonistic biological effects compared with AA derivatives.^[7] The vasoconstrictive and chemotactic potency of LTB₅ is 2 orders of magnitude lower than the activity of LTB₄.^[8] In addition, the generation of proinflammatory PAF is reduced by EPA via interference with the PAF precursor pool.^[9] Figure 1 provides an overview of the experimentally and clinically relevant possibilities of eicosanoid pathway modulation.

2. Involvement of the PLA₂ Family in the Inflammatory Process

Activation of the PLA₂ family is a key step in the production of precursors for the biosynthesis of inflammatory lipid mediators. Inhibition of this enzyme could result in the suppression of 3 important classes of inflammatory lipids (PGs, LTs and PAF), which offers an attractive therapeutic approach to the design of novel agents for the treatment of inflammation and tissue injury. The PLA₂ family is a series of enzymes involved in phospholipid catabolism. More than 150 PLA₂ amino acid sequences are currently available in protein sequence databases.

PLA₂ exists in both extracellular and intracellular forms. Secretory PLA₂ (sPLA₂) are Ca⁺⁺-dependent enzymes (molecular weight 14 kD, regulated by millimolar amounts of Ca⁺⁺) which are classified in 2 groups on the basis of their primary structures.^[10] Secretory nonpancreatic PLA₂ has been implicated in the pathogenesis of articular inflammation in rheumatoid arthritis, whereas pancreatic PLA₂ contributes to the tissue damage associated with acute pancreatitis. The cytosolic PLA₂ (cPLA₂) is an 85.2 kD enzyme with substrate specificity for AA. It is found in most cells and tissues and is regulated by Ca⁺⁺ in the micromolar range.^[11] cPLA₂ plays an important role in both the rapid and the prolonged cellular responses occurring during inflammatory processes.

Accordingly, in the past few years it has been proposed that PLA₂ inhibitors be applied to the control of inflammatory diseases. A tremendous

Table I. PLA₂ inhibitors and their inhibitory effects

Inhibitors	Reported inhibition of
Natural compounds	
Steroids	<i>In vitro</i>
Lipocortin-1	PLA ₂ I + II
Manoalide	<i>In vivo</i>
BMS-181162	PMA- and PLA ₂ -induced
Scalaradial	skin inflammation
Aristolochic acid	oedema and cellular infiltration
YM-265671	
YM-26734	
Thielocin A1β	
Thielocin B3	
Synthetic compounds	
3-Acrylic acid derivatives	<i>In vitro</i>
	PLA ₂ II
Dehydroabietylamine derivatives	<i>In vivo</i>
WAY-121520	rat paw oedema
	eicosanoid formation
	PMA-induced ear oedema
	bronchospasm
<i>Abbreviations:</i> PLA ₂ = phospholipase A ₂ ; PMA = phorbol ester (inflammatory stimulus).	

number of inhibitors have been claimed to be inhibitors of PLA₂ activity. PLA₂ inhibitors are currently being investigated, using classical inflammatory models.^[12] Table I shows selected inhibitory agents with marked *in vivo* activity. For adequate treatment it has been found necessary to apply a cell-impermeable PLA₂ inhibitor which affects cell activity at the membrane but does not enter the cell. Yedgar et al.^[13] demonstrated improvement in bleomycin-induced lung injury in hamsters after treatment with carmellose (carboxymethylcellulose) - linked phosphatidylethanolamine.

To date, only a few interventional studies with PLA₂ antagonists have been performed. Baboons which were immunised with a neutralising monoclonal anti PLA₂-II antibody showed significantly attenuated hypotension after treatment with viable *Escherichia coli*.^[14] Moreover, lung vascular leakage in rats due to gut ischaemia and reperfusion was blunted.^[15]

In discussing PLA₂ inhibition, it must be kept in mind that not only the formation of subsequent proinflammatory lipid mediators is prevented but also the generation of thromboregulatory, vasodilative and antiaggregatory PGI₂ and PGE₂ (fig. 1). To what extent PLA₂ inhibitors will reach therapeutic significance in inflammatory diseases will need to be elucidated in further clinical studies.

3. Platelet Activating Factor (PAF)

PAF, a PLA₂-dependent phospholipid, is an extraordinarily potent mediator of shock^[16] and inflammation. It exerts its biological effects by activating the PAF receptor, consequently stimulating protein kinase C and increasing intracellular Ca⁺⁺. PAF is found in most biological fluids and is synthesised in most cell types (fig. 2). Microvascular permeability is markedly increased by PAF, allowing fluids to leak out of the circulation. In the area of haemodynamic effects, PAF is negatively inotropic and lowers arterial blood pressure. It is a potent platelet aggregator and leucocyte activator, and it strongly promotes AA metabolism. It has been proposed that it plays a crucial role in the pathogenesis of rheumatoid arthritis, asthma, endotoxin shock and acute renal transplant rejection.

In animal models, PAF caused bronchoconstriction and increased airway resistance, pulmonary hypertension and gastrointestinal ulceration. Hence, selective PAF inhibition was investigated with a variety of PAF receptor antagonists, which were used in different animal models of sepsis and gave promising results^[17,18] (table II). Anti-inflammatory effects of PAF antagonists on experimental models of arthritis have been published^[19] indicating the modulation of different proinflammatory cytokines. Data obtained in a model of immune complex arthritis demonstrated controversial regulatory effects of the PAF antagonist bepafant (WEB-2170) on eicosanoid release. Whereas PGE₂ and tumour necrosis factor (TNF) levels dropped, LTB₄ release was increased.^[20] A clinical trial carried out by Hilliquin and co-workers^[21] revealed improvement of rheumatoid arthritis after

administration of another PAF receptor antagonist, ginkgolide B (BN-50730).

Dhainhaut et al.^[22] performed a placebo-controlled, double-blind study including 262 patients with sepsis syndrome. Besides their standard supportive therapy, patients received the PAF receptor antagonist BN-52021 twice daily (120mg) over 4 days, or placebo. The overall 28-day mortality in the BN-52021 group did not differ significantly from the placebo group but in the subgroup of patients with Gram-negative sepsis BN-52021 significantly reduced mortality (57% placebo vs 33% BN-52021). Subsequent studies (n = 608) did not confirm any benefit from PAF receptor antagonism on the overall mortality.^[23]

Table II. Inhibitors of platelet activating factor (PAF) and reported inhibitory effects

Natural compounds	
Terpenes	
ginkgolides A, B, C, M, J	platelet and leucocyte aggregation, hypotension, oedema, vasoconstriction, cardiovascular and renal effects
Lignans	
kadsurenone	platelet aggregation, hypotension, bronchoconstriction, cardiac effects, leucocyte degranulation
Gliotoxins	
FR-900452	platelet aggregation
FR-49175	bronchoconstriction
Synthetic compounds	
Structurally related to PAF	
e.g. CV-3988, SR-27417, ONO-6240, RO-193704	platelet aggregation, hypotension, endotoxin shock, bronchoconstriction, oedema, gastric ulceration, LPS-induced lung injury
Unrelated to PAF structure	
thiazoles, e.g. RP-48740, RP-52629	platelet aggregation, hypotension, bronchospasm, hyperfibrinolysis, gastric ulceration
triazolobenzodiazepines, e.g. apafant (WEB-2086), rocepagant (BN-50730), flumazenil, TCV-309	shock-induced immunosuppression, bronchoconstriction, platelet and leucocyte aggregation, oedema, hypotension, anaphylaxis, gastric ulceration, cytokine release, rheumatoid arthritis

Abbreviation: LPS = lipopolysaccharide.

Controversial results have been obtained from asthmatic patients^[24,25] and individuals with psoriasis.^[26] Decreased serum levels of interleukin (IL)-8 and IL-6 were detected after treatment with the PAF antagonist lexipafant in human acute pancreatitis.^[27] After the encouraging animal studies with PAF antagonists, the few existing clinical trials in fact demonstrated improvement of rheumatic conditions but did not show beneficial effects on survival rates in sepsis. Hence, it remains to be elucidated whether or not PAF-receptor antagonists can reach significance in the therapy of the critically ill patient.

4. Prostaglandins

A variety of substances that inhibit the COX pathway have been investigated, including non-steroidal anti-inflammatory drugs (NSAIDs). These are commonly used for the treatment of inflammation, pain and fever. More than 25 NSAIDs are currently available. These compounds are believed to act via inhibition of the COX enzyme, which catalyses the conversion of AA to the prostaglandins and thromboxane (fig. 1). Although available NSAIDs are efficacious anti-inflammatory agents, serious adverse effects limit their use.

Two forms of COX have been identified, a constitutively expressed COX-1 and a cytokine-inducible COX-2. It has been suggested that NSAID toxicity is due to inhibition of COX-1, whereas therapeutic properties derive from COX-2 inhibition at the site of inflammation.^[28,29] Therefore, selective COX-2 inhibitors such as SC-58125 may exert anti-inflammatory effects without gastrointestinal toxicity^[30] (table III). Recent clinical trials have evaluated the efficacy of COX-2 inhibitors in the therapy of arthritis, pointing towards sufficient symptom relief with an improved gastrointestinal tolerability.^[31] Moreover, evidence has accumulated that COX-2 inhibition could suppress the growth of colorectal cancer.^[32]

Studies investigating the effect of COX inhibitors in septic conditions demonstrated that ibuprofen was able to attenuate most of the adverse consequences of endotoxin administration and to

prolong survival in an animal model.^[33] Bernhard et al.^[34] recently reported reduced levels of PGI₂ and thromboxane in septic patients after administration of ibuprofen. Fever, tachycardia, oxygen consumption and lactic acidosis were blunted, whereas the development of shock, acute respiratory distress syndrome (ARDS) and mortality rate were unaltered.^[34]

While ibuprofen not only inhibits inflammatory COX products such as thromboxane but also the vasodilator PGI₂, another interesting approach is the inhalational application of PGI₂ in the therapy of acute respiratory distress to improve the ventilation-perfusion ratio (V/Q) in the lung.^[35] Aerosolised PGI₂ selectively induces pulmonary vasodilation and redistribution of blood flow from shunt areas to well ventilated regions, thereby increasing oxygenation in severe ARDS.^[35] It appears that PGI₂ is a valuable tool in the therapy of V/Q mismatch. The beneficial and adverse effects of COX inhibition suggest the combination of systemic COX-2 inhibition and additional supplementation with aerosolised PGI₂ supplementation in acute lung failure, to control inflammation.

A further approach to the selective reduction of COX-induced vasoconstriction and platelet aggregation without blockade of PGI₂ is to antagonise TXA₂ synthesis. In a model of coronary thrombosis, Guth and Müller^[36] demonstrated antithrombotic properties of samixogrel (DTTX-30SE), a

Table III. Cyclooxygenase (COX) inhibitors

Preference		Effects
COX-1	COX-2	
Piroxicam	Diclofenac	Improvement of pain, oedema, fever, tachycardia, O ₂ consumption
Sulindac	Meloxicam	
Aspirin (acetylsalicylic acid)	NS-398	lactic acidosis
Indomethacin	L-745337	Reduction of platelet aggregation mucosal prostaglandin production (COX-1 inhibition) colorectal cancer growth (COX-2 inhibition)
Ibuprofen	SC-58125	

Table IV. Effects of leukotriene (LT) receptor antagonists and 5-lipoxygenase inhibitors

LT receptor antagonists	5-lipoxygenase inhibitors	Improvement of
Cinalukast	Zileuton (A-64077)	Asthmatic reaction to inhaled LTs and PAF
Zafirlukast (ICI-204219)	Bay-x-1005	Bronchoconstriction
L-648051	BW-755C	Peak flow rate
L-649923	ICI-211965	Forced expiratory volume
LY-293111	ZD2138 (ICID-2138)	Symptoms of asthma
MK-571	Quiflapon (MK-0591)	Rhinitis/rhinorrhoea
Pranlukast (ONO-1078)	MK-886	Global disease scores in psoriasis
Pobilukast (SKF-104353)	Piriprost	Symptoms of inflammatory bowel disease
RG-12525	R-68151	Reduced requirement for β_2 -agonists
SC-41930	Lonapalene (RS-43179)	
Montelukast		
Tomelukast		
Verlukast		

Abbreviation: PAF = platelet activating factor.

combined TXA₂ receptor antagonist and synthase inhibitor.^[36] Thus, exclusive inhibition of TXA₂ generation might be a helpful tool in preventing vasoconstriction and platelet aggregation.

5. Leukotrienes

LTs are potent proinflammatory agents involved in the pathophysiology of various inflammatory diseases such as asthma, psoriasis, rheumatoid arthritis and ulcerative colitis.^[37] Therefore, many anti-LT compounds have been developed which selectively block either LT receptor sites or enzymes related to their biosynthesis. Table IV gives a synopsis of these drugs and their effects. Both categories of agents have been shown to decrease bronchial obstruction in asthma,^[38,39] suggesting that LTs and the 5-lipoxygenase products of AA are involved in sustaining the acute airway response that occurs after bronchial provocation in patients with mild to moderate asthma.

LT antagonists and 5-lipoxygenase inhibitors seem to be promising therapeutic tools but they are unlikely to dominate the further therapy of asthma. One of the main advantages for their use is that they can be given orally.^[40] Nickerson-Nutter and Medvedeff^[41] demonstrated the efficacy of the combination of LT synthesis inhibitors and cyclooxygenase inhibitors in models of rheuma-

toid arthritis. With regard to the chemotactic properties of LTB₄, specific receptor antagonists have been designed to control LTB₄ effects. It has been demonstrated that LY-293111 reduces upregulation of the macrophage and neutrophil adhesion molecule CD11b/CD18.^[42] Moreover, this LTB₄ receptor antagonist decreased the number of neutrophils in bronchoalveolar lavage fluid of patients with allergen-sensitive asthma.^[43] LTB₄ antagonism could be a therapeutic approach in LTB₄-dependent disorders, such as ulcerative colitis or psoriasis.

To date, no data are available concerning the use of these agents in septic patients. Whether the inhibition of LTs might be useful as a strategy for controlling proinflammatory lipid mediators will need to be assessed in future clinical studies.

6. Impact of ω -3 Fatty Acid Supplementation on Lipid Mediator Generation

After the epidemiological studies of Dyerberg et al.,^[44] in which it was shown that Greenland Eskimos have a lower incidence of thrombosis, coronary heart disease and myocardial infarction, interest was focused on ω -3-PUFAs, which are contained in fish oils. Numerous studies have been carried out, which showed beneficial properties of

ω -3-PUFAs in various diseases (table V).^[45] In our own studies we demonstrated that parenteral ω -3-PUFAs were rapidly incorporated into lung tissue and reduced both vascular resistance and endothelial permeability in the pulmonary circulation, thus blunting oedema formation.^[46]

The beneficial effects of ω -3-PUFAs seem to be related to the uptake of EPA into cellular membranes after dietary or parenteral application, and its subsequent metabolism. In states of inflammation, EPA is released to compete with AA for metabolism at the cyclooxygenase and 5-lipoxygenase levels (fig. 1). The metabolites of EPA (pentaene-LTs, triene-PGs and TXA₃) have less proinflammatory and chemotactic potency than the substances derived from AA (tetraene-LTs, diene-PGs and TXA₂). Considering the massive synthesis of lipid mediators during inflammatory reactions, supplementation of parenteral or enteral feeding with ω -3 fatty acids seems to be a promising therapeutic approach in inflammatory disorders, acting by modulating the lipid mediator spectrum.

7. Conclusions

Lipid mediators are 'local mediators' which act in the intercellular microenvironments, where they reach considerable levels. They are released from various tissues and cells and usually develop their effects at the site of production because of their short half-life and rapid enzymatic inactivation. Numerous mediators stimulate the lipid mediator cascade generating pro-inflammatory eicosanoids which increase their own synthesis via positive feedback loops. As a consequence, cascade systems which are essential for host defence may become self-perpetuating and independent of the original stimuli, and finally cause tissue damage. Research efforts of the past few decades have resulted in the development of therapeutic interventions at different sites of the inflammatory reaction. To date, a broad spectrum of different enzyme inhibitors and receptor antagonists has been investigated, showing a variety of effects on the course of diseases. Animal studies and *in vitro* investigations have revealed important beneficial anti-inflamma-

Table V. Effects of dietary supplementation with ω -3 fatty acids (fish oil) in various diseases^[45]

Disorder	Effect of ω -3 fatty acids
Coronary heart disease	Reinfarction rate, coronary sclerosis and restenosis after PTCA decreased
Sepsis	Incidence of nosocomial infections and length of hospital stay reduced
Lipid disorders	Increase of high density lipoprotein (HDL) levels
Neoplastic diseases	Modulation of oncogene expression
Diabetes mellitus	Improvement of rheology and neuropathies
Rheumatoid arthritis	Improvement of clinical condition
Psoriasis	Improvement of clinical condition
Ulcerative colitis	Improvement of clinical condition
Signal transducing	Blunted formation of inflammatory cytokines and mediators
HIV	Decreased HIV replication
Peritonitis	Survival after peritonitis improved (mouse)
Bacteraemia	Improvement of alveolar and liver macrophage function (rat) as well as rapid termination of experimental bacteraemia (rabbit)
Endotoxaemia	Improvement of splanchnic blood flow (rat)
Acute lung injury	Decrease of capillary leakage (rabbit)

Abbreviations: HIV = human immunodeficiency virus; PTCA = percutaneous transluminal coronary angioplasty.

tory and immune modulating properties of lipid mediator antagonism.

Inflammation and critical illness is a multifactorial process. Thus, it seems unlikely that pharmacological intervention to modulate the release of lipid mediators will be the magic bullet to improve patient outcome. The research efforts of recent years, however, contribute to a better understanding of the pathophysiological impact of lipid mediators in inflammatory disorders and offer new therapeutic approaches.

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