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The benefit of docosahexaenoic acid for the adult brain in aging and dementia



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ABSTRACT

Keywords:

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A brief overview of the evidence for omega-3 fatty acids and, in particular, of docosahexaenoic acid (DHA), involvement in cognition and in dementia is given. Two studies are presented in this regard in which the key intervention is a DHA supplement. The first, the MIDAS Study demonstrated that DHA can be of benefit for episodic memory in healthy adults with a mild memory complaint. The second, the ADCS AD trial found no benefit of DHA in the primary outcomes but found an intriguing benefit for cognitive score in ApoE4 negative allele patients. This leads to a consideration of the mechanisms of action and role of ApoE and its modulation by DHA. Given the fundamental role of ApoE in cellular lipid transport and metabolism in the brain and periphery, it is no surprise that ApoE affects n-3 PUFA brain function as well. It remains to be seen to what extent ApoE4 deleterious effect in AD is associated with n-3 PUFA-related cellular mechanisms in the brain and, more specifically, whether ApoE4 directly impairs the transport of DHA into the brain, as has been suggested.

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1. Introduction

A fairly substantial literature now underpins the positive relationship between long chain n-3 fatty acid intake and protection from cognitive decline as well as dementia. For example, a lower plasma concentration of docosahexaenoic acid (DHA, 22:6n-3) has been associated with cognitive decline in both healthy elderly people [1,2] as well as in patients with Alzheimer's disease (AD) [3,4]. The Framingham study related decreased plasma phosphatidylcholine DHA content to increased cognitive decline and rates of dementia [4]. Another aspect of the relationship between long chain n-3 fatty acids and cognition is the literature relating fish intake to cognitive decline. There have been many such epidemiological studies, some quite large with both positive results and some null studies. The VA Normative Aging Study found an association between fish intake and the Mini Mental State Examination (MMSE) in over 1000 healthy men of median

age 68 [5]. The PAQUID Study observed a 35% reduction in risk of AD in 1600 French adults over 68 years of age who consumed only one fish meal a week or more [6]. Morris et al. have also shown an association of decreased AD risk with fish eating in Americans [7].

Intervention studies of fish oil or EPA/DHA supplementation have recently been reviewed [8]. A recent meta-analysis of 10 randomized, controlled trials that included studies of aging healthy adults as well as those with mild dementia or AD primarily with DHA as the intervention indicated positive results for patients with mild cognitive impairment [9]. Several epidemiological studies have suggested that ApoE4 allele negative patients benefit from DHA supplementation and that ApoE4 allele patients may not [10–12]. In addition, some recent imaging studies have shown an association of brain structural features with omega-3 intake. Raji et al. observed that weekly fish consumption was positively associated with gray matter volumes in several substructures including hippocampus and cingulate and orbitofrontal cortices [13]. The use of fish oil supplements was associated with higher mean hippocampal and cerebral cortex gray matter volumes as well as better cognitive scores (ADAS-cog and MMSE) in those with normal cognition [14]. Such cross-sectional studies are not conclusive but the associations that they suggest are then good candidates for interventional studies using randomized clinical trial methodology.

Abbreviations: DHA, docosahexaenoic acid; AD, Alzheimer's disease; ApoE, apolipoprotein E; CNS, central nervous system; LDLR, low-density lipoprotein receptor; VLDLR, very low-density lipoprotein receptor; LRP, LDLR-related proteins; BBB, blood brain barrier; CSF, cerebrospinal fluid

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2. Results

One key study in the domain of benefits of DHA for brain function is the MIDAS study, an acronym for Memory Improvement after DHA Study [15]. This was a randomized, controlled, multi-center trial of cognitive outcome in 485 healthy elderly patients. The intervention was 900 mg of algal DHA/d vs. corn/soy oil placebo capsules over a 24 week period. The primary endpoint was the score in the Paired Associate Learning (PAL) test from CANTAB. This is a computer generated, objective test that is sensitive to early episodic memory changes. Secondary endpoints included various tests of cognitive function, Activity of Daily Living (ADL) skills, plasma fatty acid analysis, safety and tolerability. Subjects were > 55 years of age and the population had a mean age of 70 years. The subjects had a subjective memory complaint and were screened for age related cognitive decline by means of the Logical Memory subtest of the Wechsler Memory Scale and also the MMSE. The cut offs for these tests were as follows: subjects had an immediate (≤ 28) or delayed (≤ 15) recall score that was ≥ 1 standard deviation below the mean of younger subjects of 25–35 years, and also had an MMSE > 26. Subjects were excluded who reported taking omega-3 supplements, consuming > 200 mg/d DHA in their diets, used medications for AD, major anti-psychotic or anti-depressant medications, had major medical conditions or who abused alcohol or drugs.

There was a significant improvement in the primary outcome, the PAL test, in the DHA supplemented group (Table 1). After 24 weeks, there were 4.5 fewer errors made in the DHA group while the placebo effect produced only 2.4 fewer errors in the placebo group. There were significant differences also in two of the measures of verbal recognition memory, the immediate and delayed recall, but not in the free recall (Table 1). No differences were detected between groups in tests for pattern recognition or spatial working memory nor in geriatric depression [15].

This was an impressive demonstration in a RCT of considerable size that DHA provided a benefit to the elderly for episodic memory and measures of visual recognition memory. When compared to normative data vs age, it could be estimated that the improvement in the PAL measure corresponded to that of being 7 years younger, whilst the controls appeared to be 3.6 years younger. In addition, the cognitive changes (PAL score) were significantly correlated with plasma DHA content which was increased from baseline values to the extent of 3.2 percentage points, expressed as a weight percent of total fatty acids. No erythrocyte data was obtained in this study.

Adverse events and serious adverse events were carefully monitored in this study and there were no significant differences between groups in this regard, nor were there differences in hematological or clinical chemistry measures. There was however a significant decrease in heart rate observed in the DHA group of -3.2 bpm (vs. -1 in the placebo group).

Since the MIDAS Study was published in 2010, there have been five studies of healthy adults involving memory related measures and with DHA/EPA as the key intervention and with the number of subjects greater than 100. Of these, three studied young adults of age 35 years or less [16–18] and two studied middle aged to elderly individuals [19,20]. Dangour et al. reported no changes in cognitive measure such as the California Verbal Learning Test in 70–79 year old adults after providing an experimental treatment of 700 mg/d of EPA/DHA [19]. However, as the authors noted, over the 24 months period of the study, the subjects experienced no decline in cognitive function; thus, it does not seem possible to measure a benefit of a supplement on declining cognitive function [21]. In a study of 176 healthy young adults of 18–45 years of age who were given 1.16 g/d of DHA or placebo, Stonehouse et al. that reaction times for both episodic and working memory improved and episodic memory improved in women and working memory in men [20]. In a rather large study of 285 young women, age 18–25, Benton et al. gave 400 mg/d of DHA and found no differences in a series of measures of mood and cognitive function [16]. Jackson et al. tested 1 g/d of EPA- or DHA- rich fish oils in 18–35 year old healthy adults on a series of cognitive tests and found effects in both directions on the Stroop test and some apparent benefit of the EPA-rich fish oil on subjective mental fatigue [17]. It is worth mentioning that Lee et al., when providing a larger dose of 1.74 g/d of EPA/DHA for 12 months found a benefit for several measures of memory function in a small group of 36 more elderly patients with mild cognitive impairment [22]. Also, Witte et al. studied executive functions and neuroimaging in a group of 65 healthy subjects age 50–75 years of age given 2.2 g/d of n-3 PUFA in a randomized, controlled trial design [23]. They observed a benefit in executive function including verbal fluency. They also observed changes in white matter microstructural integrity which they interpreted to be beneficial as well as increases in gray matter volume in the frontal, temporal, parietal and limbic areas primarily within the left hemisphere. These authors demonstrated an increase in the omega-3 index (erythrocyte EPA+DHA) as well as in the erythrocyte EPA content.

It appears that benefits of DHA are best observed during aging where there is some decrement in cognition, e.g., a mild cognitive impairment or memory complaint or perhaps when a person is exposed to certain chronic physical or mental stressors. A limitation of these interventional studies is that they can only address limited aspects of memory. In the case of the MIDAS study, the PAL task is considered to be a measure of episodic memory, one of many different aspects of the clinical construct of memory.

There has also been a major trial of DHA in patients with AD as reported by Quinn et al. in 2010 [18]. This study was performed under the auspices of the National Institutes of Health by the Alzheimer's Disease Cooperative Study group and so was a

Table 1
Positive results in cognitive testing in the MIDAS trial.

Cognitive test	Baseline score mean \pm SD	Wk 24 score mean \pm SD	Wk 24, change from baseline mean \pm SE	P value
CANTAB PAL				
DHA	13.4 \pm 11.6	8.8 \pm 9.9	-4.5 \pm 0.64	0.032
Placebo	12.1 \pm 10.9	9.7 \pm 10.4	-2.4 \pm 0.62	
Verbal recognition memory, immediate, (total correct)				
DHA	10.8 \pm 1.5	11.0 \pm 1.4	0.2 \pm 0.11	0.018
Placebo	10.9 \pm 1.5	10.9 \pm 0.0	0.4 \pm 0.11	
Verbal recognition memory, delayed, (total correct)				
DHA	10.4 \pm 1.8	10.7 \pm 1.5	0.3 \pm 0.11	0.012
Placebo	10.5 \pm 1.8	10.7 \pm 1.8	0.1 \pm 0.11	

Taken from Reference [13], Table 2.

multi-center trial involving 51 centers and a total of 555 patients screened and 402 randomized with a 60:40 distribution across the DHA and placebo groups. It was a randomized, controlled trial in mild to moderate severity of AD as defined by a MMSE score within the 14–26 range. The dosage was 2 g of algal DHA/d given over an 18 months period and a corn/soy oil placebo. The primary outcome measures were the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating (CDR) sum of boxes. Secondary measures included the MMSE and the ADCS Activities of Daily Living (ADCS-ADL) scale. There was a preplanned sub-analysis of the ApoE4 negative allele group.

The results of the Quinn et al. study indicated that DHA had no significant benefit for the cognitive tests, the global score, activities of daily living and, in a subset, of brain atrophy although compliance was believed to be good. There were no significant increases in adverse events with the DHA treatment. The fascinating finding in this study came from the preplanned comparison of those patients with and without the ApoE4 allele. Patients in the ApoE4 negative group had a significantly ($p=0.03$) lower decline in the mean change in ADAS-cog score over 18 months [18]. This was observed in 61 patients in the DHA group vs. 48 in the placebo group; a subset size that demonstrates the magnitude of this effect. Indeed, it is indicated to redo this study in just ApoE4 negative group to test whether cognition can in fact be observed in AD patients of mild to moderate severity. This study implicates ApoE4 as a key modulator of the disease in regards to the efficacy of DHA treatment and raises many questions about the mechanism of action and the role of this system. This relationship has been observed in other studies as well. For example, the APOE3/E4 status has also been shown to influence the results of clinical trials with medium chain triglycerides [24], intravenous immunoglobulins [25], and bapineuzumab [26]. Interactions between treatment and APOE status were also initially reported with glitazone, statins and cholinesterase inhibitors but not confirmed in larger studies [27–31]. One limitation of AD studies thus far has been the lack of studies specifically targeted to APOE variants or possibly other genotypes as a selection criteria for the patient group.

3. Discussion

3.1. ApoE: molecular aspects in AD

Despite overwhelming evidence of its key role in AD pathogenesis, the exact mechanisms by which ApoE4 accelerates the onset of cognitive impairment continue to elude us. Nevertheless, very important molecular clues have been gathered over the years. Three common human ApoE polymorphisms have been identified, designated E2, E3, and E4, which differ by single amino acid interchanges at residues 112 and 158. The prevalence of the E2, E3 and E4 alleles coding for these ApoE isoforms in the general population is ~7, ~78 and ~15%, respectively [32–35]. The arginine residue at position 112 in ApoE4 reduces stability of the protein and impairs binding to receptors and other proteins [33,36]. In the brain, ApoE is primarily synthesized by astrocytes [37], although neurons also produce the protein under select conditions [38]. Because ApoE does not readily cross the blood brain barrier (BBB) due to its large size, the liver-produced peripheral pool of ApoE is distinct from CNS-synthesized ApoE [33]. ApoE can interact with various receptors, such as low-density lipoprotein receptor (LDLR), LDLR-related proteins (LRPs), SORL1/LR11, and very low-density lipoprotein receptor (VLDLR), which are all present in the brain, in neurons, astrocytes and microglia of the brain parenchyma, but also in capillary endothelial cells at the blood-brain barrier (BBB) [33,37,39]. Thus, circulating ApoE can influence the brain by interacting with BBB-expressed receptors,

whereas CNS-borne ApoE may act directly on receptors located on pericytes, astrocytes, neurons and microglia.

Not surprisingly, to decipher the role of ApoE in AD, most early research was centered on the role of ApoE on the production, accumulation and clearance of A β , given the importance of this peptide in the amyloid hypothesis of AD [33,34,40,41]. The observation of ApoE-amyloid complexes in AD brain [42], the strong binding avidity of ApoE to A β [43,44] and the relationship detected between the ApoE genotype and brain levels of plaques/A β [45–47] initially fueled the hypothesis that ApoE4 acts by binding A β , subsequently increasing its neurotoxicity. To directly study the role of ApoE alleles, lines of transgenic mice expressing either one of the three human ApoE isoforms have been developed and quickly emerged as invaluable tools [33,36,48]. Interestingly, the association between ApoE4 and increased A β concentrations in cerebral tissue has been confirmed in these knock-in mice [49–51]. Additional in vivo and in vitro data support a scheme in which ApoE binds to A β and promote its clearance and degradation, a mechanism becoming less effective in the presence of either lower total ApoE levels, ApoE4 genotype, or both [40,52–56]. A more recent report suggests however that molecular interactions between ApoE and A β are not needed for ApoE4 to further A β clearance from the brain [57]. Still, these data are hard to reconcile with recently reported results showing that genetically increasing human ApoE levels, regardless of isoform status, rather increased A β accumulation in transgenic mice [58,59]. Neuroimaging studies add to the orchestra of conflicting data on the link between ApoE expression and brain amyloid load [60–63]. Finally, it should be kept in mind that the relationship between ApoE and A β , if it does exist, might be consequential or accidental rather than causal, since reduced ApoE levels (see below) and increased A β are both observed in AD, and may be independently associated with its pathogenesis.

3.2. ApoE: gain or loss of function?

An inescapable question in APOE research is whether the expression of ApoE4 increases AD risk through a gain or a loss of function, or a combination of both [33,40].

In support of a possible gain of function, ApoE4-specific neurotoxic truncated fragments generated after proteolysis of the full length protein have been shown to cause mitochondrial dysfunction, cytoskeletal alterations, as well as tau hyperphosphorylation [41,64,65]. Studies comparing ApoE3/E4 bigenic mice versus ApoE4 single-transgenic mice also support a dominant negative effect of ApoE4 [66]. Other sets of experiments suggest isoform-specific interactions of human ApoE to various form of A β or tau may underlie the deleterious impact of ApoE4 in AD, compared to other isoforms [53,56,67–69]. To add more complexity to gain of function hypotheses, any effect interpreted as putative deleterious effects of ApoE4 may also be explained in part by a lack of protective effect of ApoE3 or E2 in ApoE4 carriers, as exemplified in different studies [55,70–72].

Indeed, up to now, the evidence pointing toward a loss of neuroprotective function of ApoE in ApoE4 carriers is difficult to cast away. It was discovered a long time ago that human ApoE4 carriers display lower concentrations in total ApoE in the brain, a post-mortem finding that has been replicated many times [45,73–76]. Consistent observations have been made in the plasma [77–79]. Such a loss of ApoE has been replicated in human ApoE4-targeted replacement mice when compared to ApoE2 or ApoE3, as measured in brain tissue, plasma and CSF [51,80–84]. Interestingly, alteration in the ApoE protein is not a consequence of changes in mRNA expression, which is rather increased or unchanged in ApoE carriers [85–87], hinting toward post-translational mechanisms. Indeed, animal and in vitro experiments have suggested that

enhanced degradation or defective lipidation of the ApoE4 protein compared with ApoE3 stand as possible explanations for a reduction in total ApoE in tissue [81,88]. Brain ApoE concentrations are also decreased in AD brain [45,74,89] and plasma [90], further arguing for a loss of ApoE activity in AD. Again, ApoE mRNA levels remain increased or unchanged in AD compared to age-matched controls [89,91,92], arguing against the specific death of ApoE-expressing cells or a change in mRNA expression. The fact that ApoE concentrations are lower in AD and in ApoE4 carriers is no surprise since the ApoE4 allele is more frequent in the AD population [32,35]. Lastly, a recent report showed that hippocampal ApoE concentrations correlate with spatial memory retention in ApoE knock-in mice [80]. Whatever the underlying mechanism may be, the key conclusion is that the magnitude of the ApoE4-induced decrease in total ApoE concentrations is so important that it cannot be dissociated from any specific function of ApoE4 in AD.

3.3. ApoE and lipids

From the scientific knowledge accumulated thus far, it has become clear that ApoE is the primary apolipoprotein synthesized within the CNS, where it plays a critical role in lipid transport and metabolism. For example, ApoE and its receptor pathways appear to be essential to fulfill cholesterol requirements of the majority of brain cells [34]. Cholesterol is present in high concentrations in the brain [93], where it is essential in maintaining neuronal health, particularly during synaptogenesis and related processes [34,94,95]. Although CNS cholesterol comes from *de novo* synthesis and not from the periphery, ApoE is implicated in its transport and recycling [34,37]. ApoE is also involved in the removal of excess cholesterol and its oxidized products like 24S-hydroxycholesterol out of the CNS through the BBB [33,34].

Since neurons rapidly produce ApoE during an injury response [41], it has been hypothesized that ApoE plays a critical role in delivering cholesterol to regenerating neurons [34,96]. It would be interesting to see whether a similar mechanism applies to n-3

PUFA as well. Indeed, the role of n-3 PUFA in synapse health is quite well established. In vitro data show that exposing neurons to n-3 PUFA promotes neurite outgrowth and membrane expansion [9,97–99]. Supporting in vivo data is also available from animals fed with DHA-enriched diets [100,101] or transgenetically engineered to produce endogenous DHA [102]. Evidence of a relationship between neuron size and brain DHA content has also been reported in animals as determined by electrophysiology [103] and histochemical readouts [104]. Finally, there are numerous recent studies showing that n-3 PUFA induce neuroprotection against centrally acting neurotoxins [105], while upregulating neurotrophic factors [106,107] and neurogenesis [108]. However, whether a parallel can be drawn between cholesterol and n-3 PUFA as substrates of the lipid-based mechanism underlying ApoE impact on the brain, and, more specifically, on AD pathogenesis, remains unclear. Although preliminary investigations show that ApoE deficiency can alter the relative prevalence of DHA-containing phospholipids in synaptic plasma membranes [109], data linking ApoE with the effects of n-3 PUFA on neuronal tissue is still missing. Thus, studies focusing on how ApoE may be involved in n-3 PUFA-induced neuroprotection or neuroregeneration would clearly be warranted at this time.

Brain lipids are particularly vulnerable to oxidative damage. Intriguingly, the ApoE4 genotype is associated with higher lipid peroxidation indices in the plasma [110,111] and in the brain [76,112,113] in humans and in animal models. However, no specific post-mortem relationship was detected between ApoE4 status and concentrations of DHA derivatives such as neuroprostanes in the brain of individuals with AD [114]. Nevertheless, ApoE deficiency in mice contributes to increased cerebral DHA oxidation as determined by neuroprostane quantification with gas chromatography coupled with mass spectrometry [115]. Such a role of ApoE on lipid oxidation is likely to have important implications since lipid peroxidation in diseased regions has been well established in advanced AD [116]. However, the underlying mechanisms remain unclear and deserve further investigation.

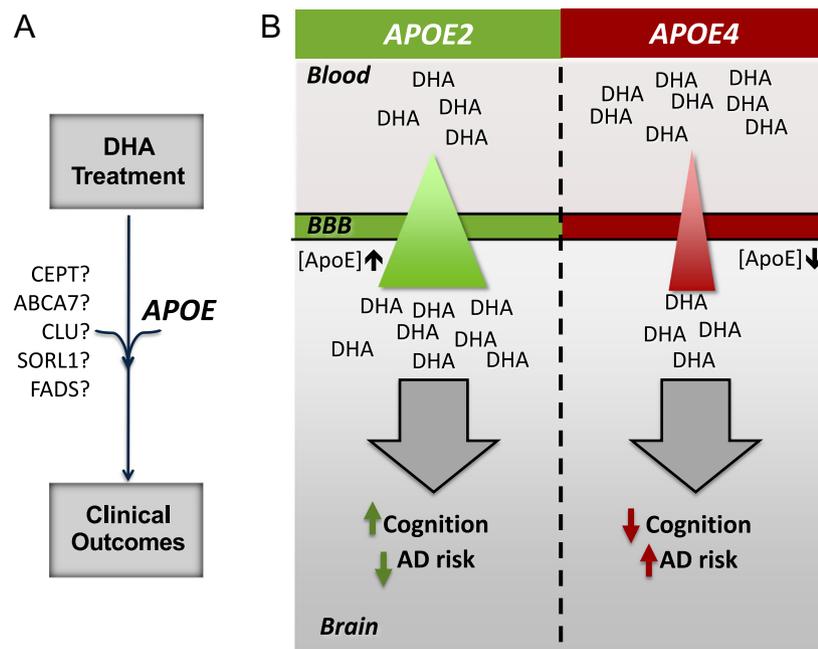


Fig. 1. (A) The nutrigenetics and pharmacogenetics of DHA: APOE genotype and possibly other genetic factors may influence the clinical outcomes of DHA supplementation trials; (B) Proposed mechanism by which the APOE status affects brain–blood barrier properties, brain DHA bioavailability and, ultimately, cognition and the risk of developing Alzheimer’s disease. **Abbreviations:** ABCA7: ATP-binding cassette sub-family A member 7; AD: Alzheimer’s disease; APOE: Apolipoprotein E; BBB: brain–blood barrier; CEPT: Cholesteryl ester transfer protein; CLU: Clusterin; DHA: docosahexaenoic acid; FADS: Fatty acid desaturase; SORL1: Sortilin-related Receptor, L.

3.4. Does ApoE regulate DHA metabolism and its transport to the brain?

As a lipid transporter, one simple way by which ApoE4 may impact n-3 PUFA cerebral function is by ultimately limiting DHA transport in the brain. Indeed, markers of AD neuropathology are sensitive to n-3 PUFA in the CNS. A high n-3 PUFA content in brain tissue is associated with reduced A β levels [117,118], reduced soluble hyperphosphorylated tau [103,117,119], higher synaptic marker levels [120–122] and improved cognitive performance [103,120,123] in animal models of AD.

Thus, ApoE4 could impact AD pathogenesis by decreasing circulating DHA concentrations or by interfering with its transport in the brain (Fig. 1). The impact of ApoE on circulating PUFA has been the subject of recent investigations. Although higher baseline EPA and DHA levels have been observed in plasma triglycerides from E4 carriers compared to ApoE3 subjects [124], another study did not detect an association between ApoE genotype and plasma DHA concentrations [125]. Comparison between old ApoE4 carriers versus noncarriers show a shorter DHA whole-body half-life in the former after an oral dose of [¹³C]-DHA [126], consistent with a faster metabolism. Thus, it has been hypothesized that ApoE4 carriers accumulate DHA in the blood, partly due to reduced metabolism. However, it is debatable whether higher n-3 PUFA plasma concentrations reflect a higher tissue bioavailability. Taking advantage of the APOE knock-in mouse, we recently reported an accumulation of DHA in the blood associated with lower concentrations in cerebral tissue of ApoE4 mice, in comparison to ApoE2 animals [83]. Such an inverse relationship between plasma and brain levels indicate that plasma concentrations may reflect defective distribution into the brain rather than being a good correlate of cerebral concentrations. Further supporting the role of ApoE in regulating cerebral DHA levels, a significant association between DHA content and ApoE concentrations was detected in the brain of AD patients [83]. Therefore, based on the evidence accumulated so far, it can be postulated that ApoE4 leads to reduced transport of DHA into the brain (Fig. 1).

Obviously, to access the brain, DHA has to cross the BBB. Despite controversies stemming from evidence suggesting the expression and functional role of fatty acid transporters at the BBB [127,128], n-3 PUFA can enter the brain by simple diffusion through the BBB [129,130]. For example, it was shown that the brain uptake of [¹⁴C]-DHA and [¹⁴C]-EPA through the BBB is not saturable, using *in situ* cerebral perfusion [130]. Despite this, long-term exposition to dietary n-3 PUFA still influence the uptake rate of [¹⁴C]-DHA in the brain, suggesting that regulatory mechanisms of DHA transport across the BBB do exist [130]. After n-3 PUFA supplementation, incorporation of EPA and DHA in the plasma free fatty acid pool was impaired in ApoE4 carriers compared to non-carriers [124]. This information may be important as free DHA unbound to plasma lipoproteins is expected to cross the BBB more readily [130–132]. Our recent work demonstrates that mice carrying ApoE4 display lower brain uptake of [¹⁴C]-DHA through the BBB and lower brain DHA concentrations [83], providing a clear mechanistic explanation for reduced brain levels of DHA in ApoE4 mice. Indeed, ApoE isoforms differ in their binding affinity for their receptor, including the low density lipoprotein receptor (LDL-R) [37,133]. Thus, it could be readily postulated that 3D molecular conformational changes could affect the capacity of ApoE to transport DHA throughout the blood circulation and, ultimately, into the brain.

Alternatively, ApoE4-induced changes in BBB function, resulting in DHA transport failure and lower brain accumulation, remains an intriguing possibility (Fig. 1). A collection of recent evidence suggests that ApoE is essential for the maintenance of BBB integrity. Disruption of the BBB accompanied by increased

permeability as a function of age has been reported in ApoE knockout [134,135]. Changes in morphology of the cerebral microvasculature, such as a thickening of the basal membrane found in AD [136–138] and in animals models [139,140], was also shown to depend on ApoE genotype in humans [141,142]. More recent work confirms that the lack of ApoE leads to BBB breakdown, whereas ApoE4 increases BBB susceptibility to injury in mice [143]. The ApoE4-induced BBB disruption is proposed to trigger neuronal dysfunction and perhaps initiate neurodegenerative changes [143]. Decreased interaction of ApoE4 with low density lipoprotein receptor-related protein 1 (LRP1) at the BBB and tight junction impairments are among the main suspected mechanisms [143,144]. Our recent data in ApoE mice also support the hypothesis that the ApoE4 genotype induces changes in the BBB, leading to reduced DHA uptake by the brain [83] (Fig. 1). Therefore, in the light of data linking ApoE with lipid transport and BBB dysfunction, it could be speculated that ApoE4 expression leads to defective transport of lipids into the brain. The main long-term consequence would be reduced distribution of n-3 PUFA in the brain [83]. Interestingly, a lower brain bioavailability of DHA could explain the lack of protective effect of DHA seen in clinical studies. It could also explain the lack of association between high n-3 PUFA concentration and low AD incidence reported in prospective epidemiological analyses.

In conclusion, it is becoming increasingly clear that one of the greatest challenges of AD pharmaceutical care is to intervene as early as possible in the disease, before widespread neurodegeneration begins [145,146]. This issue has been particularly raised with anti-amyloid agents [147]. Because of its relative safety compared to most other drugs in development, DHA and other nutraceuticals seem better positioned to be used as preventive tools during AD prodromal states [148]. Preventing age-related cognitive decline is likely to require intervention with a low safety risk as well. Recent advances in nutrigenetics and in the neuropathology of cognitive impairment suggest that the identification of the subgroups of persons who are most likely to benefit from DHA will be the way forward.

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