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Fatty Acids: From Membrane Ingredients to Signaling Molecules

Michio Hashimoto and Shahdat Hossain

Abstract

Fatty acid constitutes the foundation cell membranes, provides metabolic energy, affects functions of membrane-bound enzymes/receptors, conducts signaling cascades, and helps in learning-related memory cognition in mammals, including humans. Structurally, the fatty acids are of two kinds: saturated and unsaturated; the latter are again of mono- and polyunsaturated types. From nutritional perspectives, they are of essential and nonessential types. Omega-6 linoleic acid (ω -6 LLA, C18:2) and ω -3 alpha linolenic acid (ω -3 α LLN, C18:3) and ω -6 arachidonic acid [ω -6 AA, C20:4]; it is conditional] are essential fatty acids (EFAs). In addition, mammalian brains cannot biosynthesize the ω -3 docosahexaenoic acid (ω -3 DHA, C22:6) in adequate amounts because of lack of necessary enzymes. Thus, DHA is essential for the growth and development of the brains. Deficiency of DHA produces visual- and learning-related memory impairments, and neurodegeneration in the aged brains and Alzheimer's disease brains. Finally, this chapter will highlight and broaden the awareness about the essentiality of different fatty acids with a special emphasis on DHA.

Keywords: docosahexaenoic acid, eicosapentaenoic acid, arachidonic acid, alpha-linolenic acid and linoleic acid, eicosanoids, docasonoids, brain cognition

1. Introduction

The concept of fatty acid was first introduced by the French chemist Michel Eugène Chevreul as *graisse acide* (acidic fat) [1]. Fatty acids are chemically defined as carboxylic acids with either saturated or unsaturated aliphatic chains and are derived after hydrolysis of fats or oils. A fatty acid has, therefore, an acid group at one end of its molecule and a methyl group at the other end [2, 3]. Fatty acids are essential structural components of the cell; they also play important roles in energy requirements and signaling cascades in the cell. Both plant and animal cells can synthesize fatty acids. Animal cells, however, cannot synthesize some of the fatty acids; they must take them from plant sources. These fatty acids are called essential fatty acids (EFAs) in the animal body. Some fatty acids are also synthesized by lower organisms such as phytoplanktons, which act as primary members of the food chain. On the basis of the location of the double bonds from the methyl terminal position of the unsaturated fatty acids (UFAs), they are named as ω -3 and ω -6 UFAs. Biologically, fatty acids are esterified with glycerol, phosphoglycerol, and cholesterol and are referred to as triacylglycerol, phospholipids, and cholesterol esters, respectively. Esterified fatty acids can constitute the structural components

or dietary fuels for cells and organisms; they can also form complex liposomal structures (including lipoproteins) for transporting lipid components from the hepatic tissues to extrahepatic tissues and vice versa.

1.1 Saturated versus unsaturated fatty acids

Fatty acids whose aliphatic carbon chains are fully saturated with hydrogen atoms or contain only C-C single bond and/or contain no C=C double bonds are simply referred to as saturated fatty acids (SFAs). Fatty acids containing C=C double bonds are referred to as unsaturated fatty acids (UFAs). UFAs are again classified as monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs): if they contain only one C=C double bond, they are MUFAs; if they contain more than one C=C double bond, they are then called PUFAs (see **Figure 1** for detail). Because of the presence of C-C single bonds or C=C double bonds, they have characteristic structural features and differences in physical as well as chemical properties and have significant roles in the constitution of cellular membranes.

1.2 Omega-3 (ω -3) versus omega-6 (ω -6) PUFAs

The Greek letter omega (ω) is used in the systemic nomenclature of the polyunsaturated fatty acids (PUFAs). The PUFAs that have a C=C double bond between the 6th and 7th carbon position counting from the terminal methyl end are called ω -6 and those with the double bond between the 3th and 4th carbon are called ω -3 PUFAs. The letter 'n' is also used to denote the position of the double bond. The locations of double bonds in the PUFAs confer huge differences in their physical, biochemical, and physiological properties. The essential fatty acid (EFA) linoleic acid (C18:2) is of ω -6 series, while the EFA α -linolenic acid is the member of ω -3 series. Some of the beneficial effects overlap between the ω -3 and ω -6, while many effects are antagonistic to each other. ω -6 PUFAs can be found in vegetable oils and seeds, whereas ω -3 PUFA is found more in fish/marine animals, walnuts, and canola oil.

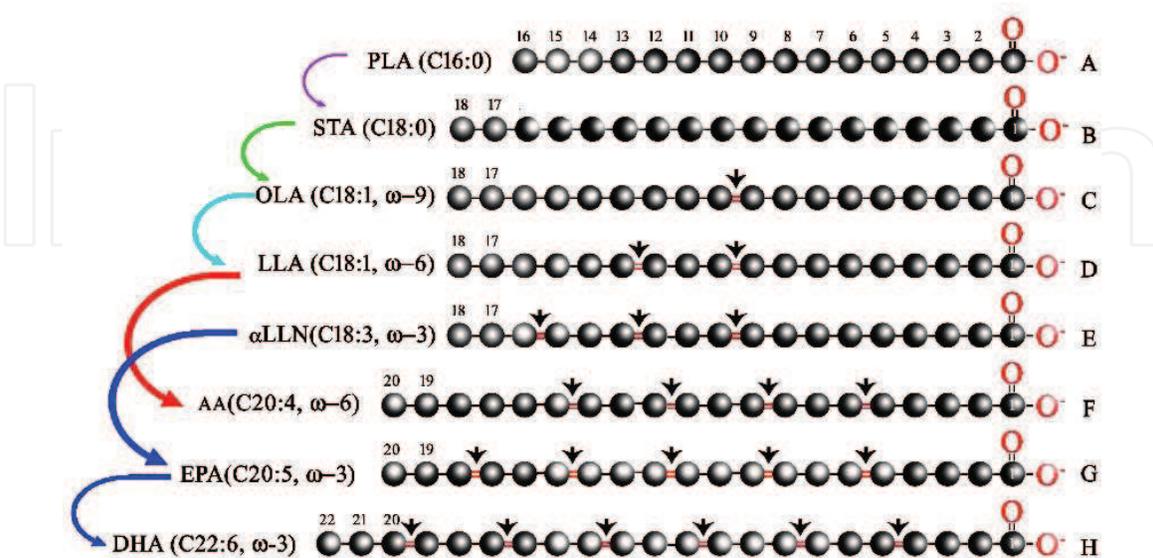


Figure 1. The straight chain structural features of the most common fatty acids. PLA = palmitic acid, STA = stearic acid, OLA = oleic acid, LLA = linoleic acid, LLN = α -linolenic acid, AA = arachidonic acid, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid. Omega (ω) is used to denote the position of double bonds from the methyl end of the fatty acid. Colored curved arrows = biological conversion is possible from the precursor by the actions of elongase/desaturase enzymes. Black arrow = indicates the position(s) of double bond.

1.3 Essential versus nonessential fatty acids

The fatty acids, which mammals cannot synthesize in their body, are known as essential fatty acids (EFAs); they must be obtained by the mammals in a preformed condition, that is, from the exogenous dietary sources. EFAs were originally designated as vitamin F, until it was realized that they must be classified with fats [4]. Of all the 18-C UFAs, two unsaturated fatty acids are found to be essential fatty acids (EFAs): they are linoleic acid (**Figure 1D**) and α -linolenic acid (**Figure 1E**). Both of them can act as precursors of very long chain polyunsaturated fatty acids (LPUFAs), such as ω -6 linoleic acid acting as the precursor of arachidonic acid (C20:4, ω -6) and ω -3 α -linolenic acid acting as the precursor of eicosapentaenoic acid (EPA, C20:5, ω -3) and docosahexaenoic acid (DHA, C22:6, ω -3). The rest are nonessential. Some examples are (common names): stearic (C18:0), oleic (C18:1), palmitic (C16:0), myristic (C14:0), and lauric acid (C12:0). Being nonessential does not actually mean that they are not important. Our body does need them to function properly; it, however, can synthesize them without receiving them directly from food.

1.4 AA (C20:4, ω -6) versus DHA (C22:6, ω -3) or EPA (C20:5, ω -3)

AA is referred to as a conditionally essential fatty acid for animals [5–7], including humans, that experience persistent deficiencies of linoleic acid (LLA, C18:2, ω -6), or during prematurity and growth, or if there is a limited capacity to convert LLA to AA [5]. However, consumption of vegetable-based oils, with large amounts of LLA, and an adequate capacity to convert LLA to AA, can eliminate the need for exogenous supply of AA, excluding it thereby from the list of essential fatty acids.

1.5 EPA (C20:5, ω -3) and DHA (C22:6, ω -3)

Both EPA and DHA are the members of ω -3 PUFA family. Both can be biosynthesized from the precursor α -linolenic acid (C18:3, ω -3, LLN). However, they are believed to act differently in different organs. For example, the differential roles of EPA and DHA have been studied in lymphocytes [8], macrophages [9], vascular smooth muscle cells [10], and endothelial cells [11]. Their differential roles have also been seen in the brains. EPA constitutes a tiny part in the unsaturated fatty acid pool of the brain. DHA, however, constitutes >17% by weight of the total fatty acids in the brain of adult rats and >33% of the total fatty acids in the retina [12]. DHA is thus referred to as essential for the growth and development of the brains, and animals have to take it in preformed form. The brain has a limited capacity to convert α LNN to DHA because of the lack of synthesizing enzymes [13, 14]. DHA plays an important role in the learning-related memory of animals, including humans.

1.6 ω -7 and ω -9 Monounsaturated fatty acids (MUFAs)

Monounsaturated ω -7 and ω -9 fatty acids are also considered to be nonessential, as majority of them are obtained from dietary sources (**Figure 2**). They can also be biosynthesized in the body. The most common ω -7s are palmitoleic acid (PA) and *cis* and *trans*-vaccenic acid (VA) (11-*cis*-octadecenoic acid). The most common ω -9s include oleic acid (OA), erucic acid (EA) and mead acid (it is a triunsaturated fatty acid). Since the human body can create ω -9 unsaturated fatty acids, there is no need to include them in diet. Full-fat grass-fed dairy, wild-caught salmon, olives, sprouted nuts, etc. are the sources of ω -7 and ω -9 unsaturated fatty acids.

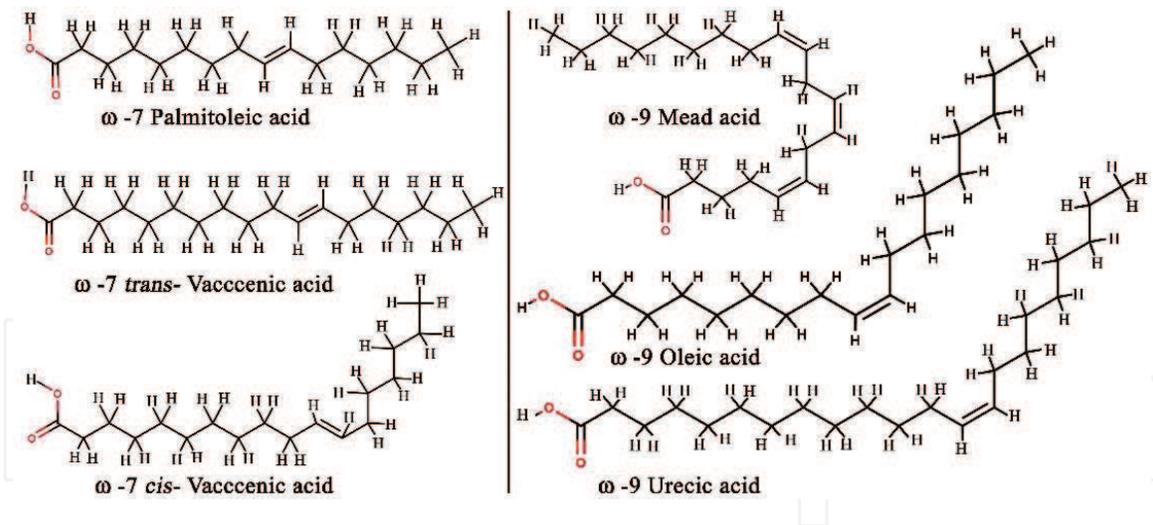


Figure 2.
The structural features of the most common ω -7 and ω -9 unsaturated fatty acids.

1.7 Cis-trans fatty acids

The naturally occurring unsaturated fatty acids have predominantly a *cis* carbon-carbon double bond ($-\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}-$). The C=C double bond typically lies on C-9 for the C18 unsaturated fatty acids. However, the artificial hydrogenation of C-18 unsaturated fatty acids such as linoleic acid (C18:2, ω -6) may produce *cis-trans* conjugated fatty acid (CLA), like isomers of *cis* Δ -9, *trans* Δ -11; *cis* Δ -9, *trans* Δ -12; and *trans* Δ -10, *cis* Δ -12. Hydrogenation may produce other forms of *trans* fatty acids (TFAs), such as *trans* Δ -8, *trans* Δ -9, and *trans* Δ -10 elaidic acid and *trans* Δ -11 vaccenic acid (**Figure 3**). *Trans* fatty acids (TFAs) are a kind of unsaturated fatty acids and also nonessential fatty acids. The primary TFAs are elaidic acid and vaccenic acid. The vaccenic acid is produced by bacteria in cattle rumen and thus may pass into humans via the milk of cows. The *trans* Δ -9 elaidic acid is the major industrial isomer of TFA [15].

The reports on the effect of CLAs on health and diseases are still scant. Raff et al. [16] reported that a 50:50 mixture of *cis* Δ -9, *trans* Δ -11 CLA and *trans* Δ -10, *cis* Δ -12 CLA caused a nonsignificant increase in SBP (by only 3 mmHg) without any effect on DBP in humans. Laso et al. [17] reported that CLA did not have any effect on blood pressure. Zock and Katan [18] reported that CLAs increase LDL-C and decrease HDL-C, thus indicating that CLA can act as a potential vascular risk factor. American Heart Association, the American Dietetic Association, the Institute of Medicine, US Dietary Guidelines, and the National Cholesterol

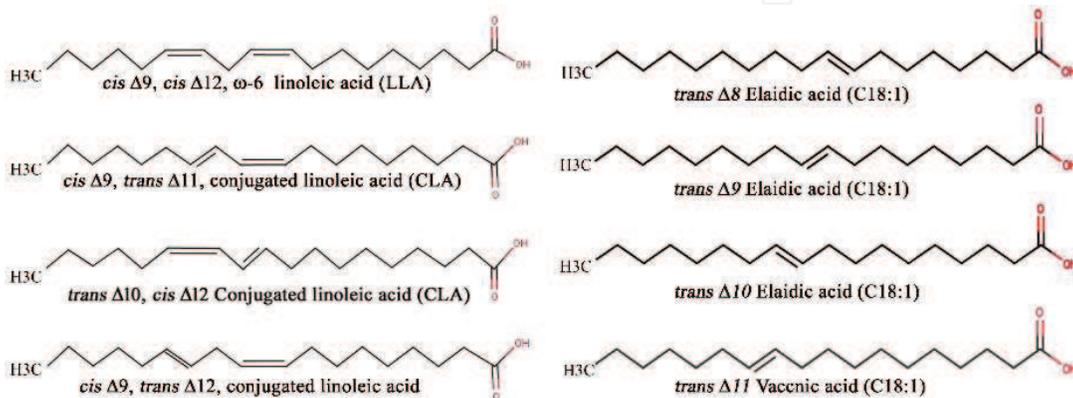


Figure 3.
The structural features of the most common *cis-trans* unsaturated fatty acids.

Education Program Adult Treatment Panel are claiming to limit *trans* fatty acids in the daily diet [19]. We have previously reported that *cis* Δ -9, *trans* Δ -11-conjugated linoleic acid promotes neuronal differentiation [20] in rats. These reports thus suggest that the effects of CLA remain to be resolved cautiously.

2. Physicochemical properties of fatty acids

Fatty acids are ubiquitous biological molecules. They are esterified to numerous complex lipid molecules, including triglycerides, phospholipids, and cholesterol esters. As being part of these molecules, fatty acids thus may govern some of their physical properties. The aliphatic chains and their lengths confer hydrophobicity to fatty acids. The hydrophobic nature of the fatty acids renders them insoluble in aqueous environments.

At very high pH, where the longer chained fatty acids are totally ionized, they form micelles, which are thermodynamically stable aggregates of molecules in aqueous solution [21]. This property confers the ionized fatty acids to detergent properties. However, to achieve a stable micelle formation, the fatty acids must be present in a solution at a pH greater than 9, which is generally unphysiologic. In fact, the most probable state of fatty acids at physiological temperature and pH is a membrane-like bilayer structure [22] (**Figure 4**, the middle one). The chain length of the fatty acid is interrelated with melting point; the higher the chain length, the lower the melting point. The double bonds in the (poly)unsaturated fatty acids further decrease their melting points [23]. This is very critical to the survival of mammals that live in extremely cold environments such as the polar areas of the earth. The presence of fatty acids in the bilayer membranes provides an excellent anisotropic solution for other membrane constituents. They confer fluidity to the membrane bilayer [24], wherein membrane-bound receptors, enzymes, and other proteins can diffuse laterally along the surface of the bilayer membrane. Phospholipids can also flip-flop between the bilayer leaflets and/or fatty acyl chains can have a vertical motion (translational motion). The word membrane fluidity can thus be referred to as the degree of stiffness or rigidity of the cellular bilayers. As saturated fatty acids are straight-chained, they can pack/stack easily with themselves and/or with the neighbor-cholesterol in the bilayer membrane. The (poly)unsaturated fatty acyl chains, on the other hand, retain bent(s) along the long axis of the chain at the position of double bonds; thus, they cannot align/stack tightly (**Figure 5**).

Consequently, they increase the degree of membrane fluidity. Therefore, the greater the degree of unsaturation of the fatty acids, the higher the fluidity of the membrane. We have previously reported the DHA, which has six double bonds, contributes to a greater extent in membrane fluidity than less-unsaturated

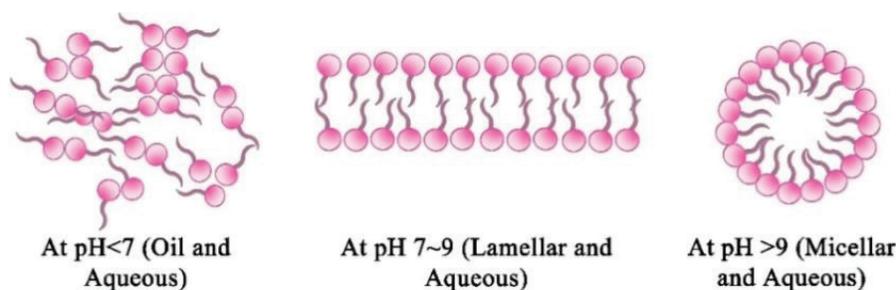


Figure 4.

The arrangements of fatty acids in aqueous environments at $T > T_c$. T = temperature. T_c = melting point of the fatty acid.

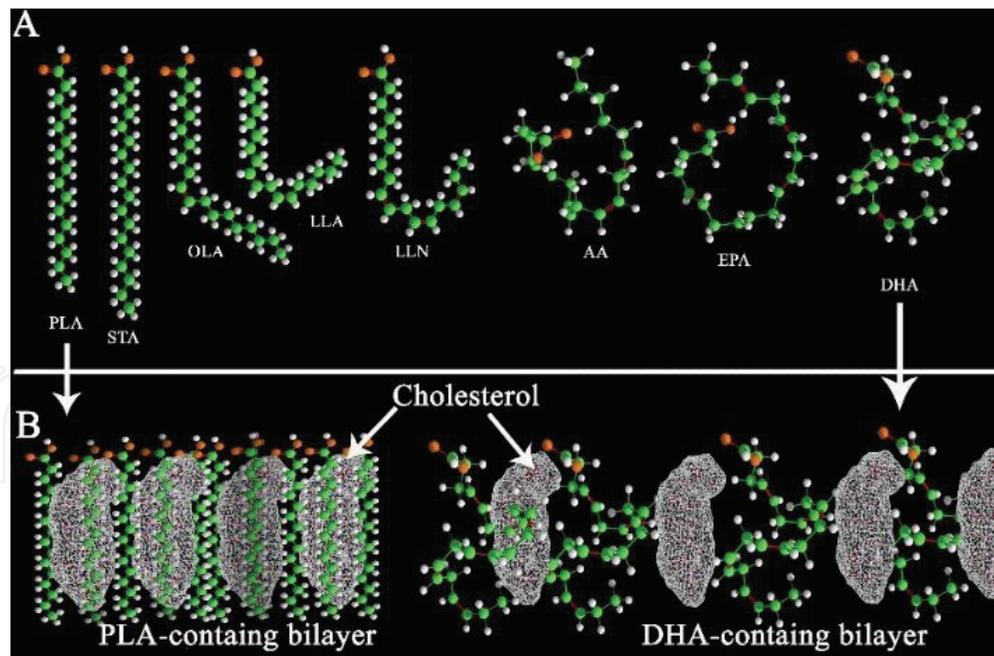


Figure 5.

The 3D structural features of the most common fatty acids (A). PLA = palmitic acid, STA = stearic acid, OLA = oleic acid, LLA = linoleic acid, LLN = α -linolenic acid, AA = arachidonic acid, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid. Double bonds of the unsaturated fatty acids are denoted by red color (in A) (B). Because of the presence of double bond(s) along the long axis of (poly)unsaturated fatty acids, they occupy more space when they are esterified in the phospholipid bilayer and loosely align with 3D cholesterol, and increase the degree of disorder (membrane fluidity). However, when straight-chained saturated fatty acids like PLA highly align (stacks) with 3D cholesterol, the degree of packing in the bilayer increases (tightens); hence, the membrane bilayer becomes more rigid, that is, less fluid.

fatty acids, such as EPA and/or saturated fatty acids [25, 26]. As a whole, the physicochemical properties of the fatty acids may affect the functions of these molecules [27], ultimately leading to altered functions of the cells and organisms.

3. Fatty acid oxidation

Fatty acids are usually oxidized by most of the cells of tissues in the body, except the RBCs. The cells of the central nervous system also do not use fatty acids for their energy requirements, using instead carbohydrates or ketone bodies. Heart cell fully depends on energy derived from fatty acid oxidation. Fatty acids constitute the principal source of energy for cells between meals, during hypoglycemia, and/or in diabetes. Beta-oxidation of fatty acids takes place in the mitochondria and, to some extent, in the peroxisomes, particularly the very long chain fatty acids [28]. Unlike in the mitochondria, beta-oxidation of fatty acid in the peroxisomes is not coupled to ATP; the high-potential electrons are rather transferred to O_2 , yielding hydrogen peroxide (H_2O_2) and generating heat. The enzyme catalase, found exclusively in peroxisomes, converts H_2O_2 into water and oxygen. H_2O_2 is also used intracellularly to digest unwanted wastes like proteins and/or to defend against intracellular foreign particles including toxins or microorganisms. All fatty acids are not oxidized at the same rates, which implicates that the purposes of cellular accumulation of fatty acids are not the same for all cells. Some fatty acids might have been exploited for energy purposes, some of them might be exploited for the structural purposes, and some of them (or their derivatives) might help the cell for the signal transductions. For example, 30–40% of all esterified fatty acids in the neural plasma membrane phospholipids consist of DHA [29], while EPA constitutes only a tiny percent of the brain total fatty acid. Among the saturated fatty acids, lauric acid (12:0) is oxidized

at the fastest rate and is the most efficient energy substrate [30]. Oleic acid (18:1) is also oxidized at a remarkably faster rate, similar to that of lauric acid. Of the ω -6 essential fatty acids studied, linoleic acid (18:2, ω -6) is oxidized at a faster rate, with arachidonic acid (20:4, ω -6) being oxidized at the slowest rate. DHA and EPA possess different oxidizing properties [31, 32]. DHA is a poor substrate for both mitochondrial and peroxisomal beta-oxidation [33], while EPA can be oxidized and to a much greater extent than DHA [33, 34]. The mechanisms of these properties are not fully elucidated, although intensive investigations are continuously going on. Furthermore, ω -3 fatty acids are incorporated into cell membranes in a highly selective manner where they act as structural components influencing fluidity of the membrane [35]. The ω -3 fatty acids also compromise themselves for enzymatic biotransformations into eicosanoids/docosanoids that act as intracellular signaling molecules and, finally, they get involved in the activity of membrane-bound enzymes, ion channels, and receptors [36]. When EPA is administered to rats, both the EPA and DHA accumulate in different organs, including brain [37], indicating EPA is elongated to DHA. DHA administration also leads to an accumulation of EPA both in the plasma and brains, however, only a tiny percent [37]. As DHA seems difficult to metabolize, we thus speculate that DHA is retroconverted to EPA for further metabolism. Therefore, EPA and DHA imply different metabolic properties in the cells of the brains.

4. Roles of ω -6 and ω -3 PUFAs in physiology

4.1 Platelet physiology

Platelets are derived from megakaryocytes and cause aggregation and play important roles in physiological conditions and pathological conditions as well. Fatty acids are enriched in the plasma membranes of platelets and thus may contribute to the physiology and pathology of platelets. Oral administration of ω -3 PUFAs to rats decreases the degree of platelet aggregation both in rats and humans [38, 39]; hence, it is evident that fatty acids may affect the platelet physiology and atherosclerosis. The mechanisms through which PUFA affects the platelet aggregation is unclear; however, it is assumed that ω -3 PUFA decreases the levels of atherogenic ω -6 PUFA particularly platelet membrane-AA, which acts as a proaggregatory fatty acid. Therefore, ω -3 prevents platelet aggregation by inhibiting PLA2 and interrupting the prostaglandin/thromboxane pathways [40, 41]. In addition, ω -3 PUFAs modulate the platelet membrane fluidity [42], specific lipid domains that hold the receptors for a variety of aggregation factors, such as ADP, thrombin, fibrin, etc. [37], and doing so, they decrease platelet aggregation.

4.2 Effects of fatty acids on hypertension

The effect of fish oil on hypertension came into light when the Norwegian under Nazi invasion had to consume more fish rather than land-based food items during WWII [43]. The Norwegian had low blood pressure, low degree of platelet aggregation, and hypocholesterolemia as well. Afterwards, in studies on the Greenlandic Eskimos, Dyerberg and Bang [44] and Fischer et al. [45] reported that the Eskimos had also a low incidence hypertension and blood cholesterol levels. Then, oil components of marine animals and fish, in particular EPA and DHA, were attributed to lower incidence of cardiovascular risk factors, such as hypertension, hypercholesterolemia, and platelet hyperaggregation. We have previously reported that oral administration of EPA and DHA to rats

(hypercholesterolemic) decreased the hypertension [46] and hypercholesterolemia [47]. The results were consistent with many other published reports [48]. To understand the mechanism(s) of action of these PUFAs, we also pretreated the rat thoracic endothelial cells with these PUFAs and some interesting data emerged from our experiments. For example, the EPA and DHA increased the plasma levels of nucleotide products including ATP, ADP, AMP, and adenosine. The blood vessels of the PUFA-fed rats exhibited less sensitivity to noradrenaline and had caused an increased release of the total purines (ATP + ADP + AMP + Adenosine), concurrently with less contractility [47]. We hypothesized that these nucleotides and their derivatives decreased the noradrenaline sensitivity to purine-receptors of the blood vessels and decreased the blood pressure. The mechanism also might be related to the EPA/DHA-induced increase in the membrane fluidity of the endothelial cells (ECs). These hypotheses led us to preincubate the cultured ECs with EPA and DHA. As expected, the PUFAs increased the membrane fluidity of the ECS [49]. The inhibitory effects of fish oil ω -3 polyunsaturated fatty acids (PUFAs) have also been reported on the expression of endothelial cell adhesion molecules [50]. Hence, the ω -3 PUFAs might have played beneficial roles in reducing hypertension in the animal models as well as in human cases who consumed fish/marine animals' oils in their everyday life.

4.3 Effects of fatty acids on hepatic functions

Saturated and/or unsaturated fatty acids are indispensable for the functions of all tissues in the mammalian body. However, an adequate balance between saturated and (poly)unsaturated and between ω -6 and ω -3 PUFAs is essential to the proper functioning of the cells. Fatty acids after their absorption in the intestinal epithelial cells are first carried to the liver, which acts as a distribution center for the whole body. Therefore, fatty acids can affect the liver functions. Inadequate amounts of essential fatty acids may cause disorders of the liver, such as fatty liver, liver cirrhosis, metabolic syndromes, hyperlipidemia, hypercholesterolemia, and other liver problems [51, 52].

Oral administration of ω -3 DHA decreases the plasma as well as hepatic cholesterol and triacylglycerol levels [53]. The mechanism through which ω -3 PUFAs decrease the plasma cholesterol is not clear; however, it is attributed to the inhibition of hepatic HMG-CoA reductase by the PUFAs, including EPA and DHA. To prove the mechanism, we determined the levels of hepatic mRNA levels of HMG-CoA reductase (yet unpublished) of the DHA-fed rats. DHA decreased the expression of HMG-CoA reductase. Our results were also consistent with numerous other published reports [54–56]. The beneficial effects also emerged at lower levels of LDL-C and TG and high levels of HDL-C. The oral administration of DHA also increased the levels of ω -3 PUFAs and decreased the levels of ω -6 AA both in the plasma and liver tissues. It might be suggested that the oral administration of PUFAs like DHA increases the degrees of oxidative stress and mammalian tissues, including the liver. However, the levels of lipid peroxide (LPO) and reactive oxygen species (ROS) were not increased, thus demonstrating that the feeding of DHA does not pose an oxidative stress to the tissues. We suggest that the oral administration of DHA rather increases the levels of antioxidative enzymes, including glutathione peroxidase and catalase, and antioxidant substrate like GSH [53]. In a similar study, the levels of antioxidative enzymes and GSH increased in the brains of hypercholesterolemic aged rats after oral administration of DHA [57]. However, there are also contradictory results where consumption of PUFA was reported to promote oxidative stress [58]. Furthermore, we isolated and purified the canalicular plasma membranes of the hepatic cells of EPA/DHA-fed rats.

These membranes allow the transport and pump bile components in-and-out of the hepatic cells. The levels of PUFAs increased in the canalicular plasma membranes, concurrent with increases in the activities of membrane-bound enzymes such as Mg^{2-} -ATPase, 5'-nucleotidase. Membrane fluidity also increased in these membranes, thus suggesting that an increased fluidity might have helped in the pumping out the cholesterol via the bile (**Figure 6**). Otherwise, the levels of fecal cholesterol could have not been increased in the feces of the fish-oil-fed rats [53].

4.4 Anti-inflammatory responses

ω -6 PUFA like arachidonic acid (AA, C20:4, ω -6) generates 2-series prostanoids, namely prostaglandins PGE₂, PGI₂, PGD₂, and PGF₂ α (largely produced by monocytes and macrophages) and thromboxanes TXA₂ and TXB₂ by COX-1/COX-2 enzymes. Prostaglandin PGI₂/PGE₂ has proinflammatory effects. AA by the action of LOX also produces leukotrienes such as 5-HETE and 5-HPETE, LTE₄, LTB₄, LTC₄, and LTD₄. They are strong proinflammatory agents and have vasoconstriction effects and platelet- and/or neutrophil- and macrophage-activating effects [59–61]. Interestingly, the eicosanoids derived from the action COX and/or LOX on EPA and DHA produces 3-series prostaglandins and thromboxanes and 5-series leukotrienes, and they are less inflammatory and even have anti-inflammatory effects, as compared to the eicosanoids derived from AA. These lipid mediators antagonize the effects of those derived from AA, thus conferring beneficial effects on inflammatory responses [62].

4.5 Effects on skeletal muscles

Skeletal muscle is the largest organ in the human body, comprising approximately 40% of total body weight [63]. This muscle has a plastic-like property and has adapting capability to physical activity. Strenuous muscle exercise increases muscle fatigue and decreases muscle strength, leading to an increase in muscle oxidative stress. It is believed that the response of skeletal muscle to exercise can be modified by the nutritional status of the muscles. There

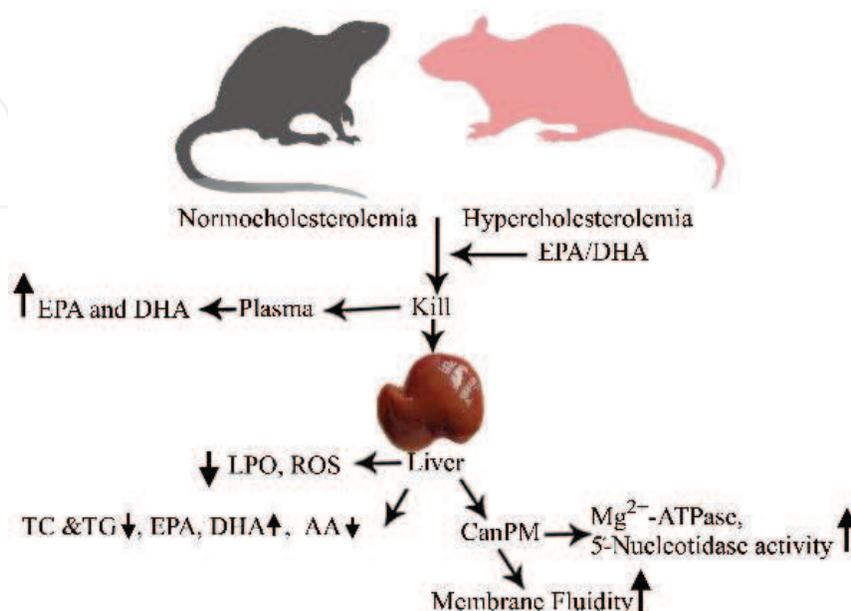


Figure 6. Effects of oral administration of EPA and DHA on the plasma and hepatic lipid profile (TC = total cholesterol, TG = triacylglycerol), LPO = lipid peroxide, ROS = reactive oxygen species, CanPM = canalicular plasma membrane of hepatic cells).

are numerous reports on the beneficial effects of EPA and DHA on muscle. Therefore, the effects of these PUFAs on muscle strength have been investigated with increasing interest. Hess et al. [64] reported that dietary algae and marine fish increase the levels of EPA and DHA in the equine skeletal muscles. Guen et al. [65] reported that DHA-enriched supplementation improves endurance exercise capacity and skeletal muscle mitochondrial function in murine skeletal muscle. Stebbins et al. [66] reported that DHA + EPA enhances skeletal-muscle blood and vascular conductance in active skeletal muscle (especially type I and IIa fibers) and that the increase in muscle blood is due to an increase in cardiac output secondary to increases in vascular conductance [66]. However, we believe that there are differential effects of PUFAs on the muscle [67]. AA deposition in the fast-twitch muscle of aging rats reduced cell volume with an increase in oxidative stress [68].

5. Effect of ω -3 DHA/EPA on brain cognition

As neurons are the structural and functional units of brain, electrochemical properties of the neurons allow them to transmit signals over long distances and send information to each other. Neurons form the basis of the brain activity and brain cognition and dictate the whole body when and how to work and maintain the behavior of the animals, including humans. Numerous reports have been published stating that the PUFAs have colossal roles in brain growth and development, learning, and memory. At the same time, deficiency of PUFAs such as DHA has been reported to cause neurodegeneration leading to impairments of memory and brain cognition.

Henriksen et al., reported that the level of DHA was low in the preterm infants (born at <33 weeks gestation, body weight < 1.5 Kg). Concurrently, the preterm infants had learning disabilities, reduced IQ, and weak visuospatial relations. However, when these infants were supplemented with DHA, they exhibited normal growth and development in terms of body weight, height, head circumference, visual acuity, and mental development [69]. The study thus suggests that DHA is important before birth. Infants (9-month-old, growth spurt period) fed with DHA-supplemented traditional formula showed higher problem-solving activities, when compared with those fed with traditional formula-only, suggesting thus that DHA also plays an important role during growth spurts and development [70]. Infant's gray matter autopsy (of human/nonhuman primate) study showed that brain DHA levels have also 40% higher in the DHA-supplemented formula-fed infants than those in the formula-fed only infant brains [29, 71]. In addition, DHA declines in aging and age-related neurodegenerative diseases such as Alzheimer's disease [72–74]. All these investigations thus suggest that DHA is important for brain cognitions, such as learning and memory, thought processes, tracing of new information, and comprehension, and that brain DHA deficiency can be recovered by the dietary DHA supplementation. Though cerebral endothelial cells and brain astroglial cells can synthesize DHA and/or α -LLN, EPA from the diet can act as precursors for the DHA; however, the endogenous synthesis or conversion of DHA is extremely low [75]. Thus, dietary DHA is the ultimate source for the DHA in the brain.

We have previously reported that oral administration of DHA for 12 weeks significantly increased the learning-related memory, as evaluated by the 8-armed-radial maze task in DHA-deficient young and old rats [76, 77]. Not only DHA increases the memory of DHA-deficient young and old rats, DHA

also had an extraordinary ability to increase the learning-related memory of Alzheimer's disease model rats [78, 79] (**Figure 7**). EPA also increased the learning-related memory, however, only after their conversion into DHA [80]. The roles of ω -6 AA on the brain cognitions have also recently been investigated; however, the results are controversial. Memory-enhancing effect of AA has been reported previously [81]. In our investigation, the ω -6 AA failed to increase memory of rats (yet unpublished). DHA always exhibited a positive effect on memory. However, the mechanisms by which DHA increases the memory remain to be clarified. Numerous mechanisms of action of DHA on memory have been proposed. DHA-induced increases in synaptic plasma membrane fluidity [26]; antioxidative effects [76–79]; anti-apoptotic effect [78]; increased expressions memory-related proteins, including postsynaptic PSD-95, presynaptic synaptophysin, NMDA-receptor unit NR2A [75], and c-fos [82]; and reductions of brain A β -burdens [83] have been attributed to the beneficial effects of DHA in the normal and AD rats, respectively. To examine the mechanism(s) of the reduction of amyloid burden, we tested whether DHA affects the *in vitro* A β peptide (A β _{25–35}, A β _{1–40}, and A β _{1–42} are the most toxic amyloids) fibrillation, a process that assumes to increase the A β deposition in the brains. We found that DHA inhibits *in vitro* A β fibrillation both at the initial stage of A β -seed formation and oligomerization and also causes dissolution of mature A β peptide fibers [84–86] (**Figure 8A**). It is thus conceivable that DHA, by decreasing the amyloid fibrillation, decreases the brain A β -burden and hence contributes to the amelioration of memory of AD model rats. DHA also caused a clearance of circulating A β s by increased lipid raft-dependent degradation pathways [87].

We later tested whether DHA affects neurogenesis, which is of great interest in the modulation of memory both in the aging and neurodegenerative Alzheimer's disease. As expected, DHA accelerated both *in vitro* and *in vivo*

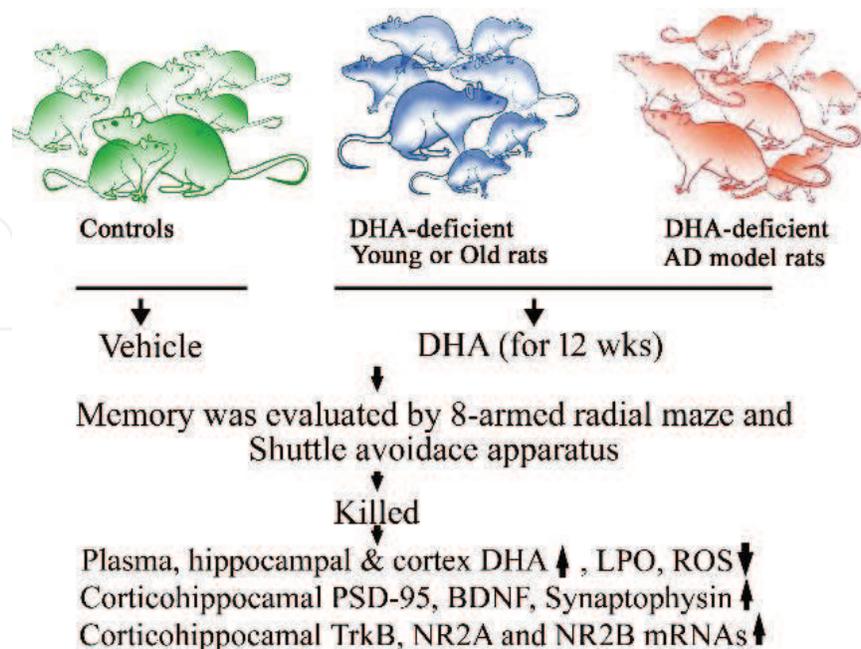


Figure 7. Effect of oral administration of DHA on the learning-related memory of DHA-deficient young/old and Alzheimer's disease model rats. Protein levels of postsynaptic density protein (PSD-95), brain-derived neurotrophic factor (BDNF), and presynaptic synaptophysin were measured. Also, the mRNA levels of BDNF-receptor tyrosine Kinase B (TrkB) and NMDA receptor units NR2A and NR2B were determined by RT-PCR to examine whether they were affected by the oral administration of exogenous DHA. All these parameters were ameliorated by the oral administration of DHA.

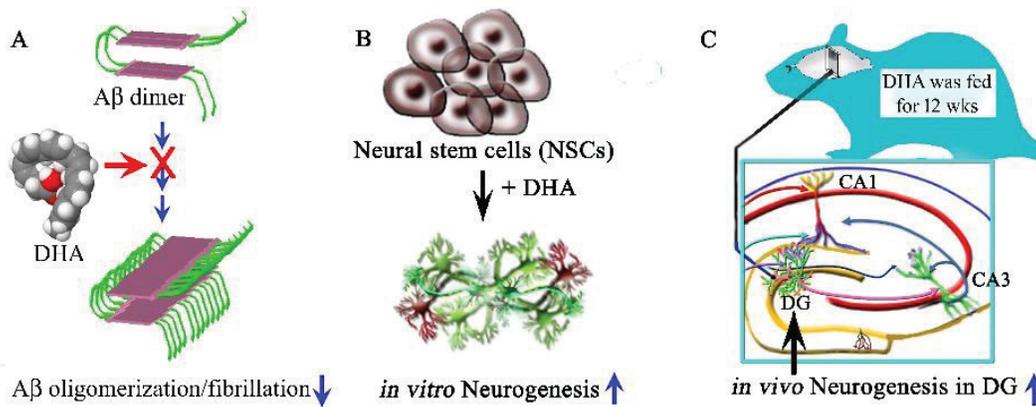


Figure 8. Effect of incubation of DHA on *in vitro* amyloid beta ($A\beta$) peptide fibrillation (A) and *in vitro* neurogenesis in NSCs culture (B) and, effect of oral administration of *in vivo* neurogenesis (C). Neurogenesis occurred primarily in the dentate gyrus (DG) region.

neurogenesis [88] (**Figure 8B, C**), which is conducive to inhibition of the impairments of memory in aging and/or AD model rats. DHA stimulated the differentiation of neural stem cells into mature neurons by triggering the activating-type bHLH transcription factors, including neurogenin, Mash1, and NeuroD and inhibiting the repressor-type transcription factor Mes1 [89]. We also reported that DHA-derived docosanoids, such as neuroprotectin D1, help increase the memory of rats [90]. Consistent with our results, Bazan et al. [91] also reported that endogenous signaling by DHA-derived mediators sustains neuronal function and protects synapses and circuits, thus demonstrating that DHA and/or its docosanoid products might act as signaling molecules during memory processing. Finally, DHA is essential for the growth and development of brain and might play crucial roles in the formation of learning-related brain cognition.

6. Conclusion

For the last several decades, fatty acid nutrition, in terms of quality, has been dramatically changed [92]. Consumption of saturated fatty acids, ω -6 PUFAs, and *trans* fatty acid intake has been increased [93]. Optimal dietary ω -6: ω -3 ratio should be around 1–4:1; however, this ratio has now increased to 10:1 to 20:1 in the Western diet [92]. Concurrently, the incidence of diseases involving inflammatory diseases, cardiovascular disease, obesity, rheumatoid arthritis, cancer, neurodegenerative, and psychiatric illnesses, such as AD and depression, are increasing with an ever-increasing rate [94]. The results of our investigations and those of the others, finally, suggest that DHA is accumulated in the synaptic plasma membranes, represses oxidative stress by increasing the anti-oxidative defense, decreases cholesterol in the detergent-insoluble membrane fraction (DIMF) of the brain tissues, increases synaptic plasma membrane fluidity, inhibits amyloid fibrillation and decreases amyloid toxicity and burden in the brain tissues, improves the neuronal morphology, increases memory-related protein substrates, and hence ameliorates the memory-related brain cognition (**Figure 9**). In conclusion, a balanced intake of ω -3 and ω -6 PUFAs is a must, as well as an increased intake of DHA, which might act as a signaling molecule to protect the brains from preterm-, postnatal-, and other age-related neurological diseases, such as Alzheimer's disease.

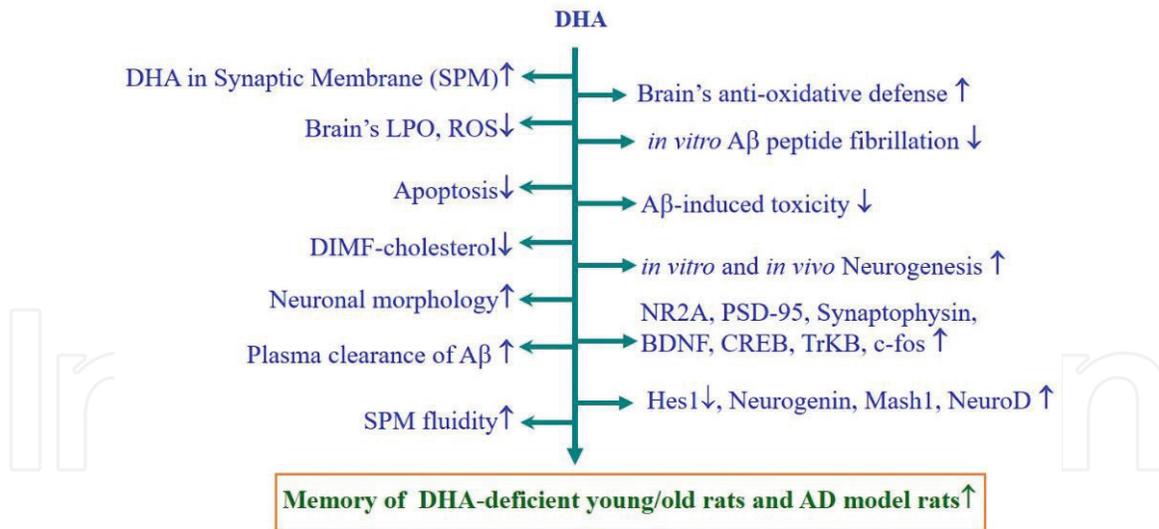


Figure 9.
 Outlines of the effect of DHA on learning-related memory of rats. SPM = synaptic plasma membrane.
 DIMF = detergent-insoluble membrane fraction. All other abbreviations are same as for other figures.

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