Aging, cognitive decline, apolipoprotein E and docosahexaenoic acid metabolism

Mélanie Plourde1,2,*

1 Department of medicine, Université de Sherbrooke, Research Center on Aging, Sherbrooke, 1036 Belvédère Sud Sherbrooke, J1H 4C4 Quebec, Canada
2 Institute of Nutrition and Functional Foods, Laval University, Québec, QC, Canada

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Abstract – In Canada, ∼17 million of adults between 30–64 years old could benefit from a prevention strategy to lower the risk of Alzheimer’s disease (AD). My group is working on a population that is particularly at risk of AD, the carriers of an epsilon 4 allele of apolipoprotein E (E4), a genetic risk. Around 20% of the population in industrial countries have this genetic risk but not all carriers will develop AD, suggesting that environmental factors modulate the clinical manifestation and risk of AD in the carriers. My group has discovered that the metabolism of docosahexaenoic acid (DHA) is disrupted during aging and in E4 carriers, a finding replicated in homoygous mice knocked-in for human E4 allele (hAPOE4). We recently showed that a diet containing DHA prevented behavioral deficits in hAPOE4 mice. Another group reported in E4 carriers that the ratio of arachidonic acid (ARA): DHA is disrupted in the plasma and constitute a preclinical marker of mild cognitive impairment/AD in E4 carriers. Using our kinetics approaches with uniformly labelled carbon 13 fatty acids, we showed that the kinetics of 13C-DHA is modified by age and E4 carriage. The kinetics of 13C- arachidonic acid was however not modified by age conversely to that of 13C-eicosapentaenoic acid (EPA). We also reported that the synthesis of 13C-DHA from 13C-EPA started 2 h after the tracer intake in older adults conversely to 7 d in young men. Whether old men needs in DHA is higher or whether their ability to use it is lower remains to be established. These differences in the DHA and EPA metabolism seems, however related to physiological modifications occurring during aging and in E4 carriers and obscure the relationship between plasma DHA and EPA levels, dietary fatty fish intake and cognitive status.

Keywords: docosahexaenoic acid / arachidonic acid / eicosapentaenoic acid / aging / cognitive decline / apolipoprotein E / kinetics

Résumé – Vieillissement, déclin cognitif, apolipoprotéine E et métabolisme de l’acide docosahexaénoique. Au Canada, 17 millions d’adultes âgés entre 30–64 ans pourraient bénéficier d’une intervention en prévention pour diminuer leur risque de développer la maladie d’Alzheimer (MA). L’un des groupes les plus à risque de développer la MA, les porteurs de l’allèle epsilon 4 de l’apolipoprotéine E (E4), est au centre des recherches menées par mon groupe. Environ 20% de la population des pays industrialisés sont porteurs d’E4 mais ce ne sont pas tous les porteurs qui développeront la MA, ce qui suggère que des facteurs environnementaux puissent moduler l’expression clinique et le risque de la MA chez les porteurs. Nous avons découvert que le métabolisme de l’acide docosahexaénoïque (DHA) est débalancé pendant le vieillissement et chez les porteurs de l’E4. Ces découvertes ont été répliquées dans un modèle de souris transgénique dont l’apolipoprotéine de souris a été remplacé par de l’E4 humaine (hAPOE4). Nous avons récemment montré qu’une diète riche en DHA prévenait les déficits comportementaux chez la souris hAPOE4. Un autre groupe a montré que le ratio acide arachidonique (ARA) : DHA était débalancé dans le plasma des humains E4 et que ce marqueur constituait un marqueur pré-clinique de déclin cognitif léger/MA chez les E4. Avec notre approche de cinétique des acides gras uniformément marqués au carbone 13, nous avons montré que les cinétiques du 13C-DHA et du 13C-eicosapentaénoïque (EPA) étaient modifiées avec l’âge et chez les porteurs de l’E4. Cependant, la cinétique du 13C-ARA n’était pas modifiée avec l’âge. Nous

*Correspondence: Melanie.Plourde2@usherbrooke.ca

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The disease is characterized by β-amyloid plaques and neurofibrillary tangles of tau protein. Together, these two components contribute to neurodegeneration. Many pharmaceutical treatments have been tried over the years but none have succeeded in delaying or limiting the progression of the disease or even treat the symptoms. However, studies involving nutritional strategies are promising. For instance, a recent review suggesting that consumption of ≥2 fish servings/weeks reduces risk of AD (Cunnane et al., 2009). Since the publication of this paper, many other prospective and randomized control trials (RCT) have been published and have reported mixed results. Most of the RCT did not find a causative effect on the consumption of fish oil. In 2013, Dacks et al. published a review of the literature showing that in participants without cognitive decline, taking an omega-3 fatty acid supplement did not gain benefit on cognition (Dacks et al., 2013). In contrast, participants with subjective cognitive complaints could experience cognitive benefits from taking omega-3 fatty acid supplements (Dacks et al., 2013). A recent study has supplemented for 2 years patients with precursor signs of Alzheimer’s disease. The active ingredient was composed of omega-3 fatty acids, uridine, choline, phosphates and B vitamins but this supplementation had no effect on cognitive scores compared to the placebo (Soininen et al., 2017). Thus, there is currently no consensus on the effectiveness of a nutritional strategy to prevent or limit the progression of cognitive decline. In the absence of an effective therapy for the treatment of Alzheimer’s disease, there is a need to clarify whether a nutritional intervention strategy alone or in combination with other treatments are effective.

The new trend in the field of Alzheimer’s disease prevention is multimodal interventions. The Finnish Geriatric Intervention Study to Prevent Impairment and Disability (FINGER) is a multimodal intervention that consists of a dietary modification to reach the targets of nutritional recommendations of Finland, aerobic exercise 2–5 times a week and muscle training 1–3 times a week, cognitive training with group sessions to explain age-related cognition changes, and computer-based exercises to perform at home. This intervention also focuses on the management of cardiovascular risks for those aged between 60 and 77 years (Ngandu et al., 2015). After 2 years of intervention, the executive functions and the execution speed were significantly higher in the group that received the intervention than in the control group, which supports that the intervention prevented cognitive decline (Ngandu et al., 2015).

Another ongoing study in France is the Multidomain Alzheimer Preventive Trial (MAPT study) which includes supplementation with omega-3 fatty acids, as well as nutritional counselling, physical exercise and cognitive stimulation. This procedure was performed for 3 years in frail patients aged 70 and over. In this study, multi-domain intervention and supplementation with omega-3 fatty acids, alone or in combination, did not prevent cognitive decline (Andrieu et al., 2017). Thus, multimodal approaches should be targeted to younger people without apparent risk factors for AD.

## 3 Dysregulation of the metabolism of long chain fatty acid during aging

Unlike saturated and mono-unsaturated fatty acids, synthesis of eicosapentaenoic acid (EPA, 20:5 omega-3) and docosahexaenoic acid (DHA, 22:6 omega-3) from its omega-3 PUFA precursor, alpha-linolenic acid (18:3 omega-3), is extremely limited in humans (Plourde and Cunnane, 2007). Thus, it is recommended that DHA be obtained from dietary sources.
sources such as fish and seafood. Intake of EPA and DHA from fish normally correlates positively with the concentrations of EPA and DHA in plasma (Vidgren et al., 1997). However, recent data suggest that EPA levels are approximately twice higher in plasma lipids of the elderly as compared to young individuals, suggesting that potential alterations in EPA incorporation and utilization occur during aging (Fortier et al., 2010). Similar results were obtained with a DHA-enriched supplement where the increase of DHA in plasma total lipids was 42% higher in the elderly compared to the young [Reviewed by (Fortier et al., 2010)]. In another study, dietary intake of 90 mg/d of DHA for 15 months was not sufficient to increase DHA in plasma total lipids of both a young elderly (aged 60–80 years old) and an old elderly (over 80 years old) group, but 180 mg/d of EPA increased the plasma EPA concentration by 53–109% (Rodriguez-Palmero et al., 1997). Moreover, a persistent significant positive correlation between EPA or DHA and age even after correction for fish intake was reported (de Groot et al., 2009), but age apparently contributed from only 2–4% to the amount of explained variance in EPA and DHA incorporation into plasma PL (de Groot et al., 2009). Whether this percentage is clinically and physiologically relevant is unknown, but it gives important indications that incorporation of EPA and DHA is altered during aging and as a consequence, it has the potential to alter the utilization and uptake of these fatty acids by tissues and organs which might enhance the risk of chronic diseases such as cardiovascular diseases and cognitive declines. Indeed, there are evidences supporting that higher omega-3 PUFA levels in the erythrocyte is associated with better cognitive functions later life (Schaef er et al., 2006) and cardiac benefits (Harris et al., 2008). Therefore, better knowledge of the biology of aging and more specifically with regards to omega-3 PUFA metabolism would help define better nutritional strategies for preventing diseases in the elderly.

To do so, there is a need to use labelled fatty acids. These fatty acids can be labeled on one or more carbons with deuterium or the fatty acid can be uniformly labeled with carbon 13 instead of carbon 12. The latter also allows to evaluate fatty acid beta-oxidation since when it is beta-oxidized, it produces carbon 13 CO₂ (13C-CO₂). The first studies using uniformly labelled carbon 13-labeled fatty acids were performed by the group of Michel Lagarde (Lyon, France) when they investigated the metabolism of 13C-DHA in young humans (Brossard et al., 1996; Lemaitre-Delaunay et al., 1999). After receiving an oral dose of 250–280 mg in 13C-DHA, 13C enrichment peaked 2 h post-dose in plasma TG when the tracer was given in the TG form, but at 6 h post-dose when the tracer was esterified to phosphatidylcholine (Brossard et al., 1996; Lemaitre-Delaunay et al., 1999). Brossard et al. have reported a 1.4% apparent retro-conversion of 13C-DHA to 13C-docosapentaenoate (22:5 omega-3) and 13C-EPA 3 d after giving the tracer (Brossard et al., 1996). These results showed the feasibility of tracing DHA metabolism in humans. However, neither the impact of aging on 13C-DHA metabolism nor its beta-oxidation was investigated. We traced 13C-DHA metabolism in six young (mean = 27 years old) and six old (mean = 77 years old) participants. We found that, 4 h post-dose, in the elderly, 13C-DHA was 4 times higher in plasma TG and free fatty acids and beta-oxidation was 1.9 times higher compared to the young (Plourde et al., 2011). Apparent retro-conversion of 13C-DHA to other 13C-omega-3 PUFA was 2.1 times higher 24 h and 7 d after tracer intake compared to the young (Plourde et al., 2011). This result can be explained by the elderly having both higher postprandial productions of very low-density lipoproteins and free fatty acid response. Hence, because DHA seems to remain transiently for longer periods of time in the blood of the old vs. the young, it may thus indicate a lower efficiency to remove DHA from the blood in the old vs. the young, resulting in lower incorporation of DHA in the membrane of cells that serve to initiate signaling pathways (Bazan, 2007). Hence, by using 13C-DHA, we were able to show postprandial alterations in the management of DHA in the old compared to the young and increased the knowledge on the biology of aging. This lower efficiency potentially results in lower incorporation of DHA in the membranes of different cells including immune cells (Rees et al., 2006; Vandal et al., 2008; Plourde, 2009; Fortier et al., 2010).

Our most recent work with tracers between old and young men was conducted with 13C-eicosapentaenoic acid (13C-EPA) or arachidonic acid (13C-ARA), two key fatty acids that are precursors of anti- and pro-inflammatory cytokines, respectively. Surprisingly, the kinetics of 13C-EPA and 13C-ARA was similar between young and old men (Leveille et al., 2017). However, one intriguing result we obtained was that in old men, synthesis of DHA from EPA started 2 h after tracer intake whereas it was delayed to 1 d in young men (Leveille et al., 2017). This result suggests that old adults might need more DHA than what was actually provided in their diet compared to the young adults. However, newly synthesized DHA accumulates in the plasma of old men for 7 d and this might be because it remains for a longer period in the plasma as suggested by our previous study with 13C-DHA (Plourde et al., 2011). Therefore, there might be a defect of cells such as immune cells in old adults to uptake EPA and DHA resulting in lower anti-inflammatory responses to insults. In the old men, 13C-EPA whole-body half-life was ~14 days and in the younger group it was ~21 days (Leveille et al., 2017). This result indicates that turn-over of EPA is ~7 days faster in older adults compared to younger adults. This is an intriguing result since epidemiological studies and the results from a previous study from our group (Plourde et al., 2009a) suggest that old adults have twice as much plasma EPA, hence, one would anticipate a lower whole-body turnover in old vs young adults. Altogether, our group provided evidence that:

- the level of plasma DHA is slightly modified by age but the metabolism of DHA is highly modified by age: why the two are disconnected needs further investigation;
- the level of EPA in the plasma of old adults is twice that of the young but the metabolism (kinetics) is only slightly modified;
- the level of ARA in the plasma is 25% higher in old vs young adults but the kinetics is not modified by age;
- are these plasma levels and kinetics imbalances obscure the potential relationship between plasma n-3 FA and cognition?

4 One genetic risk factor of AD also affecting DHA metabolism

Apolipoprotein E (ApoE) is a protein-regulating lipid transport and metabolism (Mahley, 1988). The brain has its
own pool of apoE (Pitas et al., 1987) that plays critical roles in lipid transport to neurons. The APOE gene has three isoforms: epsilon 2 (E2), epsilon 3 (E3) and epsilon 4 (E4). In humans, homozygotes for E2 genotype suffer from hypertriglyceridemia and this feature has also been reported in apoE targeted replacement mice with the human E2 (hAPOE2) (Lane and Farlow, 2005; Sharman et al., 2010). In humans, E4 is the most important genetic risk of AD (Coon et al., 2007, Bertram and Tanzi, 2009) and hAPOE4 mice have memory decline similar to that reported in humans (Bour et al., 2008; Siegel et al., 2010). Therefore, this mouse model seems to be excellent to study APOE genotype imbalances on the metabolism of lipids.

Approximately, 20% of Canadians carry the E4 allele which almost doubles their risk of late-onset AD whereas in USA, the frequency of the E4 allele is around 15% (Bullido et al., 1998). AD risk is closely linked to changes in lipid metabolism and plasma DHA levels were inversely associated to the brain Ab load (Yassine et al., 2016). Some suggest that the E4 allele induce a decrease in levels of apoE protein in the brain (i.e. loss of function) (Poirier, 2008) whereas others series of data support a gain-of-negative function in neurite deregulation, loss of synaptic plasticity and cholinergic deposition, oxidative stress, in brain, smaller neuron size and lower neuronal membrane fluidity (Nock et al., 2017). Hence, hAPOE4 might be more vulnerable to omega-3 FA deficiency. The ALA: linoleic acid (LA) ratio, an indicator of the capacity to convert ALA to DHA was ∼80% lower in the liver of hAPOE4 compared to hAPOE3 mice. We recently reviewed the neurological consequences of omega-3 FA dietary deficiency that includes a 3-fold reduction in the capillaries of the adult rat brain, smaller neuron size and lower neuronal membrane fluidity (Nock et al., 2017). Hence, hAPOE4 might be more vulnerable to omega-3 FA deficiency and this process might be accentuated during aging due to a loss of delta-6 desaturase activity as expressed by the ALA: LA ratio (Horrobin, 1981).

Another important point with regards to brain DHA uptake is that, in mice, it was shown to be not saturable at concentrations up to 100 microM suggesting that it crosses the blood-brain barrier (BBB) by simple diffusion. We showed in hAPOE4 mice, that brain 14C-DHA uptake was 24% lower in hAPOE4 than hAPOE2 mice but cortex DHA levels were lower in 13-month-old hAPOE4 mice only (Vandal et al., 2014). Abdullah et al. suggested that Mfsd2a level, a brain transport protein of lyso-phosphatidylcholine-DHA (lyso-PC-DHA), was lower in E4 carriers and in hAPOE4 mice compared to that of E3 carriers and hAPOE3 mice (Abdullah et al., 2016). Lower Mfsd2a levels correlated with lower DHA and a higher ARA levels in brain membrane (Abdullah et al., 2016). Her group also showed that E4 carriers converting to mild cognitive impairment (MCI)/AD had higher ARA: DHA ratio in PC and lyso-PC compared to cognitively normal E4 carriers and E4 non-carriers (Abdullah et al., 2017). Aldullah et al. also reported a similar higher ARA: DHA ratio in PC and lyso-PC in hAPOE4 mice compared to hAPOE3 mice supporting that this mice model also have an imbalance in DHA and ARA compartment packaging (Abdullah et al., 2017). In ~35 year-old humans, a positron emission tomography study with [1-11C]-DHA reported however, that the mean global gray matter incorporation of DHA in the brain of E4 carriers was 16% higher than in non-carriers (Yassine et al., 2017). This higher uptake was particularly emphasized in the entorhinal region, an area affected early in AD pathogenesis and it was suggested by the authors it might represent a compensatory mechanism in younger E4 carriers to cope with increased brain DHA loss thus to maintain brain DHA levels (Yassine et al., 2017). Therefore, at younger ages, E4 carriers might require more DHA than non-carriers to support brain DHA turnover and prevent accumulation of Ab peptide since it was shown that higher plasma DHA levels were inversely associated to the brain Ab load (Yassine et al., 2016). However, Abdullah et al. showed that a fish oil supplement modulate the ARA: DHA ratio in carriers and non-carriers of E4 suggesting that E4 carrier could somehow benefit from a fish oil supplement in rebalancing the ARA: DHA ratio but this may
be conditional to higher doses and longer duration than what has currently been published yet on the topic. This hypothesis is supported by our recent study in hAPOE4 mice fed a control or a diet containing DHA where the DHA diet in hAPOE4 prevented spatial memory deficits as compared to the control diet (Chouinard-Watkins et al., 2017). However, the mechanism explaining this preventive effect remains unknown (Chouinard-Watkins et al., 2017). In another study, the authors reported that the metabolic and cognitive deficits in hAPOE4 mice fed a high fat diet inducing insulin resistance were rescued by switching to a low fat diet for 1 month suggesting a functional role of dietary FA in hAPOE4 mice on top of a structural role (Johnson et al., 2017). Therefore, it seems that hAPOE4 mice could benefit from a higher consumption in DHA (Chouinard-Watkins et al., 2017) but this remains to be established in humans. A recent paper from the FINGER study, a multidomain intervention of 2 years, support this hypothesis since they concluded that healthy lifestyle changes may sustain cognition in older at-risk E4 carriers (Solomon et al., 2018). Although it do not related specifically to omega-3 fatty acid metabolism/supplementation, it indicates that AD risk can be modulated in E4 carriers and non-carriers and thus, this strategy should be encourage and developed better to be implemented in our communities.

5 Conclusion

There is currently no cure nor treatment to AD. Prevention strategies are urgently needed since the aging population will be one of the most significant forces shaping our economy and society in the next 20–30 years. Moreover, there is 15–20% of the population carrying the E4 genetic risk that increases the risk of AD. However, not all E4 carriers develop AD suggesting that lifestyle such as nutrition can modulate AD expression. We have identified that DHA metabolism is imbalanced during aging and in E4 carriers and these imbalances could limit DHA delivery to replenish brain DHA levels during aging and in E4 carriers. Our work contributes to understand how to limit these defects and help to decrease the risk of AD in E4 carriers. A reduction of even 10% in the prevalence of AD would markedly diminish the impact of this disease on society and on life quality of the aging population.

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M. Plourde: OCL

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