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Regulatory potential of *n*-3 fatty acids in immunological and inflammatory processes

H. Grimm[1]*, K. Mayer[2], P. Mayser[3] and E. Eigenbrodt[4]

[1]*Department of General and Thoracic Surgery, University of Giessen, Rudolf-Buchheim-Strasse 7, D-35385 Giessen, Germany*
[2]*Department of Internal Medicine II, University of Giessen, Klinikstrasse 36, D-35385 Giessen, Germany*
[3]*Department of Dermatology and Andrology, University of Giessen, Gaffkystrasse 14, D-35385 Giessen, Germany*
[4]*Institute for Biochemistry and Endocrinology, Veterinary Faculty, University of Giessen, Frankfurter Strasse 100, D- 35392 Giessen, Germany*

Over the last few years immunonutrition has gained increasing importance. Among other compounds lipids, especially *n*-3 polyunsaturated fatty acids, were shown to influence the immune response. The anti-inflammatory effects they exert can be induced by free fatty acids, triglyceride fatty acids, after incorporation into the membrane phopspholipid bilayer or following metabolism to eicosanoids. *n*-3 Fatty acids influence inflammatory cell activation processes from signal transduction to protein expression even involving effects at the genomic level. *n*-3 Fatty acid-mediated mechanisms decreased cytokine-induced adhesion molecule expression, thereby reducing inflammatory leucocyte-endothelium interactions and modified lipid mediator synthesis, thus influencing the transendothelial migration of leucocytes and leucocyte trafficking in general. Even the metabolic repertoire of specific immunocompetent cells such as cytokine release or proliferation is modified by *n*-3 fatty acids. Beyond this they regulate lipid homeostasis shifting the metabolic pathways towards energy supply thus optimizing the function of immune cells. Due to the regulatory impact on different processes of inflammatory and immune cell activation *n*-3 fatty acids provide positive effects on various states of immune deficiencies and diseases with a hyperinflammatory character, among which selected examples are presented.

***n*-3 Polyunsaturated fatty acids: Immunonutrition: Inflammation: Immune defence**

Introduction

Immunonutrition combining nutrition and pharmacological intervention has become of particular interest over the last few years. Among the different nutrients fat has attracted special attention. As early as 1942 the immunomodulating influence of lipids was published (Tannenbaum, 1942). Later immunological and inflammatory processes have been shown to be influenced by a selective lipid supply and the importance of polyunsaturated fatty acids (PUFA) as essential components in human nutrition has been substantiated. Among these, *n*-3 PUFA, in which the last double-bond is located between the third and fourth carbon atoms from the methyl end of the fatty acid chain, have gained increasing importance. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are scarce in Western diets but make up an appreciable part of the fat in cold-water fish and seal meat. *n*-3 PUFA have been shown to suppress (Meydani *et al.* 1991), to have no effect on (Berger *et al.* 1993) or to increase (Kelley *et al.* 1988) certain immune functions.

Essentiality and metabolism of *n*-3 fatty acids

Only algae, plants and some fungi are capable of forming *n*-3 fatty acids *de novo*, since biochemical pathways for *n*-3 fatty acid desaturation are present exclusively in the chloroplasts of these cells. Fish and other marine animals are able to elongate and desaturate these parent essential fatty acids, forming the long-chain *n*-3 PUFA (Simopoulos, 1991). α-Linolenic acid serves as substrate for EPA and DHA production in humans. However, man has only a limited capacity of synthesizing EPA from α-linolenic acid by desaturation and elongation. Long-term *n*-3 deficiency

Abbreviations: PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; PD, prostaglandin; TX, thromboxane; LT, leukotriene; PAF, platelet activating factor; ICAM, intercellular adhesion molecule; TNF, tumour necrosis factor; PPAR, peroxisome proliferator-activated receptor.

* **Corresponding author:** Dr Helmut Grimm, MD, fax +49 641 99 44709, email helmut.grimm@chiru.med.uni-giessen.de

causes neurological symptoms, retarded growth and skin lesions which are reversible upon *n*-3 fatty acid supplementation (Connor *et al.* 1991). In order to increase EPA levels, humans depend on the intake of seafood as the main source of long-chain *n*-3 fatty acids. Dietary supplementation with *n*-3 fatty acids was shown to enhance the *n*-3 to *n*-6 fatty acid ratio in membrane phospholipids of red blood cells (Brown *et al.* 1991), granulocytes (Chilton *et al.* 1993), platelets (Croset *et al.* 1992), endothelial cells, monocytes, brain cells (Tocher *et al.* 1991) and hepatocytes (Bourre *et al.* 1990). EPA and the *n*-6 arachidonic acid (AA) are competitively metabolized via the cyclooxygenase, lipoxygenase and cytochrome P 450 pathways to eicosanoids such as prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), lipoxins and epoxy-compounds. Compared to AA, EPA is the preferential substrate for lipoxygenase which explains for the higher formation of EPA-derived products at the expense of AA-derived metabolites when both free fatty acids are simultaneously available.

n-3 Fatty acids as precursors of anti-inflammatory eicosanoids

EPA-derived lipid mediators possess markedly reduced inflammatory properties (Lee *et al.* 1988). TXA 3 for example shows reduced proaggregatory and vasoconstrictive properties compared to AA-derived TXA 2, while the antiaggregatory and vasodilative efficacy of PGI 3 equals that of PGI 2. Thus, predominant prostanoid synthesis from *n*-3 fatty acids results in reduced proaggregatory and vasodilatatory effects. Beyond this, it appears that AA-derived PGE 2 potently inhibits lymphocyte proliferation much more so than the EPA-derived PGE 3 (Calder *et al.* 1992). While AA is metabolized by granulocytes, monocytes and macrophages to 4-series LT (LTB 4, C 4, D 4, E 4), potent mediators of leucocyte activation, chemotaxis and degranulation (Lee *et al.* 1985), 5-series LT with partially antagonistic properties are synthesized, when EPA serves as substrate (Lewis *et al.* 1986). Compared to LTB 4, LTB 5 possesses markedly reduced vasoconstrictive and chemotactic potencies (Lee *et al.* 1988). Even the formation of platelet-activating factor (PAF), a proinflammatory and platelet aggregating compound, is reduced by EPA which interferes with the precursor pool of PAF (Sperling *et al.* 1987).

The *n*-3 PUFA have been shown to exert beneficial effects on primary and secondary prevention of atherosclerosis, thrombosis, and embolic phenomena, hypertriglyceridemia, hypertension, autoimmune disease, and, possibly, allergy. EPA-derived PG, TX, LT, hydroxy fatty acids, and lipoxins decrease blood viscosity and platelet aggregation, increase bleeding time, and promote vasodilatation and insulin sensitivity. In addition, they inhibit very low-density lipoprotein (VLDL) formation, cell proliferation, and the inflammatory and allergic response (Harris, 1997).

Increasing evidence suggests that the opposing effects of AA and EPA may extend beyond their abilities to alter eicosanoid formation: α- linolenic acid - and EPA-rich diets in humans reduce tumor necrosis factor (TNF)-α and interleukin (IL)-1β generation from mononuclear cells (Caughey *et al.* 1996).

n-3 Fatty acids and adhesion molecules

Adhesive interactions between leucocytes and cellular or extracellular components of tissues are involved in inflammatory or immunological response mechanisms. Adhesion molecules direct the leucocyte-endothelium interactions, transendothelial migration of leucocytes and leucocyte trafficking in general (Munro, 1993). In several studies *n*-3 fatty acids have been shown to influence the expression of adhesion molecules. Culture of human endothelial cells with DHA resulted in a decreased cytokine-induced expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin associated with a reduced adherence to human blood monocytes (DeCaterina & Libby, 1996). In other *in vitro* experiments DHA inhibited TNF-α-induced expression of VCAM-1 but not ICAM-1 or E-selectin by cultured human endothelial cells (Weber *et al.* 1995). There are just a few studies dealing with the influence of dietary lipid application on the expression of adhesion molecules. Fish oil supplementation in healthy human volunteers resulted in significantly lower levels of expression of ICAM-1 and leucocyte function antigen-1 on blood monocytes (Hughes *et al.* 1996).

Modification of inflammatory cell activation by *n*-3 fatty acids

n-3 Fatty acids have been shown to influence quite a series of inflammatory processes from signal transduction to protein expression (Fig. 1, Table 1). EPA and DHA compete with LTB 4 in receptor occupancy (Yagaloff *et al.* 1995). Receptor-ligand interactions influence the structure of so called G proteins, which play an important role in signal transduction. By replacing GDP with GTP, the subunits of the G proteins dissociate activating phospholipase C. DHA inhibits TNF-α-induced phospholipase C activation (Weber *et al.* 1995). Phospholipase C triggers the phosphatidylinositol response in the course of signal transduction. During this process diacylglycerol and inositoltrisphosphate are released, activating protein kinase C which then phosphorylizes target proteins. EPA and DHA inhibit protein kinase C activation in human lymphocytes (May *et al.* 1993). AA which is released from membrane phospholipids together with diacylglycerol during signal transduction activates the transcription factor or nuclear factor NFκB, which then transmigrates into the cell nucleus and induces a number of the inflammatory genes. Fish oil-derived EPA inhibits AA-induced NFκB activation (Camandola *et al.* 1996). Following gene induction messenger RNA is produced and this process can also be inhibited by *n*-3 fatty acids (Sellmayer *et al.* 1996).

n-3 Fatty acids impair proinflammatory cytokine production by human mononuclear cells (Endres *et al.* 1989) and reduce the expression of adhesion molecules and major histocompatibility complex antigens (DeCaterina & Libby, 1996; Collie-Duguid & Wahle, 1996; Hughes *et al.* 1996; Pietsch *et al.* 1995).

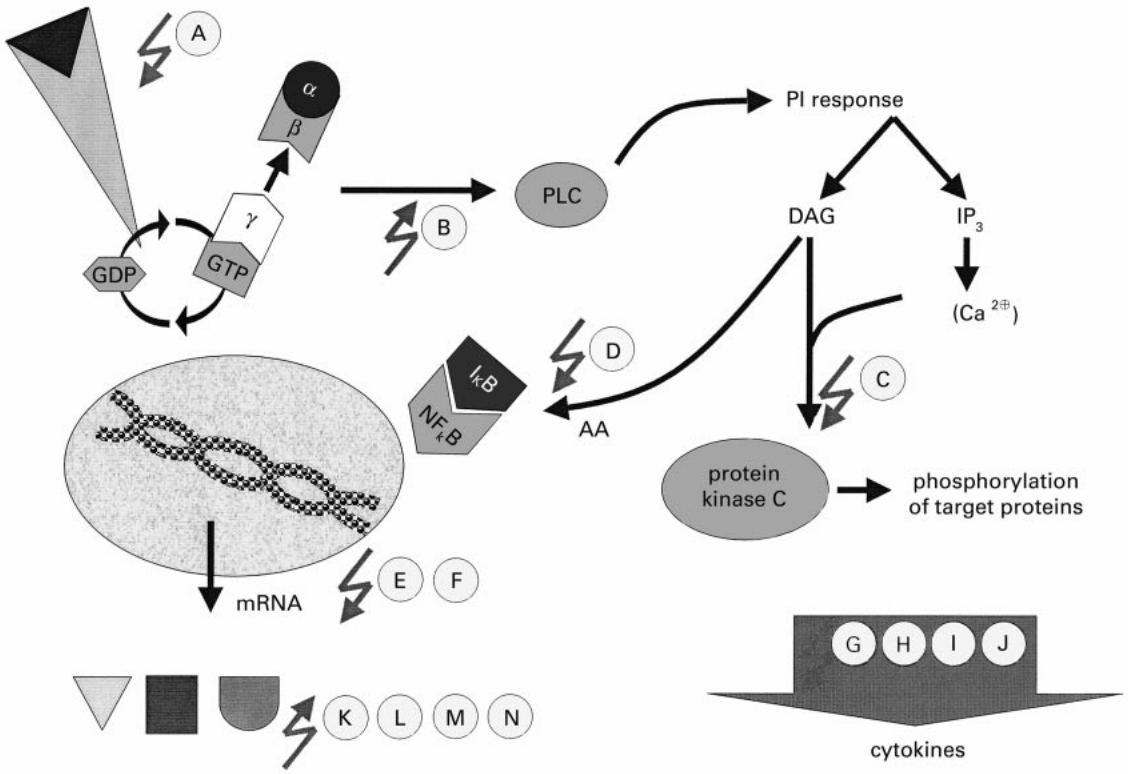

Fig. 1. Modification of cell activation by *n*-3 fatty acids.The single processes of interaction are marked with capital letters. For explanation see text and Table 1. GTP: guanosine triphosphate, GDP: guanosine diphosphate, PLC: phospholipase C, PI: phosphatidylinositol, DAG: diacylglycerol, IP3: inositoltrisphosphate, AA: arachidonic acid, NFκB: nuclear factor B or transcription factor, IκB: natural inhibitor of NFκB, mRNA: messenger RNA. The letters A - N refer to the processes described in Table 1.

Fatty acids and their metabolites regulate transcription factor function through phosphorylation, redox state or proteolytic modification or through binding of an activating ligand by the transcription factor.

n-3 Fatty acids as fuel partitioners

n-3 PUFA also act as intra- and intercellular fuel partitioners (Fig. 2). They coordinately suppress the expression of lipogenic genes and induce the transcription of genes encoding proteins of lipid oxidation and thermogenesis (Jump & Clarke, 1999; Baillie *et al.* 1999; Xu *et al.* 1999). Lipid metabolism is thereby shifted from energy storage to energy supply which is, among other things, important for the optimal function of immune cells. Peroxisome proliferator-activated receptors (PPAR) are a group of key nuclear receptors involved in lipid homeostasis (Forman *et al.* 1997; Kliewer *et al.* 1997; Devchand *et al.* 1996), which have been also identified in lymphoid tissue (Braissant *et al.* 1996). PPAR are among the family of lipid-activated transcription factors (Clarke *et al.* 1999). The amino acid sequence of PPAR indicated that they possess structural features characteristic of steroid receptors, i.e. a ligand-binding domain and a zinc finger DNA-binding domain (Issemann & Green, 1990). PPAR control the process of induction of genes encoding carnitine palmitoyltransferase (Mascaro *et al.* 1998), mitochondrial HMG-CoA synthase (Rodriguez *et al.* 1994), peroxisomal acyl-CoA oxidase (Baillie *et al.* 1999; Jump & Clarke, 1999), fatty acid binding proteins (Kletzien *et al.* 1992), fatty acid transporter and fatty acyl-CoA synthetase (Martin *et al.* 1997) and uncoupling protein 3 (Baillie *et al.* 1999). The rapidity with which PUFA modified gene transcription was consistent with a ligand-mediated event, i.e. a PUFA-binding transcription factor. *n*-3 PUFA have been shown to activate PPAR. Some fatty acids and their metabolites bind specifically to different PPAR isoforms. The EPA-derivative 8-HEPE for example is a potent activator and ligand for PPAR-α and α-linolenic acid, EPA or DHA are ligands for PPAR-α (Forman *et al.* 1997; Kliewer *et al.* 1997), PPAR-γ (Forman *et al.* 1997) and PPAR-δ (Kliewer *et al.* 1997). Apart from the PUFA their metabolites LT and prostanoids enhanced the interaction of PPAR with its DNA recognition sequence and stimulated gene transcription (Deavergne & Wahli, 1999). PGA 2, B 2, D 2 and 15 deoxy $\Delta^{12,14}$-PGI 2 are activators of PPARα, γ and δ, while PGE 2, F 2α and I 2 do not activate PPAR (Forman *et al.* 1997; Kliewer *et al.* 1997). Whereas PUFA and their metabolites upregulate genes of fatty acid oxidation and thermogenesis as ligands for PPARα, they govern lipogenic genes by a PPAR-independent mechanism. Among the lipogenic genes controlled by PUFA are hepatic glucokinase (Jump *et al.* 1994), pyruvate kinase (Liimatta *et al.* 1994), pyruvate dehydrogenase (Da Silva *et al.* 1993), acetyl-CoA carboxylase (Katsurada *et al.* 1990), fatty acid synthase (Clarke *et al.* 1990; Xu *et al.* 1999) and adipocyte fatty acid synthase (Mater *et al.* 1998).

PUFA control lipogenic gene transcription through

Table 1. Modification of cell activation by *n*-3 fatty acids

	Substrate supplemented	Type of study	Species	Effects	Reference
A	EPA, DHA	*in vitro*	pig	direct competition with LTB_4 in receptor occupancy	Yagaloff *et al.* 1995
B	DHA	*in vitro*	human	inhibition of TNF-α-induced PLC activation	Weber *et al.* 1995
C	EPA, DHA	*in vitro*	human	inhibition of lymphocyte protein kinase C activation	May *et al.* 1993
D	EPA	*in vitro*	human	inhibition of AA-induced $NF_\kappa B$ activation	Camandola *et al.* 1996
E	EPA	*in vitro*	human	inhibition of AA-induced cell growth (c-fos, Egr-1)	Sellmayer *et al.* 1996
F	DHA	*in vitro*	human	reduced induction of VCAM-1 mRNA	Weber *et al.* 1995
G	EPA	enteral	human	decreased TNF-α and IL-1 synthesis	Endres *et al.* 1989
H	Fish oil	parenteral	rat	decreased MNC TNF-α and IL-6 release	Grimm *et al.* 1994
I	DHA	*in vitro*	human	decreased IL-6 and IL-8 release	De Caterina & Libby, 1996
J	EPA	enteral	human	decreased MNC TNF-α and IL-1 S release	Caughey *et al.* 1996
K	DHA	*in vitro*	human	decreased VCAM-1, E-Selection and ICAM-1 expression	De Caterina & Libby, 1996
L	EPA, DHA	*in vitro*	human	decreased cytokine induced VCAM-1 and ICAM-1 expression	Collie-Duguid & Wahle, 1996
M	Fish oil	enteral	human	decreased MHC II expression	Hughes *et al.* 1996
N	EPA	enteral	human	decreased CD36 expression	Pietsch *et al.* 1995

another family of transcription factors, i.e. sterol regulatory binding proteins (SREBP). SREBP are anchored in the endoplasmic reticulum and nuclear envelope. Upon proteolysis SREBP-1 releases a 68 kDa peptide that translocates to the nucleus (Brown & Goldstein, 1999). The translocation of the mature form of SREBP-1 appears to be inhibited by the amount of PUFA incorporated into the membrane phospholipids (Worgall *et al.* 1998). Dietary fish oil was shown to correlate with a reduced membrane content of SREBP-1, reducing the nuclear content of 68 kDa SREBP-1 upon stimulation. There is evidence that *n*-3 PUFA suppress SREBP-1 expression by accelerating the rate of SREBP-1 mRNA decay (Xu *et al.* 1999).

In summary, *n*-3 fatty acids improve the energy supply to functionally important cells, including immune cells, since they direct fatty acids away from storage towards oxidation by functioning as ligand activators for PPARα and downregulate lipogenic gene induction by suppressing the expression and nuclear translocation of SREBP-1.

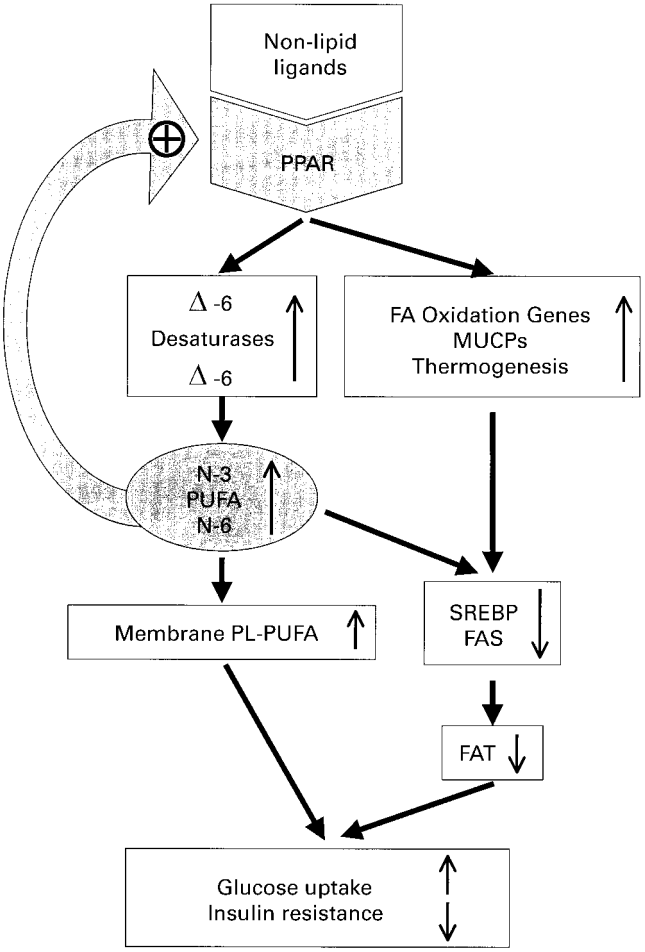

Fig. 2. Schematic representation of PUFA-mediated regulation of fuel partitioning. PUFA: polyunsaturated fatty acids, PPAR: peroxisome proliferator activated receptor, MUCPs: mitochondrial uncoupling proteins, SREBP: sterol response element-binding protein, FAS: fatty acid synthase.

Regulatory potential of *n*-3 polyunsaturated fatty acids in clinical and experimental studies

Taking into account their influence on the processes of inflammatory and immune cell function it is not surprising that *n*-3 fatty acids exert positive effects on different states of immune deficiencies and diseases with a hyperinflammatory character. Here selected examples of inflammatory disorders are presented (sepsis and psoriasis are discussed in detail in separate articles of this supplement).

Experimental transplantation

In transplantation research the prolongation of graft survival is accepted as a means of establishing the efficacy of new immunosuppressive drugs. We demonstrated that continuous infusion of a fish oil-based lipid emulsion proved to be immunosuppressive, as indicated by a 50 % prolongation of graft survival in a rat heart allotransplant model (Grimm *et al.* 1994*b*). The process of rejection is accompanied by a progressive accumulation of mononuclear cells in the graft with the amount of T-cells, especially T-helper cells characterizing the intensity of the rejection process (Häyry, 1984). In the fish oil-treated rats the number of infiltrating cells, i.e. polymorphonuclear neutrophils and the particularly important CD 4+ and CD 8+ T-cells (Mason & Morris, 1986), was reduced by up to 50 % compared with the controls (Grimm *et al.* 1995). Decreased graft infiltration coincided with a diminished fraction of T-cells circulating in the peripheral blood, indicating a reduced T-cell recruitment due to fish oil. This traffic of lymphocytes before being trapped in allografts alters the profile of peripheral blood mononuclear cells, which is used clinically for cytoimmunological monitoring (May *et al.* 1990). Proliferation and graft infiltration of immunocompetent cells depend on cytokine-regulated cell-cell interactions. Mitogen-stimulated TNF-α release by mononuclear cells harvested from fish oil-treated rats was significantly reduced compared with the controls (Grimm *et al.* 1994*a*), an effect demonstrated by others upon enteral administration of fish oil (Endres *et al.* 1989). The observed inhibition of proliferation and graft infiltration of immunocompetent cells in the fish oil group is at least partially explained by the reduced cytokine release by mononuclear cells and the diminished recruitment of T-cells from lymphatic compartments. Furthermore, T-lymphocyte proliferation has been shown to be inhibited *in vitro* by an increased concentration of free fatty acids via an eicosanoid-independent mechanism (Calder *et al.* 1992). Interestingly, fish oil infusion led to a 2·5-fold increase in free plasma fatty acid concentration compared to soybean oil-infused controls (Grimminger *et al.* 1996). Artificial lipid aggregates are known to activate the endothelial lipoprotein lipase, including translocation of this enzyme from its cellular binding sites into the vascular compartment (Peterson *et al.* 1990). Individual components of the free fatty acid pool might have influenced the rejection process by inhibiting the mobilization of polymorphonuclear granulocytes (PMN). When compared with the *n*-6 product LTB 4, which mediates adhesion, diapedesis and chemotaxis of PMN (Goetzl & Pickett, 1980), LTB 5 synthesized from free EPA is almost inactive. Free AA and EPA derived from an intercellular fatty acid exchange among active inflammatory cells (Chauncee *et al.* 1988) are metabolized to lipid mediators via cooperative eicosanoid synthesis. The considerable increase in free plasma EPA (>30 μmol/l), exceeding by 2-fold free AA concentration, upon fish oil infusion in our model, is assumed to result in a preferential synthesis of 5-series LT by neutrophils stimulated in this natural environment (Grimminger *et al.* 1992). This causes a shift in LT generation toward EPA-derived products which explains the reduced PMN graft infiltration due to fish oil infusion, since LTB 5 possesses a more than 10-fold reduced chemotactic and PMN-activating capacity as compared with LTB 4 (Leaf & Weber, 1988). Lipid-mediator generation toward EPA-derived products in response to fish oil was even more pronounced in platelets isolated from their plasma compartment. *Ex vivo* stimulation of these thrombocytes led to an approximately 1:1 release of TXA 3 to TXA 2, which reflects the highest 3-series to 2-series prostanoid ratio ever reported. By comparison, dietary *n*-3 fatty acid supplementation for several months resulted in 5–15 % generation of TXB 3 in relation to TXB 2 by human thrombocytes stimulated *ex vivo* (Fisher & Weber, 1983). Release of the potent vasoconstrictor and platelet aggregator TXA 2 was shown to be increased during acute rejection in experimental transplantation (Foegh, 1988). The considerable shift from TXA 2 to TXA 3 generation following fish oil infusion must be anticipated to have contributed to the prolonged allograft survival, since TXA 3 lacks the prorejection properties of TXA 2 (Leaf & Weber, 1988).

Experimental lung injury

In acute and chronic pulmonary inflammation *n*-3 PUFA have been shown to exert beneficial effects.TXA 2-mediated pulmonary hypertension, vascular leakage and subsequent lung edema induced by cytokines and LT characterize the adult respiratory distress syndrome (Conolly & Repino, 1997), an acute inflammatory lung disorder. In an experimental model of acute lung injury the infusion of free AA caused a marked aggravation of pulmonary edema formation and circulatory disorders due to 4-series LT and 2-series prostanoid generation (Grimminger *et al.* 1997). In contrast, vascular leakage was attenuated by the infusion of free EPA paralleled by the generation of 5-series LT. In accordance EPA-rich diets were shown to be organ-protective in different models of septic lung failure or bleomycin-induced lung injury (Mancuso *et al.* 1997; Murray *et al.* 1991).

Rheumatoid arthritis

This inflammatory disorder with idiopathic etiology involves multiple synovial joints. A reduction of morning stiffness and tender joints was observed in patients upon dietary fish oil supplementation (Kremer, 1996) paralleled by lower serum levels of IL-1β. Fish oil seems to have a beneficial effect in stable rheumatoid arthritis and should be regarded as an adjuvant therapeutic perspective if combined with conventional therapy.

Inflammatory bowel disease

Lipid mediators and cytokines are involved in the development of chronic lesions observed in ulcerative colitis and Crohn's disease (Thyssen *et al.* 1996; Vilaseca *et al.* 1990). In experimental models fish oil proved to be effective in reducing inflammatory eicosanoid generation and in attenuating organ damage (Campbell *et al.* 1997). In a rat model intravenous infusion of an α-linolenic acid-rich lipid emulsion decreased LTB 4 generation (Inui *et al.* 1996*a*) and reduced the macroscopic damage of the colon wall (Inui *et al.* 1996*b*). In accordance with the proposed benefits of *n*-3 PUFA epidemiological data correlate the increased incidence of Crohn's disease in Japan with an increased ratio of dietary *n*-6 to *n*-3 PUFA (Shoda *et al.* 1996). Enteric-coated fish oil preparations employed in a study on Crohn's disease showed a benefit for high-risk patients in remission in terms of a markedly reduced relapse rate and reduced laboratory indicators of inflammation (Belluzzi *et al.* 1996).

In ulcerative colitis dietary fish oil was shown to improve the histological findings (Stenson *et al.* 1992) and to reduce the requirement for antiinflammatory drugs, including steroids (Aslan & Triadafilopoulos, 1992; Hawthorne *et al.* 1992). Fish oil proved to be particularly effective as an additive drug in active disease (Hawthorne *et al.* 1992) and prolonged standard therapy-induced remissions without offering advantages as the sole agent in maintenance therapy (Loeschke *et al.* 1996). In summary, fish oil might have additive effects in the treatment of ulcerative colitis when taken together with 5-aminosalicylic compounds.

Concluding remarks

In the 1970s *n*-3 fatty acid research was launched with the observation that Greenland Eskimos, a population that consumes large amounts of fatty fish and marine animals, showed a low mortality rate from coronary heart disease (Bang *et al.* 1971; Kromann & Green, 1980). An increased bleeding time was reported and a lower risk of thrombus formation hypothesized. Meanwhile *n*-3 fatty acids were demonstrated to influence a series of cellular and molecular processes. They were shown to be metabolized by the same enzymatic pathways as *n*-6 fatty acids resulting in the production of antithrombotic as well as antiinflammatory eicosanoids with inhibiting effects particularly on platelets and PMN. Beyond this, *n*-3 fatty acids once incorporated into membrane phospholipids influence membrane fluidity and the structure of membrane receptors. They are even involved in the process of transmembranal signal transduction and were shown to regulate the activity of various transcription factors thus influencing cell function even at a genomic level. Based on these properties *n*-3 fatty acids play a role in the regulation of cell surface protein expression, cell-cell interactions, cytokine release and energy supply from lipids. On the basis of these manifold mechanisms it is not astonishing that *n*-3 fatty acids influence the function of specific and unspecific immune cells and exert beneficial effects in diseases with a hyperinflammatory character. They even turned out to be immunosuppressive in an experimental transplant model. This repertoire of anti-inflammatory and immunosuppressive properties holds further promise that *n*-3 fatty acids might be integrated as adjunct therapeutic measures in a variety of hyperinflammatory or autoimmune diseases.

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