Docosahexaenoic acid

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Abstract

Docosahexaenoic acid (DHA) is a long chain, highly unsaturated omega-3 (n-3) fatty acid. It has a structure that gives it unique physical and functional properties. DHA is metabolically related to other n-3 fatty acids: it can be synthesized from the plant essential fatty acid α-linolenic acid (ALA). However this pathway does not appear to be very efficient in many individuals, although conversion of ALA to DHA is much better in young women than in young men. Furthermore, young infants may be more efficient converters of ALA to DHA than many adults, although conversion rate is variable among infants. Many factors have been identified that affect the rate of conversion. The implication of poor conversion is that preformed DHA needs to be consumed. DHA is found in fairly high amounts in seafood, especially fatty fish, and in various forms of n-3 supplements. The amount of DHA in seafood and in supplements varies. Breast milk contains DHA. DHA is found esterified into complex lipids within the bloodstream, in adipose stores and in cell membranes. Its concentration in different compartments varies greatly. The brain and eye have high DHA contents compared to other organs. DHA is especially concentrated in the grey matter of the brain and in the rod outer segments of the retina. In the brain DHA is involved in neuronal signalling while in the eye it is involved in the quality of vision. DHA is accumulated in the brain and eye late in pregnancy and in early infancy. A lower DHA content is linked to poorer cognitive development and visual function. DHA affects cell and tissue physiology and function through numerous mechanisms, including alterations in membrane structure and function, in membrane protein function, in cellular signalling and in lipid mediator production.

Key words: Docosahexaenoic acid, Fish, Fish oil, Omega-3, Pregnancy, Lactation, Life course

Key messages

- Docosahexaenoic acid (DHA) is a bioactive omega-3 polyunsaturated fatty acid that influences membrane structure and function, cell signalling and communication mechanisms, gene expression and lipid mediator production

- DHA is found at high concentrations in the human brain and eye, where it is linked to better development and function

- Maintenance of DHA concentration is important throughout the life course but pregnancy, lactation and infancy are vulnerable periods, where insufficient DHA supply can impact mental and visual development and performance

Introduction

Docosahexaenoic acid (DHA) is a long chain, highly unsaturated omega-3 (n-3) fatty acid (see Box). It has 22 carbons in its acyl chain, which includes 6 double bonds. Chemically it can be described as all-*cis*-4,7,10,13,16,19-docosahexaenoic acid, with the numbers 4, 7, 10, 13, 16 and 19 referring to the carbon atoms in the acyl chain that bear double bonds when the carboxyl or alpha-carbon is counted as number 1 (Figure 1). DHA is shown in the common fatty acid nomenclature as 22:6ω-3 or 22:6n-3, with the ω-3 (or n-3) indicating the position of the first double bond in the acyl chain, in this case counting the methyl or omega-carbon as number 1 (Figure 1). The common name for DHA, which is rarely used, is cervonic acid. Fatty acyl chains with no double bonds, such as in saturated fatty acids, are straight and pack together tightly. Introduction of a *cis* double bond into an acyl chain introduces a "kink" into the chain, making it less easy for such chains to pack together and lowering their melting point. As the acyl chain of DHA contains six *cis* double bonds, it becomes highly twisted (Figure 1), giving it unique physical properties and resulting in a very low melting point (-44°C). DHA is metabolically related to other n-3 fatty acids. It can be synthesized from the plant-derived alpha-linolenic acid (ALA; 18:3n-3) or obtained directly from the diet. In common with other fatty acids, DHA is most often found linked via its carboxyl group into a more complex lipid structure such as a triglyceride, phospholipid or cholesteryl ester. Here, the pathway of DHA biosynthesis, dietary sources of DHA, the status (i.e. concentration) of DHA at different sites in the human body and the response of those sites to increased DHA intake, and selected actions of DHA at the molecular and cellular levels will be described. DHA plays vital roles in the structure and function of the brain and eye and an appropriate supply during fetal life and in infancy is essential to assure optimal development.

Biosynthesis of DHA

ALA is an essential fatty acid. It is synthesised in plants and in many lower organisms and is found in the human diet mainly as a component of green leaves; some nuts, seeds and vegetable oils; and foods made from or containing those ingredients. There is a metabolic pathway that links ALA to DHA (Figure 2). This pathway involves a series of enzyme catalysed elongation and desaturation reactions. Elongation enzymes, called elongases, add pairs of carbon atoms to the growing acyl chain, in this case converting an 18 carbon fatty acid into a 22 carbon one, while desaturase enzymes insert double bonds into the acyl chain, in this case converting a fatty acid with three double bonds in its acyl chain into one with six double bonds. These reactions occur predominantly within the endoplasmic reticulum. The pathway is believed to mainly occur within the liver, but there is some evidence that other tissues, including brain and testis, have high expression of the genes encoding the relevant enzymes.

The initial step in the pathway is the conversion of ALA to stearidonic acid (18:4n-3), catalysed by delta-6-desaturase, which is generally considered to be the rate limiting reaction in the pathway. Delta-6-desaturase is encoded by the gene fatty acid desaturase 2 (*Fads2*). Stearidonic acid is converted to 20:4n-3 by the addition of 2 carbons by the enzyme elongase-5, encoded by fatty acid elongase 5 (*Elovl5*). 20:4n-3 is then converted to eicosapentaenoic acid (EPA; 20:5n-3) by insertion of a

double bond catalysed by delta-5-desaturase, which is encoded by the gene fatty acid desaturase 1 (*Fads1*). EPA can be elongated by elongase 2 (encoded by *Elovl2*) to form n-3 docosapentaenoic acid (DPA; 22:5n-3) and then to 24:5n-3 followed by desaturation that again uses delta-6-desaturase activity to form 24:6n-3. This desaturation seems to be catalysed by the same delta-6-desaturase as in the first step of the pathway. 24:5n-3 is then translocated from the endoplasmic reticulum to the peroxisome where it undergoes one round of β-oxidation to form DHA.

It is important to note that the same enzymes are active in the metabolism of the n-6 fatty acid family, converting the essential n-6 fatty acid linoleic acid (18:2n-6) to arachidonic acid (20:4n-6) and on to n-6DPA (22:5n-6). Thus, competition exists between the conversion of n-6 and n-3 fatty acids. The rate limiting enzyme, delta-6-desaturase, has a preference for ALA over linoleic acid. However, this may be more than offset by the greater abundance of linoleic acid than ALA in most human diets, meaning that the metabolism of the former is favoured.

In addition to availability of the essential fatty acid substrates and the competition between them, a number of other factors have been demonstrated to regulate the pathway. These include the availability of several trace elements including zinc and iron, since the enzymes involved in the pathway require these as co-factors; sensitivity to insulin; female sex hormone status; polymorphisms in *Fads* genes which control gene expression and enzyme activity; and epigenetic modification of *Fads* and *Elovl* genes, which will affect their expression. Other nutrients, metabolites and hormones, and ageing may also affect the pathway. Measurements of EPA and DHA status reveal differences among some population subgroups, for example between men and women [1,2] and among individuals with different *Fads* polymorphisms [3], that are likely to reflect different activities of the biosynthetic pathway. There has been much interest in the reported differences in EPA and DHA status between men and women. Studies using stable isotopes to trace metabolism of ALA have demonstrated that the conversion of ALA to both EPA and DHA is more efficient in young women than in young men [4,5]. In men, conversion of ALA to EPA has been reported to be between 0.3% and 8%, and conversion to DHA < 1%, whereas in women up to 21% conversion to EPA and up to 9% conversion to DHA

have been reported. It has been suggested that the higher rate of conversion in women may be because of their greater requirement to produce DHA during pregnancy and lactation. Infants may be more effective at converting ALA to DHA than adults, and newborn infants appear to be better at synthesising DHA than older infants [6].

Dietary sources of DHA

Along with EPA and n-3DPA, DHA is found in fairly high amounts in seafood and products derived from seafood. Table 1 reports typical values for the content of DHA in various seafoods [7]. It is evident that there is at least a ten-fold range in content of DHA per portion (i.e., per serving) of seafood, with fatty fish able to provide as much as 1 to 1.75 g of DHA per portion. Examples of fatty fish are mackerel, salmon, trout, herring, tuna, and sardines. In comparison lean fish like cod, haddock, and plaice, typically provide about 0.1 to 0.2 g of DHA per portion. Although tuna is a fatty fish, canned tuna has had the oil removed during processing and so is low in content of n-3 fatty acids including DHA (Table 1). Meat and blubber of sea mammals like seals and whales is also rich in n-3 fatty acids including DHA, although these are not usually eaten by most humans. Likewise, some organ meats like brain are rich in DHA but again these are rarely eaten in most populations. DHA is found in modest amounts in animal-derived foods like eggs and meat (Table 1). Human breast milk and other mammalian milks contain DHA. Analysis of data from 65 studies of over 2400 women from around the globe gave a mean concentration of DHA in breast milk as 0.32% of total fatty acids by weight with a range of 0.06 to 1.4% [8]. The highest breast milk DHA concentrations were in coastal populations and were associated with marine food consumption [8].

Because fatty fish are the richest dietary source of DHA, DHA intake is heavily influenced by fish consumption. In most Western populations the distribution of fatty fish consumption is bimodal, with a relatively small proportion of the population (e.g. 15 to 25%) being regular fatty fish consumers. Thus, typical intakes of DHA across a population are likely to be low. Data from over 10,000 Australian adults identified a mean daily intake of DHA of 106 mg, with DHA contributing about 60% of n-3 LCPUFA intake [9]. By comparison mean daily intakes of EPA and n-3 DPA were 56

and 25 mg, respectively [9]. However, the median intake of DHA was only 15 mg/day [9], the large differences between mean and median intakes reflecting the non-normal distribution of the intake data. Median daily intakes of EPA and n-3 DPA were 8 and 6 mg, respectively [9]. A more recent study using an updated nutrient composition database mean daily intake data for DHA of 100 mg, which was 40% of n-3 LCPUFA intake [10]. Again, median intakes were lower, being about 50% of the mean. An interesting observation from these studies is that meat (including poultry) provides 40 to 45% of EPA+n-3DPA+DHA consumed by typical Australian adults, with fish and seafood products providing 45 to 50% [10].

DHA is also present in fish body (aka fish), fish liver, algal and krill oils, in concentrated supplements, and in pharmaceutical grade preparations designed for controlling blood triglyceride levels. Table 2 summarises the DHA content of typical preparations of these sources. It is clear that the use of supplements, whether these are over-the-counter or prescribed, can substantially increase intake of DHA. DHA-rich oils from algae or tuna are used in infant formulas.

DHA status
DHA concentration in different metabolic and anatomical compartments
DHA is transported in the bloodstream as a component of lipoproteins (within triglycerides, phospholipids and cholesteryl esters) or as a non-esterified ("free") fatty acid (largely due to release from adipose tissue stores or from spill-over of lipase-mediated hydrolysis of circulating lipoproteins). DHA can be stored in adipose tissue esterified into triglycerides. DHA is found in all cell membranes esterified into phospholipids and other complex lipids. Table 3 lists some reported concentrations of EPA and DHA in different metabolic or anatomical compartments in humans [11-23]. It is evident that the absolute and proportional contribution of EPA or DHA to the total fatty acids present within any of the compartments listed in Table 3 differs both between the two fatty acids and between compartments. Most often DHA is present at a higher concentration than EPA. This is especially true in specific regions of the brain and eye, where DHA makes a significant contribution to the fatty acid complement and EPA is virtually absent.

DHA is highly concentrated in the human brain and eyes

More than 50% of the dry weight of the human brain is lipid, particularly structural lipid (i.e. phospholipids). The most abundant fatty acids in the brain are DHA, arachidonic acid and adrenic acid [24,25]. The human brain and retina contain an especially high proportion of DHA relative to other tissues and little EPA [24,25,26] (Table 3). For example, DHA was reported to contribute an average of 18% of fatty acids to adult human brain grey matter [14], while Makrides et al. [15] reported average DHA contents of about 8% and 12% of fatty acids for human infant cerebral cortex and retina, respectively. In the latter study the contributions of EPA were < 0.05% and 0.1%, respectively [15]. Within cell membranes, EPA and DHA are distributed differently among the different phospholipid components and in the brain and eye specific phospholipids are especially rich in DHA. For example, DHA was reported to contribute an average of 36% of fatty acids in mammalian brain grey matter phosphatidylserine [25] and an average of 22% of fatty acids in retina phosphatidylcholine [26]. DHA contributes 50 to 70% of the fatty acids present in the rod outer segments of the retina [26]. These rod outer segments contain the eyes' photoreceptors.

The human brain growth spurt occurs from approximately the beginning of the third trimester of pregnancy to 18 months after birth. The amount of DHA in the brain increases dramatically during the brain growth spurt. In humans, brain weight increases from about 100 g at 30 weeks of gestation to about 1100 g at 18 months of age [27]. Over this period the DHA content of the brain increases from 900 μg/g (90 mg in total) to 3,000 μg/g (3,300 mg total) [28,29]. This represents a 35-fold increase in total brain DHA. The estimated rate of accretion of DHA into the human brain in the last trimester of pregnancy is 15 to 22 mg/week [30]. This is also the most active period of brain cell division. Thus, it is believed that an adequate supply of DHA during this period is essential for normal growth, neurological and visual development and function, and learning behaviour [29].

DHA concentration during pregnancy
There is a significant linear relationship between the DHA contents of maternal and umbilical cord plasma phospholipids. This suggests that maternal plasma phospholipids are an important source of DHA for the fetus and that maternal plasma

phospholipid DHA concentration determines DHA supply to the fetus. An increase in maternal plasma DHA concentration occurs during pregnancy [71] (Figure 3) and this increase precedes the increase in DHA accretion by the brain. The extent of the increase differs among pregnant women in different countries [32], perhaps indicating dietary differences during the pre-pregnancy period. Al et al. [33] reported that maternal plasma phospholipid DHA content was lower in women who had had multiple pregnancies than in those in their first pregnancy. This may indicate that maternal body stores are important in maintaining plasma DHA status but that these may be eroded by multiple pregnancies.

Even though maternal and fetal blood DHA concentrations are highly correlated, DHA is concentrated in the fetal circulation and in fetal tissues [34], a process sometimes referred to as biomagnification (Figure 4). Placental adaptation to ensure efficient DHA transfer from the maternal to the fetal circulation is an important part of the biomagnification process; this is discussed in detail elsewhere [34]. Furthermore, there are observations that the placenta can synthesise DHA from ALA [34], which would allow for in situ provision of DHA to help meet the demands for DHA imposed by pregnancy.

Effect of increased DHA intake on DHA status
Increasing intake of DHA increases its status in many body compartments
Increased intakes of DHA (and EPA) from fish or from n-3 supplements are reflected in increased proportions of both fatty acids in blood lipid, blood cell and many tissue compartments. This has been reported many times for total plasma or serum lipids or for the complex lipid components of plasma or serum (i.e. triglycerides, phospholipids and cholesteryl esters) and is also well described for erythrocytes, platelets and leukocytes (see [35] for references). There are also descriptions of increased proportions of DHA (and EPA) in human tissues, including skeletal muscle [18,19], heart [16], gut mucosa [22] and adipose tissue [11,36] when their intake is increased. These compartments all show a dose- and time-dependent incorporation of both EPA and DHA [11,13,35,36], but the precise pattern depends upon the specific location [37,38] (Figure 5). Pools that are turning over rapidly show faster incorporation of both EPA and DHA than slower turning over pools. Thus, plasma lipids incorporate EPA and DHA more quickly than blood cells do [11,36], whilst

amongst blood cells, leukocytes have been usually shown to incorporate EPA and DHA more quickly than erythrocytes. Modification of human brain fatty acid composition is more difficult than for other tissues, especially beyond childhood. However, Makrides et al. demonstrated that the DHA concentration of the cerebral cortex of breast-fed infants who would have received DHA via breast milk is higher than that of infants who had not been breast fed [15].

The higher status of EPA and DHA achieved through increased intake is maintained so long as the higher intake of EPA and DHA is maintained. If, after a period of increased intake of EPA and DHA, intake returns to the earlier lower levels, then EPA and DHA status decline, eventually returning to earlier levels (Figure 5). This is well described for blood lipids, platelets, leukocytes and erythrocytes (see [35]). However, just as the incorporation of EPA into different pools is faster than the incorporation of DHA, the loss of EPA is faster than the loss of DHA (see [35]). One interpretation of this preferential retention of DHA, is that DHA is structurally and/or functionally preferred over EPA and that metabolic mechanisms have evolved to preserve it.

Increasing maternal and fetal DHA status during pregnancy
With the recognition that maternal supply of DHA to the fetus is important and that fetal and infant DHA status is a major contributor to optimal visual and brain development and function investigations of ways to increase maternal DHA status have been made. Clearly the simplest way to do this would be to increase maternal DHA intake from fish or from supplements. Regular consumption of fatty fish resulted in higher maternal erythrocyte DHA content [39,40]. Connor et al. [41] reported that consumption of sardines and fish oil by women from week 30 of pregnancy resulted in higher DHA contents of maternal plasma and erythrocytes 4 weeks later than observed in women taking placebo. In that study, a total of 3 g long chain n-3 PUFAs including 1.1 g DHA were supplied per day. A similar intake of long chain n-3 PUFAs (2.7 g/day) and of DHA (1.1 g/day) provided as fish oil from week 30 of pregnancy resulted in higher DHA contents of maternal plasma phospholipids and of umbilical cord vein and artery at birth [42]. Fish oil providing 3.3 g/day n-3 LCPUFAs (including 2.2 g/day as DHA) from week 20 of pregnancy resulted in higher DHA contents of maternal erythrocytes at weeks 30 and 37 of pregnancy and at 6 weeks post-partum

[43]. Furthermore the DHA content of cord blood erythrocytes was 40% higher than in the placebo group [43]. A much lower intake of DHA (200 mg/day) from week 15 of pregnancy resulted in higher DHA content of maternal plasma erythrocytes at week 28 of pregnancy and at birth, although there was no effect on DHA content of cord blood plasma or erythrocytes [44].

Increasing status of DHA in human breast milk

After a baby is born it is important that a supply of preformed DHA is continued. Breast milk DHA content can be increased by maternal supplementation with fish oil [45], DHA-rich oil [46,47] or n-3 LCPUFA rich eggs [47] or by increased maternal fatty fish consumption [48]. Harris et al. [45] gave lactating women 5 g/day fish oil for 28 days or 10 g/day fish oil for 14 days or 47 g/day fish oil for 8 days. Levels of DHA in breast milk were 0.1% of total fatty acids at baseline and 0.5, 0.8 and 4.8% of fatty acids after 5, 10 and 47 g/day fish oil, respectively. Hawkes et al. [46] gave lactating women placebo, "low" dose DHA (300 mg/day) or "high" dose DHA (600 mg/day) from day 3 post-partum for 4 weeks. They found that the DHA content of maternal plasma, maternal mononuclear cells, breast milk and breast milk cells increased in relation to DHA intake. In another low dose approach, Jensen et al. [47] compared fish oil, algal oil and eggs as a source of DHA for incorporation into breast milk: lactating women (two weeks after giving birth) received about 200 mg/day DHA from the oils or eggs for 4 weeks. This resulted in an increase in DHA in maternal plasma phospholipids (from 2.5 to about 4% of total fatty acids) and in breast milk (from about 0.2 to about 0.4% of total fatty acids). Furthermore, infant plasma phospholipid DHA increased from about 3.6 to about 5% of total fatty acids. This demonstrates that increased consumption of DHA by lactating women results in increased DHA in breast milk subsequently elevating infant DHA status. The Salmon in Pregnancy Study investigated the effect of consumption of two portions of salmon per week from week 20 of pregnancy until delivery [12]. This intervention resulted in higher breast milk DHA than seen in women in the control group who did not eat fatty fish [48] (Figure 6).

Mechanisms of action of DHA
Cell membranes containing DHA within phospholipids have unique functional properties

Phospholipids are quantitatively the major lipid component of cell membranes. Fatty acids in the phospholipids play important roles assuring the correct environment for membrane protein function, maintaining membrane order ("fluidity"), and influencing formation of signalling platforms termed lipid rafts. Membrane phospholipids are substrates for the generation of second messengers like diacylglycerols, lysophospholipids and PUFAs themselves [49]. DHA is a constituent of cell membrane phospholipids and it imparts unique physical and chemical properties on the phospholipid and any signalling molecules that are produced from it [49]. Because of its highly unsaturated nature, DHA adopts a three dimensional shape that is different from that of other common membrane fatty acids (Figure 1). This shape strongly influences membrane order and has an impact on membrane protein function and on the assembly of lipid rafts (Figure 7). Hence, the DHA content of a cell membrane can have a significant influence on cellular behaviour and responsiveness to signals, which may be electrical, chemical, hormonal or antigenic in nature. Within the brain DHA has important actions in regulating intracellular signalling [50]. Perhaps the single best example of the unique role that cell membrane DHA has in a physiological function relates to the role of the rod in the retinal photoreceptor [51]. The cells of the rod outer segment have an exceptionally high content of DHA in their membranes (50 to 70% of fatty acids) [26]. The DHA is a component of phospholipids that cluster around the protein rhodopsin which receives the light signal. When the signal is received, rhodopsin undergoes a conformational change that initiates a signal transduction cascade. The physical nature of DHA within the membrane facilitates the conformational change [51]. Studies with rhodopsin imbedded in artificial membrane bilayers demonstrate that phospholipids containing two DHA molecules are greatly superior to phospholipids containing one or no DHA molecules, even when they contain other highly unsaturated fatty acids such as n-6DPA or arachidonic acid [52].

DHA can act via cell surface and intracellular receptors

Peroxisome proliferator activated receptors

Peroxisome proliferator activated receptors (PPARs) are transcription factors; they regulate gene expression and so play a role in cell and tissue responses to the environment. There are several isoforms of PPARs; PPAR-α and PPAR-γ are the

most well understood. PPARs act by forming a heterodimer with the retinoic-X-receptor, the ligand for which is cis-9-retinoic acid. PPAR-α is expressed mainly in the liver, and is involved in regulating hepatic metabolic responses. The transcription of genes encoding several key enzymes of β-oxidation and of lipoprotein metabolism have been shown to be regulated by PPAR-α. Thus, activation of PPAR-α results in partitioning of fatty acids towards hepatic oxidation and away from triglyceride synthesis. PPAR-γ is expressed in adipose tissue, where it is involved in regulating adipocyte differentiation and metabolic responses of adipocytes including promoting insulin sensitivity, and in inflammatory cells, where it is involved in regulating the production of inflammatory mediators, having an anti-inflammatory action. PPARs are activated by non-covalent binding of ligands which include n-3 LCPUFAs and various lipid mediators. DHA can induce and activate PPARs [53] and upregulate a number of PPAR target genes [54], which may be at least partly responsible for the ability of DHA to lower fasting plasma triglyceride concentrations [55], to increase insulin sensitivity [56], and to reduce inflammation [57].

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G-protein coupled receptors
Several membrane associated G-protein coupled receptors (GPRs) are able to bind fatty acids differentially according to structural features of those fatty acids. GPR40 and GPR120 can both bind long chain fatty acids and are active in signal transduction. Oh et al. [58] reported that GPR120 is highly expressed on adipocytes and on inflammatory macrophages. Macrophage GPR120 was shown to be involved in anti-inflammatory signalling, inhibiting activation of the prototypical pro-inflammatory transcription factor nuclear factor kappa B [58]. DHA (and EPA) promoted GPR120-mediated gene activation, and several anti-inflammatory actions of DHA did not occur in GPR120 knockdown cells. Oh et al. [57] also demonstrated that DHA promoted the translocation of the glucose transporter GLUT4 to the surface of cultured adipocytes and that this was associated with enhanced glucose uptake. These effects were abolished by GPR120 knockout, suggesting that GPR120 mediates at least some of the metabolic actions of DHA.

DHA is a substrate for biosynthesis of bioactive mediators

PUFAs including linoleic acid, dihomo-gamma-linolenic acid (20:3n-6), arachidonic acid, EPA, n-3DPA, n-6DPA (22:5n-6) and DHA all give rise to bioactive lipid mediators formed through the cyclooxygenase and lipoxygenase pathways [57]. These mediators have many actions, but are most well recognised for their roles in inflammation, immunity, platelet reactivity, and smooth muscle contraction. Historically, most attention has been given to the prostaglandins, thromboxanes and leukotrienes, produced from arachidonic acid. Like EPA, DHA has some actions to reduce the production of these mediators, which may be an important mechanism by which DHA can affect inflammation, immunity, blood clotting and so on. More importantly however, new families of bioactive lipid mediators produced from both EPA and DHA have been discovered. These mediators are able to induce resolution of inflammation (i.e., "turn inflammation off") and to promote immune function, thereby assisting with host defence and diminishing the pathological effect of inflammation [59,60]. They include the resolvins produced from EPA (E-series) and DHA (D-series) and protectins and maresins produced from DHA. Protectins are also referred to as neuroprotectins when generated within neural tissue, where they appear to have an important role [59,60]. The synthesis of resolvins, protectins and maresins involves the cyclooxygenase and lipoxygenase pathways, with different epimers being produced in the presence and absence of aspirin [59,60]. Figure 7 shows the outline of the pathway of DHA conversion to these mediators. D-series resolvins and protectins have been described in human plasma [61], adipose tissue [62] and breast milk [63]. The biological effects of resolvins, protectins and maresins have been examined extensively in cell culture and in animal models [59,60]. Resolvin D1 and D2 and protectin D1 have each been demonstrated to have potent anti-inflammatory and inflammation resolving actions in these model systems [59,60], acting through specific G-protein coupled receptors.

Summary and conclusions

DHA is a long chain, highly unsaturated n-3 fatty acid. It has a structure that gives it unique physical and functional properties. DHA is metabolically related to other n-3 fatty acids: it can be synthesized via EPA from the plant essential fatty acid ALA. However this pathway does not appear to be very efficient in many individuals, although conversion of ALA to DHA is much better in young women than in young men. It also appears that young infants may be more efficient converters of ALA to

DHA than many adults, although conversion rate is variable among infants. Many factors have been identified that affect the rate of conversion of ALA to DHA. These factors include n-6 fatty acid levels, availability of several trace elements, sensitivity to insulin, female sex hormone status, and polymorphisms in, and epigenetic modification of, the genes encoding the various enzymes involved in the pathway. The implication of poor conversion is that DHA needs to be consumed preformed. Along with EPA and n-3DPA, DHA is found in fairly high amounts in seafood, especially fatty fish, and in various forms of n-3 supplements. The amount of DHA in seafood and in supplements varies. Breast milk contains DHA. DHA is found esterified into complex lipids within the bloodstream, in adipose stores and in cell membranes. Its concentration in different compartments varies greatly. The brain and eye have high DHA contents compared to other organs. DHA is especially concentrated in the grey matter of the brain and in the rod outer segments of the retina. In the brain DHA is involved in neuronal signalling while in the eye it is involved in visual quality. DHA is accumulated in the brain and eye late in pregnancy and in early infancy. A lower DHA content is linked to poorer cognitive development and visual function. Thus, it is vital that pregnant and lactating women and infants consume sufficient preformed DHA to support brain and eye development and function. Increased intake of DHA by pregnant women and by infants results in higher DHA concentration in most body compartments. Breast milk DHA concentration is strongly influenced by dietary DHA intake. DHA affects cell and tissue physiology and function through numerous mechanisms, summarized in Figure 7. These include alterations in membrane structure and function, in membrane protein function, in cellular signalling and in lipid mediator production. In addition to the effects on neuronal signalling and vision, DHA reduces inflammation, improves immune function, and optimises cellular metabolism. Through these effects DHA acts to lower the risk of insulin resistance, metabolic syndrome, hyperlipidemia, and cardiovascular disease.

Conflicts of interest

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Table 1. Typical DHA content of selected fish, other seafood and meats. Data are taken from Ref. 7. Note that both DHA content and portion size may vary.

Food	DHA (g/100 g food)	Typical adult portion size (g)	DHA (g/portion)	Contribution of DHA to EPA+n-3DPA+DHA (%)
Mackerel	1.10	160	1.75	55
Canned pilchards	1.20	110	1.32	45
Canned sardines	0.68	100	0.68	40
Salmon	1.3	100	1.3	60
Trout	0.83	120	1.0	55
Herring	0.69	120	0.82	50
Cod	0.16	120	0.19	65
Haddock	0.10	120	0.12	65
Plaice	0.10	130	0.13	35
Canned tuna	0.14	45	0.06	75
Crab	0.45	85	0.38	45
Prawns	0.04	60	0.02	35
Mussels	0.16	40	0.06	25
Beef	< 0.01	90	<0.01	<25
Lamb	0.02	90	0.02	25
Pork	0.01	90	<0.01	<25
Chicken	0.03	100	0.03	50

Table 2. Typical EPA and DHA contents of fish oils and other n-3 supplements.

Food	EPA (mg/g oil)	DHA (mg/g oil)	EPA+DHA (mg/g/oil)
Cod liver oil	110	90	200
Krill oil	140	65	205
Standard fish oil	180	120	300
Typical 45% fish oil concentrate	270	180	450
Tuna oil	110	350	460
Algal oil used in infant formula	0	>400	>400
Typical 60% fish oil concentrate	360	240	600
Epanova® (N-3 free fatty acid concentrate)	550	200	750
Omacor®/Lovaza® (N-3 ethyl ester concentrate)	460	380	840
Vascepa® (EPA ethyl ester concentrate)	1000	0	1000

Table 3. Typical EPA and DHA concentrations reported in different compartments in humans. Data are taken from the selected references and are not exhaustive.

Population	Compartment	Units	EPA	DHA	Reference
Generally healthy men and women aged 18 to 45 years; UK	Plasma triglycerides*	μmol/L‡	4	10	A.L. West and P.C. Calder, unpublished data
Generally healthy men and women aged 20 to 80 years; UK	Plasma triglycerides*	% of fatty acids	0.3	0.8	[11]
Generally healthy men and women aged 18 to 45 years; UK	Plasma phospholipids*	μmol/L‡	40	120	A.L. West and P.C. Calder, unpublished data
Generally healthy men and women aged 20 to 80 years; UK	Plasma phospholipids*	% of fatty acids	1.2	3.6	[11]
Healthy pregnant women aged 18 to 40 years; week 38 of pregnancy; UK	Plasma phospholipids*	% of fatty acids	0.4	3.8	[12]
Newborn infants (umbilical cord); healthy pregnancies; UK	Plasma phospholipids	% of fatty acids	0.3	6.4	[12]
Generally healthy men and women aged 18 to 45 years; UK	Plasma cholesteryl esters*	μmol/L‡	55	40	A.L. West and P.C. Calder, unpublished data
Generally healthy men and women aged 20 to 80 years; UK	Plasma cholesteryl esters*	% of fatty acids	1.0	0.6	[12]
Generally healthy men and women aged 18 to 45 years; UK	Plasma non-esterified fatty acids*	μmol/L‡	0.9	3.4	A.L. West and P.C. Calder, unpublished data
Generally healthy men and women aged 20 to 80 years; UK	Plasma non-esterified fatty acids*	% of fatty acids	0.4	1.6	[12]
Generally healthy men and women aged 20 to 80 years; UK	Red blood cells	% of fatty acids	2.3	5.2	[12]

Generally healthy men and women aged 20 to 80 years; UK	Platelets	% of fatty acids	1.1	2.0	[12]
Generally healthy men aged 18 to 40 years; UK	Blood neutrophils	% of fatty acids	0.6	1.6	[13]
Generally healthy men and women aged 20 to 80 years	Blood mononuclear cells (mainly lymphocytes)	% of fatty acids	0.8	1.9	[11]
Men mean age 68 years with no evidence of dementia	Brain grey matter	% of fatty acids	Not reported	18	[14]
Men mean age 68 years with no evidence of dementia	Brain white matter	% of fatty acids	Not reported	4	[14]
Breast fed term infants who had died at mean age 4 months; Australia	Cerebral cortex	% of fatty acids	< 0.1	8	[15]
Breast fed term infants who had died at mean age 4 months; Australia	Retina	% of fatty acids	0.1	12	[15]
Men mean age 55 years who had received a heart transplant; USA	Cardiac muscle	% of fatty acids	0.2	1.5	[16]
Mainly men mean age 60 years undergoing cardiac surgery; Australia	Cardiac muscle phospholipids	% of fatty acids	0.5	4.8	[17]
Healthy men mean age 21 years; UK	Skeletal muscle	% of fatty acids	0.6	1.5	[18]
Healthy men and women aged 25 to 45 years; USA	Skeletal muscle phospholipids	% of fatty acids	0.7	1.9	[19]
Men and women aged 38 to 41 years undergoing surgery; Chile	Liver	% of fatty acids	0.4	6.8	[2]
Men and women aged 23 to 63 years undergoing surgery; Chile	Liver phospholipids	% of fatty acids	4.8	15.1	[21]
Patients with	Colonic mucosa	% of fatty	0.3	1.7	[22]

inflammatory bowel disease; UK		acids			
Generally healthy men and women aged 20 to 80 years; UK	Subcutaneous adipose tissue	% of fatty acids	0.2	0.2	[11]
Generally healthy men mean age 34 years; Iran	Spermatozoa	% of fatty acids	0.6	9.6	[23]

*Blood collected after an overnight fast

[‡]Absolute n-3 PUFA concentrations will be affected by the concentrations of blood lipids and lipoproteins; these data are for healthy non-obese adults.

Figure legends

Figure 1. Different depictions of the structure of DHA. DHA has 22 carbons and six *cis* double bonds in its hydrocarbon (acyl) chain. The α-carbon is the carbon of the terminal carboxyl group (COOH) and the ω-carbon is the carbon of the terminal methyl (CH$_3$) group.

Figure 2. The metabolic pathway of conversion of α-linolenic acid to DHA showing the enzymes involved.

Figure 3. The change in DHA concentration (mg/L) in plasma phospholipids during human pregnancy. Maternal blood was collected from the same women at different time points in pregnancy. Data are taken from Al et al. [31] and represent the mean values from 110 women.

Figure 4. DHA concentration (as % of total fatty acids) in maternal blood plasma lipids in late pregnancy and in umbilical cord blood plasma at birth. Maternal blood was collected at week 38 of pregnancy. Data are previously unpublished and represent mean values from 50 pregnancies. PL, phospholipid, TG, triglyceride; CE, cholesteryl ester.

Figure 5. DHA concentration (as % of total fatty acids) in plasma phospholipids and peripheral blood mononuclear cells from older subjects supplemented with DHA (720 mg/day) for 12 weeks. Blood was collected at baseline and after 4, 8 and 12 weeks of supplementation with near pure DHA (algal source) and again 4 weeks after stopping supplementation. Data are taken from Thies et al. [37,38] and represent mean values from eight healthy older subjects (age 58 to 71 years).

Figure 6. **Effect of eating salmon during pregnancy on DHA concentration (as % of total fatty acids) in human breast milk.** Pregnant women consumed two portions of salmon per week from week 20 of pregnancy until birth. The control group reported very low or no consumption of fatty fish. Breast milk was collected at days

1, 5, 14 and 28 after giving birth. Data are taken from Urwin et al. [48] and represent mean values from 7 to 27 samples depending upon group and time point.

Figure 7. A schematic summary of the mechanisms of action of DHA. PPARs, peroxisome proliferator activated receptors.