Fish or Chips?
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Cell membranes are not simply barriers separating intracellular from extracellular space. Rather, they represent a dynamic high-turnover system that adapts to current demands. During inflammation, prostaglandins and leukotrienes are formed from membrane-derived phospholipids. Encouraging improvements in critically ill patients were observed after nutritional replacement of long-chain omega-6 fatty acids with long-chain omega-3 fatty acids, contained in fish oil.

Since the epidemiological studies of Dyerberg et al. (3) in the early 1970s, which demonstrated that Greenland Inuit eating diets high in fish oil have a lower incidence of thrombosis, coronary heart disease, and myocardial infarction, interest has been focused on omega-3 polyunsaturated fatty acids (PUFA). Compared with a Caucasian control group, the content of omega-3 PUFA (contained in fish oil), especially of cis-5,8,11,14,17-eicosapentaenoic acid (EPA), was increased in thrombocytes of Greenland Inuit. Since then, numerous studies have been carried out in vitro as well as in vivo that showed fewer inflammatory properties of omega-3 PUFA compared with omega-6 PUFA (5) in various diseases, such as coronary heart disease, lipid disorders, neoplastic diseases, and diabetes mellitus. The inflammatory reaction is characterized by the stimulation of humoral and cellular mediator systems and the release of a great variety of inflammatory mediators, which result in alterations in microvascular tone and capillary wall permeability. Lipid mediators (Fig. 1) are essentially involved in the regulation of these complex processes. Arachidonic acid (AA)-derived prostaglandins such as PGE2 and PGI2 enhance the formation of an inflammatory edema (tumor), are favored by their vasodilative properties (rubor), and contribute to the development of hyperalgesia at the site of inflammation (dolor). Fatty acid peroxides and leukotrienes increase the local capillary wall permeability and are potent chemoattractants for neutrophil granulocytes, resulting in a further accumulation of phagocytes in the microcirculation at the site of action. The current review focuses on the experimental and clinical evidence of anti-inflammatory effects of omega-3 PUFA, outlines the mechanisms of action, and delineates therapeutic implications.

Origin and metabolism of biologically relevant fatty acids

Eicosanoids are “local mediators” and may be generated in almost all tissues and in circulating leukocytes (5). They usually develop their effects at the site of production because of their short half-life and rapid enzymatic inactivation (5). The precursors of eicosanoids are lipid compounds of cellular membranes (Fig. 2). The activation of membrane-linked phospholipase A2 in the case of inflammation induces the mobilization of fatty acids, particularly AA, from the membrane lipid pool for the synthesis of eicosanoids at the site of cellular damage or inflammation.

Unsaturated fatty acids are divided into mono- and polyunsaturated fatty acids. Depending on the position of the first double bond, counted from the methyl end, the fatty acids are further subdivided into omega-3, omega-6, and omega-9 PUFA. Omega-6 PUFA, however, are essential for humans and must be nutritionally provided (2). Omega-6 PUFA, such as linoleic acid (C18:2) and AA (C20:4), are contained in plant oils and adipose tissues of mammals, which make up the major fraction of PUFA in the diet of the population of industrialized countries (Fig. 3).

Our title question—"Fish or Chips?"—is obviously answered in favor of "chips" by the majority. Accordingly, the composition of human cell membranes in industrialized populations shows a predominance of omega-6 PUFA. The main source for the human supply of EPA and docosahexaenoic acid (DHA) is sea fish (15). Therefore, populations with major dietary intake of sea fish incorporate large amounts of omega-3 PUFA into their cellular reservoirs, which partly replaces omega-6 PUFA. Diets enriched with omega-3 PUFA result in a change of the omega-3-to-omega-6 ratio in the membrane fatty acid composition of erythrocytes, neutrophils, platelets, endothelial cells, monocytes, and brain and liver cells in favor of pentanoic acids.

Mechanisms of action

The products of the classical inflammatory cascade systems—coagulation, complement, the kallikrein-kinin system, and others—activate eicosanoid synthesis. In individuals with relevant dietary intake of omega-3 PUFA, AA is predominantly released from the phospholipid pool of cellular membranes, which is metabolized by two major pathways of proinflammatory mediators (Fig. 2). The vaso- and bronchoconstrictive metabolite thromboxane A2 (TXA2) is produced via the cyclooxygenase pathway. The TXA2-induced vaso- and bronchospasm prevails over the relaxing effects of simultaneously generated prostacyclin (PGI2) and PGE2 on smooth muscle cells of vessels and bronchioli. The type of eicosanoid formed depends on the enzyme pattern of the respective cells (Fig. 1). Although TXA2 is produced mainly in platelets and macrophages, PGI2 is derived from endothelial cells. PGE2 is
predominantly synthesized in the renal medulla, whereas mast cells are the main source for PGD₂. Besides the described cyclooxygenase pathway, AA is also metabolized via the lipoxygenase pathway (Fig. 2), thereby forming the leukotrienes (LTB₄, LTC₄, LTD₄, LTE₄) and other eicosanoids, which increase capillary permeability and attract neutrophils via chemotactic properties. LTB₄ is produced in neutrophils and macrophages, whereas eosinophils and mast cells form LTC₄, LTD₄, and LTE₄, which have formerly been termed slow-reacting substance of anaphylaxis (SRS-A). In the case of increased membrane lipid content of omega-3 PUFA, EPA will, for example, compete with AA for metabolic action with

<table>
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<tr>
<td>SFA</td>
<td>3-Series Prostanoids: TXA₂, PGE₂, PGD₂</td>
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<td>MUFA</td>
<td>5-Series Leukotrienes: LTD₄, LTC₄-LTE₄</td>
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<tr>
<td>OA (C18:1)</td>
<td>n3 PUFA (EPA C20:5)</td>
</tr>
<tr>
<td>n6 PUFA (AA C20:4)</td>
<td>n9 PUFA (DHA C22:6)</td>
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FIGURE 1. Sites of synthesis and profiles of action of the most important arachidonic acid (AA) metabolites in leukocytes, platelets, and endothelial cells. LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; TX, thromboxane.

FIGURE 2. Differential metabolism of saturated fatty acids (SFA) and mono- (MUFA) and polyunsaturated fatty acids (PUFA) via cyclooxygenase and 5-lipoxygenase after inflammatory activation of phospholipase A₂ (PLA₂). PLA₂ releases fatty acids from membrane triglycerides (scissors). EPA, eicosapentaenoic acid; OA, oleic acid; n3, n6, and n9, omega-3, -6, and -9 PUFA, respectively.
cyclo- and lipoxygenase pathways (Fig. 2). The EPA-derived metabolites have lower biological activity compared with the analogous AA derivatives. Whereas AA is metabolized by cyclooxygenase to diene prostanoids (prostaglandins and thromboxane) and by lipoxygenase to 4-series leukotrienes and hydroxyeicosatetraenoic acids, EPA is converted by cyclooxygenase into trien-prostanoids. Compared with the AA-derived TXA2, the EPA-derived cyclooxygenase product of the 3-series thromboxane TXA3 has considerably reduced proaggregatory and vasoconstrictive properties, whereas PGI3 possesses similar antiaggregatory and vasodilative effects compared with PGI2. Moreover, EPA represents a preferred substrate for the 5-lipoxygenase (5). After the enzymatic conversion of EPA, the 5-series leukotrienes (LTB5, LTC5, LTD5, LTE5) are generated; these leukotrienes have partially antagonistic biological effects compared with AA derivatives. Because of less intrinsic activity, the vasoconstrictive and chemotactic potency of LTB5 is two orders of magnitude lower than the activity of LTB4 (5).

Although the impact of omega-3 fatty acids on lipid mediator generation has been greatly clarified, the understanding of subcellular effects is still limited. Omega-3 PUFA affect biophysical characteristics of cellular membranes by alteration of the membrane phospholipid composition and the content of cholesterol, which improves membrane fluidity. The associated increase in the deformability of blood cells might account for improvements of blood rheology after fish oil intake. Furthermore, omega-3 PUFA modify the function of membrane-linked enzyme systems, signal transducing, and receptor functions. Recent work of Lee and coworkers (10) demonstrated that activation of general proinflammatory pathways, such as NF-κB and cyclooxygenase-2 expression by saturated fatty acids and inhibition of this induction by PUFA, is mediated through a common signaling pathway derived from toll-like receptor 4 (Tlr-4). Tlr-4 conveys signals as a part of innate immunity from the endotoxin receptor (CD14) on the surface of macrophages to the inner cell. As a result of downregulation of nuclear transcription factors, formation of cytokines such as TNF-α and IL-1 in monocytes might be reduced after fish oil. Omega-3-PUFA therefore seem to interfere with early inflammatory signal transduction processes and thus to be capable of blunting hyperinflammation.

Nutritional and epidemiological studies

Since the discovery of the significance of omega-3 PUFA in the incidence of cardiovascular diseases (3), numerous other effects have been reported. In particular, the antiarteriosclerotic effects of omega-3 PUFA have been intensively investigated (5, 12, 14). The correlation between high plasma omega-6 lipid concentrations and the development of arteriosclerosis is well known. In this context, it was shown that a high fish oil diet reduced hyperplasia of arterial intima and coronary sclerosis, resulting in reduced rates of restenosis after coronary angioplasty. The underlying mechanisms might include downregulation of microinflammatory processes in the vessel wall (Fig. 2), offering protection from reactive intima hyperplasia. With respect to diabetic vascular occlusive disease and neuropathies, omega-3 PUFA showed protective effects on the vessel wall and improvement of blood rheology, both associated with an improved metabolic situation in these tissues. The reason for these findings could be the reduced formation of platelet-derived growth factor from the vascular endothelium after consumption of omega-3 PUFA or...
increased release of the “endothelium-derived relaxing factor” nitric oxide (14). Nitric oxide in combination with vasodilative prostaglandins promotes the relaxation of the smooth muscle of arteries and resistance vessels.

Early onset effects of omega-3 PUFA in acute inflammation

In contrast to the many previous studies investigating the effects of long-term (weeks, months) nutrition with omega-3 PUFA, more recent interest has focused on the question of whether or not omega-3 PUFA are integrated into the phospholipid pool even after short-term intravenous application and whether they induce organ-protective effects by means of their metabolites after inflammatory stimulation. Under conditions of inflammatory reactions of different origins, humoral and cellular mediator systems are locally activated. In severe diseases, such as the systemic inflammatory response syndrome (SIRS) or sepsis, hyperinflammation may result in subsequent severe tissue injury, culminating in multiple organ failure. In this regard, the lung with its large alveolar and vascular surfaces is exceptionally susceptible to inflammatory damage. Various clinical circumstances (sepsis, multiple blood transfusions, pulmonary contusion, aspiration, etc.) can induce the acute respiratory distress syndrome (ARDS). Neutrophils and macrophages are activated by selectin and β2-integrin-related interactions with the endothelium. Subsequent release of proinflammatory AA metabolites results in capillary damage, increased capillary permeability, and, consequently, lung edema. By means of the above-discussed mechanisms, omega-3 PUFA seem to be capable of blunting or inhibiting hyperinflammatory processes associated with ARDS, as is shown below.

In isolated and cell-free perfused rabbit lungs, a relevant uptake of the omega-3 fatty acids EPA and DHA into the tissue was observed as early as 3 h after lung perfusion with 1% fish oil emulsion in the perfusion buffer (1). During inflammatory stimulation of the lungs, induced by calcium ionophore A23187, which triggers AA metabolism via transmembraneous Ca2+ influx, the rise of pulmonary arterial pressure was considerably blunted. The lung weight increase was reduced by 50% compared with controls receiving either saline or omega-6 PUFA, indicating reduced edema formation (9). The latter observations after omega-3 PUFA were paralleled with a considerable reduction of the capillary filtration coefficient (ml·min⁻¹·mmHg capillary pressure⁻¹ per 100 g lung weight]) as an indicator of vascular permeability (9). These data correlated with an increased synthesis of EPA-derived cysteinyl leukotrienes, whereas the AA-derived leukotrienes and TXA2 were only detectable in small quantities. Compared with controls, treatment with omega-3 PUFA did not influence release of vasodilatory prostacyclin.

The potential clinical impact of these findings (1, 9) was assessed in a cohort of patients with ARDS by Gadeck and the Enteral Nutrition in ARDS Study Group in 1999 (4). Because of the improvement of pulmonary gas exchange, lower inspiratory oxygen concentrations and lower levels of positive end-expiratory pressure were able to ensure adequate oxygen delivery compared with controls (4). As a result, the patients’ number of respirator-free days after omega-3 PUFA increased and the length of hospital stay was shortened. Data from our own investigations in patients after major abdominal surgery revealed that short-term intravenous application of omega-3 PUFA improved liver function (Fig. 4, Ref. 6) without untoward effects on platelet function and coagulation (7). Moreover, omega-3 PUFA helped to maintain the balance between pro- and anti-inflammatory cytokines (6) and thus prevented hyperinflammatory complications. Amelioration of liver functions might be explained by an increase of hepatoprotective blood flow and thereby improved bacterial defense (13) after omega-3 PUFA.

In view of the clinical consequences, these findings point toward prophylactic and acute therapeutic effects in inflammatory diseases, which seem to be attainable by simple rearrangement of nutritional components. As a result, consensus conferences of the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition, and the American Society for Clinical Nutrition recognized the therapeutic value of omega-3 PUFA-containing nutrition and suggested larger-scale clinical investigations (8, 12).

Conclusions

Lipid membranes are not rigid barriers separating intracellular from extracellular space. Rather, they represent a dynamic high-turnover system, adapting to current demands. Membrane-derived lipids are local mediators that act in intracellular microenvironments, where they quickly reach considerable concentrations. Numerous mediators stimulate the generation of proinflammatory eicosanoids, which increase their own synthesis via positive feedback loops. As a consequence, cascade systems, which are essential for host defense, may become self-perpetuating, independent of the original stimulus and may ultimately cause tissue damage. Rapid control of those hyperinflammatory conditions might be achieved with omega-3 PUFA contained in fish oil, even in critically patients, by shifting the eicosanoid profile to diene prostanooids and pentane leukotrienes.

![Figure 4](http://physiologyonline.physiology.org/fig10_2003_01.png)
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References


