EDITORIAL

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Anna Wiktorowska-Owczarek[B, D, F], Małgorzata Berezińska[B, D],
Jerzy Z. Nowak[A, B, E]

PUFAs: Structures, Metabolism and Functions*

Department of Pharmacology and Toxicology, Medical University of Lodz, Poland

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Polyunsaturated fatty acids (PUFAs) include two series of fatty acids: omega-6 and omega-3 series. PUFAs have amphiphatic properties: hydrophilic head and hydrophobic tail. Such structure and other properties of unsaturated fatty acids are responsible for exerting the following biological action: maintaining cell-membrane fluidity, inhibiting inflammatory processes, decreasing secretion of proinflammatory cytokines by monocytes/macrophages, decreasing susceptibility to ventricular rhythm disorders of the heart, improving functions of vascular endothelial cells, inhibiting blood platelet aggregation and decreasing triglyceride synthesis in the liver. In an organism, aracidonic acid (ARA) is converted to prostanoids series 2 (PGE2, PGI2, TXA2) and leukotrienes series 4 (LTB4, LTC4, LTD4) which are endowed with pro-inflammatory potential and are able to induce platelet aggregation and vasoconstriction. The metabolism of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) gives prostanoids series 3 (PGE3, PGI3, TXA3) and leukotrienes series 5 (LTB5, LTC5, LTD5); this group of eicosanoids shows anti-inflammatory, antiplatelet and antiarrhythmic properties (**Adv Clin Exp Med 2015, 24, 6, 931–941**).

Key words: polyunsaturated fatty acids, ARA, EPA, DHA.

Adequate development, both physical and intellectual, depends to a great extent on proper nutrition. Therefore, a diet should be varied and should include proper amounts of proteins, carbohydrates, fats, vitamins and mineral content. Fats are an essential element of the diet, which are mostly used as a highly energetic material. Some data described an association between low mortality rate among the Eskimos due to cardiovascular reasons and their diet rich in polyunsaturated fatty acids (PUFAs) derived from sea fish, which has focused attention to other important functions of this group of compounds in the human body [1, 2]. Studies on the use of fish oils in the prevention and treatment of cardiovascular diseases as well as in psychiatric and ophthalmological disorders have been undertaken. Omega-3 fatty acid derivatives play a significant role in the process of blood coagulation, in inflammation, regulation of blood vessel contractility and proper brain and eye retina functioning. Thus, they are necessary not only for adequate growth and development of the human body but also for the functioning of the adult organism. The results of studies on omega-3 fatty acids have aroused interest in the possibility of increasing their level in the human body through proper nutrition as well as through modified food and diet supplements.

The intake of dietary supplements containing omega-3 fatty acids has increased in all countries of the world because of their beneficial effects on the human body, which have been recommended by different medical specialists and the media [4, 56, 60]. The aim of the present study is to present the most important facts regarding the structure and metabolism of polyunsaturated fatty acids and their therapeutic application.

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The Structure and Nomenclature of Fatty Acids

Fats (lipids) are a heterogeneous group of compounds built up of carbon and hydrogen atoms, possessing a tsmall number of oxygen-containing functional groups. Because of their specific molecular structure, they have amphipatic (amphiphilic) properties: hydrophilic head and hydrophobic (lipophilic) tail – such a structure affects their arrangement within the cellular membrane. Lipids are divided into simple and complex compounds (waxes – lanoline, cetaceum, beeswax). Simple fats include esters of fatty acids and various alcohols. In the case of lipids, glycerol is an alcohol that contains three hydroxyl groups at three present carbon atoms, which according to stereospecific numbering are defined as sn-1, sn-2 and sn-3

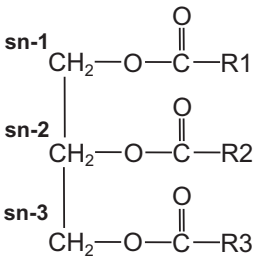

Fig. 1. Glycerol – stereospecific numbering

(Fig. 1). Depending on the number of attached acids, mono- (1 acid), di- and triacylglycerols are formed. Simple triacylglycerols are characterized by the presence of one type of acid; however, there are two or three types of acids in mixed triacylglycerols. Fatty acids are the main components of membrane lipids and most frequently contain 12 to 24 carbon atoms forming hydrocarbon chains. They may be represented by saturated (without double bonds), monounsaturated (one double bond) and polyunsaturated (with two or more double bonds) fatty acids – Fig. 2 presents polyunsaturated fatty acids omega-3 and omega-6 series [3–5].

Fatty acids commonly occurring in nature possess usual names (e.g. palmitic acid, linoleic acid, arachidonic acid), however due to a variety of forms and great possibilities of conversions, definite rules regarding nomenclature of such structures have been implemented. The order of numbering carbon atoms in aliphatic fatty acids starts with the carboxyl group; and carbon in this group (COOH) is defined as C1, and further numbering is as follows: C2, C3, etc. According to another classification, carbon attached to the carboxyl group, i.e. C2 is defined by the Greek letter alpha – α, C3 – β, C4 – γ etc., and the carbon atom furthest from the COOH group is defined by the letter omega – ω. When we start counting from carbon ω to the first

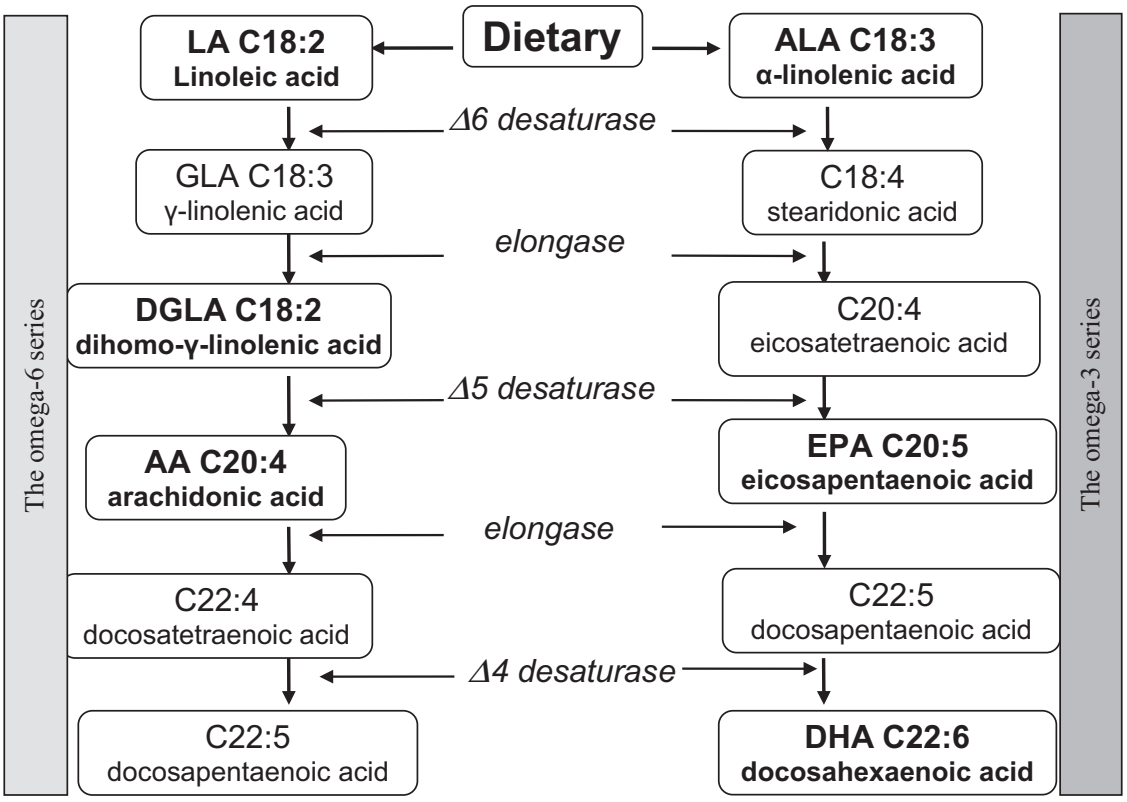

Fig. 2. Pathways of biosynthesis of unsaturated fatty acids omega-6 and -3 series

double bond between carbon atoms in the hydrocarbon chain (-C = C-), we can determine the affiliation of acid to series of omega-3, omega-6 or omega-9 fatty acids. The chemical structure of fatty acids is presented in the following way: the number of carbon atoms (e.g. C22), the number of double bonds and the group ω; e.g. docosahexaenoic acid is defined as C22 : 6ω-3, which means that it possesses 22 carbon atoms and six double bonds and it belongs to the group of omega-3 (possesses the first double bond when we count from the end at the third carbon atom) [3–5].

Metabolism of Fatty Acids

Saturated fatty acids such as palmitic (C16:0) or stearic (C18:0) acid, which mainly provide energy, are produced in the human and other mammal organism. The formation of malonyl coenzyme A (malonyl-CoA) and acetyl-CoA is a fundamental stage of fatty acid synthesis. The elongation process takes place with the involvement of fatty acid synthase. However, some mammals including *Homo sapiens* do not possess enzymes (or possess them in slight amounts) capable of creating double bonds in fatty acid chains at a place further than at carbon C9. The human being is not able to produce linoleic (LA; C18 : 2ω-6) and α-linolenic acid (ALA; C18 : 3ω-3) in the sufficient amounts to meet the requirements for these compounds, thus they are named exogenous acids. These two compounds give rise to the others, and all of them constitute a group of essential unsaturated fatty acids of high physiological significance (Fig. 2). Looking through literature reports the reader can find rich nomenclature connected with this group, such as polyunsaturated fatty acids (PUFAs), essential fatty acids (EFAs) or long-chain polyunsaturated fatty acids (LCPUFAs). The human exhibits the ability to elongate these two exogenous acids to a slight but de facto insufficient degree; however, the requirement for them is higher than 'endogenous' supply [3–5].

Linoleic and α-Linolenic Acid Elongation

The omega-6 series derives from linoleic acid and includes arachidonic acid (AA or ARA; C20 : 4ω-6), the last one being docosapentaenoic acid (DPA; C22 : 5ω-6). Administration of α-linolenic acid into the body enables to form omega-3 fatty acid series such as eicosapentaenoic acid (EPA; C20 : 5ω-3) and docosahexaenoic acid (DHA; C22 : 6ω-3). Biosynthesis of these acids requires the involvement of Δ-6, Δ-5 desaturases (enzymes forming double bonds) and elongases (elongating hydrocarbon chain) occurring in the endoplasmic reticulum. The last stage of conversions, i.e. β-oxydase, requires translocation of substrates to peroxysomes. Omega-9 series of fatty acids also competes for the same enzymes and these reactions result in a final formation of eicosatrienoic acid (C20 : 3:ω-9) from oleinic acid (C18 : 1:ω-9), which is not so important as the remaining two series because it can be totally synthesized by humans from saturated stearic acid. Moreover, a high concentration of eicosatrienoic acid, which normally occurs in trace amounts, indicates deficiency of substrates for the synthesis of omega-3 and omega-6 series of polyunsaturated fatty acids; this value might thus have a diagnostic importance. The same enzymes participate in conversion of fatty acids of all three series, showing functional connections between metabolic paths of omega-3, -6 and -9 acids, which depend on competing for enzymes and regulating a given stage of transformation based on a negative feedback through a direct or indirect product [3, 4, 6].

Biosynthesis of Eicosanoids

As a result of exogenous conversions of omega-3 and omega-6 families of fatty acids, such compounds as arachidonic (ARA), docosahexaenoic (DHA) and eicosapentaenoic acid (EPA) are formed, which are precursors of mediators of a wide physiological importance (Fig. 3). Eicosanoids (prostaglandins and leukotrienes) are products of the arachidonic and eicosapentaenoic acid metabolism; their names derive from the Greek world – *eikosi* – twenty, as their precursor contains 20 carbon atoms. Arachidonic acid affected by cyclooxygenase (COX) undergoes conversion into prostaglandin E_2 (PGE_2), which is an inflammatory mediator, prostacyclin I_2 (PGI_2), responsible for blood vessel dilation and thromboxane A_2 (TXA_2) activating blood platelet aggregation and vasospasm. Due to lipoxygenase (LOX) action, 4-series leukotrienes are formed, which play a crucial role in the development and maintenance of the inflammatory response. Eicosapentaenoic acid (EPA, C20 : 5ω-3) is metabolized in a similar way with the participation of the same enzymes, i.e. cyclooxygenase and lipoxygenase, however its metabolic products are different: 3-series prostanoids and 5-series leukotrienes of different properties mostly antiinflammatory (PGE_3, LTA_5, LTB_5, LTC_5, LTD_5), antiaggregatory (TXA_3) and vasodilative (PGI_3) [3, 6–8]

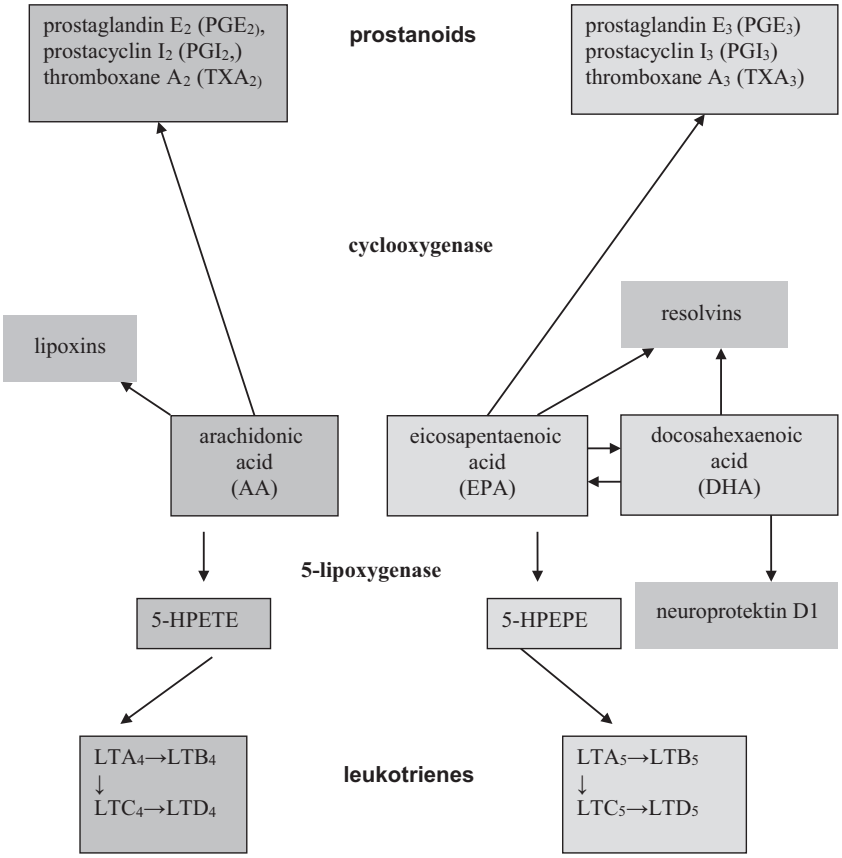

Fig. 3. Metabolic pathways of a polyunsaturated fatty acids omega-6 and omega-3 series

Formation of Compounds Capable of Inducing Extinction of Inflammatory Processes

Prostanoids and leukotrienes are mobilized in response to damaging stimulus, i.e. inflammation. Acute inflammation that lasts for a relatively short time is a beneficial process in which threatening factors are removed and functions as well as tissue structures are restored. Inflammatory resolution/ /extinction is an important active stage, which is mediated by small molecules that are the products of the omega-6 and omega-3 acid metabolism. Under the influence of lipoxygenases (LOX: LOX-5, LOX-15 and LOX-12) ARA, EPA and DHA acids undergo conversion into lipid mediators actively extinguishing the inflammatory process such as lipoxin A4 and B4 (LXA4 and LXB4 – arising from ARA), E-series resolvins (RvE1 and RvE2) – generated from eicosapentaenoic acid and D-series resolvins (RvD1, RvD2, RvD3 and RvD4) generated from docosahexaenoic acid [9, 10]. Furthermore, at least two oxylipins are formed from DPA-ω6 acid, which also have properties extinguishing inflammation. At the same time, a particular involvement of acetylsalicylic acid (ASA), commonly named aspirin/polopirin, has been observed, which acetylates cyclooxygenase-2 (COX-2), and ASA-COX2 in turn metabolises ARA, EPA and DHA acids into intermediate products, which next form lipoxins and E- and D-series resolvins with participation of lipoxygenases. COX-2 acetylation inhibits formation of prostanoids produced by this enzyme; however, it maintains the ability to synthesize 15R-hydroxyeicosatetraenoic acid, which is next converted into resolvins through activated inflammatory cells. To emphasize the role of ASA in the initiation of these conversions, the achieved products are preceded by the symbol 'AT' derived from aspirin triggered: aspirin-triggered lipoxin – ATL, aspirin-triggered resolvin E –ATRvE or aspirin-triggered resolvin *D* –ATRvD [11–13]. The described above ASA functions indicate an important role of this drug as an anti-inflammatory agent, which not only inhibits the initiation of the inflammatory process but participates in the extinction of ongoing inflammation as well.

DHA, influenced by lipoxygenase (LOX), is also converted into other compounds with protective potentials, i.e. protectins PD1 (D1 indicates derivation from DHA and no. 1 defines the first compound in this series). The protectin produced in the central nervous system is named neuroprotectin, NPD1, which has neuroprotective properties. NPD1 occurs in photoreceptors and retinal

pigment epithelium (RPE); it is responsible for the inhibition of expression and activity of proinflammatory factors and proapoptotic caspase-3, as well as for the stimulation of antiapoptotic factors (i.e. proteins of Bcl-2 family) [14–19].

There is still another path of the DHA conversion affected by lipoxygenases, which leads to the formation of the next group of compounds, maresins, having antiinflammatory activity. Until now, only one compound from this group, MaR1, has been determined. The term "maresin" derives from the initial letters of the words macrophage, resolution, inflammation – which describe the site of formation of this compound and its biological function. Biological activity of MaR1 includes multidirectional interactions leading to the limitation of polynuclear leukocyte aggregation in the area of inflammation resulting from the stimulation of phagocytic activity of macrophages [13, 20, 21].

Oxidation of Polyunsaturated Fatty Acids

Due to double bonds (–C = C–), PUFAs are especially susceptible to oxidation by radicals produced in excessive amounts during the oxidative stress (homeostasis disorders resulting in intensive production of radical oxygen species that are not sufficiently deactivated by antioxidants). Lipid peroxidation without the enzyme involvement comprises the following processes: initiation, propagation and termination. The process of initiation depends on the $OH^{\bullet}$ reaction with PUFA, as a result of which a lipid radical is produced, which in reaction with oxygen provides LOO• (a radical of lipid peroxide), having the ability to detach hydrogen from other molecules and to generate subsequent radicals L•. Such radicals undergo conversion into alcoxylic radicals LO•, in the presence of iron Fe^{2+}, and next into peroxylic radicals that are decomposed into reactive aldehydes: 4-hydroxynonenal, 4-hydroxyhexanal, malonic dialdehyde and acroleins, defined as secondary toxic transmitters. Omega 6-series fatty acids, such as linoleic or arachidonic acid, are mainly converted into 4-hydroxy-2-nonenal (HNE), and omega-3 acids (EPA, DHA) into 4-hydroxy-2-hexanal (HHE) [22–24]. Monoperoxides are always primary products of PUFAs, which are defined as lipid peroxides with an additional group of LOOH. The number of monoperoxides that can be generated from unsaturated fatty acids depends on the number of double bonds (n) and can be represented by the following formula: 2n-2, which means that 2 monoperoxides with –OOH groups will generate from linoleic acid (18 : 2) at the 9^{th} and 13^{th} carbon atom (9-OOH, 13-OOH). On the basis of the above formula, 6 different monoperoxides are produced from arachidonic acid (20 : 4) – 8 from EPA (20 : 5) and 10 from DHA (22 : 6). As a consequence of PUFA oxidation, changes in the physical properties of the cell membrane (a decrease in electric potential differences on both sides of the membrane) occur, which results in the loss of functioning and structural integrity of the cellular membrane [21–23].

Lipids are attacked by free radicals in a special way. The conversions described above, which occur under the influence of radical oxygen species (ROS), are not the only ones because Morrow et al. [25] in 1990 discovered isoprostanes, the compounds resembling prostaglandins, which are generated from arachidonic acid due to ROS oxidation, irrespectively of cyclooxygenase (COX). Further studies revealed that due to peroxylic transformations, isoprostanes of different types can arise both *in vitro* as well as *in vivo* conditions from omega-3 series of PUFAs, such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids [26, 27]. Isoprostanes derived from DHA within the tissues of the central nervous system are named neuroprostanes; what is interesting, there are more of them as compared to other isoprostanes [28]. In *in vivo* conditions and in the presence of increased partial pressure of oxygen from arachidonic acid, additional compounds of the isofuran structure and DHA-structurally similar compounds called neurofurans are formed [29]. Their higher concentration has been found in the cerebral cortex of animals used as a model of Alzheimer disease [30]. Even the first observations regarding free-radical formation of isoprostanes from arachidonic acid suggested that these compounds might be mediators of oxidative stress. Such a suggestion has been confirmed by further research on free-radical formation of isofurans and neurofurans in biological fluids such as urine, blood or cerebrospinal fluid. Thus, the measurement of iso/neurofuran concentration may be a reliable biomarker of intensity of oxidative stress and lipid peroxidation in the cell/tissue/organism, and a biomarker of an advanced process of neurodegeneration in the nervous tissue [27, 29]. There are some suggestions that supplementation of fish oil containing a high amount of EPA provides antiinflammatory properties also as a result of considerable reduction in forming isoprostanes (F_2-IsoPs) from arachidonic acid with strong proinflammatory activity [30].

Fatty Acid Functions

Omega-3 and omega-6 fatty acids play definite functions in the organism and their new functions are still being discovered. On the basis of

unsaturated fatty acid conversions in the human body, their role in forming prostanoids and leukotrienes have been observed. When they arise from ARA, like PGE_2, PGD_2, or 4-series leukotrienes, they exhibit proinflammatory activity that is commonly known and described in the reports which discuss the mechanisms of nonsteroidal anti-inflammatory drug action.

Basic studies have indicated that DHA and EPA acids are beneficial for the human body exerting the following biological action [31]:

– maintaining cell-membrane fluidity,
– inhibiting inflammatory processes,
– decreasing secretion of proinflammatory cytokines by monocytes/macrophages,
– decreasing susceptibility to ventricular rhythm disorders of the heart,
– improving functions of vascular endothelial cells,
– inhibiting blood platelet aggregation,
– decreasing triglyceride synthesis in the liver.

Omega-3 Fatty Acid Effects on Cell-Membrane Fluidity

The membrane of the cell as well as of mitochondria and other cellular elements is built up of proteins and lipids which contain saturated or unsaturated fatty acids. Saturated fatty acids have simple 'tails' because they do not possess double bonds. They are densely packed, so there is no space between the chains, resulting in a rigid membrane. The presence of unsaturated fatty acids with numerous double bonds (occurring in nature in the *cis* conformation) causes 'tail'/hydrocarbon chain bending, which in turn results in forming free spaces and affects membrane fluidity and elasticity.

Polyunsaturated docosahexaenoic acid (DHA) commonly occurs in cellular and plasma membranes of the organism. Its high amount has been particularly found in the brain tissue and the retina (up to 50% and 60–80% membrane phospholipids, respectively). DHA can occur in the free state or combined with phosphatidylethanolamine (PEA) and phosphatidylocholine (PC), as well as with phosphatidylserine (PS) [5, 32].

DHA in the cell membranes (membrane 'rafts' are especially rich in DHA) exerts influence on their physical properties – ensures their proper fluidity, and also affects the proper functioning of membrane receptors, ion channels and transporting proteins, i.e. elements involved in adequate cell reactivity, its ability to react to stimuli and in intercellular communication [33].

Omega-3 Fatty Acid Effects on Anti-Inflammatory Activity

Omega-3 and omega-6 PUFAs are incorporated into cell membranes. They are released from membrane phospholipids and constitute substrates for eicosanoid synthesis, i.e. prostaglandins, prostacyclins, thromboxanes and leukotrienes.

Eicosanoids arising from arachidonic acid (omega-6) induce an inflammatory response by 2-series prostanoids synthesize. PGE_2 may also induce anti-inflammatory effect by increasing lipoxin production by inducing 15-LOX (lipooxygenase) [19]. Arachidonic acid-derived eicosanoids are responsible for proaggregation and vasoconstriction effect (TXA_2 and TXB_2) and proliferation of cancer cells (especially of breast, colorectal and prostate cancers) [7].

3-series prostanoids and 5-series leukotrienes arising from fatty acids of omega-3 series (mainly from EPA) possess weaker inflammation inducing properties or even anti-inflammatory properties, which means that the body response to factors inducing infection, impairment or inflammation depends on the composition of the cell membrane. When the proportions are favourable for omega-3 PUFAs, the response to inflammatory factors is weaker. Production of lipoxins and resolvins, as well as oxylipins from both groups of polyunsaturated fatty acids allows to extinct the ongoing inflammatory process; lack of such reaction may contribute to the development of autoimmune diseases, chronic inflammation or excessive tissue damage and development of various diseases whose pathogenesis is associated with inflammatory disease. Omega-3 acid derivatives may also have antithrombotic activity counteracting blood vessel narrowing and inhibiting carcinogenesis [34, 35].

Omega-3 fatty acids have anti-inflammatory and anti-allergic activity, predominantly through the inhibition of excessive immune response, competing for mutual enzymes with omega-6 fatty acids in the metabolic pathway. They decrease the synthesis of proinflammatory compounds (LTB_4, PGE_2, IL-1, TNF) as well as stimulate the synthesis of cytokines with anti-inflammatory action (IL-2, TGF). Alleviation of inflammatory symptoms has been observed after the administering omega-3 acid preparations in the case of rheumatoid arthritis, ulcerative colitis, asthma, psoriasis and other autoimmune diseases. Moreover, there are some reports showing that they can also alleviate the course of inflammatory processes of the bacterial or viral origin [8, 36, 37].

Omega-3 Fatty Acid Effects on Cardiovascular System

Omega-3 fatty acids beneficially affect lipid metabolism. EPA and DHA decrease the triglyceride level in the plasma by 30% and in the case of patients with hyperglyceridemia even by 80%. They also decrease the level of total and LDL fraction cholesterol, while increasing HDL fraction level [37, 38].

DHA and EPA normalize blood pressure through the rise in the level of prostacyclins and endothelium-derived relaxing factor (EDRF) – nitrogen oxide (NO), belonging to vasodilated factors, as well as through the reduction in the level of tromboxane A_2 (TXA_2), a strong vasoconstrictor, and PGE_2 (stimulates renin production and reversed sodium resorption). Hypotensive activity can be also caused by beneficial changes in the lipid composition of the cell membrane at the receptor sites for vasoactive hormones and by the weakened response to them. A correlation has been found between the acid composition in the fatty tissue and the blood pressure value; an increase in α-linolenic acid in the fatty tissue by 1% was associated with a drop in the systolic pressure by 5 mm Hg. A complete hypotensive activity develops after 3–4 weeks of omega-3 acid consumption [36–40].

Omega-3 acids have antithrombotic activity. They prolong the bleeding time by decreasing the platelets tendency towards adhesion and aggregation. This activity results from inhibiting the synthesis of prothrombotic compounds such as TXA_2 and PAF (platelet-activating factor), decreasing fibrinogen concentration, increasing prostacyclin level and activity of the tissue plasminogen activator as well as of angiotensin III [41–43]. Omega-3 PUFA not only potentiate platelet response to antiplatelet drugs, but also reduce thrombin formation. In coronary artery disease, it was found that in patients who received omega-3 PUFA together with aspirin and clopidogrel fibrin clots had a less compact structure, which made it less resistant to lysis [44, 45].

Due to omega-3 fatty acids, stabilization of the atheromatous plague takes place. In subjects using omega-3 supplementation, thicker fibrous capsule of the plaque and less inflammation have been observed. Beneficial changes may occur even in old atheromatous plaques. Some reports can be found in the literature, which indicate that omega-3 supplementation may contribute to a decrease in the incidence of restenosis after coronary angioplasty and to a decrease in the incidence of vessel closure after coronary arterial bypass graft surgery [46, 47].

Moreover, omega-3 acids play an important role in prevention of sudden death caused by arrhythmia in patients with ischemic heart disease. They function as modulators affecting calcium flow *via* type L channels and controlling calcium release from the endoplasmic reticulum. Thanks to the presence of omega-3 fatty acids, elongation of the refraction period (by 150%) and elevation in the threshold of cardiomyocyte excitability (the power of electrical stimulation required for inducing a functional potential increases by 50%) have been noted. Long-term administration of omega-3 fatty acids at the dose of 1 g per day leads to a decrease in the rate of hospitalization and death risk due to heart rhythm disorders [48, 49].

Omega-3 Fatty Acids Effects on the Nervous System

DHA plays an essential role in a proper functioning of the nervous system of adults, as well as in its development during fetal life and childhood. It is one of the main constituents of phospholipids in neuron cell membranes, especially in the synapse. Omega-3 fatty acids are also indirectly involved in the synthesis of serotonin and dopamine [50]. They seem to have a protective function in mood impairments. Moreover, some reports state that they may exert a beneficial effect on concentration and hyper-reactivity in children with developmental coordination disorders (DCD) [51]. Some researchers think that the consumption of omega-3 fatty acids by subjects with psychic disorders may provide health benefits not only due to their protective activity exerted on the nervous system but also due to alleviation of metabolic adverse effects of psychotropic medications and obesity frequently occurring in this group of patients [52].

DHA also appears in high amounts in the eye retina. The most important function performed by DHA in the eye is the role of a substrate for the earlier described compounds that have cytoprotective and anti-inflammatory activities including neuroprotectin NPD-1. DHA is involved in the structure of plasmic membranes of photoreceptors, and especially their outer segments (POS). Moreover, the presence of DHA in POS is essential for proper functioning of visual pigments (e.g. rhodopsin) [4]. However, in certain situations, such as the occurrence of oxidative stress, DHA easily undergoes peroxidation and decomposes into smaller seven-carbon fragments, from which immunogenic conjugates (adducts) arise after binding protein molecules (e.g. albumins). Such molecules mobilize the immune system and can generate autoaggression reactions, which in consequence can lead to age-related macular degeneration (AMD). An example of a seven-carbon compound is 4-hydroxy-7-oxohept-5-enoic acid (HOHA), which is

further converted into 2-(ω-carboxyethyl) pyrrole (CEP) and conjugated with the protein molecule (adduct CEP-protein). Peroxidative fragmentation and formation of immunogenic adducts are likely to be also associated with EPA and other acids or even all PUFAs consumed with food or in a form of diet supplementation. However, free radicals are also generated as a result of DHA oxidation, whose unfavourable action depends on local possibilities of their neutralization through antioxidative protection systems [23, 24]. The above situation demonstrates that PUFAs are very important constituents for adequate functioning of the nervous system or the vision organ, however due to their special susceptibility to oxidation they can give rise to molecules exerting adverse effect on the above mentioned structures and contribute to the development of various diseases. Therefore, supplementation with DHA and other long-chain PUFAs should be combined with antioxidant compounds, e.g. vitamins E and C as well as lutein and zeaxanthin, the latter ones are especially recommended for subjects at risk of AMD development.

Fatty Acids in Diet

Omega-3 and omega-6 PUFAs are also defined as essential polyunsaturated fatty acids (EFA), which emphasizes their significant role in the functioning of the organism and the necessity of supplying it with food. EFAs are absorbed in the digestive tract (diet, supplementation), reach the liver, where they are esterified into phospholipids and next they are released into the bloodstream in the form of lipoproteins. EFAs are necessary for proper growth, development and functioning of all tissues and organs, especially the retina, brain and heart. Taking into consideration the importance of EFAs, and particularly omega-3 series, for proper functioning of the human body, the international health organizations highlight the need for constant and regular consumption of about 200 mg of DHA/day by adults in the form of various foods rich in DHA and EPA or pharmacological preparations containing these acids [5, 53].

Marine fish predators are the richest food sources of DHA and EPA. Other types of fish like salmons, herrings, sardines, mackerels, tunas, halibuts, flounders and trout contain ω-3 series of fatty acids in slightly lower amounts. They also occur in different seafoods and algae. Cultivated microalgae, *Cryptehecodinium cohnii,* are one of ω-3 acid sources, whose oil contains 40% of DHA (i.e. DHASCO – DHA Single Cell Oil) – the product which has obtained a positive opinion of the United States Food and Drug Administration (US FDA) and is recommended to be given to infants and small children. Another recommended source of fatty acids is the oil produced by microalgae *Schizochytrium* sp., containing 40% of DHA, 2.5% of EPA and additionally 15% of docosapentaenoic acid (DPA), belonging to ω-6 (DPA-ω6) acids. It has been stated that bioequivalence and effectiveness of supplementation are similar to those achieved by taking capsules containing oils from both types of algae and do not differ from an equivalent portion of ready to eat salmon. In different countries, food enriched with small amounts of fatty acids, i.e. bread, milk products, margarine or juice, has been produced. These products are regarded as functional food, which beneficially affects the human body owing to the presence of bioactive components (natural or added), regardless of its nutritional properties [54, 55].

Numerous national and international health organizations dealing with health protection recommend regular consumption at least 500 mg/ /day of EPA and DHA [56]. The National Group of Experts in their recommendations regarding consumption and supplementation of diet with omega-3 fatty acids advise adults to take fatty acids, DHA and EPA, in the amount from 0.5 do 1.5 g (mean 1 g) per day. In order to achieve beneficial health effects, the ratio of omega-6 to omega-3 fatty acids in the diet should be 4 : 1 [4, 31]. Because omega-3 acids decrease platelet aggregation in the blood, which prolongs the time of bleeding, their simultaneous application with anticoagulation and antiplatelet drugs may potentiate the response to drugs [45, 57, 58]. Therefore, in patients taking these drugs, an additional dose of omega-3 fatty acids should not exceed 1 g per day. This dose, which may be covered by food, exerts cardioprotective action. In patients with high risk of cancer, cardiac, rheumatoid and neurodegenerative diseases, the EPA and DHA dose can be increased up to 1.5 g per day. In the treatment of hypertriglicerydemia, omega-3 fatty acids can be used as supplements under the physician's control at a dose of 2–4 g/day (capsules containing 465 mg of EPA and 375 mg of DHA in the form of ethylene esters) [59]. It is particularly beneficial to consume omega-3 fatty acids in everyday diet, combined with statin or fibrate treatment – this combination is recommended especially in mixed dyslipidemias [60]. According to the FDA data, consumption up to 3 g of omega-3 fatty acids per day should not induce side effects; however, higher doses should be reserved for special situations (specified therapeutic indications) and used under the physician's supervision [4, 31].

The best solution for people who do not have any special indications for fatty acid supplementation seems to be the consumption of fatty acid-rich

natural products, e.g. a meal containing fatty sea fish twice a week, what approximately corresponds to 500 mg/day of EPA + DHA + DPA. The European Food Safety Authority (EFSA) draws attention to the fact that due to the growing environmental pollution unlimited consumption of meat of large fish predators (especially tuna, shark, marlin and pike) may lead to the excessive exposure to mercury [61]. Since toxic activity of mercury compounds is most dangerous for fetuses, infants and small children, women planning to be pregnant, pregnant women, breastfeeding mothers and younger children are advised to choose smaller species of fish that do not cumulate such a high amount of pollutants. In this group of people possibilities of supplementation with PUFA preparations should be considered.

Conclusions

Unsaturated fatty acids of omega-6 and omega-3-series are not synthesized by humans in the sufficient amounts and must be provided with food. That is why they are called essentials. Sea fish oil is a source of DHA and EPA, which considerably limits their availability in the diet as compared to omega-6 fatty acids present in plants. However, omega-3 series fatty acids exhibit particularly beneficial effect on proper functioning of the brain, cardiovascular system or the eye retina, owing to the presence and the number of double bonds in the molecule. Double bonds, so significant for molecular properties, easily enter into reactions with radicals, which promotes their oxidation and changes their characteristics. At the same time, it is worth emphasizing that no significant adverse reactions of this group of compounds have been reported. At the same time, it should be remembered that they cannot replace a pharmacological therapy. However, due to their involvement in maintaining heath they should be supplied in proper amounts, if possible in an adequately balanced diet or as pharmacological preparations, i.e. diet supplements that should also contain compounds possessing the properties of lipophilic antioxidants, e.g. vitamin E.

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Address for correspondence:

Anna Wiktorowska-Owczarek
Department of Pharmacology and Toxicology
Medical University of Lodz
Żeligowskiego 7/9
90-752 Łódź
Poland
E-mail: anna.wiktorowska-owczarek@umed.lodz.pl

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