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Dietary DHA and health: cognitive function ageing

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Abstract

DHA is a key nutritional *n*-3 PUFA and needs to be supplied by the human diet. DHA is found in significant amounts in the retinal and neuronal cell membranes due to its high fluidity. Indeed, DHA is selectively concentrated in the synaptic and retinal membranes. DHA is deemed to display anti-inflammatory properties and to reduce the risk of CVD. Consumption of larger amounts of DHA appears to reduce the risk of depression, bipolar disorder, schizophrenia and mood disorders. Conversely, it has been shown that loss of DHA from the nerve cell membrane leads to dysfunction of the central nervous system in the form of anxiety, irritability, susceptibility to stress, dyslexia, impaired memory and cognitive functions, and extended reaction times. DHA plays an important role in ensuring a healthy ageing, by thwarting macular degeneration, Alzheimer's disease, and other brain disorders at the same time as enhancing memory and strengthening neuroprotection in general. A reduced level of DHA is associated with cognitive decline during ageing. Different mechanisms for this fundamental DHA role have been put forward. Namely, neuroprotectin D1, a DHA derivative, may support brain cell survival and repair through neurotrophic, anti-apoptotic, and anti-inflammatory signalling. Many of the effects of DHA on the neurological system may be related to signalling connections, thus leading to the study of the related signalolipidomics. Therefore, the present review will focus on the influence of DHA deficiency upon ageing, with specific emphasis upon neurological disorders related to cognitive function and mental health.

Key words: DHA: Marine sources: Ageing: Cognitive disorders: Mental health

Introduction

In developed countries, population ageing is a major demographic trend and will remain so in the next decades. Accordingly, health issues concerning the elderly have increased in importance and have entailed an ever-growing level of economic costs. Among these health issues, loss of memory and alterations in behaviour associated with declining brain function have a large impact on society and the economy. These changes with ageing are also key symptoms of degenerative brain diseases, such as Alzheimer's disease (AD) and other dementia forms[1]. Furthermore, there are many forms of chronic debilitating brain disorders besides dementias. It has been claimed that in the next years the impact of the wide array of brain disorders will possibly surpass that of CVD and cancer taken together[2]. Therefore, it is of paramount importance to achieve a deeper knowledge of the conditions for optimal brain function and cognition. It is important to point out that prevention is more effective than treatment in curbing the societal and economic costs. Taking this into account, nutrition may have a very significant role for this objective. In fact, there are aspects associated with nutrition that affect the risk of cognitive function decline and neural and psychiatric outcomes.

DHA, one of the most important marine *n*-3 PUFA, may have a strong influence on brain health[1]. Indeed, consumption of larger amounts of *n*-3 PUFA, particularly DHA, appears to reduce the risk of depression[3], including postpartum depression, bipolar disorder (manic depression), schizophrenia, and mood and behaviour disorders[4]. It has also been hypothesised a connection between DHA in the diet and in the nerve cell membrane and the risk of dysfunction of the central nervous system in the form of anxiety[5], irritability, susceptibility to stress[6], dyslexia[7], stereotypic behaviour, aggressiveness[8], reduced learning capacity[4], impaired memory and cognitive functions, and extended reaction times[9].

The present review will focus on the role of DHA in the nervous system and cognitive function as well as in the prevention of cognitive decline associated with ageing. The state-of-the-art in these scientific areas of research will be analysed taking into account the DHA chemical form (Fig. 1), that is, the wider chemical structure where DHA is bound (TAG, NEFA, ethyl ester

Abbreviations: AD, Alzheimer's disease; ALA, α-linolenic acid; β-APP, β-amyloid precursor protein; FA, fatty acid; MCI, mild cognitive impairment; NeuroPs, neuroprostanes; NPD1, neuroprotectin D1; PC, phosphatidylcholine; PL, phospholipid; RCT, randomised controlled trial; RDI, recommended daily intake.

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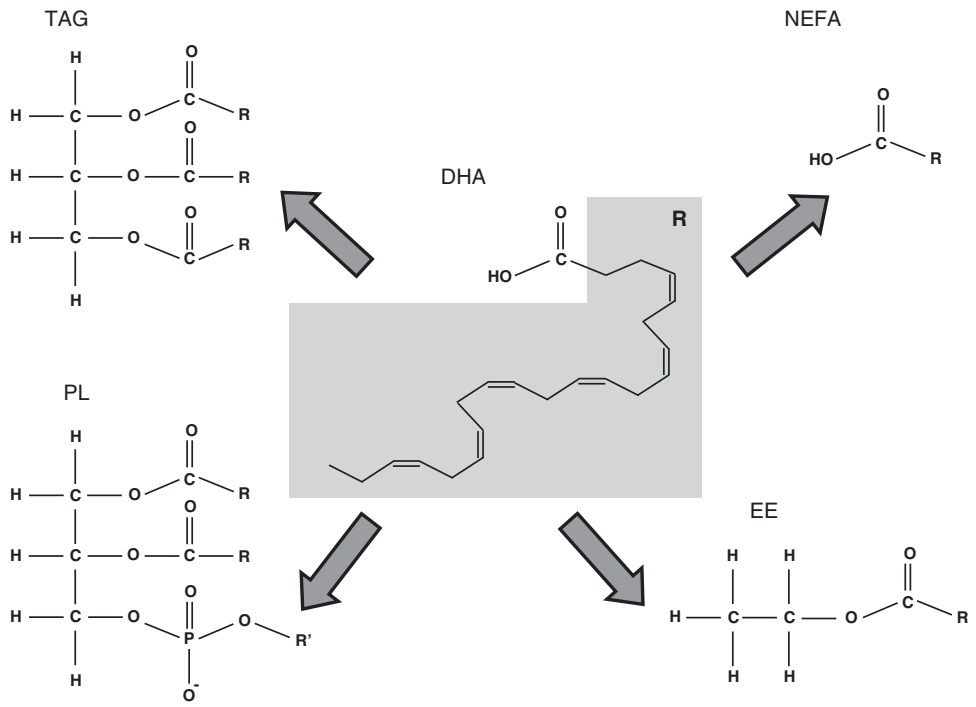

Fig. 1. Chemical structure of the different chemical forms in which DHA may be found. PL, phospholipid; R', choline, serine, ethanolamine, etc.; EE, ethyl ester.

and phospholipid (PL)) and its effects on DHA bioaccessibility and bioavailability.

DHA and its role in cognitive ageing: evidence discussion

Ageing and the cognitive function decline associated with it pose a great challenge to societies in developed countries. The loss of cognitive abilities may vary immensely in kind and degree and may affect not only elderly, but also middle-aged individuals. In the most serious situations, pathologies are identified. As aforementioned, there are many forms of chronic debilitating brain disorders, nutrition being a possible key to the prevention and mitigation of some of their effects. DHA plays an important role in ensuring healthy ageing, by possibly thwarting macular degeneration, AD and Parkinson's disease, and other brain disorders at the same time as enhancing memory and strengthening neuroprotection in general. A reduced level of DHA in the blood is associated with cognitive decline during ageing[10]. An overview of the various studies concerning the impact of DHA on AD (and other cognitive decline situations) as well as on healthy individuals is presented in Table 1.

There are several important studies correlating dietary DHA and cognitive function ageing effects. These studies relate to different human populations that can be healthy or presenting mild cognitive impairment (MCI)/AD/other cognitive function disorders.

Some interesting studies, either observational or randomised controlled trials (RCT), have been carried out with healthy populations[11–13]. For instance, in a community-dwelling cohort, levels of α-linolenic acid (ALA), EPA and DHA were assessed in serum PL of volunteers not taking fish oil supplements[11,14]. It was found out that only the associations between serum PL DHA and non-verbal reasoning and working memory remained after adjustment for participant education and vocabulary. Moreover, DHA increased cognitive performance in an RCT involving mentally healthy individuals older than 55 years[13,15]. Daily supplementation of 900 mg of algal (*Schizochytrium* sp.) DHA for 24 weeks was associated with significantly lower paired associative learning errors than the placebo case. Similar results were attained by an RCT study[12] on executive functions and neuroimaging in a group of healthy subjects whose age ranged between 50 and 75 years. The authors registered a benefit in executive function including verbal fluency. They also found alterations in white matter microstructural integrity (interpreted as beneficial) as well as increases in gray matter volume in the frontal, temporal, parietal and limbic areas[12]. In a large cohort of Chinese adults (average age of 65 years; part of the Singapore Longitudinal Aging Studies (SLAS)), daily consumption of fish oil supplements was associated with higher Mini-Mental State examination scores and a lower risk of cognitive decline over a 1·5-year period[16].

All these studies involving healthy subjects have some drawbacks. In fact, while the study by Witte *et al.*[12] involved a very small population (*n* 65), the SLAS did not control the level of DHA intake. Therefore, both studies' conclusions are weakened by these shortcomings. The study by Yurko-Mauro *et al.*[13] seems better designed and more robust than others and clearly points to positive effects of 0·9 g DHA/d. However, the study by Velho *et al.*[17] did not find an effect of any PUFA on cognitive function. Hence, though studies on healthy elderly seem to point to a beneficial net effect of DHA on cognitive ageing, evidence is still far from convincing, further studies being required.

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Table 1. Overview of some significant intervention and observational studies concerning the effects of DHA on the cognitive decline due to ageing

Type of study	Study length (months)	Subjects (*n*)	Age (years)	DHA intake (g/d)	DHA source/form	Outcome	Reference
Observational study	–	280	35–54	–	–	Positive association between DHA and non-verbal reasoning and working memory in healthy volunteers	(11)
Prospective cohort study	18	1475	≥55	–	Fish oil/TAG	Daily consumption of fish oil supplements was associated with higher Mini-Mental State examination scores and lower cognitive decline	(16)
Cross-sectional and prospective study	5–12	187	>65	–	–	The exact effect of *n*-3 PUFA intake on cognitive function of elderly was unclear, warranting further study	(17)
Randomised controlled trial	6	65	50–75	–	Fish oil/TAG	DHA (and other *n*-3 PUFA) was beneficial in executive function including verbal fluency in healthy subjects	(12)
Randomised controlled trial	6	485	≥55	0·9	Algal/TAG	DHA associated with significantly lower paired associative learning errors in healthy subjects	(13)
Randomised controlled trial	6	23	55–90	0·7	Fish oil/TAG	DHA improved Alzheimer's Disease Assessment Scale score in subjects with mild cognitive impairment	(18)
Randomised controlled trial	3	21	68·1 (SD 6·3)	0·2	–	DHA improved immediate memory and attention score in subjects with mild cognitive impairment	(19)
Randomised controlled trial	12	36	≥60	1·3	Fish oil	DHA provided benefit for several measures of memory function in subjects with mild cognitive impairment	(20)
Observational study	31	186	65–84	–	–	Only high DHA and other *n*-3 PUFA intake evidenced a borderline non-significant trend for a protective effect against the development of mild cognitive impairment	(23)
Observational study	48	397	55–90	–	Fish oil	Although a causal effect of fish oil supplement use on cognition cannot be concluded from results, they highlight the need for future research	(22)
Observational study	–	5395	≥55	–	–	DHA was not associated with AD risk	(29)
Observational study	–	815	65–94	–	–	DHA was associated with reduced risk of AD	(25)
Observational study	–	899	55–88	–	–	Top quartile of plasma phosphatidylcholine DHA was associated with reduced risk of AD	(26)
Randomised controlled trial	6	23	55–90	0·7	Fish oil/TAG	DHA produced no difference in Alzheimer's Disease Assessment Scale score in AD subjects	(18)
Randomised controlled trial	3	8	67·0 (SD 6·3)	0·2	–	DHA did not improve immediate memory and attention score in AD patients	(19)
Randomised controlled trial	18	402	76 (SD 8·7)	2·0	Algal/TAG	DHA provided benefit for cognitive score in ApoE4 allele-negative AD patients	(32)

AD, Alzheimer's disease.

For individuals with MCI, some interesting studies[18–20] have also been carried out. The evidence has been recently reviewed[21]. Namely, the Memory Improvement After DHA Study (MIDAS) demonstrated that DHA may be advantageous in healthy adults with a mild memory complaint[13], thereby emphasising the role of prevention. Another study, Lee *et al.*[20], has reported a benefit for several measures of memory function in a group of elderly patients with MCI. Furthermore, in an RCT study, DHA provided benefit for several measures of memory and attention score in subjects with MCI[19]. However, in a study by Daiello *et al.*[22], it was concluded that a causal effect of fish oil supplement use on cognition was not proven, further research being warranted. On the other hand, in the Italian Longitudinal Study on Aging, there was no significant effect on the protection against the development of MCI[23]. These latter studies oppose the view that benefits of DHA are easier to detect during ageing whenever there is some MCI or memory complaint or possibly if an individual is under the influence of some physical or mental stressors[21].

A critical appraisal of these studies relating to MCI raises doubts about the beneficial action of DHA on MCI onset and development. The more positive results were attained in studies with small populations (thirty-six or lower)[18–20]. The studies with larger populations (186 or higher) did not show significant results[22,23], but they were observational studies where high DHA intakes were not tested by a significant share of the subject set. Accordingly, the protective role of DHA in MCI is still dubious.

Nevertheless, the effects of DHA on cognitive ageing, MCI and dementia other than AD have been more supported by evidence than those on AD. Whereas, according to some authors, DHA improved cognitive abilities in individuals with MCI, the effects on AD patients were not obvious[10,18,19]. Indeed, it has been mentioned that once AD is clinically evident, supplementation trials show no significant effect of DHA on AD[24]. Nevertheless, several prospective observational studies clearly point to a protective effect of higher DHA intake against risk of AD[25,26]. Hence, prevention is more effective than treatment. This assessment of the observational studies has been shared by different review papers[24,27,28]. On the other hand, there are other observational studies that did not find any association between DHA intake and AD risk[29]. A meta-analysis reviewing the association of *n*-3 PUFA and DHA with AD incidence found no significant evidence[30]. However, in some populations, such as the Dutch[29], fish consumption and DHA intake are quite low[31], thus entailing statistical problems given the very low number of subjects with a DHA intake high enough to reduce AD incidence. Furthermore, another interesting study[32], the Alzheimer's Disease Cooperative Study, found out that DHA did not produce any benefit in the primary outcomes, but observed a benefit for cognitive score in ApoE4 allele-negative patients. Indeed, AD patients in this group had a significantly lower decline in the Alzheimer's Disease Assessment Scale score over 18 months with a daily dosage of 2 g of DHA.

A comparison between the studies concerning DHA and AD (Table 1) shows that some studies do not have a representative population sample[18,19] and, as such, their significance is quite weakened. The Dutch study[29] seems much more solid and representative. The other observational studies are more modest and show beneficial DHA effects on AD that were not found in the Dutch study[25,26]. The RCT study by Quinn *et al.*[32] may harbinger a new generation of studies that are supported by *a priori* genetic analysis. This will provide much more insight. Meanwhile, evidence connecting DHA intake and containment of AD progression after its onset is very insufficient.

Whether healthy or MCI or AD subjects, the assessed studies do not provide incontrovertible outcomes. It is possible that the beneficial effects of DHA concern solely AD and MCI prevention and be entirely absent once clinical conditions, especially if severe (AD), are already present. But, results do not allow for such conclusion. Perhaps, more importantly, future studies should always separate population groups in accordance to their genes, since some causal links may only occur in specific genotypes. Studies encompassing larger populations and longer periods are also warranted.

DHA and its role in cognitive ageing: dose–response and mechanisms

The calibration of the DHA dosages for achieving a significant response is another issue that requires new studies. Some of the daily DHA dosages are quite high. For instance, in order to achieve 2 g/d of DHA, a daily meal of 130 g of Atlantic mackerel or 120 g of Atlantic salmon may be required (Table 2). Therefore, it would be difficult to achieve such high DHA intakes without supplements. Moreover, in future RCT, the issue of DHA bioavailability (see the 'Dietary sources of DHA, bioaccessibility and bioavailability' section) should be taken into account – for instance, the same DHA dosage given to different individuals can lead to different levels of bioavailable DHA as a result of changes in the functioning of the digestive system due to age and disease – and a better selection of DHA supplements (including chemical binding form) should be ensured.

For those studies involving AD patients, it has been observed that though DHA intake is low, brain DHA levels are frequently similar to the controls, thus suggesting that low DHA intake leads to low plasma DHA, but does not necessarily decrease brain DHA[24]. Accordingly, these authors have claimed that animal models involving dietary *n*-3 PUFA deficiency in order to deplete brain DHA may not be adequate in AD research. Moreover, it has been claimed that the fatty acid (FA) profile of plasma total lipids is not an appropriate measure of DHA status in AD because it seems to mask lower DHA in plasma PL offset by higher DHA in plasma cholesteryl esters[33,34]. Hence, it is of paramount importance to analyse DHA in each lipid class. AD has been associated with changes in plasmalogen choline as well as in the amount of DHA found in different PL[35].

In the mechanistic analysis of the link between DHA and cognitive function, it should be noted that DHA is by far the main *n*-3 PUFA present in the brain – its content within brain FA is 12–15 %[36] – where it is predominantly located in neuronal membranes of the grey matter, especially in synapses[24]. In addition, the brain FA-binding protein preferentially binds DHA (and other *n*-3 PUFA)[37], leading to higher levels of DHA incorporation in the molecular structures of the membranes[38].

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Table 2. Average DHA content (mg/100 g) in different marine sources, not subjected to any culinary process[112,113,130–132]

Category	Product	DHA content (mg/100 g)	DHA richness
Bivalves	Common cockle	215	Poor
	Grooved carpet shell	55	Poor
Cephalopods	Common cuttlefish	38	Poor
	Common octopus	129	Poor
	European squid	417	Medium
	Flying squid	225	Poor
Crustaceans	Norway lobster	77	Poor
	Red shrimp	28	Poor
	Rose shrimp	29	Poor
Fish	Alfonsino	48	Poor
	Atlantic cod	42	Poor
	Atlantic mackerel	1580	Rich
	Atlantic salmon	1773	Rich
	Auxillary seabream	327	Medium
	Black scabbardfish	171	Poor
	Blackspot seabream	490	Medium
	Chub mackerel	2128	Rich
	Common sole	29	Poor
	European conger	425	Medium
	European eel	3447	Rich
	European hake	155	Poor
	European plaice	153	Poor
	Gilthead seabream	1207	Rich
	Greater forkbeard	26	Poor
	Horse mackerel	363	Medium
	Ling	21	Poor
	Meagre	147	Poor
	Monkfish	38	Poor
	Northern bluefin tuna	420	Medium
	Rainbow trout	387	Medium
	Red porgy	45	Poor
	Rubberlip grunt	79	Poor
	Sardine	1169	Rich
	Sea bass	599	Rich
	Silver scabbardfish	460	Medium
	Smooth hound	51	Poor
	Swordfish	829	Rich
	Thornback ray	44	Poor
	Wreckfish	418	Medium
Microalgae	*Amphidinium sp.* S1*	677	Poor†
	*Isochrysis galbana NIVA-4/91**	1580	Medium†
	Prorocentrum triestinum S2*	752	Poor†
	Thraustochytrium aureum ATCC 34304	6590	Rich†
Seaweeds	*Ascophyllum nodosum**	40	Poor
	*Fucus spiralis**	83	Poor
	*Fucus vesiculosus**	91	Poor
	*Laminaria digitata**	16	Poor
	*Pelvetia canaliculata**	127	Poor

* For microalgae and seaweeds, DHA contents are given in mg/100 g DM.
† For microalgae and seaweeds, richness was assessed assuming 20% DM as is usually the case in seafood.

DHA is supplied to the central nervous system by the liver, where DHA attained from food is taken up and distributed to other organs[39]. Besides, though there is evidence suggesting the expression and functional role of FA transporters at the blood–brain barrier[40], DHA can reach the brain by simple diffusion through this barrier[41]. On the other hand, the dietary level of α-linolenic acid (ALA; 18 : 3*n*-3), a precursor of DHA, does not correlate well with the level of DHA in the human body, making it advisable, for instance, to supplement the nursing mother's diet with DHA[42]. Furthermore, it should be remarked that plasma or erythrocyte DHA does not correlate well with DHA in the brain cells[24,43–45].

DHA is highly enriched in the PL of the synaptic plasma membrane and synaptic vesicles[46]. Regarding this issue, it is worth analysing the pathways leading to the synthesis of some important PL. Phosphatidylcholine (PC), a fundamental brain PL, is synthesised through the Kennedy pathway[47] from three precursors: choline, a pyrimidine, and, typically, a PUFA (either DHA or other PUFA). Phosphatidylethanolamine (PE) may be synthesised from a PUFA and a pyrimidine. These precursors act by enhancing the substrate saturation of enzymes that bring about the incorporation of the precursors in PC and phosphatidylethanolamine[48]. In accordance with this, it has been reported that synaptic proteins and PL are increased in gerbil brain by joint administration of uridine and DHA[48]. Furthermore, it was found that continuous supply of DHA, but not arachidonic acid (20 : 4*n*-6), may lead to an increase in brain phosphatide and synaptic protein levels according to animal models[49]. Phosphatidylserine is also very important and abundant in the human brain and typically contains significant amounts of DHA[50]. It is known that throughout childhood development DHA is accumulated within the brain PL, PC and phosphatidylethanolamine[51].

Differently from EPA, DHA is not a source for eicosanoid synthesis, rather exerting influence directly and indirectly. DHA can also be converted to EPA by a retroconversion reaction, thereby leading to the formation of various eicosanoid metabolites[52]. The DHA derivatives produced by oxidation reactions have also importance and are usually termed docosanoids[53]. Such compounds bear resemblance to eicosanoids and are deemed as potential mediators of the biochemical processes in the central nervous system[53]. DHA may also generate *trans*-4-hydroxy-2-hexenal (4-HHE) as a result of peroxidation. This oxidation product, 4-HHE, has been shown to be toxic to primary cultures of cerebral cortical neurons[54]. The formation of 4-HHE seems to follow an oxidation pathway different from that generating docosanoids. Hence, DHA may undergo different biochemical transformations as a function of the prevailing conditions and lead to distinct effects on the central nervous system.

Docosanoids include neuroprotectin D1 (NPD1), maresins, neuroprostanes (NeuroPs), and related 22-C derivatives[55]. The NeuroPs are structurally related to prostaglandins and constitute a large family of oxidised cyclopentanoid derivatives. NeuroPs are derived through a cascade of non-enzymic radical reactions from the non-enzymic peroxidation of DHA in neurons[56]. However, it has also been shown that lipoxygenase inhibitors block the synthesis of many docosanoids[57]. Interestingly, it has been suggested that these DHA derivatives might be neuroprotective[58]. The research into the role of NPD1 has brought forth evidence of such a neuroprotective effect[59].

NPD1 is attained from the selective oxygenation of DHA by the enzyme 15-lipoxygenase-1[60]. NPD1 leads to homeostatic signalling in response to cellular and systemic imbalances[61]. In particular, the positive regulatory actions of NPD1 together with DHA follow different interdependent mechanisms[62–65]. First, membrane properties encompassing lipid bilayer fluidity and membrane rafts are important for their biophysical characteristics. Another mechanism involves the recruitment and up-regulation of anti-apoptotic members of the *Bcl-2* gene family. Moreover, the

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modulation of kinase-mediated *Bcl-2* gene family phosphorylation is affected. The activation of inflammatory signalling mediators (for instance, the PG-synthesising arachidonic FA enzyme cyclo-oxygenase-2) is repressed. Finally, the expression of proapoptotic signalling is also repressed.

Different mechanisms for the DHA role as a protective agent against cognitive decline have been put forward. Namely, NPD1 may support brain cell survival and repair through neurotrophic, anti-apoptotic and anti-inflammatory signalling. Indeed, many of the effects of DHA on the neurological system may be related to signalling connections, thus leading to the study of the related signalolipidomics. However, the action of NPD1 as a possible modulating agent of transport mediated by ApoE and its effect on β-amyloid precursor protein (β-APP) processing, soluble amyloid precursor protein α fragment (sAPP-α) or amyloid-β peptide speciation, generation, and secretion during ageing, and in cytokine-, hypoxia- and oxidation-stressed human brain cell models of AD are not fully understood. DHA itself has been linked to these events[64,66,67]. It is still unsettled if, under those conditions, NPD1 is formed from DHA or if there are alternative mechanisms for DHA action[63].

However, there are aspects of the NPD1 action that need to be better understood, such as, the impact on the biophysics and kinetics of the membrane-embedded secretase-mediated cleavage mechanisms of β-APP[66,68]. Moreover, the effect of NPD1 on specific secretase activities is a still unexplored field, which deserves more attention, given its importance to the design of more effective and selective amyloid-β peptide-lowering agents[68,69].

The Alzheimer's Disease Cooperative Study AD study[32] also suggests other biochemical interactions of DHA, given the sensitivity of ApoE4 allele-negative patients to DHA. It is known that ApoE can interact with various receptors in the brain, in neurons, astrocytes and in capillary endothelial cells at the blood–brain barrier[70,71]. ApoE4 is a lipid transporter, which may limit DHA transport in the brain. A comparison between old ApoE4 carriers with ApoE4 allele-negative individuals (carrying ApoE2 or ApoE3 alleles) points to a shorter DHA whole-body half-life in the former after an oral dose of [^{13}C] DHA[72]. It has been reported that an accumulation of DHA in the blood is associated with lower concentrations in cerebral tissue of ApoE4 mice, taking ApoE2 animals as a reference[73]. Such an inverse relationship between plasma and brain DHA contents suggests that plasma levels[74] may reflect defective distribution in the brain rather than being a good correlate of brain DHA content. So, it seems that ApoE4 leads to less DHA being transported into the brain, thereby causing a deleterious effect in AD[21].

A further mechanism relating DHA dietary intake and cognitive function ageing may involve the role of DHA in inflammatory processes. Indeed, DHA and EPA are deemed to display some anti-inflammatory properties[75,76], thereby offsetting the pro-inflammatory effects of *n*-6 PUFA[76]. For diseases having a recognised central role of inflammation to the pathology such as asthma or rheumatoid arthritis, DHA supplementation in the diet may be protective. The DHA-derived docosanoids are potent endogenous anti-inflammatory and pro-resolving chemical mediators[77]. They may reduce chronic inflammation by attenuating NF-kB, thereby modulating the expression of pro-inflammatory cytokines. On the other hand, abundant evidence indicates that inflammatory processes are active in AD[78]. Epidemiological studies indicate a lower prevalence of AD in individuals treated with non-steroidal anti-inflammatory drugs, but clinical trials have not yielded strong effects[79]. It is known that AD is related to the activation of microglia by different factors, including β-APP and pro-inflammatory cytokines[80]. Microglia increase the levels of some cytokines, such as IL-6, and TNF-α, which may generate deviations from the normal neuronal function[81].

Besides, DHA incorporation into the cell membranes modulates the efficiency of numerous membrane transporters and enzymes[82]. The incorporation of DHA into cell membranes is of great importance, since many essential cellular processes take place in and on membranes[83]. These processes are affected by the biochemical and biophysical properties of organelle membranes. Precisely, the lipid composition of these membranes influences the membrane properties, which, in turn, decisively exert an effect upon the activity of membrane-embedded proteins[84]. For instance, membrane thickness can affect the location of proteins.

DHA may also affect directly the physical properties of membranes, which depend on PL that are known to have a large importance in the neural membranes. For instance, PL, such as glycerophospholipids and sphingolipids, and sterols are prominent lipid classes in the membranes, but there is a large diversity of other minor lipid components[85]. The physical properties of membranes are affected both by the head groups and the hydrocarbon chains of lipid molecules. These effects can be tremendous not only on the properties, but also on the processes occurring within the membranes, even with subtle changes in lipid composition[83]. For instance, while a hypothetical bilayer of PC with two chains of a SFA such as stearic acid (18 : 0) displays a packed ordered state without any diffusion of lipid substances, a bilayer of PC with two DHA chains exhibits a more disordered state with freely moving lipid molecules[86,87]. Moreover, longer FA chains and a higher content of sphingolipids and sterols in the membrane correlate with an enhanced thickness[88]. It has also been observed that asymmetric distribution of glycerophospholipids and sphingolipids between the two leaflets of the neural membrane may lead to dynamic lipid substructures[46]. Therefore, the connections between DHA and the membrane physical properties are another important research field deserving further scientific studies.

Future research on the mechanistic aspects connecting DHA and AD as well as other cognitive ageing disorders should also identify and quantify relevant biomarkers in the plasma and cerebrospinal fluid, bridging the gap between docosanoids, cytokines and neuronal cell changes.

DHA and the cognitive function

The effects of DHA on cognitive ageing need an understanding of the multiple connections between DHA and the highest degrees of brain activity. Several studies have been conducted

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regarding this subject (Table 3). A deficient level of DHA is related with changes in the operation of cognitive function, namely, in ageing, hyperactivity, AD, schizophrenia and peroxisomal diseases[55]. Conversely, higher dietary intake of DHA is linked to better brain health[89]. Indeed, DHA is enriched in synaptic membranes, being able to change their fluidity as well as neurotransmitter and receptor densities. These mechanisms whereby DHA affects neural cells have already been described in previous section, but more studies on their details and the way that DHA positively affects cognitive function are warranted. There are several studies of a medical nature pointing to the positive effect of DHA on cognitive function[89], but the full understanding of the underlying biochemistry remains elusive.

Many studies relate to human cognitive function evolution as a result of ageing. For instance, a study on the effects of a 90 d DHA supplementation (252 mg/d) on cognitive function in a healthy ageing population did not find any significant impact[90]. Besides, it has been argued that there is greater evidence for DHA playing a preventive rather than curative role in dementia[27]. This role may be more important in unhealthy populations, for instance, in patients with type 2 diabetes[91]. Namely, it is not clear if an adequate brain DHA level can be kept in obesity and insulin-resistant states. Indeed, it is quite possible that the DHA level becomes inadequate, given evidence of greater cognitive decline in individuals with insulin resistance[92]. Moreover, it has been reported[93] that reference memory-related learning ability is positively correlated with DHA-derived docosanoids in aged rats. The same study did not find a significant correlation for EPA-derived mediators. Moreover, dietary DHA improves the learning-related spatial memory of DHA-deficient rats[94,95].

There is a lack of robust evidence to evaluate the effect of DHA in diet on the cognitive performance of young healthy adults. Some of the trials that have been done seem to present experimental design shortcomings. For instance, a placebo control is absent[96], sample size is small[97] and duration is too short[98,99]. On the other hand, a cross-sectional study on adults aged between 30 and 70 years old showed a positive association between DHA blood levels and scores on cognitive performance tests[11]. Against this backdrop, a recent work involving RCT has shown that DHA supplementation has improved both memory and reaction time in healthy young adults[9]. It should be remarked that the habitual diet of these young adults (age range 18–45 years) was low in DHA. Moreover, response was modulated by sex – whereas DHA improved episodic memory in women, it improved reaction times of working memory in men[9]. Another recent study provided compelling initial evidence that dietary factors affect the connection between physical activity and cognitive performance[100]. In particular, high levels of DHA relative to arachidonic acid reduced the negative effects of lower physical activity on performance. The results of these two studies may be related to the fact that DHA accumulates in areas of the brain involved in memory and attention such as the cerebral cortex and hippocampus[101,102]. Nevertheless, further observational studies and RCT are warranted in order to achieve a higher degree of certainty and a deeper understanding of the connections.

Table 3. Summary of the main studies concerning DHA and cognitive function

Type of study	Objectives	Individual characteristics	Mechanism involved	Main findings	Reference
Randomised controlled trial	Investigate whether a DHA supplement affects cognitive performance in healthy adults	176 healthy adults (18–45 years)	–	DHA supplementation improved memory and reaction time of memory in adults whose diet was low in DHA	(9)
Randomised controlled trial	Study effect of DHA on cognitive function and visual acuity in elderly	74 healthy participants (45–77 years)	–	90 d DHA supplementation raised plasma DHA, no significant effects of DHA on cognitive functioning	(90)
Animal experimental trial	Advance understanding of the impact of hyperinsulinaemia on brain fatty acid profile	24 5-week-old male Zucker rats	–	Deposition of DHA was limited in forebrain of young obese rats fed a diet without DHA	(91)
Animal experimental trial	Investigate whether administration of *n*-3 PUFA improves cognitive abilities	24 aged male Wistar rats	Benefits through increased brain DHA-derived docosanoids	DHA and other *n*-3 PUFA effectively improved the reference memory-related ability	(93)
Animal experimental trial	Test hypothesis that chronic administration of DHA may improve rat learning ability	36 inbred male Wistar rats	DHA may balance the deleterious effects of amyloid-β peptides	DHA administered for 12 weeks reduced the increase in reference and working memory errors in amyloid β-infused rats	(94)
Animal experimental trial	Evaluate whether fish oil supplementation improves reference/working memory	24 male Sprague–Dawley rats	–	DHA is critical for the development and maintenance of learning memory performance	(101)
Observational study	Test possible associations between DHA and other *n*-3 PUFA and cognitive function	280 volunteers (35–54 years) free of neuro-/psychiatric illness	Derivatives of DHA and not EPA/ALA have a long-term action throughout the lifespan	In covariate-adjusted regression models, higher DHA was related to better performance on reasoning tests	(11)
Observational study	To evaluate the interaction of physical activity and DHA regarding cognitive function	344 participants (30–54 years)	–	A diet high in DHA might mitigate the effects of lower levels of physical activity on cognitive performance	(100)

ALA, α-linolenic acid.

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Dietary sources of DHA, bioaccessibility and bioavailability

The large importance of DHA makes this an essential FA in human nutrition. Diets should be formulated in order to ensure an adequate level of DHA supply. The main source of DHA is seafood, particularly marine fish and shellfish[103]. DHA is found in the flesh of both lean and oily fish, with much greater amounts in the latter, and in the liver of some lean fish species, such as cod. There is also fish oil prepared from these raw materials rich in DHA[76]. There are also non-marine sources of DHA. However, DHA contents are only comparable with lean fish in the case of some meat-processing by-products and especially enriched foods. An overview of the DHA content in different sources and their characteristics is presented in Tables 2 and 4. Since meat, cereals and milk are more important in the Western diet, DHA intake is low[104]. Indeed, for a total of approximately 100 mg DHA/d, fish and seafood products are the largest contributor with 69·9 mg/d, followed by meat products with 19·6 mg/d, and egg products with 5·1 mg/d.

DHA is present primarily as TAG and, to a lesser extent, as NEFA in fish and derived unrefined raw oils[105]. In krill oil, a third fraction is found, since a substantial percentage of *n*-3 PUFA (and DHA) is bound in PL[105]. Pharmaceutical-grade, highly concentrated fish oil supplements with DHA bound in ethyl ester, are also available[76].

Oily fish, such as herring, salmon and sardine, are the richest sources of DHA[106]. According to these authors, of thirty-seven commonly consumed types of fish products, DHA is the main *n*-3 PUFA, being on average 65 % of total *n*-3 PUFA[107]. It should be remarked that DHA content in fish usually varies with the overall *n*-3 PUFA content. Three main classes of fish products may be differentiated on the basis of DHA content: relatively poor DHA sources (black scabbardfish, catfish, hake, megrim, tilapia); moderately rich DHA sources (halibut, pollock); and very rich DHA sources (herring, mackerel, salmon, sardine), corresponding to the approximate ranges <300, 300–500, and >500 mg/100 g, respectively[106–111].

For a more detailed presentation of DHA concentrations in different marine sources, Table 2 based on the Portuguese Institute for the Sea and Atmosphere (IPMA) extensive database[111,112] and different papers[113] can be consulted. The six highest DHA contents are found in the European eel, chub mackerel, Atlantic salmon, Atlantic mackerel, gilthead seabream (wild) and sardine, all exceeding 1000 mg/100 g[111,112].

The American Heart Association's recommended daily intake (RDI) is 500 mg EPA + DHA for individuals without CHD[114]. The European Food Safety Agency has advised 250 mg of EPA + DHA[115] and reference values for the EPA + DHA RDI are typically in the 250–500 mg range[116]. Specifically for DHA, an RDI of 250 mg has been put forward by ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail)[117]. A single weekly meal of 150 g of chub mackerel, Atlantic salmon or sardine may be more than enough to meet this DHA RDI (250 mg/d). For seafood moderately rich in DHA, the consumption of two to three weekly meals of 150 g may also be enough.

The level of DHA in a portion of food that is eaten may be quite different from the bioaccessible level, that is, the DHA concentration that is released from the food matrix into the intestinal lumen after digestion and is available for absorption[118,119]. On the other hand, bioavailability is usually defined as the fraction of an oral dose of a substance that reaches the systemic circulation[120]. The bioaccessible content is always equal or higher than the bioavailable content[118]. Bioaccessibility is usually determined by *in vitro* simulations of human digestion[118,121]. For bioavailability, according to the definition given above, cell lines and transwell assays are used for mimicking the intestinal lining barrier[122] and cell cultures simulating the relevant liver tissues may also be used[123]. Bioaccessibility and, as a consequence, bioavailability of DHA may depend on the chemical binding form (DHA bound in ethyl ester, TAG or PL) (Fig. 1), matrix effects (fat and other components content in food), and, in the case of DHA in supplements, galenic form (microencapsulation, emulsification, etc.)[105].

DHA biosynthesis routes

Besides dietary DHA and the bioaccessibility/bioavailability issues, DHA may be biosynthesised in the human body. However, for healthy and non-vegetarian humans, despite the

Table 4. Non-marine DHA dietary sources and their main characteristics, advantages and drawbacks

Category	Product	DHA content (mg/100 g)	Product characteristics, advantages and drawbacks
Milk*	Cows' milk, basal diet	0–10	Readily available, but extremely low content
	Cows' milk, special diet	10–30	Available, but very low content
	Cows' milk, enriched	30–50	Available, but still very low content
Eggs†	Chicken eggs, basal diet	20–40	Readily available, but very low content
	Chicken eggs, enriched diet	90–180	Available, low content
Meat‡	Lamb, muscle	10–20	Readily available, but very low content
	Pork, muscle	10–50	Readily available, but very low content
	Beef	10–20	Readily available, but very low content
	Rabbit, muscle	10–30	Readily available, but very low content
	Chicken, basal diet	10–30	Readily available, but very low content
	Chicken, linseed diet	20–50	Readily available, but very low content
Animal by-products§	Pork, subcutaneous fat	60–320	Available, nutritionally unbalanced, low content
	Pork, viscera	10–50	Available, but very low content

* Values from Fonollá *et al.*[133] and Klop *et al.*[134].
† Values from Lemahieu *et al.*[135].
‡ Values from Woods & Fearon[136] and Zotte & Szendrö[137].
§ Values from Sobol *et al.*[138].

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availability of the necessary enzymes, there is extremely limited synthesis of DHA in adults[124,125]. Unless induced by several years of a vegetarian diet, the human enzymic machinery is very inefficient in converting, for instance, ALA to EPA and DHA. Even with a diet deficient in DHA, the brain cells' ability to synthesise DHA from ALA is very low[126]. One study indicates a very low share of plasma ALA, < 0·2 %, deployed to the synthesis of DHA via EPA[124]. Indeed, it has been claimed an extremely low level of conversion of the precursor ALA to EPA, < 5 %[127], and to DHA, < 0·05 %[128]. Several enzymes are required to elongate and desaturate ALA or other shorter and less unsaturated *n*-3 PUFA into DHA. Research has found evidence suggesting that DHA formation may be regulated independently of other FA in the pathway and that DHA binding to PPARα suppresses transcription of the Δ-6 desaturase gene, thereby down-regulating conversion of ALA to DHA[129]. Indeed, it should be noted that the rate-limiting step in DHA synthesis is precisely the desaturation of ALA by Δ-6 desaturase. An overview of the possible routes for attaining DHA in the human organism, taking into account enzyme action, conversion rates, genetic factors, and dependence on the starting *n*-3 PUFA, is presented in Table 5.

Conclusions

DHA is mainly found in seafood, being rich sources of DHA such as marine fish and shellfish. Oily fish such as herring, salmon, sardine and tuna provide the highest amount of DHA per meal. DHA intake may be associated with several health endpoints ranging from inflammatory processes, asthma and rheumatoid arthritis to CVD and diabetes mellitus as well as to depression and cancer. Particularly, DHA has an important role in the nervous system, which is highlighted by its prominence in neural tissues. DHA may lead to the formation of docosanoids such as NeuroPs or NPD1. Namely, the action of NPD1 in the central nervous system is influential in different ways. It is known that NPD1 leads to homeostatic signalling in response to cellular and systemic imbalances. Nevertheless, much needs to be known about the mechanisms and roles of NPD1. For instance, NPD1 as a possible modulating agent of transport mediated by ApoE and its effect on β-APP processing is not fully understood. In spite of this, there seems to be some protection against cognitive decline with ageing and even improved memory and reaction time in healthy young adults. Indeed, for ageing-related MCI, some studies suggest that DHA may improve cognitive abilities. Nonetheless, for healthy subjects or MCI and AD patients, the evidence is still not convincing. In this context, it is worthwhile noting that for ApoE4 allele-negative AD patients, DHA produced a benefit in the cognitive score. Future studies should take the DHA bioavailability issue into account in order to achieve better results. On the other hand, research should try to separate the role of DHA and of EPA through studies using DHA only instead of fish oil rich also in EPA. Moreover, DHA in each main lipid class should be quantified instead of global DHA. Finally, future RCT and observational studies should always take into account the genetic traits of the population, since some effects may only be detected in subgroups with specific alleles.

Table 5. Possibilities for attaining DHA from different precursors in the human organism, conversion rates associated with DHA synthesis, genetic factors and performance in producing DHA for each precursor

Precursor studied	Main findings	Conversion rates	Genetic factors	Level of conversion of the precursor to DHA	Reference
ALA	The conversion of [^{13}C]ALA to longer-chain fatty acids was determined, yielding low conversion rates	–	–	< 0·05 %	(128)
	A dairy fat matrix providing ALA is better than a vegetable fat mixture to increase brain DHA accretion in young rats	–	–	–	(139)
	DHA synthesis from ALA is inhibited by diets high in PUFA	–	–	–	(140)
	Studies on rats pointed to dietary PUFA < 3 % for maximal DHA conversion from ALA		–	About 1 %	(141)
	The limited incorporation of dietary ALA into the hepatic phospholipid pool contributes to the low conversion of ALA into EPA, being an obstacle for DHA synthesis				
	DHA formation was highest at a linoleic acid (18 : 2*n*-6):ALA ratio of 1:1, gene expression of PPARα involved in ALA elongation was higher in the presence of ALA solely	–	PUFA and their derivatives help regulate expression of Δ-5 and Δ-6 desaturase genes	About 0·7 %	(142)
	The apparent synthesis of DHA was consistently low and not influenced by the intakes of ALA	–	–	<0·01 %	(143)
	Typical diets which are significantly higher in ALA compared with EPA yield similar daily DHA synthesis despite a higher synthesis-secretion coefficient from EPA	0·068 nmol/min	–	–	(144)
	The efficiency of conversion for individual steps in the desaturation/elongation route was estimated from kinetic analysis of ^{2}H-labelled fatty acids	–	–	About 0·05 %	(124)
	Binding of DHA to PPARα suppresses transcription of Δ-6 desaturase and down-regulates conversion of ALA to DHA	–	5′-Flanking region with a direct repeat (DR-1) regulates Δ-6 human desaturase gene	–	(129)
SDA (18 : 4*n*-3)	Dietary SDA increased EPA concentration but not DHA concentration in erythrocyte and in plasma phospholipids (relative effectiveness was 1·0:3·0:0·07 for EPA:SDA:ALA)	–	–	–	(145)
EPA	Typical diets which are significantly higher in ALA compared with EPA yield similar daily DHA synthesis despite a higher synthesis-secretion coefficient from EPA	0·120 nmol/min	–	–	(144)

ALA, α-linolenic acid; SDA, stearidonic acid.

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