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Topical issue on:

LIPIDS & BRAIN IV: LIPIDS IN ALZHEIMER'S DISEASE
LIPIDS & BRAIN IV: LES LIPIDES DANS LA MALADIE D'ALZHEIMER

REVIEW

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Dietary arachidonic acid: a Janus face actor in brain and Alzheimer's disease?

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Abstract – Arachidonic acid is the second polyunsaturated fatty acid in brain and the first one belonging to the ω -6 series. Dietary intakes of arachidonic are between 50 and 300 mg/day in western diets but they might be underestimated. Triglycerides from fat would provide similar amounts than phospholipids of lean meat. Alzheimer's disease is an age-associated degenerative disease and a critical health concern worldwide. Amyloid- β peptide oligomers are presently recognized as the main and earliest agents of Alzheimer's disease although their neurotoxicity requires the presence of tau protein. We and others established that the arachidonic-specific cytosolic phospholipase A₂ is critical for the amyloid- β peptide oligomer neurotoxicity. Then, we showed that an arachidonic acid-rich diet increases the mouse sensitivity to the amyloid- β peptide oligomer deleterious effect without major increase of arachidonic acid levels in brain. This suggests that dietary arachidonic acid can exert its effects in brain through peripheral modifications. Involvement of systemic sub-inflammation and gut-brain communications are discussed based on the recent literature. The various data suggest that dietary arachidonic acid should be taken into account in the design of preventive strategies against Alzheimer's disease.

Keywords: arachidonic acid / inflammation / brain / diet / Alzheimer's disease

Résumé – L'acide arachidonique alimentaire : un acteur à deux faces dans le cerveau et la maladie d'Alzheimer ? L'acide arachidonique est le second acide gras polyinsaturé cérébral et le premier de la série des ω -6. Les apports alimentaires d'acide arachidonique varient entre 50 et 300 mg/jour dans les régimes occidentaux mais pourraient être sous-estimés. Les triglycérides de la partie grasse des viandes fourniraient des quantités similaires aux phospholipides de la partie maigre. La maladie d'Alzheimer est une maladie neurodégénérative associée à l'âge et un problème de santé publique majeur dans le monde. Les oligomères de peptides β amyloïde en sont désormais reconnus comme l'agent principal, bien que la présence de la protéine tau est nécessaire à leur action. Avec d'autres auteurs, nous avons établi que la phospholipase A₂ cytosolique, spécifique de l'acide arachidonique, assure les effets neurotoxiques des oligomères de peptide β amyloïde. Nous avons ensuite montré qu'un régime riche en acide arachidonique augmente la sensibilité des souris aux effets de ces oligomères, sans augmentation majeure de ses niveaux cérébraux. Ceci suggère que cet acide gras peut agir sur le cerveau par des effets périphériques comme une sub-inflammation dont le rôle dans la relation intestin-cerveau est discutée dans la littérature. Les apports alimentaires d'acide arachidonique devrait être intégrés dans la prévention de la maladie d'Alzheimer.

Mots clés : acide arachidonique / inflammation / cerveau / régime alimentaire / maladie d'Alzheimer

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Abbreviations

AD	Alzheimer's disease
AICD	Activation-induced cell death
APP	Amyloid precursor protein
ARA	Arachidonic acid
A β peptide	Amyloid-beta peptide
BACE 1	Beta-secretase 1 precursor
CD33	Cluster of differentiation 33
CD36	Cluster of differentiation 36
cPLA2	Cytosolic phospholipase A2
DHA	Docosahexaenoic acid
GFAP	Glial fibrillary acidic protein
LDL	Low density lipoprotein
LNA	Linoleic acid
NFT	Neurofibrillary tangles
PSD95	Postsynaptic density protein 95
PUFAs	Polyunsaturated fatty acids
SNAP25	Synaptosomal-associated protein 25
SNARE	Soluble N- ϵ -thylmaleimide-sensitive-factor attachment protein receptor
TLR	Toll-like receptor
TREM2	Triggering receptor expressed on myeloid cells 2

1 Introduction

While the influence of docosahexaenoic acid [DHA] in Alzheimer's disease [AD] or other neurodegenerative diseases focused the interest of scientific and medical communities, few works were devoted to the role of arachidonic acid [ARA] in these diseases. However, ARA is the second polyunsaturated fatty acids [PUFA] and the main member of the ω -6 series in brain, representing approximately 20% of the neuronal fatty acids. In addition, ARA is converted in various eicosanoid which are important mediators in the various phases of inflammation, having pro- or anti-inflammatory activities and is involved in synaptic transmission as retrograde messenger (Nishizaki *et al.*, 1992) and regulator of SNARE formation (Rickman and Davletov, 2005). Furthermore, ARA is considered as an essential fatty acid at least in the maturation of brain in the pre- and post-natal periods.

It is well admitted that memory alterations are caused by synaptic dysfunctions in the AD early steps. Neuro-inflammation contributes to the AD early synaptic dysfunctions and the neuronal death in the late steps of the disease. Therefore, ARA is putatively involved in AD through its role in synaptic signal and in inflammatory process and regulation of its brain levels could be a target in the fight against AD occurrence and progression. Despite its putative role in the maintenance of brain functions, excessive dietary ARA intake could lead to higher brain incorporation and favour dysregulation of ARA mobilization and conversion into pro-inflammatory mediators. However, ARA content in western diets were poorly studied until now, which makes difficult the evaluation of their impact on AD risk.

We will first examine, in this review, the present knowledge about the ARA place in the current western diets. After a short overview about the AD molecular actors of AD

Table 1. Evaluation of dietary arachidonic acid intakes. Few studies evaluated ARA dietary intakes in a limited number of countries and reported a large range of values.

Sources	Range
Jonnalagadda <i>et al.</i> , 1995	100 mg/day
Mann <i>et al.</i> , 1995	< 150 mg/day
Tokudome <i>et al.</i> , 1999	139–168 mg/day
Kuriki <i>et al.</i> , 2002	130–150 mg/day

and the role of neuro-inflammation, we will present recent data about ARA contribution to AD mechanisms including ours. On this basis, we will propose some hypothesis on the ARA-associated mechanisms in AD.

2 Arachidonic acid in the current western diets

Several studies were performed in the 1990s to evaluate the ARA daily intake in the western diets and its main sources in food. According to these studies, ARA daily intakes are in a wide range from 100 to 200 mg/day (Jonnalagadda *et al.*, 1995; Mann *et al.*, 1995). Studies on Japanese population reported a narrower but compatible range of values between 100 and 200 mg/day (Tokudome *et al.*, 1999; Kuriki *et al.*, 2002). This wide range of daily intakes (see Tab. 1 for comparison of the various studies) in western diets could make difficult the determination of ARA contents in currently consumed foods as suggested by some works about the ARA underestimation at least in American diet (Taber *et al.*, 1998). ARA is provided directly from some food components such as red meat, chicken, eggs but also fish (<http://appliedresearch.cancer.gov/diet/foodsources/fattyacids/table4.html>, data from the National Health and Nutrition Examination Survey 2005–2006 USA). For example, a recent study established that ARA plasma concentration is associated with the consumption of red meat in the Singapore Chinese population (Seah *et al.*, 2017). Although membrane phospholipids are frequently considered as the main source of ARA, Li *et al.* (1998) reported that meat fat and triglycerides provide similar or even higher ARA amounts especially in white meat, chicken or pork. The case of chicken or other poultry has to be considered since they are frequently consumed in many countries and higher ARA content in poultry improve the taste of the meat (Kiyohara *et al.*, 2011; Takahashi *et al.*, 2012). Methods of raising and feeding poultries could therefore increase dietary ARA intakes in humans.

ARA also results from the conversion of its precursor linoleic acid [LNA], i.e. the elongation by elongases and desaturation by Δ and Δ 6 desaturases. LNA is much more abundant in human food than ARA. The European Food Safety Authority [EFSA] recommended in 2009 the consumption of 2 g/day of α -linolenic acid and 10 g/day of LNA (European Food Safety Authority, 2009) which corresponded to an increase of the previous recommendations for ω -3 and ω -6 daily intakes (2 g/day and 6 g/day respectively in 1992). In parallel, the World Health Organization recommended that 0.5–2% and 2.5–5% of energy should be provided by ω -3 and

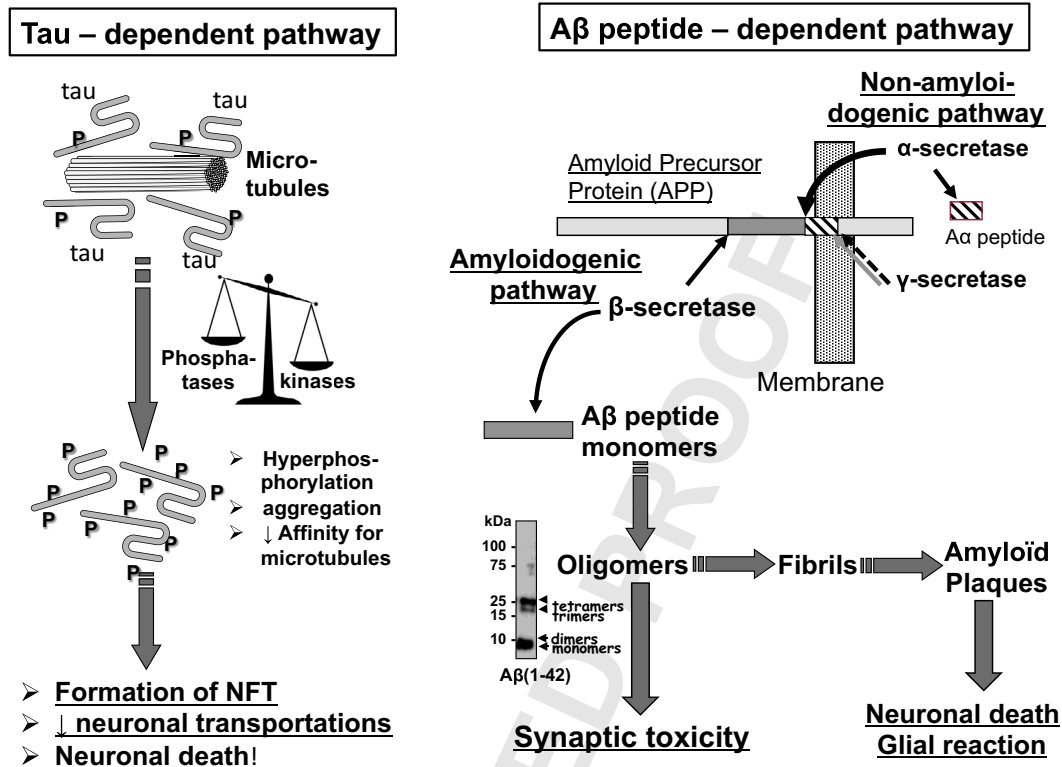


Fig. 1. Roles of tau and Aβ oligomers in AD. The tau-dependent pathway is associated to hyperphorylation and aggregation of tau-proteins inducing alterations of neuronal transportations and finally, neuronal death. The Aβ peptide-dependent pathway is associated to Aβ peptide production and toxic oligomer formation which alter synaptic functions. In a final step, Aβ peptide oligomers aggregate into amyloid plaques from oligomers which contribute to glial reaction and neuronal death.

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169 ω-6 PUFAs, respectively (i. e. 1.5–6 g/day and 7.5–15 g/day of
 170 ω-3 and ω-6 PUFAs, respectively) (FAO/WHO, 2008). In
 171 France, the National Individual study on Alimentary Con-
 172 sumptions [INCA] showed that the French people eat on
 173 average 9 g/day of LNA (ω-6) and 0.9 g/day of linolenic acid
 174 (ω-3) while the US daily average intakes are 18 g and 2 g of
 175 LNA and linolenic acid, respectively, according the
 176 2012 USDA study (USDA, 2012). A few studies investigated
 177 the rate of conversion of consumed LNA into ARA in adults
 178 and their data indicated that this conversion poorly contributes
 179 to the ARA amounts found in plasma or in liver (Adam *et al.*,
 180 2008). On the contrary, the brain ARA requirement of the fetal
 181 baboon are met by dietary maternal LNA (Su *et al.*, 1999),
 182 which suggest that the brain development period must be
 183 considered separately from what happen in adult organism.
 184 Additional worldwide studies are needed to provide more
 185 precise evaluation of the daily ARA intake, the LNA
 186 contribution to the ARA amounts found in peripheral organs
 187 as well in brain and the main food sources of ARA.

3 Main molecular actors of Alzheimer’s disease and contribution of neuro-inflammation

AD was originally defined in 1906 by Alois Alzheimer by the presence of two histological pathognomonic signs in brain of affected patients:

- neurofibrillary tangles (NFTs);
- amyloid plaques (Berrios, 1990).

Neurofibrillary tangles are formed by aggregation of hyperphosphorylated tau protein filaments while amyloid plaques result from aggregation of amyloid-β [Aβ] peptide (Fig. 1). Tau protein physiologically associates to microtubules in mature neurons and play an important role in neuronal signalling and axonal transport (Nisbet *et al.*, 2015; Chong *et al.*, 2018). Hyperphosphorylation of tau in AD probably result from a disequilibrium between kinase (CDK5, GSK3β, ERK2 and/or other still unidentified kinases) and phosphatase activities (Gong *et al.*, 2000) and facilitate the formation of tau helical filaments which finally aggregate into NFTs. In addition, hyperphosphorylation of tau decrease its affinity for microtubules which drastically alters the axonal transportations (Iqbal *et al.*, 1994). The importance of tau dysregulation is highlighted by the correlation between the clinical symptoms and the extension of NFTs through the various brain regions (the entorhinal cortex in the earliest steps, then in the limbic system and the hippocampus the neocortex in the latest stages of AD) (Silverman *et al.*, 1997).

The amyloid plaques are formed by aggregates of amyloid-β [Aβ] peptide. The Aβ peptide is produced by the amyloidogenic cleavage of the transmembrane amyloid precursor protein [APP] which function is still unknown. In this amyloidogenic way, the N-terminal portion of APP is

cleaved by the major β -secretase BACE1 while the C-terminal portion of APP is cleaved by the γ -secretase, both the cleavage releasing the A β peptide and two other N-terminal (sAPP β) and C-terminal (AICD) fragments (Vassar *et al.*, 1999). There are two major forms of A β peptide: A β ₁₋₄₀, which is the most abundant form (90%) and A β ₁₋₄₂ (10%), which is the most toxic form. Since the clinical symptoms are not correlated with the number and size of the amyloid plaques (Lue *et al.*, 1999), many authors concluded in the early 2000s that amyloid plaques is not the engine of the pathological process but a late symptoms. They postulated that the A β oligomers, formed by the A β peptides before their fibrillization and deposition into plaques, are the initial agent of AD. This hypothesis is presently largely recognized since numerous studies demonstrated that these A β oligomers induce early synaptotoxicity and damages to neuronal networks, leading to memory impairment (Gong *et al.*, 2003; Lacor *et al.*, 2007; Shankar *et al.*, 2008). Despite numerous works, the relationship between tau and A β peptide oligomers is still poorly known. Several studies established that the pathological effects induced by the A β peptide oligomers required the presence of intact tau (Vossel *et al.*, 2010; Mairet-Coello *et al.*, 2013). Although it is still a subject of debate, A β peptide oligomers appear as the earliest and more specific AD agents since tau alterations are observed in many other neurodegenerative diseases (Lebouvier *et al.*, 2017).

One of the main question emerging from the tremendous numbers works on AD and A β peptide oligomers is the root cause of intracerebral accumulation of these oligomers in AD since there is no clear evidence of A β peptide overproduction in sporadic AD cases (> 99% of the AD cases) on the contrary to the genetic cases < 1% of the cases). Dysregulations of neuro-inflammatory processes could at least contribute to this accumulation. The importance of neuroinflammation in AD is supported by the findings of associations between AD and genes coding for immune receptors, such as TREM2 (Guerreiro *et al.*, 2013) and CD33 (Griciuc *et al.*, 2013). Microglial cells, which are major actors in neuroinflammation with astrocytes, recognize A β peptide oligomers through the binding to the cell-surface toll like receptors (Walter *et al.*, 2007; Liu *et al.*, 2012). Stewart *et al.* described that TLR-4 and -6 form heterodimers able to bind A β peptide as well as oxidized LDL and associate with CD36 to generate cytokine production and inflammation (Stewart *et al.*, 2010). Why microglial or astroglial cells are unable to eliminate A β peptide and impede accumulation of A β oligomers and plaque formations is still unknown. Whether neuroinflammation is just reactive to the presence of undesirable A β peptide oligomers or whether an active contributor to AD pathological processes is also an opened question. But many recent data highlighted neuroinflammation as an important actor and a therapeutic target against AD (Ardura-Fabregat *et al.*, 2017).

4 Arachidonic acid in brain functions and Alzheimer's disease: an essential lipid or a pathological agent?

ARA is usually considered as an essential fatty acid especially for brain development in association with DHA. To date, few studies provided some evidenced to support this

hypothesis. Since ARA and its precursor LNA are very abundant in human food and maternal milk, no drastic deficiency has been described on the contrary to DHA, which is 10–20-fold less abundant. Some studies in humans or in primates indicated that blood ARA levels are not influenced by diet on the contrary to DHA in humans (Ghebremeskel *et al.*, 2000; Diau *et al.*, 2005; Lauritzen *et al.*, 2015) and suggested that DHA/ARA ratio is strictly maintained (Ghebremeskel *et al.*, 2000). However, a slower growth has been observed in case of low ARA levels (Ghebremeskel *et al.*, 2000). Several studies performed on rodents indicated that maternal ARA supplementation could compensate the alterations of cognitive abilities in pups induced by maternal metabolic diseases such as streptozotocin-induced diabetes (Zhao *et al.*, 2011) and diet/APO-E*3 leiden genotype-induced obesity (Arnoldussen *et al.*, 2016). A decrease of obesity was observed in the APO-E*3 leiden adult mice with a combination of ARA and DHA supplementation but not with DHA alone (Wielinga *et al.*, 2012). Studies on $\Delta 6$ desaturase knockout mice showed that supplementation with both DHA and ARA are necessary to compensate the PUFAs deficiencies in brain and the effects on motor activity and coordination during development (Hatanaka *et al.*, 2016; Harauma *et al.*, 2017). But, long-term administration of ARA in adult mice maintained under ω -3 deficient diet increases the severity of motor coordination alterations indicating that preservation of adequate DHA intake are necessary in any case (Harauma *et al.*, 2015). It is important to emphasize that sex should be considered for these studies about dietary lipid intake and brain functions since brain lipid composition and diet influence differ in male and female mice (Rodriguez-Navas *et al.*, 2016).

Higher dietary ARA intakes or ARA diet supplementation counteract the reduction of cognition and synaptic activity which are observed in healthy aged rodents (McGahon *et al.*, 1997; McGahon *et al.*, 1998; Kotani *et al.*, 2003; Okaichi *et al.*, 2005). An ARA positive effect has also been reported on neurogenesis in rodent hippocampus (Tokuda *et al.*, 2014) but it is difficult to transpose these data in humans whose neurogenesis is weak especially during aging. On the contrary, we observed a negative influence of dietary ARA in a murine AD model. We previously showed that A β oligomers activate, in neuronal cells, cytosolic phospholipase A₂ (cPLA₂) which specifically releases ARA from membrane phospholipids (Kriem *et al.*, 2005). We then showed that cognitive abilities and expression of the synaptic proteins PSD95 and SNAP25 are preserved in cPLA₂^{-/-} mice after an intracerebroventricular injection (ICV) of A β oligomers while they are drastically altered in wild-type mice after this treatment (Desbène *et al.*, 2012). By breeding cPLA₂^{-/-} mice and transgenic AD model mice overproducing A β peptide, Sanchez-Mejia *et al.* (2008) also showed that the reduction of cPLA₂ reduce the neurotoxicity of A β peptides. Since cPLA₂ specifically hydrolyze ARA containing phospholipids, we assumed that higher dietary ARA intakes could lead to higher ARA brain incorporation and favor its release by A β peptide oligomer-activated cPLA₂. Therefore, we studied the effects of a single ICV of A β peptide oligomers in mice fed with a 1% ARA containing diet for 12 weeks (Thomas *et al.*, 2017). We also used a control diet in which oleic acid replaced ARA (see Fig. 2 for the experimental layout of this study). Both ARA-rich and control diets contained adequate amounts

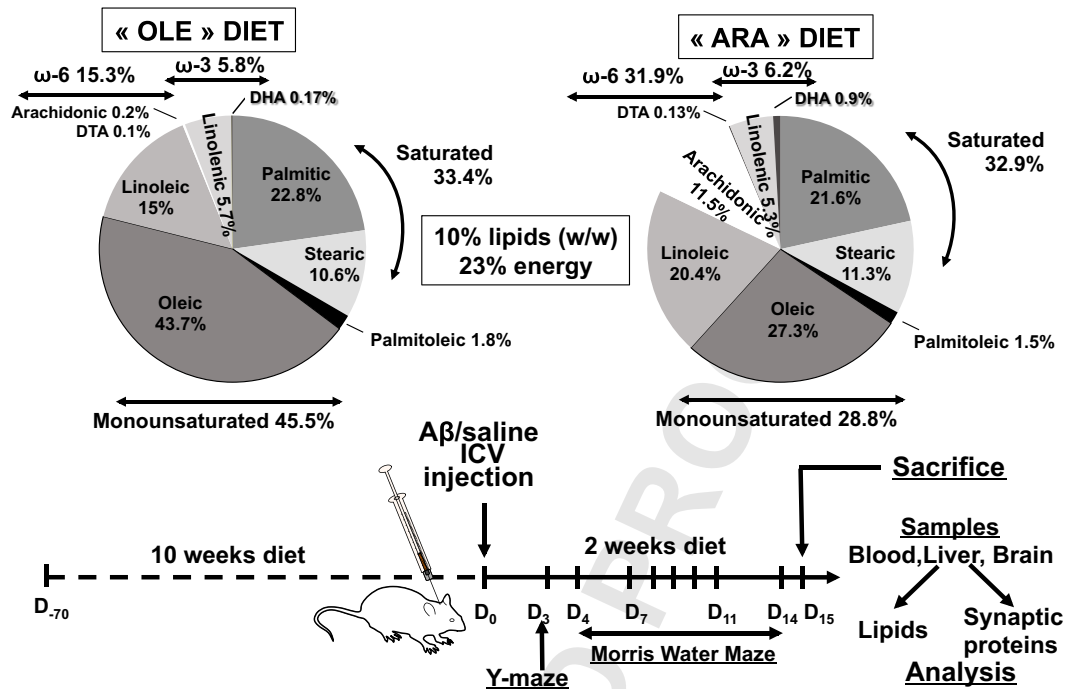


Fig. 2. Experimental layout of [Thomas *et al.* \(2017\)](#) study. In this study, two groups of mice were fed for 12 weeks either with an oleic acid rich diet (control OLE diet) or an ARA-rich diet (ARA diet). The two diets contained similar amounts of saturated and ω-3 fatty acids. In the OLE diet, oleic acid replaces the excess of ω-6 fatty acids (mainly ARA). At week 10, the two groups of mice were submitted to intracerebroventricular injections of Aβ(1-42) peptide oligomers or saline solution (control). Cognitive abilities were measured by using the Y-maze (short term memory) and the Morris Water maze (long term memory) tests. Mice were sacrificed at the end of week 12 and blood, liver and brain samples were collected for protein (synaptic proteins in brain) and lipid analyses.

of **ARA** and linolenic acid for murine needs. We observed a drastic reduction of learning abilities, reduction of AMPA receptor expression levels and increase of the astrocytic marker GFAP expression after Aβ peptide oligomer ICV in mice fed with the ARA-rich diet compared to the control group. These negative effects of dietary ARA are consistent with those of [Amtul *et al.* \(2012\)](#) who reported that a 2% ARA containing diets increased of Aβ₁₋₄₂ production and deposition in transgenic AD-model CRND8 mice after 21 weeks. By contrast, [Hosono *et al.* \(2015a, 2015b\)](#) described an improvement of cognitive alterations and a reduction of amyloid plaques by supplementation with ARA in 17-month-old Tg2576 mice. The authors did not observe the same positive results with DHA supplementation. But in this transgenic AD-model, the Aβ peptide overproduction due to mutant human APP overexpression leads to massive amyloid deposition and drastic alterations of cognitive abilities before the age of 12 months. In the early step of sporadic AD, there is no evidence of Aβ peptide overproduction and memory alterations are not caused by amyloid plaque formation but to the synaptotoxicity of Aβ oligomers. Our single Aβ oligomer ICV model is supposed to reproduce this early synaptotoxicity ([Youssef *et al.*, 2008](#)). The two groups ([Hosono *et al.*, 2015a, 2015b](#); [Amtul *et al.*, 2012](#)) who studied the effects of dietary ARA did not show any result about the modification of brain lipids and/or ARA brain incorporation. In our study, we measure reproducible but small increase of ARA levels in ARA diet-fed mice. This minor increase compared to the large modifications that we observed in blood and liver, do not

support the existence of a drastic release of free ARA in brain and its direct influence on brain inflammation or synaptic functions. Dietary ARA could increase the brain sensitivity to Aβ oligomer toxicity through the transmission of inflammatory signals from the peripheral compartment to brain (see [Tab. 2](#) for the comparison of the studies on the role of dietary ARA).

5 Dietary arachidonic acid: an actor of chronic sub-inflammation from gut to brain?

The role of acute or chronic systemic inflammation in the AD progression emerged quite recently in literature and was initially focused on the circulation of pro-inflammatory cytokines ([Holmes *et al.*, 2009](#)). The usually admitted dogma that increased ARA levels increase eicosanoid production was supported by some works ([Whelan *et al.*, 1993](#); [Whelan *et al.*, 1997](#)) but this eicosanoid production is not automatically associated to cytokine secretion ([Kelley *et al.*, 1997](#)). Dietary ARA has been mainly involved in two chronic pathologies in which inflammation plays a critical role: bowel disease and obesity. Conversion of arachidonic acid into pro-inflammatory leukotriene was early recognized as a key event in Bowel disease ([Nielsen *et al.*, 1987](#)). But more recent works indicated that dietary ARA is rather protective against colitis progression ([Ramakers *et al.*, 2008](#); [Knoch *et al.*, 2010](#)). ARA might favour obesity by acting on the differentiation of brite adipocytes which are energy-dissipating cells ([Pisani *et al.*, 2014](#)). In addition, ARA impairs hypothalamic leptin signal, thus

Table 2. Experimental features and main data of the previous studies on the role of arachidonic acid in AD. We previously showed the mice in which the expression of the main ARA releasing enzyme cPLA₂ has been suppressed, are resistant to the neurotoxicity of the A β peptide oligomers. By contrast, an ARA-rich diet increase the sensitivity of the mice to the neurotoxicity of the A β peptide oligomers. Two other teams studied the role of dietary ARA and reported conflicting results.

Sources	Main experimental features	Main experimental data
Desbène <i>et al.</i> , 2012	cPLA ₂ ^{-/-} mice	→ cognitive abilities in cPLA ₂ ^{-/-} mice
Thomas <i>et al.</i> , 2017	ICV injection of A β peptides Balb/c mice 1% ARA diet for 12 weeks	→ PSD95 and SNP25 in cPLA ₂ ^{-/-} mice ↘ Learning abilities ↘ AMPA Receptors
Amtul <i>et al.</i> , 2012	ICV injection of A β peptides CRND8 mice 2% ARA diet for 21 weeks	↗ GFAP ↗ A β ₁₋₄₂ production and deposition
Hosono <i>et al.</i> , 2015a, 2015b	Tg2576 mice ARA Supplementation of the diet 4%	↘ Cognitive alteration ↘ Amyloid plaques

395 promoting obesity (Cheng *et al.*, 2015). However, there is still
396 a debate about the ARA influence on obesity-associated
397 inflammation (Suitor *et al.*, 2017). The role of intestinal
398 microbiota should be considered to reconcile the various data
399 on dietary ARA effects on systemic chronic sub-inflammation
400 in obesity, Bowel disease or chronic pathologies pro-
401 inflammatory. For example, Zhuang *et al.* (2017) recently
402 showed that dietary ARA favour obesity and by acting on the
403 hypothalamus-liver-adipocytes axis but the effect is modulated
404 by sex and intestinal microbiota, female mice being less
405 pejoratively affected. This result should be related to the
406 current work on the relationship between the gut microbiota
407 and Alzheimer's disease (for review see Jiang *et al.*, 2017).
408 Therefore, the role of gut microbiota, gut-brain communi-
409 cations, systemic inflammation and its transmission to brain
410 through the blood-brain barrier should be further investigated
411 to design preventive strategies against AD (Fig. 3).

412 5 Conclusion

413 AD prevention is a critical challenge to stop the increasing
414 AD prevalence worldwide. Nutrition is one of the main tools in
415 preventive strategies, but risk factor must be more precisely
416 characterized. On this point of view, ARA contribution to
417 western diet and AD risk should be more extensively studied.
418 Several preclinical works including ours suggest that ARA
419 could favour AD occurrence and progression although other
420 studies indicated that ARA could play a positive role in
421 physiological aging. Additional studies are required on the
422 various mechanisms induced by high dietary intakes including
423 modulation of inflammation, modification of the gut micro-
424 biota, influence on the gut-blood and blood-brain barriers. It
425 is noticeable that a correlation between ARA and cholesterol
426 consumption and higher risk of occurrence of Parkinson's
427 disease has been reported in the japan population (Miyake
428 *et al.*, 2010) which suggest that dietary ARA could be a target
429 in preventive strategies against other neurodegenerative
430 diseases.

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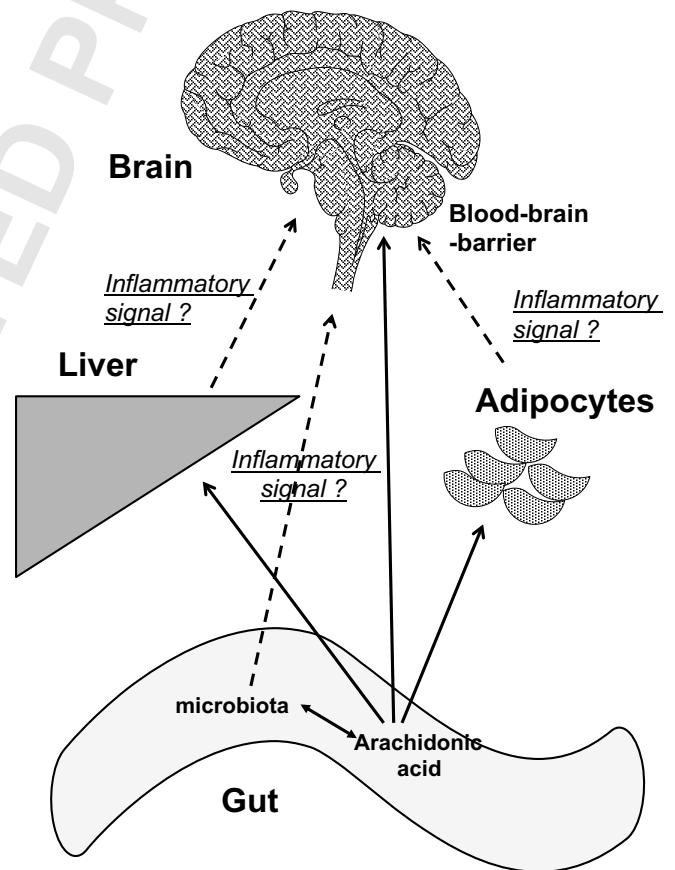


Fig. 3. Putative roles of gut-brain communications, gut microbiota and systemic inflammation in the dietary arachidonic acid effects on the sensitivity to the A β peptide oligomer neurotoxicity. ARA has an impact directly or indirectly on the brain. An ARA-rich diet can modify the composition of intestinal microbiota to induce inflammatory mediators and thus, have effects on the A β peptide oligomer neurotoxicity. Indeed, arachidonic acid can affect the brain by going liver, adipocytes and inflammatory mediators.

434 *Conflicts of interest.* The authors declare that they have no
435 conflicts of interest in relation to this article.

References

- Adam O, Tesche A, Wolfram G. 2008. Impact of linoleic acid intake on arachidonic acid formation and eicosanoid biosynthesis in humans. *Prostaglandins Leukot Essent Fatty Acids* 79: 177–181.
- Amtul Z, Uhrig M, Wang L, Rozmahel RF, Beyreuther K. 2012. Detrimental effects of arachidonic acid and its metabolites in cellular and mouse models of Alzheimer's disease: structural insight. *Neurobiol Aging* 33: 831.e21–831.e31.
- Ardura-Fabregat A, Boddeke EWGM, Boza-Serrano A, *et al.* 2017. Targeting neuroinflammation to treat Alzheimer's disease. *CNS Drugs* 31: 1057–1082.
- Arnoldussen IA, Zerbi V, Wiesmann M, *et al.* 2016. Early intake of long-chain polyunsaturated fatty acids preserves brain structure and function in diet-induced obesity. *J Nutr Biochem* 30: 177–188.
- Berrios GE. 1990. Alzheimer's disease: a conceptual history. *Int J Geriatr Psychiatry* 5: 355–365.
- Cheng L, Yu Y, Zhang Q, Szabo A, Wang H, Huang XF. 2015. Arachidonic acid impairs hypothalamic leptin signaling and hepatic energy homeostasis in mice. *Mol Cell Endocrinol* 412: 12–18.
- Chong FP, Ng KY, Koh RY, Chye SM. 2018. Tau proteins and tauopathies in Alzheimer's disease. *Cell Mol Neurobiol*, in press.
- Desbène C, Malaplate-Armand C, Youssef I, *et al.* 2012. Critical role of cPLA2 in A β oligomer-induced neurodegeneration and memory deficit. *Neurobiol Aging* 33: 1123.e17–1123.e29.
- Diau GY, Hsieh AT, Sarkadi-Nagy EA, Wijendran V, Nathanielsz PW, Brenna JT. 2005. The influence of long chain polyunsaturated fatty acid supplementation on docosahexaenoic acid and arachidonic acid in baboon neonate central nervous system. *BMC Med* 3: 11.
- European Food Safety Authority. 2009. Scientific opinion: labelling reference intake values for n-3 and n-6 polyunsaturated fatty acids. *EFSA J* 1176: 1–11.
- FAO/WHO. 2008. Interim summary of conclusions and dietary recommendations on total fat & fatty acids, in expert consultation on fats and fatty acids in human. Geneva, pp. 10–14.
- Ghebremeskel K, Crawford MA, Lowy C, *et al.* 2000. Arachidonic and docosahexaenoic acids are strongly associated in maternal and neonatal blood. *Eur J Clin Nutr* 54: 50–56.
- Gong CX, Lidsky T, Wegiel J, Zuck L, Grundke-Iqbal I, Iqbal K. 2000. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain. Implications for neurofibrillary degeneration in Alzheimer's disease. *J Biol Chem* 275: 5535–5544.
- Gong Y, Chang L, Viola KL, *et al.* 2003. Alzheimer's disease-affected brain: presence of oligomeric A beta ligands (ADDLs) suggests a molecular basis for reversible memory loss. *Proc Natl Acad Sci U S A* 100: 10417–10422.
- Grieciu A, Serrano-Pozo A, Parrado AR, *et al.* 2013. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* 78: 631–643.
- Guerreiro R, Wojtas A, Bras J, *et al.* 2013. TREM2 variants in Alzheimer's disease. *N Engl J Med* 368: 117–127.
- Harauma A, Tomita M, Muto D, Moriguchi T. 2015. Effect of long-term administration of arachidonic acid on n-3 fatty acid deficient mice. *Prostaglandins Leukot Essent Fatty Acids* 95: 41–45.
- Harauma A, Yasuda H, Hatanaka E, Nakamura MT, Salem N Jr, Moriguchi T. 2017. The essentiality of arachidonic acid in addition to docosahexaenoic acid for brain growth and function. *Prostaglandins Leukot Essent Fatty Acids* 116: 9–18.
- Hatanaka E, Harauma A, Yasuda H, *et al.* 2016. Essentiality of arachidonic acid intake in murine early development. *Prostaglandins Leukot Essent Fatty Acids* 108: 51–57.
- Holmes C, Cunningham C, Zotova E, *et al.* 2009. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 73: 768–774.
- Hosono T, Mouri A, Nishitsuji K, *et al.* 2015a. Arachidonic or docosahexaenoic acid diet prevents memory impairment in Tg2576 Mice. *J Alzheimers Dis* 48: 149–162.
- Hosono T, Nishitsuji K, Nakamura T, *et al.* 2015b. Arachidonic acid diet attenuates brain A β deposition in Tg2576 mice. *Brain Res* 1613: 92–99.
- INCA 2. Étude Individuelle Nationale sur les Consommations Alimentaires. 2006–2007.
- Iqbal K, Alonso AC, Gong CX, Khatoon S, Singh TJ, Grundke-Iqbal I. 1994. Mechanism of neurofibrillary degeneration in Alzheimer's disease. *Mol Neurobiol* 9: 119–123.
- Jiang C, Li G, Huang P, Liu Z, Zhao B. 2017. The Gut Microbiota and Alzheimer's Disease. *J Alzheimers Dis* 58: 1–15.
- Jonnalagadda SS, Egan SK, Heimbach JT, Harris SS, Kris-Etherton PM. 1995. Fatty acid consumption patterns of Americans: 1987–1988 SDA Nationwide Food Consumption Survey. *Nutr Res* 15: 1767–1781.
- Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Mackey BE, Kyle D. 1997. Effects of dietary arachidonic acid on human immune response. *Lipids* 32: 449–456.
- Kiyohara R, Yamaguchi S, Rikimaru K, Takahashi H. 2011. Supplemental arachidonic acid-enriched oil improves the taste of thigh meat of Hinai-jidori chickens. *Poult Sci* 90: 1817–1822.
- Knoch B, Barnett MP, McNabb WC, *et al.* 2010. Dietary arachidonic acid-mediated effects on colon inflammation using transcriptome analysis. *Mol Nutr Food Res* 54(Suppl. 1): S62–S74.
- Kotani S, Nakazawa H, Tokimasa T, *et al.* 2003. Synaptic plasticity preserved with arachidonic acid diet in aged rats. *Neurosci Res* 46: 453–461.
- Kriem B, Sponne I, Fifre A, *et al.* 2005. Cytosolic phospholipase A₂ mediates neuronal apoptosis induced by soluble oligomers of the amyloid-beta peptide. *FASEB J* 19: 85–87.
- Kuriki K, Nagaa T, Imaeda N, *et al.* 2002. Discrepancies in dietary intakes and plasma concentrations of fatty acids according to age among Japanese female dietitians. *Eur J Clin Nutr* 56: 524–531.
- Lacor PN, Buniel MC, Furlow PW, *et al.* 2007. Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. *J Neurosci* 27: 796–807.
- Lauritzen L, Fewtrell M, Agostoni C. 2015. Dietary arachidonic acid in perinatal nutrition: a commentary. *Pediatr Res* 77: 263–269.
- Lebouvier T, Pasquier F, Buée L. 2017. Update on tauopathies. *Curr Opin Neurol* 30: 589–598.
- Li D, Ng A, Mann NJ, Sinclair AJ. 1998. Contribution of meat fat to dietary arachidonic acid. *Lipids* 33: 437–440.
- Liu S, Liu Y, Hao W, *et al.* 2012. TLR2 is a primary receptor for Alzheimer's amyloid β peptide to trigger neuroinflammatory activation. *J Immunol* 188: 1098–1107.
- Lue L, Kuo YM, Roher AE, *et al.* 1999. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. *Am J Pathol* 155: 853–862.
- Mairet-Coello G, Courchet J, Pieraut S, *et al.* 2013. The CAMKK2-AMPK kinase pathway mediates the synaptotoxic effects of A β oligomers through Tau phosphorylation. *Neuron* 78: 94–108.
- Mann NJ, Johnson LG, Warrick GE, Sinclair AJ. 1995. The arachidonic acid content of the Australian diet is lower than previously estimated. *J Nutr* 125: 2528–2535.

- 561 McGahon B, Clements MP, Lynch MA. 1997. The ability of aged rats
562 to sustain long-term potentiation is restored when the age-related
563 decrease in membrane arachidonic acid concentration is reversed.
564 *Neuroscience* 81: 9–16.
- 565 McGahon B, Murray CA, Clements MP, Lynch MA. 1998. Analysis
566 of the effect of membrane arachidonic acid concentration on
567 modulation of glutamate release by interleukin-1: an age-related
568 study. *Exp Gerontol* 33: 343–354.
- 569 Miyake Y, Sasaki S, Tanaka K, *et al.* 2010. Dietary fat intake and risk
570 of Parkinson's disease: a case-control study in Japan. *J Neurol Sci*
571 288: 117–122.
- 572 Nielsen OH, Ahnfelt-Rønne I, Elmgreen J. 1987. Abnormal
573 metabolism of arachidonic acid in chronic inflammatory bowel
574 disease: enhanced release of leucotriene B₄ from activated
575 neutrophils. *Gut* 28: 181–185.
- 576 Nisbet RM, Polanco JC, Ittner LM, Götz J. 2015. Tau aggregation and
577 its interplay with amyloid- β . *Acta Neuropathol* 129: 207–220.
- 578 Nishizaki T, Nomura T, Matsuoka T, Tsujishita Y. 1992. Arachidonic
579 acid as a messenger for the expression of long-term potentiation.
580 *Biochem Biophys Res Commun* 254: 446–449.
- 581 Okaichi Y, Ishikura Y, Akimoto K, *et al.* 2005. Arachidonic acid
582 improves aged rats' spatial cognition. *Physiol Behav* 84: 617–623.
- 583 Pisani DF, Ghandour RA, Beranger GE, *et al.* 2014. The ω 6-fatty
584 acid, arachidonic acid, regulates the conversion of white to brite
585 adipocyte through a prostaglandin/calcium mediated pathway.
586 *Mol Metab* 3: 834–847.
- 587 Ramakers JD, Mensink RP, Verstege MI, te Velde AA, Plat J. 2008.
588 An arachidonic acid-enriched diet does not result in more colonic
589 inflammation as compared with fish oil- or oleic acid-enriched
590 diets in mice with experimental colitis. *Br J Nutr* 100: 347–554.
- 591 Rickman C, Davletov B. 2005. Arachidonic acid allows SNARE
592 complex formation in the presence of Munc18. *Chem Biol* 12:
593 545–553.
- 594 Rodriguez-Navas C, Morselli E, Clegg DJ. 2016. Sexually dimorphic
595 brain fatty acid composition in low and high fat diet-fed mice. *Mol*
596 *Metab* 5: 680–689.
- 597 Sanchez-Mejia RO, Newman JW, Toh S, *et al.* 2008. Phospholipase
598 A₂ reduction ameliorates cognitive deficits in a mouse model of
599 Alzheimer's disease. *Nat Neurosci* 11: 1311–1318.
- 600 Seah JY, Gay GM, Su J, *et al.* 2017. Consumption of red meat, but not
601 cooking oils high in polyunsaturated fat, is associated with higher
602 arachidonic acid status in Singapore Chinese adults. *Nutrients* 9.
603 pii: E101.
- 604 Shankar GM, Li S, Mehta TH, *et al.* 2008. Amyloid-beta protein
605 dimers isolated directly from Alzheimer's brains impair synaptic
606 plasticity and memory. *Nat Med* 14: 837–842.
- 607 Silverman W, Wisniewski HM, Bobinski M, Wegiel J. 1997.
608 Frequency of stages of Alzheimer-related lesions in different
609 age categories. *Neurobiol Aging* 18: 389–392.
- 610 Stewart CR, Stuart LM, Wilkinson K, *et al.* 2010. CD36 ligands
611 promote sterile inflammation through assembly of a toll-like
612 receptor 4 and 6 heterodimer. *Nat Immunol* 11: 155–161.
- 613 Su HM, Corso TN, Nathanielsz PW, Brenna JT. 1999. Linoleic acid
614 kinetics and conversion to arachidonic acid in the pregnant and
615 fetal baboon. *J Lipid Res* 40: 1304–1312.
- Suitor K, Payne GW, Sarr O, *et al.* 2017. Arachidonic acid promote
white adipose tissue inflammation in Fads2^{-/-} mice fed low fat
diets. *Prostaglandins Leukot Essent Fatty Acids* 126: 84–91.
- Taber L, Chiu CH, Whelan J. 1998. Assessment of the arachidonic
acid content in foods commonly consumed in the American diet.
Lipids 33: 1151–1157.
- Takahashi H, Rikimaru K, Kiyohara R, Yamaguchi S. 2012. Effect of
arachidonic acid-enriched oil diet supplementation on the taste of
broiler meat. *Asian-Australas J Anim Sci* 25: 845–851.
- Thomas MH, Paris C, Magnien M, *et al.* 2017. Dietary arachidonic
acid increases deleterious effects of amyloid- β oligomers on
learning abilities and expression of AMPA receptors: putative role
of the ACSL4-cPLA₂ balance. *Alzheimers Res Ther* 9: 69.
- Tokuda H, Kontani M, Kawashima H, Kiso Y, Shibata H, Osumi N.
2014. Differential effect of arachidonic acid and docosahexaenoic
acid on age-related decreases in hippocampal neurogenesis.
Neurosci Res 88: 58–66.
- Tokudome Y, Imaeda N, Ikeda M, Kitagawa I, Fujiwara N, Tokudome
S. 1999. Foods contributing to absolute intake and variance in
intake of fat, fatty acids, and cholesterol in middle-aged Japanese.
J Epidemiol 9: 78–90.
- USDA nutrient intakes from food: mean amounts consumed per
individual, by gender and age. 2012. What we eat in America,
NHANES 2009–2010. USDA, Agricultural Research Service.
- Vassar R, Bennett BD, Babu-Khan S, *et al.* 1999. Beta-secretase
cleavage of Alzheimer's amyloid precursor protein by the
transmembrane aspartic protease BACE. *Science* 286: 735–741.
- Vossel KA, Zhang K, Brodbeck J, *et al.* 2010. Tau reduction prevents
Abeta-induced defects in axonal transport. *Science* 330: 198.
- Walter S, Letiembre M, Liu Y, *et al.* 2007. Role of the toll-like
receptor 4 in neuroinflammation in Alzheimer's disease. *Cell*
Physiol Biochem 20: 947–956.
- Whelan J, Li B, Birdwell C. 1997. Dietary arachidonic acid
increases eicosanoid production in the presence of equal amounts
of dietary eicosapentaenoic acid. *Adv Exp Med Biol* 400B:
897–904.
- Whelan J, Surette ME, Hardardóttir I, *et al.* 1993. Dietary
arachidonate enhances tissue arachidonate levels and eicosanoid
production in Syrian hamsters. *J Nutr* 123: 2174–2185.
- Wielinga PY, Harthoorn LF, Verschuren L, *et al.* 2012. Arachidonic
acid/docosahexaenoic acid-supplemented diet in early life
reduces body weight gain, plasma lipids, and adiposity in
later life in ApoE*3Leiden mice. *Mol Nutr Food Res* 56:
1081–1089.
- Youssef I, Florent-Bécharde S, Malaplate-Armand C, *et al.* 2008. N-
truncated amyloid-beta oligomers induce learning impairment
and neuronal apoptosis. *Neurobiol Aging* 29: 1319–1333.
- Zhao J, Del Bigio MR, Weiler HA. 2011. Maternal arachidonic acid
supplementation improves neurodevelopment in young adult
offspring from rat dams with and without diabetes. *Prostaglan-*
dins Leukot Essent Fatty Acids 84: 63–70.
- Zhuang P, Shou Q, Lu Y, *et al.* 2017. Arachidonic acid sex-
dependently affects obesity through linking gut microbiota-driven
inflammation to hypothalamus-adipose-liver axis. *Biochim Bio-*
phys Acta 1863: 2715–2726.

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