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Mini-review

The essential role of lipids in Alzheimer's disease

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ABSTRACT

In the absence of efficient diagnostic and therapeutic tools, Alzheimer's disease (AD) is a major public health concern due to longer life expectancy in the Western countries. Although the precise cause of AD is still unknown, soluble β-amyloid (Aβ) oligomers are considered the proximate effectors of the synaptic injury and neuronal death occurring in the early stages of AD. Aβ oligomers may directly interact with the synaptic membrane, leading to impairment of synaptic functions and subsequent signalling pathways triggering neurodegeneration. Therefore, membrane structure and lipid status should be considered determinant factors in Aβ-oligomer-induced synaptic and cell injuries, and therefore AD progression. Numerous epidemiological studies have highlighted close relationships between AD incidence and dietary patterns. Among the nutritional factors involved, lipids significantly influence AD pathogenesis. It is likely that maintenance of adequate membrane lipid content could prevent the production of Aβ peptide as well as its deleterious effects upon its interaction with synaptic membrane, thereby protecting neurons from Aβ-induced neurodegeneration. As major constituents of neuronal lipids, *n*-3 polyunsaturated fatty acids are of particular interest in the prevention of AD valuable diet ingredients whose neuroprotective properties could be essential for designing preventive nutrition-based strategies. In this review, we discuss the functional relevance of neuronal membrane features with respect to susceptibility to Aβ oligomers and AD pathogenesis, as well as the prospective capacities of lipids to prevent or to delay the disease.

1. Introduction

Alzheimer's disease (AD) is a progressive dementia that manifests in early stages as a profound inability to form new memories. Age is the major risk factor for the non-familial form of AD (up to 99% of cases), which at least partly explains the dramatic increase in AD prevalence in countries where life expectancy is growing [1]. Many questions about pathogenesis of this devastating disease still remain unanswered and satisfying therapeutic options are few [2]. Given the heavy individual and societal burdens inflicted by AD, there is enormous medical need for the development of novel therapeutic strategies that target or even better prevent from the mechanisms leading to dementia. In this context, it becomes essential to identify the molecular actors and pathways involved in AD pathogenesis.

Due to the progressive and – yet – irreversible nature of AD, very early stages (preclinical and mild cognitive impairment) may be due to synaptic dysfunction caused by Aβ peptide under soluble oligomeric form, long before widespread synaptic loss and neurodegeneration. Indeed, clinical studies have shown that soluble Aβ levels rather than amyloid deposits are better correlated with dementia severity [3]. Furthermore, in the brain of AD patients, Aβ oligomeric forms mainly target synapses affected early in the pathogenesis [4]. Cognitive deficits appear before amyloid deposition in AD transgenic mice models [5], which strongly implicate

Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; ARA, arachidonic acid; $cPLA_2$, cytosolic phospholipase A_2; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LOX, lipoxygenase; LTP, long-term potentiation; PS1, presenilin-1; PUFA, polyunsaturated fatty acid; S1P, sphingosine-1-phosphate; SMase, sphingomyelinase.

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soluble forms of Aβ whose intracerebral injection inhibits long-term potentiation (LTP), a paradigm for memory [6], as well as cognitive functions [7].

Fusogenic properties of soluble Aβ suggest that interaction with plasma membrane occurs among the initial events leading to impairment of synaptic functions and subsequent neurodegeneration [8]. It is thus essential to identify the biological factors that could modulate these early interactions and their noxious consequences. Besides age and gender, education level and social activities, dietary parameters represent common risk factors for neurodegenerative and cardiovascular diseases, leading to the idea that nutrition could offer powerful tools for delaying onset of AD or slowing its progression. Among them, lipid status has been identified as a key parameter in AD pathogenesis by numerous epidemiological, clinical, animal or cellular studies [9]. This is especially the case for docosahexaenoic acid (DHA; *n*-3, C22:6), a fatty acid essential for cerebral functions and whose decline has been reported in the brain and plasma of AD patients [10].

2. Lipids influence neuronal susceptibility to amyloid stress

2.1. Membrane architecture is determinant for Aβ neurotoxicity and production

A growing body of evidences supports the notion that membrane destabilization by Aβ oligomers may represent the primary mechanism of pathogenesis. Indeed, exposure to soluble Aβ causes a rapid and reversible leakage of calcium that can be inhibited by anti-oligomer antibody. Such an increased lipid bilayer conductance without forming discrete pores suggests that Aβ oligomers could directly induce a profound remodelling of plasma membrane. In that way, we have shown that exogenous cholesterol and DHA protect cortical neurons in primary cultures from Aβ-induced apoptosis, while cholesterol depletion increases Aβ-oligomers neurotoxicity [11,12]. Since steric incompatibility of the rigid steroid moiety for highly disordered DHA chain promotes lateral segregation of lipids into rafts [13,14], it can be deduced that membrane lipid status is strongly involved in neuron susceptibility to Aβ oligomers and therefore represents a goal for prevention. Accordingly, it is well known that inheritance of apolipoprotein ε4 allele (ApoE4) is a major risk factor for sporadic AD [15]. ApoE proteins belong to the family of plasma lipid-binding proteins involved in triglycerides and cholesterol transport and delivery, but it is also worthy to note that ApoE proteins also contribute to the clearance of Aβ peptide through binding to lipoprotein receptors [16].

Although the link between ApoE4, cholesterol and AD is still not clear, it becomes obvious that cholesterol can modulate AD pathogenesis by influencing Aβ production and neurotoxicity [9]. Aβ peptides are derived from proteolytic cleavage of the membrane-bound amyloid protein precursor (APP). APP is metabolised by two possible pathways: the non-amyloidogenic pathway involves a sequential cleavage of APP by α- and β-secretases, leading to the release of a secreted neurotrophic APP ectodomain called sAPPα, while the amyloidogenic pathway results in Aβ release as well as loss-of-function of truncated sAPPα [17]. As the α- and β-secretases compete for the same substrate, distribution of APP between the two alternative pathways is thus tightly regulated. Numerous studies support the hypothesis that dynamic partitioning of APP and its proteolytic enzymes in different membrane domains could be the main regulatory mechanism involved (Fig. 1). Accordingly, it was found that β- and γ-secretase activities are concentrated and optimized in lipid rafts, while α-secretase and APP are mainly found in non-raft regions [18]. Consistent with that, depletion in cholesterol which is highly enriched in rafts has been demonstrated to decrease Aβ production [19], leading to the exciting perspectives of statin-based treatment as a mean to lower cholesterol levels. Statins have been reported to reduce AD risk [20,21] and to prevent Aβ-induced neuronal loss and memory impairment [22], but contradictory data have also been published [23]. This suggests that the appropriateness of statin therapy is not established at this time [24,25] and the fact that a moderate decrease in cholesterol levels results in increased Aβ production in primary hippocampal neurons [26] indicates that the link between cholesterol and AD requires to be more clearly elucidated.

In this context, DHA has been recently demonstrated to promote the non-amyloidogenic pathway, resulting in reduced Aβ levels in AD cellular models [27]. Though dietary DHA clearly leads to

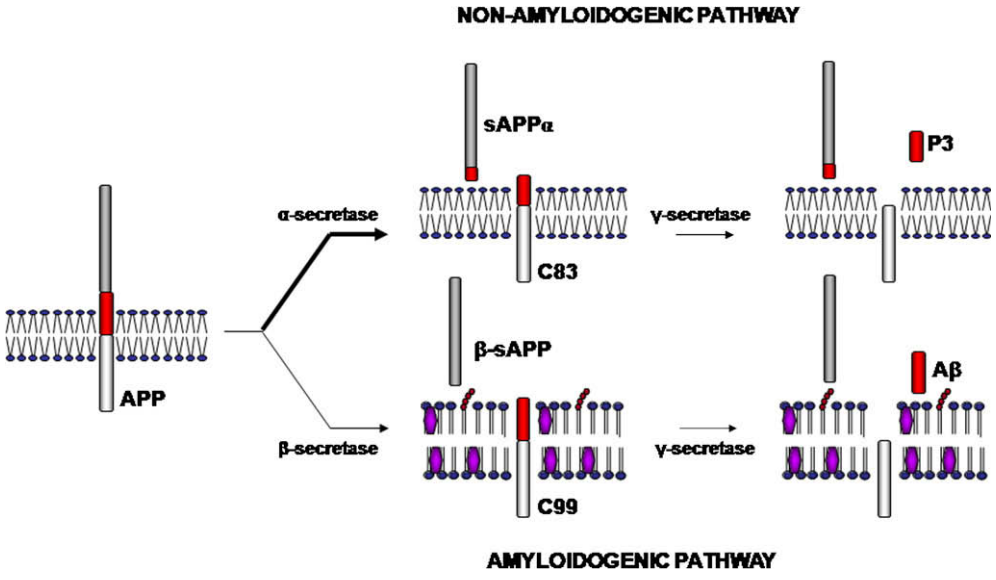

Fig. 1. Alternative processing of APP. APP is mainly metabolised through the non-amyloidogenic pathway involving a sequential cleavage by α- and β-secretases, leading to release a secreted neurotrophic protein called sAPPα. On the other hand, the amyloidogenic pathway requires β- and γ-secretase activities and leads to Aβ production. This pathway mainly occurs in rafts represented here by membrane domains enriched in cholesterol (purple hexagons) and gangliosides (with red tails).

enrichment of neuronal phospholipids, its precise influence on membrane structure is still debated as it has been detected in cholesterol-rich domains [28] albeit its non-raft physiochemical properties [14]. These data altogether suggest that membrane lipid status is strongly involved in APP processing and that any perturbations could lead to deleterious cascades. Management of lipid status thus represents a very promising objective for preventing Aβ interaction with membrane and deleterious outcomes, as well as Aβ production in the central nervous system.

2.2. Neuronal cell death induced by Aβ oligomers involves lipid mediators

2.2.1. Phospholipase A_2–arachidonic acid pathway

Initiation of inflammatory processes takes place during the earliest stages of AD and is associated with an increase in free fatty acid levels, suggesting that phospholipases may play a crucial role in the production of second messengers involved in deleterious cascades [29]. Accordingly, increased immunoreactivity of the cytosolic calcium-dependent phospholipase A_2 ($cPLA_2$) is observed in AD cortex as compared with that of age-matched control subjects. Treatments of primary culture of cortical neurons with low concentrations of Aβ oligomers lead to a precocious activation of $cPLA_2$ and rapid arachidonic acid (ARA; *n*-6, C20:4) release, demonstrating that neuro-inflammatory cascades could be initiated by soluble Aβ [30]. Indeed, ARA acts as a second messenger that directly regulates a number of cellular processes, including apoptotic pathways, and serves as a precursor for the production of eicosanoids, a variety of other lipid mediators. Inhibition of $cPLA_2$ activation or expression upon exposure to Aβ oligomer has been shown to significantly protect neurons from subsequent cell death, which suggests that the control of $cPLA_2$ activity could be an interesting therapeutic target for AD.

2.2.2. Sphingomyelinases–ceramide pathway

Altered sphingolipid metabolism has been reported in AD brain, including elevated acid sphingomyelinase (SMase) and acid ceramidase associated with lower sphingomyelin levels and higher ceramide and sphingosine levels [31]. Ceramides and sphingosine are important second messengers that regulate diverse cellular processes, including cell growth and differentiation, and display potent proapoptotic properties. Once produced, ceramides could also form signalling platforms that have been shown to cluster receptor molecules transmitting apoptotic stimuli into the cell [32]. *In vitro*, Aβ oligomers induce the activation of both neutral and acid SMases through a redox-sensitive $cPLA_2$–ARA dependent pathway, which results in apoptotic cell death [33]. Ceramides have also been shown to stabilize the β-site APP cleaving enzyme BACE-1, thereby promoting Aβ production [31]. Interestingly, sphingosine-1-phosphate (S1P), an anti-apoptotic molecule able to inhibit Aβ-induced ASM activation and subsequent neuronal apoptosis, is also decreased in AD brain [31,33]. It is likely that elevated ceramides and sphingosine as well as lower S1P create a proapoptotic environment in AD brain that takes part in neuronal death (Fig. 2).

3. DHA supplementation studies strongly suggest potential for AD prevention

3.1. DHA prevents neuronal cell death through various protective mechanisms

Since conversion from α-linolenic acid to DHA is very low in human, DHA is now increasingly considered an essential fatty acid that must be provided from diet [34]. This is especially true in elderly whose neuronal membranes often display a deficit in DHA [10]. Several studies have established that moderate fish consumption as a proxy of *n*-3 polyunsaturated fatty acids (PUFAs) is associated with a reduced risk of impaired cognitive functions. This neuroprotective effect is usually described to rely on 4 distinct and interconnected molecular mechanisms: (*i*) regulation of gene expression, (*ii*) anti-oxidative and (*iii*) anti-inflammatory effects, as well as (*iv*) membrane remodelling.

3.1.1. Regulation of gene expression

The first reported effect of dietary PUFA-induced differential gene expression pattern in the brain has been reported on myelination process [35]. A nutrigenomic approach has then revealed significant changes in the expression of several genes including the

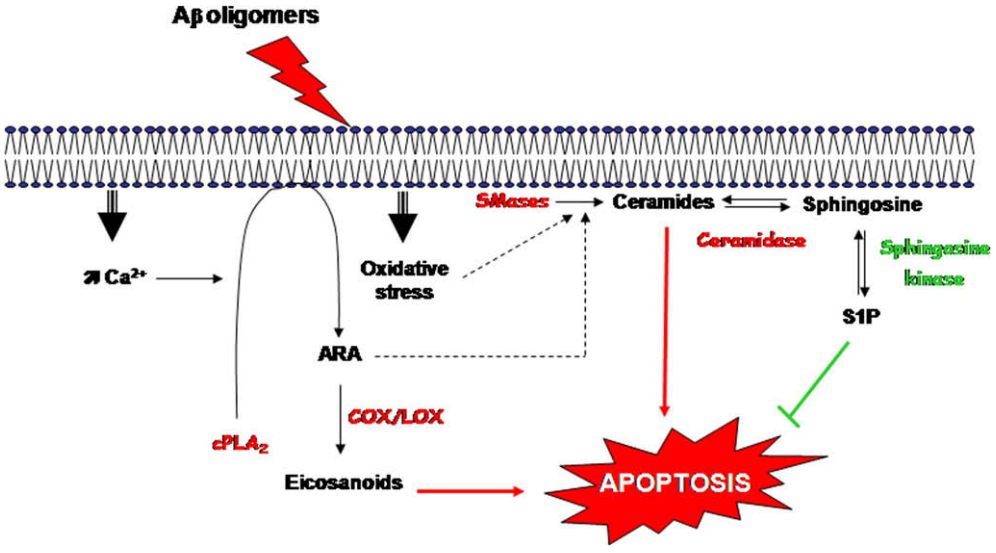

Fig. 2. Lipid mediators in Aβ neurotoxicity. This cartoon depicts the pivotal contribution of lipids in signalling of apoptotic cell death induced in neurons exposed to Aβ oligomers. Upon their interaction with the lipid bilayer, a very rapid cellular response is initiated, involving an oxidative stress and a calcium influx that leads to $cPLA_2$ activation and subsequent ARA release. Besides the pro-inflammatory cascade mediated by COX/LOX-produced eicosanoids, ceramide-enriched membrane domains are favoured thanks to SMase activation, detrimentally to sphingolipids and especially to S1P whose production and cell protective properties are prevented.

gene encoding the Aβ-scavenger transthyretin in hippocampus of aged rats fed with fish oil [36]. The number of genes whose expression has been modified as well as the extent of these modifications depends on the conditions of the supplementation, which suggests that high PUFA intake must be well fitted in terms of both duration and level to have a significant effect on human health.

3.1.2. Oxidative stress

Increasing levels of oxidative stress markers appear early in AD pathogenesis implying soluble Aβ oligomers. Some reports have concluded that DHA or fish oil supplementation can result in antioxidant effects in rat corpus striatum [37] as well as in hippocampus and cortex of an AD model rat [38]. However, DHA provided as free fatty acid failed to prevent the oxidative stress induced *in vitro* in neurons exposed to soluble Aβ peptides and rather seems to favour oxidation, radical formation and subsequent damages [12], which could at least partially be explained by the high unsaturation degree of this fatty acid.

3.1.3. Inflammatory process

Keeping in mind the importance of the inflammatory processes in AD and the beneficial impact of dietary intake of DHA on inflammatory diseases such as asthma, it was worth to explore whether DHA could modulate $cPLA_2$ pathway. *In vitro*, DHA pretreatment of neurons does not prevent Aβ-induced ARA release, suggesting that DHA does not inhibit $cPLA_2$ activation, while neurons are fully protected from Aβ when cultured in media supplemented with DHA and pretreated with a $cPLA_2$ inhibitor [12]. However, recent work demonstrated that DHA and eicosapentaenoic acid (EPA; *n*-3, C20:5) are converted to bioactive mediators named docosatrienes and resolvins, respectively [39]. The main potent member of DHA metabolites is neuroprotectin D1 and has been reported to decrease Aβ peptide production as well as apoptosis induced *in vitro* by Aβ oligomers [40]. Interestingly, sAPPα can induce neuroprotectin D1 generation, which allows linking the decrease in the latter to the reduced production of sAPPα observed in AD brain.

3.1.4. DHA and membrane incorporation

Due to its physicochemical features, DHA enrichment results in higher membrane fluidity and subsequently modulated activity of membrane-associated proteins, as well as vesicle formation and fusion. This could allow DHA modifying membrane architecture, especially the number of lipid rafts as well as their distribution and composition. In our *in vitro* model, protection of rat cortical neurons from Aβ-induced apoptosis is observed by supplementing the culture medium with nanomolar DHA concentrations, which likely results in DHA enrichment of specific phospholipid species or membrane microdomains [12]. Accordingly, immunocytochemical analysis of raft-specific partners such as ganglioside M1 and flotillin-1 shows a membrane disorganisation in cortical neurons exposed to soluble Aβ oligomers, whereas normal intense fluorescence labelling is obtained in neurons pretreated with DHA [41]. This could suggest that the apoptosis induced by Aβ oligomers involves structural and qualitative changes in lipid microdomains that could be prevented in DHA-enriched membranes. Appropriate studies to assess this hypothesis are in progress in our laboratory.

3.2. DHA supplementation potential has been proven in Alzheimer's disease models

Numerous dietary supplementation studies have been reported in the literature. They mostly differ by the animal model, the route of administration, the nature, the dose and the source of the PUFA provided (purified DHA under ethyl-ester or phospholipid form, DHA + EPA, fish oil…) and the duration of the supplementation, as summarised in Table 1. Most studies were performed either using intra-gastric administration of purified ethyl-ester-DHA or fish oil emulsified in 5% gum Arabic solution at concentrations ranging

Table 1
Summarised description of *n*-3 PUFA dietary supplementation studies in aging/AD animal models.

Model	Route of administration and daily dose of DHA	Duration	Main effects of DHA/*n*-3 PUFAs/fish oil	References
Young and aged rats	High-*n*-3 PUFA diet 10 mg DHA/d (from tuna oil)	2 months	Reversion of age-related impairments in LTP and depolarisation-induced glutamate transmitter release	McGahon et al. (1999) [42]
Adult male rats progeny from female depleted or not in PUFAs	High-*n*-3 PUFA diet (from tuna oil or egg phospholipids)	2–3 months	Enhancement of the potassium chloride-evoked release of acetylcholine in rat hippocampus	Aid et al. (2005) [43]
Young and aged rats	Intra-gastric injection of purified ethyl-ester-DHA (10 mg DHA/d)	2 months	Reversion of age-related alterations of phospholipid profiles	Little et al. (2007) [44]
5-week old male rats	Intra-gastric injection of purified ethyl-ester-DHA (300 mg/kg/d)	3.5 months	Improvement of spatial cognition, increase in Fos expression in rat CA1 hippocampus	Tanabe et al. (2004) [45]
25-week old rats	Intra-gastric injection of purified ethyl-ester-DHA (300 mg/kg/d)	3 months	Increased synaptosomal membrane fluidity, protection from learning/memory impairments in Aβ-infused rats	Hashimoto et al. (2006) [46]
18-month old rats	Intra-gastric injection of purified ethyl-ester-DHA (300 mg/kg/d)	0.5 month	Promotion of neurogenesis *in vitro* and *in vivo*	Kawakita et al. (2006) [47]
Adult gerbils	Intra-gastric injection of purified ethyl-ester-DHA (50–300 mg/kg/d)	1 month	Increase in dendritic spine density in hippocampus	Sakamoto et al. (2007) [48]
15-month old female mice	Intra-gastric injection of purified ethyl-ester-DHA (50–100 mg/kg/d)	1.7 months	Improvement of age-related cognitive impairments, increase in BDNF levels in hippocampus	Jiang et al. (in press) [49]
3-week old male mice	Palm oil (*n*-3-deficient) or sardine oil (*n*-3-abundant) diet chow	12 months	Higher DHA level in brain, membrane synaptic fluidity and maze-learning ability	Suzuki et al. (1998) [50]
6-month old female 2 × Tg mice (APP × PS1)	High-DHA (0.5% DHA) diet chow	3 months	Decrease in Aβ load	Oksman et al. (2006) [51]
17-month old Tg2576 mice	High-DHA (0.6% DHA) diet chow	3.5 months	Protection from dendritic pathology and behavioural deficits, increased anti-apoptotic BAD phosphorylation	Calon et al. (2004) [52]
17–19-month old Tg2576 mice	High-DHA (0.6% DHA) diet chow	3.5 months	Reduction of amyloid burden	Lim et al. (2005) [53]
3-month old 3 × TgAD mice	High-DHA, [DHA + DPA] or [DHA + AA] diet chow (*n*-6/*n*-3 = 1/1)	3, 6 or 9 months	Amelioration of Aβ and Tau pathology (after 3 months) *via* a mechanism involving PS1 levels	Green et al. (2007) [54]
2-month old 2 × Tg mice (APP × PS1)	High-*n*-3 diet chow including 4% of menhaden fish oil (*n*-6/*n*-3 = 3.8/1)	4 months	No improvement or protection of cognitive performance	Arendash et al. (2007) [55]

from 100 to 300 mg/d/kg, or using DHA-enriched diet chow comparing low DHA or high-*n*-6/*n*-3 molar ratio to high-DHA-diet. It should be noted that elevated *n*-6/*n*-3 diets could induce pro-inflammatory conditions and must hence be interpreted carefully or compared with a well-fitted standard diet adjusted to present adequate *n*-6/*n*-3 ratio ranging from 4/1 to 10/1 [56].

3.2.1. Beneficial impact of DHA in aging model

Changes in lipid composition such as the age-related decline in DHA content can affect the biophysical features of the neuronal cell membranes with subsequent cell signalling, enhancing their sensitivity to various stresses. Depolarisation-induced neurotransmitter release is particularly decreased in synaptosomes prepared from the hippocampus of aged rats compared with those from young animals. This decline is at least in part explained by an increase in membrane rigidity and results in a poorer ability to sustain LTP and promote synaptic plasticity [42]. It was also demonstrated that a 2-month feeding program reversed the age-related impairment of LTP, which could be due either to an increase in synaptosomal fluidity [46] or to optimisation of ion channelling favoured by a more appropriate membrane environment [43]. Accordingly, some studies based on supplementation of young and older rats with a daily dose of 10 mg of DHA have reported an increase in the unsaturation index of old rat cortical tissue to levels similar to those observed in young animals, which thereby normalises age effect [44]. This response was associated with a replenishment of the DHA-containing species, especially phosphatidylinositol and phosphatidylserine, which could have important implications for DHA biological functions since these species are known to be involved in cell signalling and apoptosis. Improvement of age-induced cognitive impairment could also be explained by the formation of new dendritic spines. As a matter of fact, a daily administration of DHA, but not of ARA was demonstrated to lead to a significant increase in spine density in the primary apical dendrites of CA1 pyramidal neurons associated with higher expression of pre- and post-synaptic proteins in hippocampus, a pivotal structure for memory process [48]. These authors also highlighted the synergistic effect of DHA and phosphatide precursors such as UMP or CDP-choline (citicoline) in terms of neurogenesis and dendritic spine formation. The latter is of particular interest as PC is the major phospholipid in the brain and provides the PC moiety needed to synthesise sphingomyelin. However, almost all precursors required by the brain being obtained from the circulation, their blood levels can affect the overall rate of PC-synthesis and thus influence synaptogenesis and dendritic formation [57].

3.2.2. Beneficial impact of DHA in AD models

Two types of methods are basically used to investigate DHA potential benefits against AD pathogenesis: acute Aβ-oligomer brain exposure in Aβ-infused rat or AD transgenic mice models. Depending on the transgene(s) involved, contradictory data were obtained, especially for AD mice models. Indeed, while a DHA-diet was shown to reduce amyloid burden and prevent from dendritic pathology in Tg2576 mice [52,53] as well as in 3-month old 3 × TgAD mouse models [54], no improvement in cognitive performances of (APP)-sw + PS1 double transgenic mice was observed [55]. However, it is worth to note here that these AD mice models have been conceived to mimic Aβ overproduction as observed in genetic cases of the familial form of disease and therefore constitute a rather poor model for early stages of the widespread sporadic disease. For this reason, several studies were designed by using acute Aβ-oligomer exposure only. Intra-gastric administration of purified ethyl-ester-DHA emulsified in 5% gum Arabic solution at 300 mg/kg/d was reported to preserve the learning capacities of Aβ-infused rats from impairment induced by Aβ oligomers. This neuroprotective effect was shown to be associated with a decrease in cholesterol/phospholipids molar ratio and in lipid peroxidation, as well as an increase in synaptosomal DHA content and in the number of newborn neurons in the entire granule cell layer of *dentate gyrus* [46,47]. More recently, a new AD mouse model has been validated in our laboratory, based on a single stereotaxic injection of picomoles of soluble Aβ oligomers in the brain lateral ventricle, very close to the hippocampus [7]. Such a mouse then displays synaptic dysfunction and cognitive deficits, but neuronal death and neuroinflammation have not been detected. This model closely resembles the earliest AD stages and therefore represents a precious tool for evaluating the neuroprotective potential of preventive approaches. Preliminary and unpublished data obtained from this model indicate that dietary supplementation with very low doses of DHA fully preserves the learning and memory capacities from impairment induced by Aβ-oligomer injections.

4. Conclusion

Sporadic Alzheimer's disease is a pathology whose onset relies upon the coincidence of a complex pattern of risk factors that could render neurons particularly susceptible to soluble Aβ oligomers. In the brain of individuals prone to declare AD, neurons very likely exhibit poor intrinsic resistance capacities that presumably result at least partially from accumulation of oxidative damage as postulated by the free radical theory of aging [58]. However, a substantial body of evidence is growing, leading to consider that AD pathogenesis can also be favoured as a consequence of altered lipid status, similarly to other age-related syndromes including cardiovascular diseases, diabetes and obesity. Therefore, AD could reasonably be considered a lipid metabolism disease whose associated dysfunctions accumulate for years as a result of deteriorated nutritional quality of the Western diet. Along with longer lifespan, this would lead to pathological brain ageing and explain elevated prevalence of AD in our countries.

Interestingly, all these devastating afflictions can be appropriately prevented by nutritional strategies, leading to predictable modifications in the lipid content and status of target tissues and brain particularly. Numerous studies have provided the exciting emerging evidence that DHA is a potent neuroprotective fatty acid that can prevent neuronal damage and cell death *in vitro* and protect elderly as well as animal models from age- and Aβ-induced cognitive impairments *in vivo*. Elucidation of the molecular mechanisms and pathways responsible for these effects still requires further investigations, for instance in order to explain the highly heterogeneous effects reported in the literature for which *apoE* genotype may be in part responsible as a possible determinant of lipid responsiveness to DHA or fish oil intervention. Nonetheless, DHA already appears a central compound in the view of designing well-being diets for seniors. As membrane impairment also seems to be a key event in other afflicting diseases, dietary lipids could be regarded as valuable ingredients whose protective effects could be of essential interest for designing new preventive strategies based on nutritional approaches. This challenge is especially urgent for AD due to the lack of really efficient therapeutic drugs and protocols.

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