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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 polysaturé 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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After a short overview about the AD molecular actors of AD knowledge about the ARA place in the current western diets. However, ARA content in western diets were poorly studied mobilization and conversion into pro-inflammatory processes and regulation of its brain levels and in inflammatory activities and inflammatory mediators. ARA also results from the conversion of its precursor 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 acids. In addition, ARA is converted in various eicosanoid acids. In addition, ARA is converted in various eicosanoid acids.

### 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 acids 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 postnatal 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 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 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 poultry 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

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### Abbreviations

- AD: Alzheimer’s disease
- AICD: Activation-induced cell death
- APP: Amyloid precursor protein
- ARA: Arachidonic acid
- Aβ 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
- PUFA: Polysaturated fatty acids
- SNAP25: Synaptosomal-associated protein 25
- SNARE: Soluble N-εthylmaleimide-sensitive-factorattachment protein receptor
- TLR: Toll-like receptor
- TREM2: Triggering receptor expressed on myeloid cells 2

### 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.

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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.
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:

- 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 activities (Gong et al., 2000) and facilitate the formation of tau helical filaments which finally aggregate into NFTs. In addition, 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 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 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: Aβ40, which is the most abundant form (90%) and Aβ42 (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 fibrillation and deposition into plaques, are the initial agent of AD. This hypothesis is presently largely recognized since numerous studies demonstrated that these Aβ 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 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; Mairet-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 questions 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 highlighted neuroinflammation as an important actor and a therapeutic target against AD (Ardua-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 evidence 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-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 PUFA 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 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 intracerebroventricular 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...
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 replace 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.

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-inflammation in 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.

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