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Does aging change docosahexaenoic acid homeostasis? Implications for the challenge to cognitive health in the elderly

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Abstract

Epidemiological studies fairly convincingly suggest that higher intake of fish and omega-3 fatty acids present in fish is associated with reduced risk for age-related cognitive decline (ARCD). Normally, docosahexaenoic acid (DHA) in plasma is positively associated with DHA intake. However, despite being associated with lower fish and DHA intake, unexpectedly, ARCD is not consistently associated with lower plasma DHA. Furthermore, DHA is often slightly but significantly higher in plasma and erythrocytes in the elderly without ARCD compared to young adults. Higher plasma DHA in the elderly may be a sign that their fish or DHA intake is higher but we show here that various aspects of DHA homeostasis also change with age. Our supplementation and tracer studies show that DHA metabolism, e.g. transit through the plasma and apparent retroconversion but not beta-oxidation, is different in healthy elderly compared to healthy young adults. Apolipoprotein E4 increases the risk of ARCD, possibly in part because it changes DHA homeostasis. Therefore, independent of differences in fish intake, changing DHA homeostasis may contribute to making the elderly more susceptible to cognitive decline despite them having similar or sometimes higher plasma DHA than in younger adults. Key words: aging, cognitive decline, dietary, docosahexaenoic acid, omega-3 fatty acid

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Does Aging Change Docosahexaenoic Acid Homeostasis?

Implications for the Challenge to Cognitive Health in the Elderly

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Abstract

Epidemiological studies fairly convincingly suggest that higher intake of fish and omega-3 fatty acids present in fish is associated with reduced risk for age-related cognitive decline (ARCD). Normally, docosahexaenoic acid (DHA) in plasma is positively associated with DHA intake. However, despite being associated with lower fish and DHA intake, unexpectedly, ARCD is not consistently associated with lower plasma DHA. Furthermore, DHA is often slightly but significantly higher in plasma and erythrocytes in the elderly without ARCD compared to young adults. Higher plasma DHA in the elderly may be a sign that their fish or DHA intake is higher but we show here that various aspects of DHA homeostasis also change with age. Our supplementation and tracer studies show that DHA metabolism, e.g. transit through the plasma and apparent retroconversion but not beta-oxidation, is different in healthy elderly compared to healthy young adults. Apolipoprotein E4 increases the risk of ARCD, possibly in part because it changes DHA homeostasis. Therefore, independent of differences in fish intake, changing DHA homeostasis may contribute to making the elderly more susceptible to cognitive decline despite them having similar or sometimes higher plasma DHA than in younger adults.

DHA and aging-related cognitive decline

Cognitive health in the elderly is an increasingly important preoccupation for public health institutions globally. This preoccupation is all the more acute given the lack of effective medical treatment for the various types of cognitive decline associated with aging including 'Alzheimer's disease'. Because the various forms of cognitive decline in the elderly are increasingly recognised as a heterogeneous conditions (Whitehouse *et al.* 2011), we prefer the general term - aging-related cognitive decline (ARCD). Conditions linked to the metabolic syndrome, particularly insulin resistance and type 2 diabetes, are major risk factors for cognitive decline in the elderly (Hao et al. 2011). Since the metabolic syndrome is preventable at least in adolescents and younger adults, in theory, prevention should be able to play a key role in the reducing the risk of ARCD. Nutrition and physical activity are key elements of prevention in reducing the susceptibility to the metabolic syndrome and type 2 diabetes. Omega-3 fatty acids such as docosahexaenoic acid (DHA) are amongst the nutrients of particular interest relative to optimal glucose metabolism, especially for cognition (Cunnane *et al.* 2009; Pifferi *et al.* 2010; Cunnane *et al.* 2011).

Our aim here is to draw attention to an apparent dichotomy: On the one hand, there is the relatively solid evidence that low fish and low DHA intake are common in ARCD; on the other hand, there is the lack of consistent evidence that brain or plasma omega-3 fatty acids, particularly DHA, are any different in ARCD than in age-matched controls (Cunnane *et al.* 2009). Furthermore, some studies show a benefit on cognitive function of higher intake of fish or DHA

in the elderly (Beydoun et al. 2007; Dullemeijer et al. 2007), but others did not observe any difference in cognitive performance (Van De Rest *et al.* 2008; Dangour *et al.* 2010). These observations seem contradictory and counter-intuitive: Why is it that if fish intake is low in ARCD, and if fish intake is an important predictor of plasma DHA, that plasma DHA is not more consistently reported to be lower in ARCD? Equally if not more importantly, can omega-3 supplements correct an apparent DHA deficit in the elderly and thereby reduce the risk of ARCD and, if so, under what conditions, because presently the outcomes of such studies have not been too promising (Freund-Levi *et al.* 2006; Fotuhi *et al.* 2009; Quinn *et al.* 2010).

We have previously raised some methodological issues that may contribute to this apparent dichotomy between the epidemiological versus the biological evidence for a protective role of fish and/or DHA in ARCD (Cunnane *et al.* 2009) and will discuss here some potential biological reasons for this inconsistency. Our focus here is not so much on ARCD *per se* but on the healthy elderly because clear indications are emerging that omega-3 fatty acid, at least DHA, metabolism changes in the elderly with no symptoms of ARCD.

Plasma DHA response to a DHA-rich supplement

We and others have observed that the healthy elderly tend to have 10-15% higher DHA and eicosapentaenoic acid (EPA) in plasma (Dewailly *et al.* 2003; Crowe *et al.* 2008; Fortier *et al.* 2010; Yanagisawa *et al.* 2010) and red blood cells (De Groot et al. 2009), but there are exceptions (Babin *et al.* 1999; Sfar *et al.* 2010). Somewhat higher plasma DHA may be due in part to higher DHA intakes in the elderly (Meyer *et al.* 2003; Buyken *et al.* 2010). Given that we

have not tracked DHA intakes in our elderly study participants (Fortier et al. 2010), we did not know whether the higher plasma EPA and DHA were due to higher fish and seafood intake in the elderly or to an aging-related change in DHA metabolism. We decided to probe the possibility of an aging-related change in DHA metabolism with a simple three week supplementation study in which participants received about 680 mg DHA /day, which is about 4-5 times usual intake in many developed countries (Kris-Etherton *et al.* 2009; Lucas *et al.* 2010; Meyer 2011). Participants were screened to eliminate those already consuming high amounts of fish or fish oil supplements. Interestingly, despite almost identical fasting DHA at baseline, after 3 weeks supplementation, the elderly participants had a 42% higher plasma response to the same supplement as the young participants (Figure 1) ((Vandal *et al.* 2008). This was a preliminary indication to us that perhaps DHA metabolism was changing with healthy aging, e.g. independently of ARCD.

Carbon-13-labelled DHA transit through plasma

The fish oil supplementation study (Vandal *et al.* 2008) led us to examine metabolism of carbon-13 (^{13}C)-DHA in the healthy elderly. Again, we were surprised to see a very significant difference in the transit of a single oral 50 mg dose of ^{13}C-DHA through the plasma with repeated blood sampling over a 4 week study period. The elderly had slower DHA transit in the form of higher ^{13}C-DHA enrichment in all plasma lipid pools examined. This slower clearance was observed in the pools rapidly labeled in the first hours after the oral dose, ex. free fatty acids and triglycerides, as well as in those pools increasingly labeled days to weeks later, ex.

phospholipids and cholesteryl esters (Figure 2) (Plourde *et al.* 2011). These results support the idea that higher plasma DHA (fasting or response to a fish oil supplement) in the elderly is not necessarily an indication of 'better' DHA metabolism, better DHA status or even higher intake of DHA; it may well be that aging changes DHA homeostasis in a way that slows down its transfer to tissues including the brain thus increasing its levels in plasma, at least transiently. This apparent delay in DHA transport into tissues may underlie and contribute to the increased susceptibility to cognitive decline in the elderly.

Other components of homeostasis

^{13}C-DHA provides an opportunity to measure other components of DHA homeostasis besides plasma levels, including beta-oxidation, retroconversion, and conversion to bioactive metabolites. One day after an oral dose of ^{13}C-DHA, about 7% of it is completely beta-oxidized to CO_2 (Plourde et al. 2011), which is about 30% of the beta-oxidation of the same dose of ^{13}C-linoleic acid and about 25% of that of ^{13}C-alpha-linolenic acid given under the same conditions. Seven days after giving the oral dose of ^{13}C-DHA, about 35% is beta-oxidized (Figure 3), whereas ^{13}C-linoleic acid and ^{13}C-alpha-linolenic acid are beta-oxidized at 40% and 70%, respectively (McCloy *et al.* 2004). Up to seven days post-dose, beta-oxidation of ^{13}C-DHA does not seem to be affected by healthy aging. However, the apparent retroconversion of ^{13}C-DHA to ^{13}C-EPA is roughly doubled (from 2.0 to 4.3 %) in the healthy elderly. Based on our one month study, apparent retroconversion appears to draw no more than 5-7% of ^{13}C-DHA metabolism (Plourde *et al.* 2011).

Genotype (apo E)

Whalley et al (2008) were the first to suggest that apolipoprotein (apo) E genotype might affect DHA metabolism; they reported that cognitive decline was associated with lower erythrocyte omega–3 fatty acid content only in the presence of the apo E4 allele. We have also observed that apo E genotype influences plasma EPA and DHA after a fish oil supplement, with apo E4 significantly reducing the rise in plasma DHA after 6 wk of fish oil supplementation that provided 1.9 mg/d of EPA and 1.1 mg/d of DHA (Plourde *et al.* 2009).

We have not yet assessed the relationship between DHA metabolism and apo E genotype in the elderly but given that apo E4 predisposes to various forms of ARCD (Song *et al.* 2009; Leoni 2011), this interaction bears further scrutiny. As suggested by Whalley et al (2008), one potential explanation of a relation between omega-3 fatty acids and apo E genotype would be increased oxidative stress that catabolises DHA. Studies *in vitro* (Miyata *et al.* 1996; Jolivalt *et al.* 2000) and in mice (Ramassamy *et al.* 2000) and humans (Kharrazi *et al.* 2008) suggest that apo E4 carriers have greater susceptibility to oxidative damage and lower antioxidant defenses.

Relation between dietary and plasma DHA

If lower habitual fish and/or DHA intake increase the risk of ARCD (reviewed by Cunnane et al. 2009) but this is not reflected by lower plasma DHA in ARCD, then the relation between dietary and plasma DHA in the elderly and in ARCD needs further attention. Our preliminary assessment of several published papers on this topic shows the anticipated and relatively

consistent positive, dose-dependent relation between DHA intake and plasma DHA (Figure 4) (Blonk et al. (1990). We believe that a crucial point needing verification is whether ARCD is associated with a leftward shift in the diet-plasma relationship for DHA (Figure 5). This possibility is suggested by at least three observations: (i) the lack of consistently lower plasma DHA in the elderly with ARCD (Cunnane *et al.* 2009), (ii) the higher plasma DHA and ^{13}C-DHA response in the healthy elderly (Vandal *et al.* 2008; Plourde *et al.* 2011), and (iii) the similar plasma DHA levels but lower DHA intake in those with ARCD (Lopez et al. (2010). We see this as a topic for fruitful investigation and, at the moment, draw no firm conclusion as to whether this key component of DHA homeostasis, i.e. plasma response to habitual dietary DHA intake, is altered by healthy aging or cognitive decline in the elderly.

Conclusions

Although both prospective and cross-sectional epidemiological studies clearly associate ARCD with lower fish and DHA intake, ARCD is not consistently associated with lower plasma DHA (Cunnane et al 2009). Indeed, DHA is often slightly but significantly higher in plasma and erythrocytes in the elderly compared to young adults even though the former are at increased risk of ARCD. Higher plasma DHA in the elderly is not necessarily a sign that their fish intake is higher; we review here several of our studies showing that DHA homeostasis appears to change with age. Our tracer and supplementation studies show that DHA metabolism, i.e. transit through the plasma and apparent retroconversion, changes with aging in the absence of ARCD. Apo E4 increases the risk of ARCD, and our studies show that this may be in part because it

changes DHA homeostasis. Independent of differences in fish intake, changing DHA homeostasis may contribute to making the elderly more susceptible to cognitive decline despite them having similar or even somewhat higher plasma DHA than in younger adults. Identifying how and why DHA homeostasis changes with age may contribute to resolving the problems with clinical trials that have unsuccessfully used fish oil or DHA supplements to treat ARCD.

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FIGURES

Figure 1

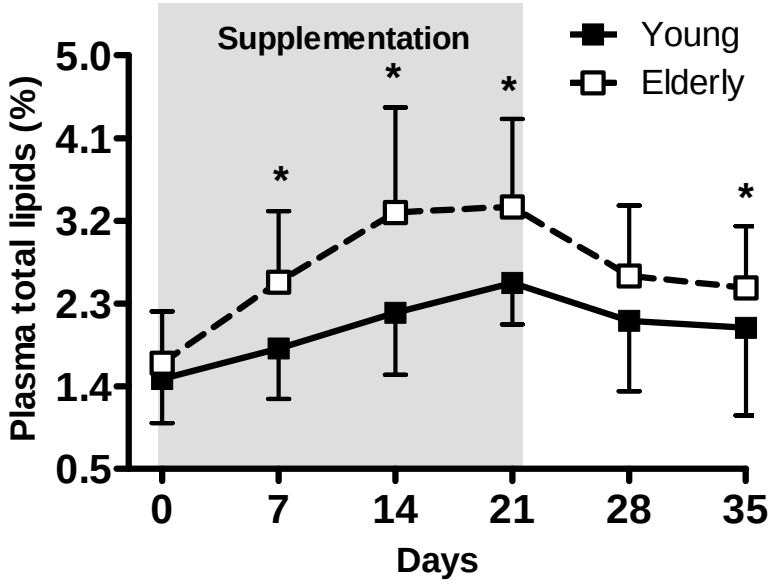

Figure 1: DHA in plasma total lipids in healthy young and elderly humans (24 ± 2 and 74 ± 4 years old, respectively) during a 3 week dietary supplementation with fish providing 680 mg/d DHA, as adapted from Vandal et al (2008). At the end of the supplementation period, plasma DHA was 42% higher in the elderly group than in the young group (* $p < 0.05$).

Figure 2

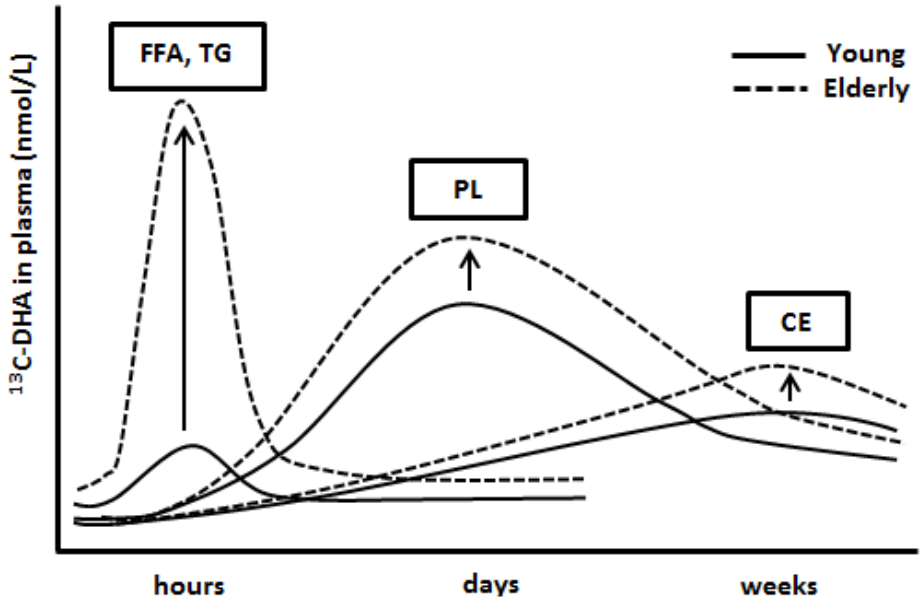

Figure 2: Healthy aging delays plasma clearance of ^{13}C-DHA as adapted from Plourde et al (2011). In the elderly, plasma tracer concentration in free fatty acids (FFA) and triglycerides (TG) was 4-5 fold higher 4 h after giving the 50 mg oral dose whereas in phospholipids (PL) and cholesteryl esters (CE), ^{13}C-DHA was 2-fold higher 1-4 weeks later (Young: 26.8 ± 2.6 years *;* Elderly 76.5 ± 2.7 years).

Figure 3

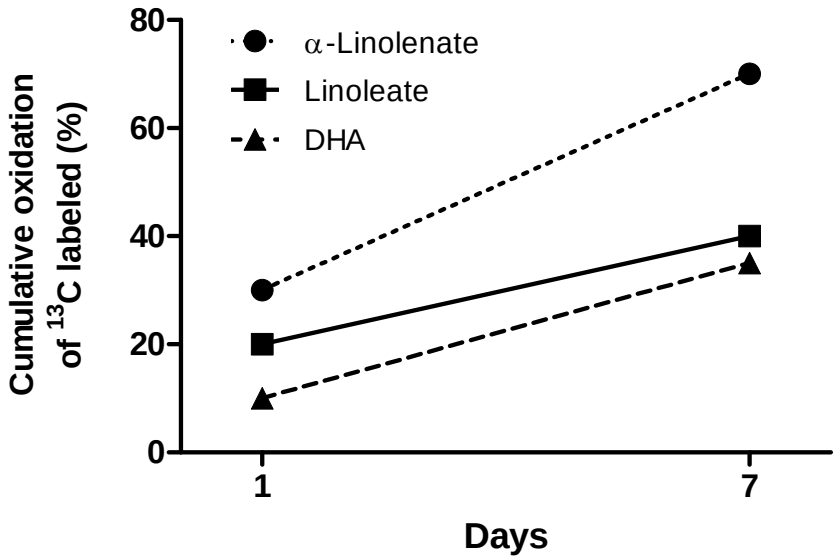

Figure 3: Slower beta-oxidation of ^{13}C-docosahexaenoic acid (DHA) compared to ^{13}C-linoleate and ^{13}C-α-linolenate over 1 and 7 d. Adapted from McCloy et al (2004) and Plourde et al (2011).

Figure 4

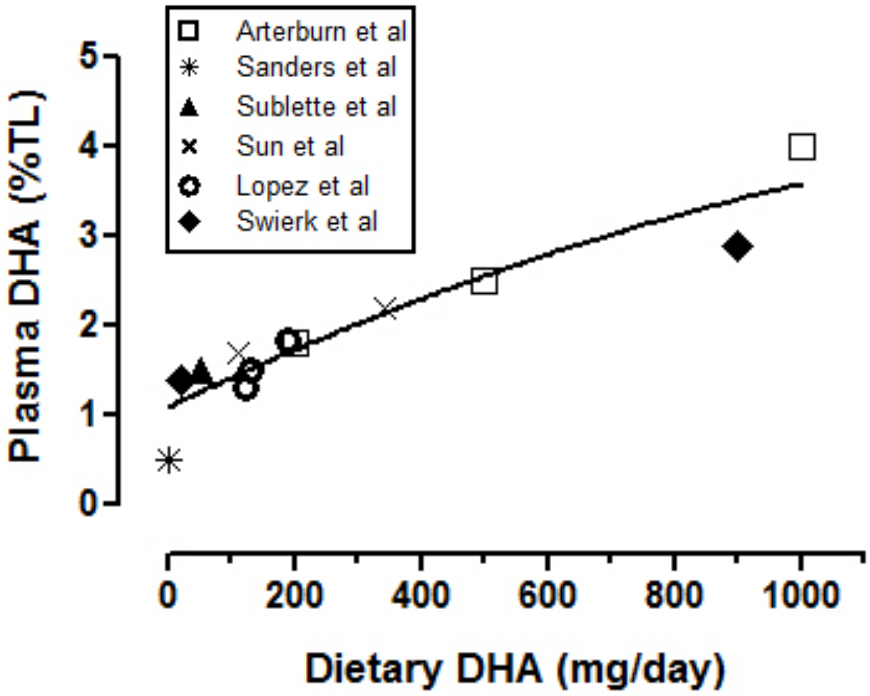

Figure 4: Near linear relation between dietary and plasma DHA at DHA intakes below 1000 mg/d (Sanders *et al.* 1989; Arterburn *et al.* 2006; Sublette *et al.* 2007; Sun *et al.* 2007; Lopez *et al.* 2010; Swierk *et al.* 2011).

Figure 5

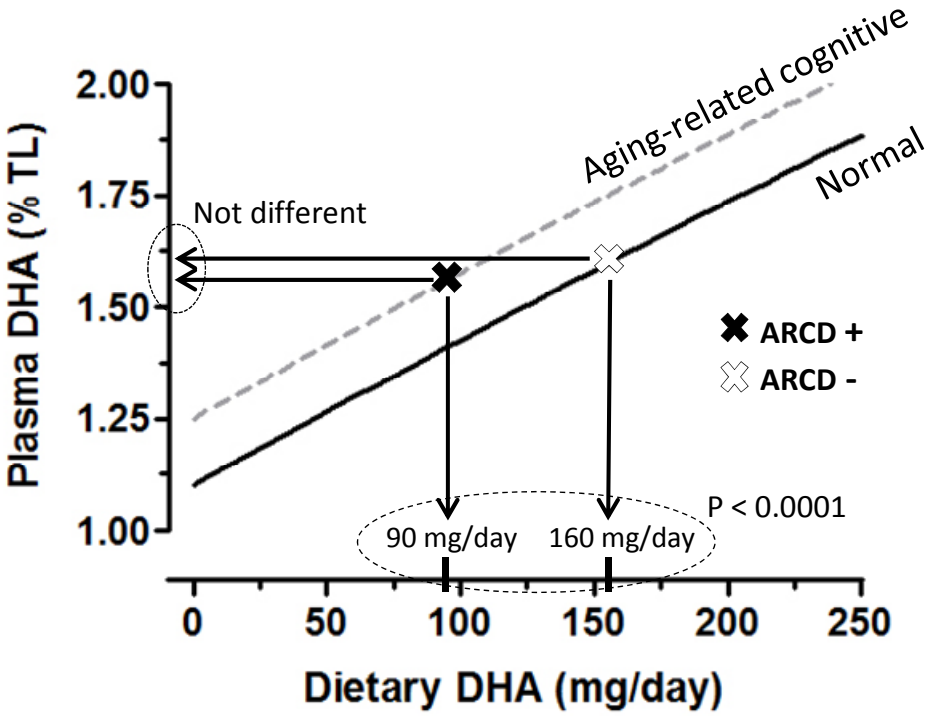

Figure 5: Dietary verses plasma DHA in aging-related cognitive decline (ARCD), based on Lopez et al (2010). In Lopez et al (2010), daily intake of 90 mg DHA in the elderly was associated with cognitive decline (ARCD+), whereas 160 mg of DHA was associated with an absence of cognitive decline (ARCD-), yet % DHA in plasma total lipids was not significantly different in the two groups. Though by no means conclusive, these data support our hypothesis that there may be a shift in DHA homeostasis in the elderly with ARCD.