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Topical issue on:

REVIEW



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 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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45 **Abbreviations**

46		
49	AD	Alzheimer's disease
50	AICD	Activation-induced cell death
52	APP	Amyloid precursor protein
54	ARA	Arachidonic acid
50	Aβ peptide	Amyloid-beta peptide
5 8	BACE 1	Beta-secretase 1 precursor
60	CD33	Cluster of differentiation 33
63	CD36	Cluster of differentiation 36
64	cPLA2	Cytosolic phospholipase A2
60	DHA	Docosahexaenoic acid
69	GFAP	Glial fibrillary acidic protein
70	LDL	Low density lipoprotein
73	LNA	Linoleic acid
74	NFT	Neurofibrillary tangles
76	PSD95	Postsynaptic density protein 95
79	PUFAs	Polyunsaturated fatty acids
80	SNAP25	Synaptosomal-associated protein 25
83	SNARE	Soluble N-éthylmaleimide-sensitive-factor at
84		tachment protein receptor
86	TLR	Toll-like receptor
88	TREM2	Triggering receptor expressed on myeloid cells
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1 Introduction

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While the influence of docosahexaenoic acid [DHA] in 91 Alzheimer's disease [AD] or other neurodegenerative diseases 92 focused the interest of scientific and medical communities, few 93 works were devoted to the role of arachidonic acid [ARA] in 94 these diseases. However, ARA is the second polyunsaturated 95 fatty acids [PUFA] and the main member of the ω -6 series in 96 brain, representing approximately 20% of the neuronal fatty 97 98 acids. In addition, ARA is converted in various eicosanoid 99 which are important mediators in the various phases of inflammation, having pro- or anti-inflammatory activities and 100 is involved in synaptic transmission as retrograde messenger 101 (Nishizaki et al., 1992) and regulator of SNARE formation 102 (Rickman and Davletov, 2005). Furthermore, ARA is 103 considered as an essential fatty acid at least in the maturation 104 of brain in the pre- and post-natal periods. 105

It is well admitted that memory alterations are caused by 106 synaptic dysfunctions in the AD early steps. Neuro-inflamma-107 tion contributes to the AD early synaptic dysfunctions and the 108 neuronal death in the late steps of the disease. Therefore, ARA 109 is putatively involved in AD through its role in synaptic signal 110 and in inflammatory process and regulation of its brain levels 111 could be a target in the fight against AD occurrence and 112 progression. Despite its putative role in the maintenance of 113 114 brain functions, excessive dietary ARA intake could lead to 115 higher brain incorporation and favour dysregulation of ARA 116 mobilization and conversion into pro-inflammatory mediators. However, ARA content in western diets were poorly studied 117 118 until now, which makes difficult the evaluation of their impact 119 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 et al., 1995	100 mg/day
Mann et al., 1995	$< 150 \mathrm{mg/day}$
Tokudome et al., 1999	139–168 mg/day
Kuriki et al., 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 ARAassociated mechanisms in AD.

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2 Arachidonic acid in the current western diets

Several studies were performed in the 1990s to evaluate the 129 ARA daily intake in the western diets and its main sources in 130 food. According to these studies, ARA daily intakes are in a 131 wide range from 100 to 200 mg/day (Jonnalagadda et al., 1995; 132 Mann et al., 1995). Studies on Japanese population reported a 133 narrower but compatible range of values between 100 and 134 200 mg/day (Tokudome et al., 1999; Kuriki et al., 2002). This 135 wide range of daily intakes (see Tab. 1 for comparison of the 136 various studies) in western diets could make difficult the 137 determination of ARA contents in currently consumed foods as 138 suggested by some works about the ARA underestimation at 139 least in American diet (Taber et al., 1998). ARA is provided 140 directly from some food components such as red meat. 141 chicken, eggs but also fish (http://appliedresearch.cancer.gov/ 142 diet/foodsources/fattyacids/table4.html, data from the Nation-143 al Health and Nutrition Examination Survey 2005-2006 USA). 144 For example, a recent study established that ARA plasma 145 concentration is associated with the consumption of red meat 146 in the Singapore Chinese population (Seah et al., 2017). 147 Although membrane phospholipids are frequently considered 148 as the main source of ARA, Li et al. (1998) reported that meat 149 fat and triglycerides provide similar or even higher ARA 150 amounts especially in white meat, chicken or pork. The case of 151 chicken or other poultry has to be considered since they are 152 frequently consumed in many countries and higher ARA 153 content in poultry improve the taste of the meat (Kiyohara 154 et al., 2011; Takahashi et al., 2012). Methods of raising and 155 feeding poultries could therefore increase dietary ARA intakes 156 in humans. 157

ARA also results from the conversion of its precursor 158 linoleic acid [LNA], i.e. the elongation by elongases and 159 desaturation by Δ and $\Delta 6$ desaturases. LNA is much more 160 abundant in human food than ARA. The European Food Safety 161 Authority [EFSA]) recommended in 2009 the consumption of 162 2 g/day of α -linolenic acid and 10 g/day of LNA (European 163 Food Safety Authority, 2009) which corresponded to an 164 increase of the previous recommendations for ω -3 and ω -6 165 daily intakes (2 g/day and 6 g/day respectively in 1992). In 166 parallel, the World Health Organization recommended that 167 0.5–2% and 2.5–5% of energy should be provided by ω -3 and 168



Fig. 1. Roles of tau and AB 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 AB peptide-dependent pathway is associated to AB peptide production and toxic oligomer formation which alter synaptic functions. In a final step, AB peptide oligomers aggregate into amyloid plaques

from oligomers which contribute to glial reaction and neuronal death.

 ω -6 PUFAs, respectively (i. e. 1.5–6 g/day and 7.5–15 g/day of 169 170 ω -3 and ω -6 PUFAs, respectively) (FAO/WHO, 2008). In France, the National Individual study on Alimentary Con-171 sumptions [INCA] showed that the French people eat on 172 01 average 9 g/day of LNA (ω -6) and 0.9 g/day of linolenic acid 173 (ω -3) while the US daily average intakes are 18 g and 2 g of 174 175 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 and their data indicated that this conversion poorly contributes 178 to the ARA amounts found in plasma or in liver (Adam et al., 179 2008). On the contrary, the brain ARA requirement of the fetal 180 baboon are met by dietary maternal LNA (Su et al., 1999), 181 which suggest that the brain development period must be 182 considered separately from what happen in adult organism. 183 Additional worldwide studies are needed to provide more 184 precise evaluation of the daily ARA intake, the LNA 185 contribution to the ARA amounts found in peripheral organs 186 as well in brain and the main food sources of ARA. 187

3 Main molecular actors of Alzheimer's 188 disease and contribution of neuro-189 inflammation 190

AD was originally defined in 1906 by Aloïs Alzheimer by 191 the presence of two histological pathognomonic signs in brain 192 193 of affected patients:

neurofibrillary tangles (NFTs);	194
amyloid plaques (Berrios, 1990).	195

- amyloid plaques (Berrios, 1990).

Neurofibrillary tangles are formed by aggregation of hyperphosphorylated tau protein filaments while amyloid plaques result from aggregation of amyloid-B [AB] 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-216 β [A β] peptide. The A β peptide is produced by the 217 amyloidogenic cleavage of the transmembrane amyloid 218 precursor protein [APP] which function is still unknown. In 219 this amyloidogenic way, the N-terminal portion of APP is 220

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cleaved by the major β-secretase BACE1 while the C-terminal 221 222 portion of APP is cleaved by the γ -secretase, both the cleavage 223 releasing the AB peptide and two other N-terminal (sAPPB) and C-terminal (AICD) fragments (Vassar et al., 1999). There 224 225 are two major forms of A β peptide: A β_{1-40} , which is the most abundant form (90%) and $A\beta_{1-42}$ (10%), which is the most 226 toxic form. Since the clinical symptoms are not correlated with 227 the number and size of the amyloid plaques (Lue et al., 1999), 228 many authors concluded in the early 2000s that amyloid 229 230 plaques is not the engine of the pathological process but a late 231 symptoms. They postulated that the A β oligomers, formed by the AB peptides before their fibrillization and deposition into 232 233 plaques, are the initial agent of AD. This hypothesis is presently largely recognized since numerous studies demon-234 strated that these AB oligomers induce early synaptotoxicity 235 and damages to neuronal networks, leading to memory 236 impairment (Gong et al., 2003; Lacor et al., 2007; Shankar 237 238 et al., 2008). Despite numerous works, the relationship between tau and AB peptide oligomers is still poorly known. 239 240 Several studies established that the pathological effects induced by the A β peptide oligomers required the presence 241 of intact tau (Vossel et al., 2010; Mairet-Coello et al., 2013). 242 243 Although it is still a subject of debate, AB peptide oligomers 244 appear as the earliest and more specific AD agents since tau 245 alterations are observed in many other neurodegenerative diseases (Lebouvier et al., 2017). 246

247 One of the main question emerging from the tremendous numbers works on AD and A β peptide oligomers is the root 248 cause of intracerebral accumulation of these oligomers in AD 249 since there is no clear evidence of AB peptide overproduction 250 251 in sporadic AD cases (>99% of the AD cases) on the contrary to the genetic cases < 1% of the cases). Dysregulations of 252 neuro-inflammatory processes could at least contribute to this 253 accumulation. The importance of neuroinflammation in AD is 254 supported by the findings of associations between AD and 255 genes coding for immune receptors, such as TREM2 256 257 (Guerreiro et al., 2013) and CD33 (Griciuc et al., 2013). 258 Microglial cells, which are major actors in neuroinflammation with astrocytes, recognize $A\beta$ peptide oligomers through the 259 binding to the cell-surface toll like receptors (Walter et al., 260 261 2007; Liu et al., 2012). Stewart et al. described that TLR-4 and -6 form heterodimers able to bind AB peptide as well as 262 oxidized LDL and associate with CD36 to generate cytokine 263 264 production and inflammation (Stewart et al., 2010). Why microglial or astroglial cells are unable to eliminate AB peptide 265 and impede accumulation of $A\beta$ oligomers and plaque 266 formations is still unknown. Whether neuroinflammation is 267 just reactive to the presence of undesirable AB peptide 268 269 oligomers or whether an active contributor to AD pathological 270 processes is also an opened question. But many recent data 271 highlighted neuroinflammation as an important actor and a 272 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 279 abundant in human food and maternal milk, no drastic 280 deficiency has been described on the contrary to DHA, which 281 is 10-20-fold less abundant. Some studies in humans or in 282 primates indicated that blood ARA levels are not influenced by 283 diet on the contrary to DHA in humans (Ghebremeskel et al., 284 2000; Diau et al., 2005; Lauritzen et al., 2015) and suggested 285 that DHA/ARA ratio is strictly maintained (Ghebremeskel 286 et al., 2000). However, a slower growth has been observed in 287 case of low ARA levels (Ghebremeskel et al., 2000). Several 288 studies performed on rodents indicated that maternal ARA 289 supplementation could compensate the alterations of cognitive 290 abilities in pups induced by maternal metabolic diseases such 291 as streptozotocin-induced diabetes (Zhao et al., 2011) and diet/ 292 APO-E^{*}3 leiden genotype-induced obesity (Arnoldussen et al., 293 2016). A decrease of obesity was observed in the APO-E^{*}3 294 leiden adult mice with a combination of ARA and DHA 295 supplementation but not with DHA alone (Wielinga et al., 296 2012). Studies on $\Delta 6$ desaturase knockout mice showed that 297 supplementation with both DHA and ARA are necessary to 298 compensate the PUFAs deficiencies in brain and the effects on 299 motor activity and coordination during development (Hata-300 naka et al., 2016; Harauma et al., 2017). But, long-term 301 administration of ARA in adult mice maintained under ω -3 302 deficient diet increases the severity of motor coordination 303 alterations indicating that preservation of adequate DHA 304 intake are necessary in any case (Harauma et al., 2015). It is 305 important to emphasize that sex should be considered for these 306 studies about dietary lipid intake and brain functions since 307 brain lipid composition and diet influence differ in male and 308 female mice (Rodriguez-Navas et al., 2016). 309

Higher dietary ARA intakes or ARA diet supplementation 310 counteract the reduction of cognition and synaptic activity 311 which are observed in healthy aged rodents (McGahon et al., 312 1997; McGahon et al., 1998; Kotani et al., 2003; Okaichi et al., 313 2005). An ARA positive effect has also been reported on 314 neurogenesis in rodent hippocampus (Tokuda et al., 2014) but 315 it is difficult to transpose these data in humans whose 316 neurogenesis is weak especially during aging. On the contrary, 317 we observed a negative influence of dietary ARA in a murine 318 AD model. We previously showed that AB oligomers activate, 319 in neuronal cells, cytosolic phospholipase A_2 (cPLA₂) which 320 specifically releases ARA from membrane phospholipids 321 (Kriem et al., 2005). We then showed that cognitive abilities 322 and expression of the synaptic proteins PSD95 and SNAP25 323 are preserved in $cPLA_2^{-/-}$ mice after an intracerebroven-324 tricular injection (ICV) of AB oligomers while they are 325 drastically altered in wild-type mice after this treatment 326 (Desbène et al., 2012). By breeding cPLA₂⁻ mice and 327 transgenic AD model mice overproducing AB peptide, 328 Sanchez-Mejia et al. (2008) also showed that the reduction 329 of cPLA₂ reduce the neurotoxicity of AB peptides. Since 330 cPLA₂ specifically hydrolyze ARA containing phospholipids, 331 we assumed that higher dietary ARA intakes could lead to 332 higher ARA brain incorporation and favor its release by AB 333 peptide oligomer-activated cPLA₂. Therefore, we studied the 334 effects of a single ICV of $A\beta$ peptide oligomers in mice fed 335 with a 1% ARA containing diet for 12 weeks (Thomas et al., 336 2017). We also used a control diet in which oleic acid replaced 337 ARA (see Fig. 2 for the experimental layout of this study). 338 Both ARA-rich and control diets contained adequate amounts 339



Fig. 2. Experimental layout of Thomas *et al.* (2017) study. In this study, two groups 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 A β (1-42) peptide oligomers or saline solution (control). Congitive abilities were measured by using the Y-maze (short term memory) and the Moorris 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 340 drastic reduction of learning abilities, reduction of AMPA 341 receptor expression levels and increase of the astrocytic 342 marker GFAP expression after AB peptide oligomer ICV in 343 mice fed with the ARA-rich diet compared to the control 344 group. These negative effects of dietary ARA are consistent 345 with those of Amtul et al. (2012) who reported that a 2% ARA 346 containing diets increased of $A\beta_{1-42}$ production and deposition 347 348 in transgenic AD-model CRND8 mice after 21 weeks. By 349 contrast, Hosono et al. (2015a, 2015b) described an 350 improvement of cognitive alterations and a reduction of 351 amyloid plaques by supplementation with ARA in 17-month-352 old Tg2576 mice. The authors did not observe the same 353 positive results with DHA supplementation. But in this transgenic AD-model, the AB peptide overproduction due to 354 mutant human APP overexpression leads to massive amyloid 355 deposition and drastic alterations of cognitive abilities before 356 the age of 12 months. In the early step of sporadic AD, there is 357 no evidence of $A\beta$ peptide overproduction and memory 358 359 alterations are not caused by amyloid plaque formation but to the synaptotoxicity of AB oligomers. Our single AB oligomer 360 ICV model is supposed to reproduce this early synaptoxicity 361 362 (Youssef et al., 2008). The two groups (Hosono et al., 2015a, 2015b; Amtul et al., 2012) who studied the effects of dietary 363 ARA did not show any result about the modification of brain 364 365 lipids and/or ARA brain incorporation. In our study, we measure reproducible but small increase of ARA levels in 366 367 ARA diet-fed mice. This minor increase compared to the large modifications that we observed in blood and liver, do not 368

support the existence of a drastic release of free ARA in brain369and its direct influence on brain inflammation or synaptic370functions. Dietary ARA could increase the brain sensitivity to371 $A\beta$ oligomer toxicity through the transmission of inflammato-372ry signals from the peripheral compartment to brain (see Tab. 2373for the comparison of the studies on the role of dietary ARA).374

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

The role of acute or chronic systemic inflammation in the 377 AD progression emerged quite recently in literature and was 378 initially focused on the circulation of pro-inflammatory 379 cytokines (Holmes et al., 2009) The usually admitted dogma 380 that increased ARA levels increase eicosanoid production was 381 supported by some works (Whelan et al., 1993; Whelan et al., 382 1997) but this eicosanoid production is not automatically 383 associated to cytokine secretion (Kelley *et al.*, 1997). Dietary 384 ARA has been mainly involved in two chronic pathologies in 385 which inflammation plays a critical role: bowel disease and 386 obesity. Conversion of arachidonic acid into pro-inflammatory 387 leukotriene was early recognized as a key event in Bowel 388 disease (Nielsen et al., 1987). But more recent works indicated 389 that dietary ARA is rather protective against colitis progression 390 (Ramakers et al., 2008; Knoch et al., 2010). ARA might favour 391 obesity by acting on the differentiation of brite adipocytes 392 which are energy-dissipating cells (Pisani et al., 2014). In 393 addition, ARA impairs hypothalamic leptin signal, thus 394

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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 $cPLA_2$ 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 et al., 2012	$cPLA_2^{-/-}$ mice	\rightarrow cognitive abilities in cPLA ₂ ^{-/-} mice
	ICV injection of $A\beta$ peptides	\rightarrow PSD95 and SNP25 in cPLA ₂ ^{-/-} mice
Thomas et al., 2017	Balb/c mice	Learning abilities
	1% ARA diet for 12 weeks	AMPA Receptors
	ICV injection of Aβ peptides	∕ GFAP
Amtul et al., 2012	CRND8 mice	$\nearrow A\beta_{1-42}$ production and deposition
	2% ARA diet for 21 weeks	
Hosono et al., 2015a, 2015b	Tg2576 mice	Cognitive alteration
	ARA Supplementation of the diet 4%	Amyloid plaques

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

412 **5 Conclusion**

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

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works performed by the group and presented in this review.



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.

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

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