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Ageing and apoE change DHA homeostasis: relevance to age-related cognitive decline

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Epidemiological studies fairly convincingly suggest that higher intakes of fatty fish and *n*-3 fatty acids are associated with reduced risk of Alzheimer's disease (AD). DHA in plasma is normally positively associated with DHA intake. However, despite being associated with lower fish and DHA intake, unexpectedly, plasma (or brain) DHA is frequently not lower in AD. This review will highlight some metabolic and physiological factors such as ageing and *apoE* polymorphism that influence DHA homeostasis. Compared with young adults, blood DHA is often slightly but significantly higher in older adults without any age-related cognitive decline. Higher plasma DHA in older adults could be a sign that their fish or DHA intake is higher. However, our supplementation and carbon-13 tracer studies also show that DHA metabolism, e.g. transit through the plasma, apparent retroconversion and β-oxidation, is altered in healthy older compared with healthy young adults. *ApoE4* increases the risk of AD, possibly in part because it too changes DHA homeostasis. Therefore, independent of differences in fish intake, changing DHA homeostasis may tend to obscure the relationship between DHA intake and plasma DHA which, in turn, may contribute to making older adults more susceptible to cognitive decline despite older adults having similar or sometimes higher plasma DHA than in younger adults. In conclusion, recent development of new tools such as isotopically labelled DHA to study DHA metabolism in human subjects highlights some promising avenues to evaluate how and why DHA metabolism changes during ageing and AD.

Alzheimer's disease: Docosahexaenoic acid: Ageing: ApoE: Cognition

The cognitive and psychological health of older adults is now a major preoccupation for healthcare services and researchers alike. Alzheimer's disease (AD) is the main form of cognitive decline in older persons in Western countries[1]. Age is the main risk factor associated with AD[1], but other factors also have an effect such as a predisposing genetic polymorphism, i.e. ε4 allele of *apoE4*[2], vascular risk factors including hypertension, obesity and type 2 diabetes[1], and lifestyle including physical activity and dietary habits[3,4]. Among the nutrients closely associated with brain function, the *n*-3 fatty acids, especially DHA, have attracted special attention. Fatty fish and seafood are the most important dietary sources of both DHA and EPA. DHA is by far the predominant *n*-3 fatty acid in the brain and is present mostly in various membrane phospholipids (PL) of neurons, especially in synapses[5]. In contrast to other common dietary long-chain fatty acids, DHA is highly conserved and poorly β-oxidised[6–8]. In human subjects, DHA synthesis is relatively inefficient, especially in comparison to rodents[9].

Low intake of *n*-3 fatty acids has long been associated with higher risk of CVD[10], and also of suboptimal brain

Abbreviations: AD, Alzheimer's disease; CE, cholesteryl esters; ^{13}C-DHA, carbon-13 labelled DHA; PL, phospholipids.
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development[11]. Much effort has been focused over the past decade on whether a higher DHA intake could decrease the risk of cognitive decline in older adults, or reduce the progression from mild cognitive impairment towards AD. In general, these studies polarise in two directions: randomised clinical trials that are largely negative and epidemiological studies that are more positive[12] about the DHA's role in maintaining cognition during ageing. Thus, in general, DHA supplementation trials in AD (with or without EPA) have not so far produced any truly positive results[12–15]. Methodological issues such as dose of *n*-3 fatty acid, duration of treatment or selection criteria may well have affected the outcomes of these trials. DHA supplementation may have a greater positive effect on memory and learning in healthy adults[16], elderly with subjective cognitive complaints[17] or with mild cognitive impairment[18] than in those with AD[12,14,19]. However, prospective epidemiological studies have been more positive; they broadly show that habitually low intake of fish and/or DHA is associated with higher risk of developing AD[12,20,21]. These results are supported by the neuroprotective role of DHA reported for non-human models of neurodegenerative disease[22–26].

Studies with biological samples (human blood and brain) may be able to provide useful leads to explain the divergent results between randomised clinical trials and epidemiological studies. We have previously reviewed at some length the methodological limits on observational or intervention studies on DHA supplementation in older adults or in AD[12–15,20,21,27]; so we will review them here only briefly. We will also present an emerging framework showing that DHA homoeostasis changes in older adults and differs in carriers from non-carriers of *apoE4*, probably before the onset of cognitive decline.

DHA in plasma and post-mortem human brain

Brain DHA

In primate, pig and rodent models, when *n*-3 intake is severely deficient for extended periods, brain DHA also decreases across all cell types and regions, in association with lower scores on cognitive and behavioural tests[25,28–31]. AD is now widely associated with lower fish and DHA intake, so it would be logical that post-mortem brain samples of patients with a definitive diagnosis of AD also contained lower DHA. Indeed, in the hippocampus, which is central to memory processing and learning, AD patients reportedly do have lower DHA[32,33]. However, in the temporal and frontal cortices which are also affected in AD, DHA is almost always the same as in the controls (Fig. 1). Studies reporting lower DHA in the AD brain show that other fatty acids are also lower, particularly *n*-6 PUFA[35,41,44,46]. Thus, the effect of AD is not specific to DHA which is contrary to what would be expected if only *n*-3 fatty acid intake were deficient.

There are many potential methodological reasons for the observed lack of agreement between the apparently

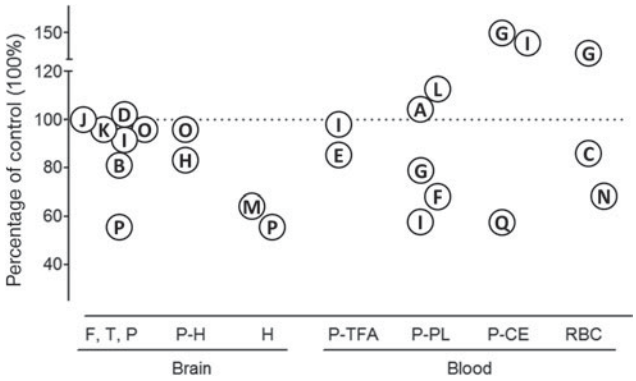

Fig. 1. Summary of the published literature on brain and blood DHA in Alzheimer's disease. The symbols represent the results of individual studies using each study's control group as the reference (100 %; dotted line). The papers from which these DHA data are obtained are as follows: A, Arsenault *et al.*[34]; B, Astarita *et al.*[35]; C, Boston *et al.*[36]; D, Brooksbank *et al.*[37]; E, Cherubini *et al.*[38]; F, Conquer *et al.*[39]; G, Corrigan *et al.*[40]; H, Corrigan *et al.*[41]; I, Cunnane *et al.*[42]; J, Fraser *et al.*[43]; K, Guan *et al.*[44]; L, Laurin *et al.*[45]; M, Prasad *et al.*[46]; N, Selley *et al.*[47]; O, Skinner *et al.*[48]; P, Söderberg *et al.*[32]; Q, Tully *et al.*[49]. F,T,P, frontal, temporal and/or parietal cortex; P-H, para-hippocampus; H, hippocampus; P-TFA, plasma total fatty acids; P-PL, plasma phospholipids; P-CE, plasma cholesteryl esters; RBC, red blood cells.

low DHA intakes in AD yet frequently normal DHA levels in the brain[12]. Crucial among these are the 'healthy' controls against which the AD cases are compared as well as the very marked extent of regional brain atrophy associated with ageing regardless of the presence of neurological disease[44,50]. Furthermore, the basis for classifying a patient as having AD, i.e. whether on clinical cognitive criteria or on neuropathological score, may not give consistent results since senile plaques are increasingly recognised as being present in a significant proportion of cognitively normal elderly persons[51–53]. Hence, there is a risk that post-mortem samples from brain banks for which cognitive status is not known at the time of death could be misclassified if based solely on neuropathological scores. It also appears that membrane PL in the cortex can tenaciously retain DHA and that a more discrete and specific subcellular pool or membrane pool of DHA may have to be measured[43]. Brain membrane DHA cycles rapidly between PL and free DHA via DHA-CoA[54,55], and the deteriorating efficacy of this process could theoretically contribute to the neurodegenerative processes. Thus, the key issue in relation to post-mortem tissue analysis is that the time to lipid extraction is rarely less than 4–5 h yet DHA turnover is on the order of minutes, if not seconds. Since the turnover of DHA towards resolvins and neuroprotectins are orders of magnitude lower than the amount of DHA in the brain NEFA pool, truly 'physiological' amounts of these products are extremely difficult to measure, especially in human subjects[23,56]. As also noted elsewhere, these and other issues severely constrain the validity and hence the utility of DHA measurements on human post-mortem brain samples[57].

Blood DHA

Lower DHA would normally be expected in the blood of those with habitually low DHA intake (whether diagnosed with AD or not). In some AD studies, lower DHA is indeed reported for plasma total lipids[38], PL[39,40,42], cholesteryl esters[49] and NEFA[58]. However, many other AD studies show no difference in plasma DHA, whether in PL or total fatty acids[34,38,42,45,59]. Some even report higher DHA in plasma PL[45] or cholesteryl esters (CE)[40,42]. Similar inconsistencies are present across DHA levels reported for the erythrocytes in AD (Fig. 1)[36,40,47]. Prospective studies also show this inconsistency: some found a strong association between lower blood DHA level and slower cognitive decline[60] or lower risk of dementia[61], whereas other did not[45,59,62]. It may be that the cognitive domain studied[63,64] and *apoE4* genotype[65,66] contribute to this scatter in the data.

DHA homeostasis during ageing and apoE

We propose that even when collected under hypothetically ideal conditions (zero delay; perfectly matched, cognitively healthy controls, etc.), data obtained from single blood samples are too limited to fully understand possible changes in DHA metabolism due to genotype, ageing or neurodegenerative disease. However, isotopically labelled DHA is emerging as a useful tool to assess how the metabolism of DHA changes with age. Indeed, in a relatively simple study design, it was clear that the clearance of a 50 mg oral dose of uniformly carbon-13 labelled DHA (^{13}C-DHA) from the blood over 1 month was much slower in healthy 76-year-old compared with 27-year-old adults[67]. These results were similar to our earlier report that the increase in plasma DHA during a short-term treatment with fish oil was higher in healthy older persons[68]. ^{13}C-DHA enrichment in plasma NEFA and TAG of older adults was most affected (four- to fivefold higher than in the young adults) but its enrichment in PL and CE ^{13}C-DHA was also affected. The doubling of ^{13}C-DHA enrichment in plasma PL and CE emerged only after about 7 d postdose, suggesting slower DHA clearance through plasma lipid classes, i.e. an altered plasma 'DHA wave' in older adults (Fig. 2)[67].

Clearly, therefore, healthy ageing seems to change DHA metabolism and, hence, homeostasis in human subjects. Notwithstanding the limited extent to which the kinetic behaviour of a tracer can be compared with a single plasma fatty acid measurement, the difference in ^{13}C-DHA homeostasis in the elderly seems to reflect the results observed in two studies in which lower DHA was reported in plasma PL yet higher DHA was reported in plasma CE of AD patients[40,42]. The minimally invasive nature of this type of experiment makes it difficult to invoke a particular mechanism but one could speculate that the changing sensitivity of endothelial lipoprotein lipase could be involved in this age-associated difference in DHA homeostasis[69].

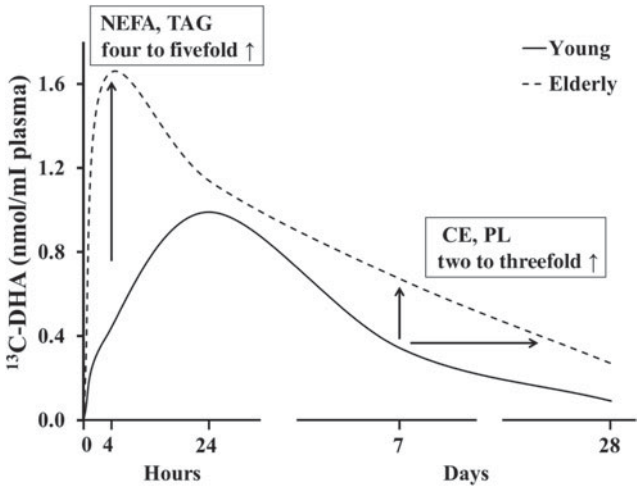

Fig. 2. Delayed plasma clearance of carbon 13-labelled DHA (^{13}C-DHA) during healthy ageing, adapted from Plourde *et al.*[67]. Plasma ^{13}C-DHA concentration was followed over 28 d after the oral administration of a single 50 mg dose of ^{13}C-DHA in young (27 years; *n* 6) and elderly (76 years; *n* 6) participants. In older adults, plasma tracer concentration in NEFA and TAG was four to fivefold higher 4 h after giving the oral dose and about twofold higher 1–4 weeks later in phospholipids (PL) and cholesteryl esters (CE).

ApoE4 carriers are at significantly higher risk of AD[70,71]. It is now emerging that the *apoE4* status also affects DHA metabolism in human subjects[27,72,73]. This interaction may help explain why the protective association of higher dietary intake of fish[74,75] or higher erythrocyte total *n*-3 fatty acids[65] is generally limited to non-carriers of *apoE4*. Measuring expired ^{13}C-CO_2 after dosing with ^{13}C-DHA permits the estimation of the whole body half-life of DHA in healthy older adults, which is of the order of 32 d in carriers of *apoE4* and 140 d in non-carriers of *apoE4*[72]. Ageing seems not to affect the whole body half-life of DHA although the small sample size makes these results still somewhat preliminary[67].

Using positron emission tomography and the tracer, ^{11}C-DHA, human brain turnover of DHA has been estimated to be about 4 mg/d, giving rise to a half-life of brain DHA of about 2·5 years[54]. Hence, the half-life of brain DHA is much longer than its whole body half-life. Perhaps further assessments of the brain or whole body half-life of DHA could provide some insight into the current ineffectiveness of DHA supplements in AD despite the fact that these supplements typically supply several fold the brain's apparent daily turnover of DHA[12].

ApoE4 seems also to supress the plasma DHA response to a fish oil supplement[73] and the metabolism of an oral dose of ^{13}C-DHA[72], an effect somewhat opposite to that observed with healthy ageing. For up to 28 d after a single oral dose of ^{13}C-DHA, carriers of *apoE4* have a slightly lower concentration of plasma ^{13}C-DHA compared with non-carriers[72]. When the tracer is given both before and again after a 5-month period

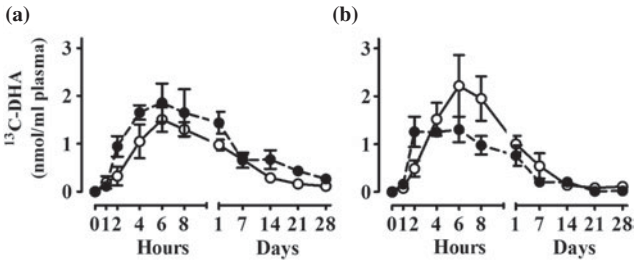

Fig. 3. Plasma carbon 13-labelled DHA (^{13}C-DHA) concentration over 28 d after a single oral dose of 40 mg ^{13}C-DHA. Results expressed as means (SEM) show the plasma ^{13}C-DHA status (a) pre- (*n* 6) and (b) post- (*n* 4) supplementation of 5 months with 1·8 g/d EPA +1·4 g/d DHA in apoE ε4 carriers (*apoE4*+; ○) and non-carriers (*apoE4*-; ●).

of DHA+EPA supplementation, the *apoE4* carriers had a greater accumulation of the tracer in plasma after supplementation compared with the non-carriers, again suggesting slower clearance of DHA to and/or use by tissues (Fig. 3). Hence, two established risk factors for AD (ageing and *apoE4*) both significantly change DHA homeostasis but possibly in different ways.

Linking dietary and plasma DHA

Habitual DHA intake is commonly estimated to be <250 mg/d[76–78] but this is a difficult and laborious measurement and subject to high day-to-day variability depending on the frequency of fish or shellfish consumption. Hence, it would be useful if DHA intake and plasma DHA were highly correlated because plasma DHA measurement is now technically simple and reliable, so it could potentially be a surrogate for dietary DHA measurement. There is indeed a good positive correlation between dietary and plasma intake for DHA consumption, especially at DHA intakes towards 1000 mg/d, during which plasma DHA rises to a maximum of about 4 % in plasma total lipids. However, DHA always seems to be present in plasma, even when DHA intake is negligible; thus, vegans consuming no known dietary sources of DHA still have about 0·5 % DHA in plasma total lipids[79]. The problem is that there are relatively few reports on which to build the relationship of dietary to plasma DHA. At DHA intakes between 0 and 50 mg/d, DHA is between 0·5 and 1·2 % of plasma total lipids, but the spread in these data is large[57]. A value of 0·5 % DHA in plasma total lipids therefore seems to be at or close to the lower limit possible of plasma DHA in healthy adults.

The AD cases we have studied had 1·0 % DHA in plasma total lipids, which empirically corroborates very low DHA intake, yet they had 'normal' DHA in the PL of brain cortical grey matter[42]. Plasma DHA does not rise in human subjects given EPA or α-linolenic acid supplements, even in vegans[80–82]. The conundrum therefore is: how are plasma (or brain) DHA levels maintained when DHA intakes are very low to negligible? We speculate that with changes in DHA metabolism and homeostasis during age-related cognitive decline, the diet–plasma relation of DHA may shift, explaining why with lower DHA intake, a population with age-related cognitive decline appears to have the same plasma DHA concentration as healthy elderly even though the availability of DHA to the tissues may be reduced[83]. The lack of an established reference lipid class in blood (PL, CE, TAG or NEFA, erythrocytes, etc.) for DHA measurements relative to intake still hampers the extent to which plasma DHA data from various reports can be compared in relation to ageing, genotype and risk of cognitive decline. This area clearly needs further research but suffice it to say that it is becoming increasingly important to take into account changing DHA homeostasis in the study of ageing population, especially in a context of age-related cognitive decline or AD.

Conclusion

We have sought to briefly highlight some of the methodological challenges and potential future directions for the study of DHA in ageing and AD. The emerging evidence for changing DHA half-life in older adults and in carriers of *apoE4* should encourage more basic research on DHA metabolism in human subjects. Molecular, cellular and animal models have contributed enormously to understanding the complexity of DHA biology, but none of them seem to represent the changes in DHA homeostasis reported in elderly human subjects. The human brain is able to strongly retain DHA in membrane PL despite very low DHA intake and advanced AD[42], so the classical dietary *n*-3 deficiency model used to probe the function of DHA in the animal brain appears inappropriate for research into AD. In human subjects, DHA in the post-mortem brain is unlikely to correctly reflect what is happening during ageing and AD, due to its fast turnover in neuronal membrane PL. Ageing- and apoE4-associated changes in DHA metabolism strongly suggest altered DHA homeostasis involving a decrease in plasma DHA clearance during age-related cognitive decline and AD. Therefore, a shift in the relationship between plasma and dietary DHA may be occurring during age-related cognitive decline and AD, one that needs to be considered when looking at plasma DHA as a measure of dietary DHA intake. In the future, the availability of innovative tools for studies of DHA half-life and metabolism in human subjects will be needed to understand in a better manner the changes in DHA metabolism occurring during human ageing and AD and the potential protective role of DHA on cognitive decline. As shown in prospective studies, a protective role of DHA in cognitive health of older persons may depend on consuming a healthy diet throughout adult life.

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Conflicts of Interest

None.

Authorship

M. H. and S. C. C. conceived and wrote the first draft with all the authors contributing to the revisions and final version of the manuscript.

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