Dietary arachidonic acid: a Janus face actor in brain and Alzheimer’s disease?
Katleen Pinchaud, Katy Maguin-Gaté, Jean-Luc Olivier

To cite this version:
Katleen Pinchaud, Katy Maguin-Gaté, Jean-Luc Olivier. Dietary arachidonic acid: a Janus face actor in brain and Alzheimer’s disease?. OCL Oilseeds and fats crops and lipids, EDP, 2018, 25 (4), pp.D406. 10.1051/ocl/2018033. hal-02452853

HAL Id: hal-02452853
https://hal.univ-lorraine.fr/hal-02452853
Submitted on 23 Jan 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
Dietary arachidonic acid: a Janus face actor in brain and Alzheimer’s disease?

Katleen Pinchaud¹, Katy Maguin-Gaté¹ and Jean-Luc Olivier¹,²,*

¹ Composés Alimentaires, Biofonctionnalités et NeurOTOxicité (CALBINOTOX, EA7488), Université de Lorraine, Faculté des Sciences et Technologies, Boulevard des Aiguillettes, 54506 Vandoeuvre-lès-Nancy, France
² Service de Biochimie-Biologie moléculaire, CHU de Nancy, 24 avenue du Mal de Lattre de Tassigny, CO n° 34, 54018 Nancy, France

Received 2 March 2018 – Accepted 28 May 2018

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 soit nécessaire à leur action. Avec d’autres auteurs, nous avons établi que la phospholipase A2 cytosolique, spécifique d’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 discuté 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

*Correspondence: jean-luc.olivier@univ-lorraine.fr, jl.olivier@chru-nancy.fr

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
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. Neuroinflammation 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 favours 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 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; Marin et al., 1995). Studies on Japanese population reported a narrower but compatible range of values between 100 and 200 mg/day (Takudome 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 content 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 Δ6 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 0.5–2% and 2.5–5% of energy should be provided by ω-3 and...
The amyloid precursor protein (APP) undergoes cleavage by two main enzymes: ß-secretase and γ-secretase (Fig. 1). In AD, hyperphosphorylation of tau protein decreases its affinity for microtubules which drastically alters axonal transportations finally leading to neuronal death. In AD, amyloid plaques are formed by aggregation of amyloid-β (Aβ) peptide and neurofibrillary tangles (NFTs) by aggregation of hyperphosphorylated tau protein. 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 split into two peptides: the Aβ peptide and the C-terminal fragment (CTF). The CTF is further degraded into smaller fragments, including the amyloidogenic peptide. The Aβ peptide is the main component of the amyloid plaques, while the CTF is involved in the formation of NFTs.

Fig. 1. Roles of tau and Aβ oligomers in AD. The tau-dependent pathway is associated to hyperphosphorylation 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.

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

AD was originally defined in 1906 by Aloïs Alzheimer by the presence of two histological pathognomonic signs in brain of affected patients:
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 Aβ peptide and two other N-terminal (sAPPβ)
and C-terminal (AICD) fragments (Vassar et al., 1999). There
are two major forms of Aβ peptide: Aβ1-40, which is the most
abundant form (90%) and Aβ1-42 (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 Aβ oligomers, formed by
the Aβ peptides before their fibrilization and deposition into
plaques, are the initial agent of AD. This hypothesis is
presently largely recognized since numerous studies demonstra-
ted that these Aβ oligomers induce early synaptic toxicity 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 Aβ peptide oligomers is still poorly known.
Several studies established that the pathological effects
induced by the Aβ peptide oligomers required the presence
of intact tau (Vossel et al., 2010; Mairat-Coello et al., 2013).
Although it is still a subject of debate, Aβ 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 Aβ peptide oligomers is the root
cause of intracerebral accumulation of these oligomers in AD
since there is no clear evidence of Aβ 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 Aβ 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 Aβ 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 Aβ peptide
and impede accumulation of Aβ oligomers and plaque
formations is still unknown. Whether neuroinflammation is
just reactive to the presence of undesirable Aβ peptide
oligomers or whether an active contributor to AD pathological
processes is also an opened question. But many recent data
highlight 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
das streptozotocin-induced diabetes (Zhao et al., 2011) and diet
APO-E3 leiden genotype-induced obesity (Arnoldussen et al.,
2016). A decrease of obesity was observed in the APO-E3
leiden adult mice with a combination of ARA and DHA
supplementation but not with DHA alone (Wielinga et al.,
2012). Studies on Δ6 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 (Hata-
aka 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 Aβ 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 intracerebroven-
tricular injection (ICV) of Aβ 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 Aβ peptide,
Sanchez-Mejia et al. (2008) also showed that the reduction
of cPLA2 reduce the neurotoxicity of Aβ 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 Aβ
peptide oligomer-activated cPLA2. Therefore, we studied the
effects of a single ICV of Aβ 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
of ARA and linoleic 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 Aβ_{1-42} 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...
promoting obesity (Cheng et al., 2015). However, there is still a debate about the ARA influence on obesity-associated inflammation (Suitor et al., 2017). The role of intestinal microbiota should be considered to reconcile the various data on dietary ARA effects on systemic chronic sub-inflammatory obesity, Bowel disease or chronic pathologies pro-inflammatory. For example, Zhuang et al. (2017) recently showed that dietary ARA favour obesity and by acting on the hypothalamus-liver-adipocytes axis but the effect is modulated by sex and intestinal microbiota, female mice being less pejoratively affected. This result should be related to the current work on the relationship between the gut microbiota and Alzheimer’s disease (for review see Jiang et al., 2017). Therefore, the role of gut microbiota, gut-brain communications, systemic inflammation and its transmission to brain through the blood-brain barrier should be further investigated to design preventive strategies against AD (Fig. 3).

5 Conclusion

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

Acknowledgements. We thank the France-Alzheimer association and the Region Loraine for their financial support to the works performed by the group and presented in this review.

Conflicts of interest. The authors declare that they have no conflicts of interest in relation to this article.
addition to docosahexaenoic acid for brain growth and function.


Cite this article as: Pinchaud K, Maguin-Gaté K, Olivier J-L. 2018. Dietary arachidonic acid: a Janus face actor in brain and Alzheimer’s disease? OCL, https://doi.org/10.1051/ocl/2018033