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Omega-3 polyunsaturated fatty acids and brain health: preclinical evidence for the prevention of neurodegenerative diseases.

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Abstract

Background

As the prevalence of neurodegenerative diseases increases steadily, the need to develop new treatment approaches intensifies and the possibility of targeting risk and protective factors to delay onset of these diseases is attracting more interest. Dietary habits stand as one of the most promising modifiable risk factors for both Alzheimer's (AD) and Parkinson's (PD) diseases.

Scope and approach

Over the last 30 years, several groups have generated data indicating that concentrations of specific brain lipids highly depend on dietary intake. Preclinical results show that treatments with omega-3 polyunsaturated fatty acids (n-3 PUFA) improve cognition, provide neuroprotection (and even neurorestoration), reduce neuroinflammation and influence neuronal function, while high-fat diets exert deleterious effects. Preclinical experiments have been conducted in well-recognized animal models of AD, PD, and ischemic stroke. ~~Beneficial effects on memory were also documented with dietary polyphenols, with possible synergies with omega-3 fatty acids~~.

Key findings and Conclusions

These studies have shown that dietary n-3 PUFA treatments consistently improve cognitive performance in animal models and may also exert disease-modifying actions. N-3 PUFA also provide protection to dopaminergic neurons in animal models of PD and possibly recovery after lesion. Furthermore, some of these effects might depend on specific diet formulations to protect long-chain fatty acids from oxidation or synergies with other nutrients. More generally, this review aims at providing evidence that adjustments in the consumption of dietary lipids alone or combined with other nutrients may be a cost-effective intervention to optimize brain function and prevent AD or PD.

Keywords : omega-3 fatty acids; Alzheimer's disease; Parkinson's disease; cognition; neuroprotection; neuroinflammation; formulation

Introduction

Neurodegenerative diseases (NDD) stand between us and the hope of successful aging. More than 40 million people worldwide are living with Alzheimer's disease (AD) or related dementia, a number expected to double by 2031(Hebert et al., 2013, Lambert et al., 2014). The rise in life expectancy has also increased the prevalence of Parkinson's disease (PD), which now affects more than 10 million people worldwide(Pringsheim et al., 2014). For both diseases, but particularly for AD due to the weaker efficacy of treatment, it is of prime importance for patients, their loved ones and the society as a whole, that we rapidly develop new therapeutic strategies. In the AD field, the majority of preclinical and clinical studies have focused on the two neuropathological markers: amyloid plaques (Aβ peptide) and neurofibrillary tangles (tau)(Gauthier et al., 2016, Katsuno et al., 2012, Scheltens et al., 2016). However, since 2004, despite marked research efforts, no new drug has yet been marketed. The failure of recent AD clinical trials can be attributed in part to the complexity of the disease, but also to the reliance on compounds, such as large biopharmaceuticals, with poor central nervous system (CNS) bioavailability(Katsuno et al., 2012, St-Amour et al., 2014, St-Amour et al., 2016, Yu & Watts, 2013).

An additional challenge to the management of NDD comes from the fact that when the diagnosis is made based on symptoms, the disease has progressed to a phase in which it is difficult to treat, and obviously too late to prevent(Calon, 2011, Cummings et al., 2007, Emery, 2011, Kivipelto & Mangialasche, 2014, Scheltens et al., 2016). Our health systems in the Western world have been built to react to clinical symptoms, when the severity of symptoms has forced patients to consult a health professional. At least for brain diseases, symptomatic treatment is the norm rather than the exception(Cummings et al., 2007, Fox et al., 2011, Herrmann et al., 2013). However, in the case of neurodegenerative diseases, there is a growing understanding that the irreversible nature of their pathophysiology may not fit so well this traditional way of responding to a health problem(Katsuno et al., 2012). Indeed, it is becoming increasingly clear that key events in AD or PD pathogenesis occur many years before symptoms. When symptoms are evident, real therapeutic opportunities may just be long gone.

Including preventive approaches will thus probably imposes itself as an inescapable principle of the medical care of NDD(Hickman et al., 2016, Katsuno et al., 2012, Kivipelto & Mangialasche, 2014, Norton et al., 2014). A valuable strategy for prevention is to identify modifiable risk factors and use this knowledge to act early to reduce the incidence of NDD(Barnes & Yaffe, 2011, Kivipelto & Mangialasche, 2014, Norton et al., 2014, St-Amour et al., 2016). There is hope that modulating environmental factors as early as possible could curb disease progression and extend quality of life before severe symptoms appear(Exalto et al., 2014, Kivipelto & Mangialasche, 2014, Ngandu et al., 2015, St-Amour et al., 2016). To address this issue there is thus a need to develop preventive tools, to intervene much earlier, using secondary or even primary prevention paradigms(Barnes & Yaffe, 2011, Kivipelto & Mangialasche, 2014, Norton et al., 2014, Scheltens et al., 2016, St-Amour et al., 2016). However, patients subjected to preventive treatments show a lower acceptance of adverse effects, higher rate of nocebo affect and, consequently, at risk of poor adherence to treatment(Barsky et al., 2002, Stathis et al., 2013, Zis & Mitsikostas, 2015). Opposition to vaccine offers a vivid example as many people are reluctant to be vaccinated against severe diseases, even despite the well-known benefit/risk balance for individuals and for the whole society(Bean, 2011). Therefore, the development of inexpensive and safe interventions, which can be used on large scale, should continue to receive growing interest from public funding agencies.

Nutrition is often considered as one of the most promising modifiable risk factors for both AD and PD, a contention fully appreciated in ongoing or published multidomain intervention studies(Gillette-Guyonnet et al., 2013, Ngandu et al., 2015, Solomon et al., 2014, Vellas et al., 2014). As a result, many

groups worldwide have been interested in the development of nutraceuticals strategies against these diseases, especially using omega-3 polyunsaturated fatty acids (n-3 PUFA)~~and polyphenols~~.(Calon & Cole, 2007, Calon, 2011, Joffre et al., 2014).

Omega-3 polyunsaturated fatty acids (n-3 PUFA): How do they reach the brain?

In the pharmaceutical world, bioavailability is determinant in the ultimate clinical efficacy of drugs and can, at least in part, be ascertained at the preclinical level. A similar approach can be taken with nutraceuticals. However, CNS diseases offer an additional challenge compared to peripheral diseases: the blood-brain barrier (BBB). The BBB is formed of tightly attached endothelial cells surrounding every microvessel feeding the brain, in close interaction with other brain cells such as pericytes, astrocytes and neurons(Cornford & Hyman, 2005, Daneman & Prat, 2015, Oldendorf et al., 1977, Weiss et al., 2009). The BBB offers protection to cerebral tissue with the consequence that most endogenous and exogenous molecules circulating in the blood cannot reach the central nervous system to exert neuroactivity. In the field of neuropharmacology, cerebral bioavailability remains one of the steepest obstacles to the development of new drugs(Henderson & Piquette-Miller, 2015, Kesselheim et al., 2015).

To exert a rapid effect on the brain, nutrients must also cross the BBB. Evidence suggests that dietary lipids are particularly bioavailable for cerebral tissue. Work largely done between 1970 and 1990 has shown that brain lipid levels are highly dependent on their intake, implying a notable exchange between the periphery and the brain. Seminal work aiming at studying the effect of deficiencies have pointed out alterations in the fatty acid (FA) composition of various subcellular fractions from the brain of rodents(Alling et al., 1974, Bourre et al., 1984, Galli et al., 1971, Sun, 1972). Later studies progressively worked on more specific FA, mostly using vegetable oils, evidencing for instance opposite effects between n-6 PUFA and n-3 PUFA(Bourre et al., 1984, Lamptey & Walker, 1976). Direct respective effects on brain concentrations of dietary long-chain PUFA such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) or arachidonic acid (ARA) have also been shown in rodents or non-human primates(Arsenault et al., 2012a, Calon et al., 2005, Diau et al., 2005, Joffre et al., 2014, Salem et al., 2001, Salem et al., 2015). Other similar diet/brain relations have been shown for other classes of FA such as mono-unsaturated fatty acids (MUFA)(Arsenault et al., 2012b, Greenwood & Winocur, 1996) or trans-fat(Cook, 1978, Phivilay et al., 2009). This sensitivity (or vulnerability) of brain tissue to dietary intake may seem surprising since it implies that a deficiency of a given FA could affect its function. From an evolutionary point of view, it suggests that the first human beings lived in an environment with sufficient supply in n-3 PUFA essential to brain function(Crawford et al., 2001, Cunnane et al., 2007).

How do PUFA enter the brain?

To the eyes of a neuropharmacologist, the chemical structure of FA suggests free diffusion across the BBB(Hamilton & Brunaldi, 2007). A relatively small molecular size, very few potential hydrogen bonds and highly lipophilic moieties are all key characteristic of brain penetrant molecules(Chikhale et al., 1994, Pardridge, 2012). Recent studies in animal models have confirmed the importance of diffusion of plasma non-esterified DHA to supply the brain(Chen et al., 2015) through a non-saturable uptake mechanism across the BBB(Calon, 2011, Ouellet et al., 2009). However, it is also clear that most DHA in the blood is bound to carriers such as albumin and/or in various esterified forms(Chen et al., 2015). An analogy can be made with cholesterol, which also has the physicochemical characteristics of a BBB permeable compound(Cattelotte et al., 2008, Do et al., 2011). Due to the binding of cholesterol to blood-borne carriers and its affinity to efflux transporters, it is well known that no significant direct exchange of cholesterol exists between the blood and the brain(Bjorkhem & Meaney, 2004). Thus, it is important to consider that DHA binding to carriers like lysophosphatidylcholine (LPC) or albumin also

148 influences the uptake into brain tissue(Hachem et al., 2016, Lemaitre-Delaunay et al., 1999, Ouellet et
149 al., 2009). In addition, BBB transporters such as FABP5 (fatty acid binding protein 5) or Mfsd2a (Major
150 facilitator superfamily domain-containing protein 2) have been shown to impact cerebral
151 concentrations of DHA(Nguyen et al., 2014, Pan et al., 2015b), perhaps by affecting its uptake through
152 the BBB(Pan et al., 2015a, Pan et al., 2015b). Overall, the current data suggest that, while plasma non-
153 esterified FA are probably the most readily available form of DHA for the brain, it remains likely that
154 exchanges of PUFA between the blood and the brain might be regulated by (lipo)proteins either located
155 in the BBB or circulating in the blood.

156 One of these potential regulators is apolipoprotein E, which exists in 3 polymorphic alleles in humans.
157 The carriage of ApoE4 has been shown to reduce the uptake of DHA in the CNS based on studies in
158 animal models(Vandal et al., 2014) or human CSF data(Yassine et al., 2016b). One the other hand, a
159 slightly higher brain DHA uptake coefficient was recently reported in a small group APOE4 carriers of
160 various age(Yassine et al., 2017), suggesting a complex interaction between APOE carriage and DHA
161 distribution and metabolism. In addition, reduced uptake of DHA has been reported in mice previously
162 exposed for months to a high-DHA diet(Ouellet et al., 2009) and in a mouse model of AD(Calon, 2011),
163 further supporting the existence of mechanism controlling the influx of PUFA at the BBB.

164

165 **Omega-3 fatty acids and Alzheimer's disease : Cognition**

166 The association between AD and cognition has been mostly investigated by correlative epidemiological
167 studies, which overall suggest that a high consumption in food rich in n-3 PUFA is associated with better
168 performance and possibly the prevention of age-related cognitive impairment or AD. Most longitudinal
169 or case-control studies show an association between n-3 PUFA consumption or blood levels with lower
170 risks of dementia or AD (reviewed in(Barberger-Gateau et al., 2011, Morris, 2016, Yassine et al., 2016a).
171 Recently, higher serum concentrations of long-chain n-3 PUFA have been associated with better
172 performance on neuropsychological tests, as reported in a cross-sectional study in a Finnish
173 cohort(D'Ascoli et al., 2016). Other recent results, presented at the Alzheimer's Association
174 International Conference in Toronto, indicate that blood DHA levels are significantly associated with
175 superior cognitive ability in two large population-based studies, totaling more than 5000 individuals(van
176 Duijn et al., 2016).

177 Results from clinical intervention studies with n-3 PUFA suggest no significant effect after the clinical
178 diagnosis of AD, but still confer limited support to a potential preventive effect(Joffre et al., 2014, Quinn
179 et al., 2010, Salem et al., 2015, Yurko-Mauro et al., 2015a). Indeed, larger randomized controlled trials in
180 individuals with age-related cognitive decline report no change or improvement in memory-related
181 endpoints(reviewed in (Joffre et al., 2014, Quinn et al., 2010, Salem et al., 2015, Yurko-Mauro et al.,
182 2015a). Four small clinical trials in MCI (mild cognitive impairment) reported possible cognitive-
183 enhancing effects (reviewed in (Joffre et al., 2014, Quinn et al., 2010, Salem et al., 2015, Yurko-Mauro et
184 al., 2015a). However, randomized controlled trials with high-DHA formulations in patients diagnosed
185 with AD have been negative(Freund-Levi et al., 2006, Quinn et al., 2010). Recently published data from
186 the MAPT trial (Multidomain Alzheimer Preventive Trial) reported no significant cognitive benefit in old
187 participants who received 800 mg/d of DHA supplementation over 3 years(Andrieu et al., 2017).
188 Nevertheless, an a posteriori analysis highlights a dose-response association between n-3 PUFA plasma
189 levels and preservation of cognitive performance (Eriksdotter et al., 2015). Finally, preclinical studies
190 with controlled diet very consistently show that increasing DHA concentrations in the brain improves
191 rodent performance in a wealth of different memory tests(Catalan et al., 2002, Joffre et al., 2014). This
192 has been confirmed in various animal models of AD-like neuropathology (Tables 1-2)(Arsenault et al.,

2011, Calon et al., 2004, Casali et al., 2015, Hashimoto et al., 2011, Hooijmans et al., 2009, Joffre et al., 2014, Oksman et al., 2006).

Omega-3 fatty acids and Alzheimer's disease : Neuropathology

DHA-induced decreases in amyloid, tau or synaptic neuropathologies have been reported in animal models of AD over the years (Table 1-2)(Arsenault et al., 2011, Arsenault et al., 2011, Calon et al., 2004, Calon et al., 2005, Casali et al., 2015, Green et al., 2007, Hooijmans et al., 2009, Joffre et al., 2014, Lebbadi et al., 2011, Lim et al., 2005, Oksman et al., 2006, Perez et al., 2010, Teng et al., 2015). More specifically, lower brain Aβ levels after a high DHA intake have been reported by at least 4 groups in amyloid protein precursor (APP)transgenic mice(Hooijmans et al., 2009, Lim et al., 2005, Oksman et al., 2006, Perez et al., 2010) and, to a lesser extent, in the tri-transgenic (3xTg-AD) model(Table 1-2)(Arsenault et al., 2011, Green et al., 2007). Other series of evidence suggest that DHA may also act more directly on neuronal function by progressively integrating cell membranes, without necessarily targeting AD neuropathology per se(Arsenault et al., 2011, Arsenault et al., 2012a, Arsenault et al., 2012b, Bruno et al., 2007). A reduction of markers of neuroinflammation has also been observed following n-3 PUFA intake, which could contribute to a therapeutic effect in NDD(Bazinet & Layé, 2014, Hopperton et al., 2016, Lalancette-Hebert et al., 2011, Trépanier et al., 2016b). On the other hand, very ~~few~~ limited evidence in humans support the contention that n-3 PUFA improves AD neuropathology. One small intervention study has reported a decreased loss of gray matter volume after treatment with a DHA/EPA combo(Witte et al., 2013) and Yassine et al (2016) showed significant associations between low serum docosahexaenoic acid (DHA) concentrations with: (i) brain amyloid load (PiB PET), (ii) smaller brain volume (MRI) and (iii) impaired nonverbal memory, in volunteers with no or mild cognitive impairment(Yassine et al., 2016a). Finally, one must keep in mind that most clinicopathological studies do not detect lower levels of DHA in the brain of AD or PD patients, in part due to the difficulty in assessing lipid levels post-mortem(Cunnane et al., 2009, Cunnane et al., 2013, Julien et al., 2006, Tremblay et al., 2011a). Overall, preclinical investigations have provided mechanistic data for a potential disease-modifying effect of n-3 PUFA in the prevention of NDD(Calon & Cole, 2007, Cole & Frautschy, 2010, Joffre et al., 2014, Salem et al., 2015).

Other fatty acids can influence AD pathogenesis

High adherence to a Mediterranean diet consisting of olive oil, nuts, unrefined cereals, fruits and vegetables has been associated with lower risk of cognitive decline using various epidemiological study paradigms(Feart et al., 2009, Panza et al., 2010, Solfrizzi et al., 1999, Solfrizzi et al., 2010). The Mediterranean diet is rich in MUFA, which are known to be reduced in AD cerebro-spinal fluid (CSF)(Fonteh et al., 2014) and to exert direct effects on the physiology of neurons within the entorhinal cortex-hippocampus loop, which is involved in learning and memory(Arsenault et al., 2012b). Oleic acid has been reported to reduce amyloid burden in transgenic APP mice(Amtul et al., 2011) and more recently to be a component of abnormal oil droplets found in 3xTg-AD (triple-transgenic) mice and AD brain(Hamilton et al., 2015). Finally, studies in animal models suggest that a high saturated fat intake, included in 'westernized' diets, contribute to significantly impair memory-related behavior and increase astrogliosis as well as signs of AD neuropathology, such as Aβ burden or, perhaps less consistently, tau phosphorylation(Barron et al., 2013, Gratuze et al., 2016, Ho et al., 2004, Julien et al., 2010, Leboucher et al., 2013, Martin et al., 2014, Refolo et al., 2000).

Omega-3 fatty acids and Parkinson's disease: neuroprotection and neurorestoration

A clear distinction can be made in the clinical care of PD compared to AD because of the availability of very efficient symptomatic treatments for the former NDD. Pharmaceutical or surgical approaches can

at least partially relieve motor symptoms of nigrostriatal dopaminergic denervation in most patients(Fox et al., 2011). However, no treatment yet can alter the progression of the neurodegenerative processes underlying PD(Meissner et al., 2011, Schapira et al., 2014). Neuroprotection, neurorescue, neurorecovery and neurorestoration are all words dear to the heart of PD 'semanticologists'. While the former can be attributed to treatment before the occurrence of nigral cell death, the 3 latter refer to disease-modifying intervention after the diagnosis. The holy grail of PD research is to develop approaches that not only stop neurodegeneration, but also actually reverse it(Meissner et al., 2011, Schapira et al., 2014).

In the last 10 years, we accumulated data in support of the neuroprotective effects of n-3 PUFA dietary intake against toxicity induced by a neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)(Bousquet et al., 2008, Bousquet et al., 2009, Bousquet et al., 2010, Bousquet et al., 2011a, Bousquet et al., 2011b, Bousquet et al., 2012, Calon & Cicchetti, 2008). While MPTP administration induced a 30% neurodegeneration of dopaminergic nigral cells in C57BL/6 mice fed a "control" high n-6 PUFA diet, no signs of cell death along with higher dopamine (DA) concentrations in the striatum were seen in mice fed a high n-3 PUFA diet(Bousquet et al., 2008). We have also noticed that several key dopaminergic markers correlated with DHA concentrations in the brain of MPTP-treated Fat-1 mice(Bousquet et al., 2011b). Increased brain-derived neurotrophic factor (BDNF) secretion may contribute to the beneficial effect of n-3 PUFA against MPTP neurotoxicity(Bousquet et al., 2009). More recently, we have shown that DHA induces a recovery of the dopaminergic system after an extensive lesion in animal models of PD(Coulombe et al., 2016). After 6-hydroxy-dopamine-induced dopaminergic denervation, a high intake in DHA led to (i) higher dopamine levels in the striatum, (ii) more numerous TH-positive dopaminergic terminals to the striatum, and (iii) larger soma perimeter and area of dopamine neurons(Coulombe et al., 2016). Although cell count remained unchanged, such an enhancement of key components of the dopaminergic system suggests that DHA-triggered compensatory mechanisms may contribute to functional recovery(Coulombe et al., 2016). Therefore, these data suggest that DHA induced neurorecovery and could be used after the diagnosis of PD.

Role of n-3 PUFA in neuroinflammatory pathways, a putative protective mechanism in neurodegenerative diseases

A compelling body of evidence has accumulated in the last 10 years linking neurodegenerative diseases with the brain innate immune system(Heneka et al., 2015, Perry et al., 2010, St-Amour et al., 2016, Wes et al., 2016). More attention has been paid to the role of microglia, the main innate immune system cells in the brain, in the etiology of AD. It is now well accepted that these cells are not only involved in protecting the brain against infection or damage(Ransohoff & Perry, 2009), but they also modulate synaptic functions in the healthy brain(Hanisch & Kettenmann, 2007). An intriguing role in synaptic pruning has been recently demonstrated during brain development and at adulthood, shedding light on the role of microglia and the complement system in the phagocytosis of unnecessary synapses and brain wiring(Kettenmann et al., 2013, Tremblay et al., 2011b). This has led to the concept that microglia/complement dysregulation, occurring during aging or a neurodegenerative process, participates to synaptic loss, not only in diseases such as AD or multiple sclerosis(Hong et al., 2016) but also as a consequence to stress(Delpech et al., 2015b) or dietary lipid unbalance(Madore et al., 2016, Nadjar et al., 2016). In addition, aging and neurodegenerative diseases are accompanied by increased production of proinflammatory factors, components of complement pathways and reactive oxygen species (ROS), which have been largely shown in animal models to be involved in neuronal death and neuropathological processes(Ransohoff, 2016, St-Amour et al., 2016). In addition to microglia senescence, microglia priming, a phenomenon linked to insult, aging, psychological or nutritional stress,

is incriminated in the persisting production of proinflammatory factors(Perry & Holmes, 2014). This long-lasting proinflammatory cytokine production in turn activates neuropathological processes of neurodegenerative diseases and promotes cognitive deficit. Recent genetic studies in AD patients have identified variants of genes involved in microglia function as risk factors of AD (TREM-2 [Triggering receptor expressed on myeloid cells 2], CR1[complement receptor 1], CD33, IL-1RAP[Interleukin-1 receptor accessory protein]), leading to the idea that the corresponding proteins could be targeted to treat AD(Colonna & Wang, 2016, Wes et al., 2016). Of note, TREM2 is of particular interest as this receptor binds lipids to control microglia activity and promote phagocytosis of Aβ(Colonna & Wang, 2016, St-Amour et al., 2016). Altogether, these data place microglia as a targetable cell to prevent and/or treat neurodegenerative diseases.

In this context, the immunomodulatory potency of long-chain n-3 PUFA (DHA and EPA) may be put to use in brain disorders that have an inflammatory component, including AD and PD(Bazinet & Layé, 2014, Joffre et al., 2014, Trépanier et al., 2016b). For example, n-3 PUFA anti-inflammatory and proresolving properties may exert a control on microglia activity and associated neuroinflammatory processes(Bazinet & Layé, 2014, Joffre et al., 2014, Layé, 2010). It has been reported that cerebral expression of proinflammatory cytokines in animal models after endotoxin administration(Delpech et al., 2015a, Delpech et al., 2015c), aging(Labrousse et al., 2012), ischemic stroke(Lalancette-Hebert et al., 2011) or increased Aβ(Hopperton et al., 2016) are reduced in rodents with higher levels of brain DHA. This anti-inflammatory effect could be due to a direct action of DHA on microglia as suggested by in vitro and in vivo data (De Smedt-Peyrusse et al., 2008, Madore et al., 2014). However, whether n-3-PUFA supplementation generates a favorable inflammatory marker profile to prevent NDD is still an open question, as it remains unclear which immune-related abnormality is a potential therapeutic target in these diseases(St-Amour et al., 2016, Yates et al., 2014). Mitigated results of fish oil supplementation on peripheral inflammatory markers in AD patients have been reported(Freund-Levi et al., 2014), although DHA levels were negatively correlated to inflammatory markers and phosphorylated tau in the CSF(Freund Levi et al., 2014). Recently, postmortem changes in n-3 PUFA derived pro-resolving mediators (SPM), known to regulate microglia activity(Hopperton et al., 2016, Rey et al., 2016, Trépanier et al., 2016a), have been reported in the brain of AD patients(Wang et al., 2015, Zhu et al., 2016). However, the role of n-3 PUFA in the promotion of a protective microglia phenotype in neurodegenerative diseases remains to be evaluated.

Intake, source and formulation of omega-3 fatty acids: conservation, bioavailability and sustainability

From a public health perspective, compared to synthetic drugs, it is an advantage that long-chain n-3 PUFA can readily be obtained from dietary sources. There is no consensus on the recommended dietary intake of EPA and DHA. The World Health Organization recommends that n-3 PUFA intake should represent 1-2% of energy/day while the European Food Safety Authority recommends 250 mg EPA+DHA/day(Aranceta & Pérez-Rodrigo, 2012, Nishida et al., 2004, Vannice & Rasmussen, 2014). In the US, no clear dietary intake recommendations has been delivered for n-3 PUFA, although in 2002 the Institute of Medicine estimated an adequate intake of 1.6 g or 1.1 g a day of n-3 PUFA (total) for healthy adult men or women, respectively(Trumbo et al., 2002, Vannice & Rasmussen, 2014). Doses of 500 mg or up to 1 g of DHA/EPA per day have been suggested by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and American Heart Association, particularly based on cardiovascular health (improvement of blood lipid profiles or treatment of coronary artery disease)(Harris et al., 2009, Lee, 2013, Meyer, 2011, Vannice & Rasmussen, 2014). However, most evidence suggests that n-3-PUFA

consumption remains lower than abovementioned doses in most countries(Lucas et al., 2010, Meyer, 2011, Papanikolaou et al., 2014, Vannice & Rasmussen, 2014, Yurko-Mauro et al., 2015b).

It is also difficult to determine a minimum effective dose of EPA and DHA, at which PUFAs would exert brain benefits. Background levels of EPA and DHA in clinical trial participants are key confounding variables(Calon, 2011, Jernerén et al., 2015). They can result from differences in nutritional intake of EPA and DHA as well as α-linolenic acid (ALA), an essential fatty acid, which is converted into DHA and EPA at varying degrees among individuals(Barceló-Coblijn & Murphy, 2009, Domenichiello et al., 2015), but also from inter-individual genetic variation in PUFA distribution and metabolism. Most studies in humans are correlative and based on declarative information, evaluated by questionnaire about food habits, or based on blood levels, which do not convey information on the exact dietary intake. Even in animal models, different doses and varying formulations have been utilized and no clear dose-response curves have been established. Therefore, more studies in animals and in humans are necessary to propose a solid recommendation for dietary n-3 PUFA intake as well as to determine a minimum effective dose, particularly when aiming at maintaining brain health.

It is increasingly recognized that marine sources of n-3 PUFA cannot fulfill global human needs in a sustainable manner(Jenkins et al., 2009, Newton & McManus, 2011). One alternative to consider is the use of the metabolic precursor of DHA, ALA, which also increases DHA concentrations in the brain(Barceló-Coblijn & Murphy, 2009, Domenichiello et al., 2015). Various plant seeds contain significant amounts of ALA and represent sustainable sources(Vannice & Rasmussen, 2014). Bioengineered plants could also produce n-3 PUFA-enriched vegetable oils, by improving synthesis of the desired PUFA(Petrie et al., 2012, Qi et al., 2004). Microalgae and biotechnology based on microalgae are also a very promising alternative to produce n-3 PUFA in a sustainable way(Adarme-Vega et al., 2012, Arterburn et al., 2007). As opposed to fish oil, canola and camelina oils extracted from seeds are very versatile because of their stability and heat resistance and are already used extensively in the food industry. Other promising sources include flaxseed/linseed or chia oils, which contains elevated levels of ALA(Vannice & Rasmussen, 2014, Vuksan et al., 2017).

Beside nutritional intake, growing evidence behind the benefits of n-3 PUFA brings a strong incentive to develop formulations to be used as supplements. Some studies suggest that specific types of formulations may provide enhanced bioavailability while others do not(Ghasemifard et al., 2015, Sanguansri et al., 2015, Yurko-Mauro et al., 2015b). Since the expected benefits of LC n-3-PUFA likely require chronic consumption, it is unclear how slight differences in initial bioavailability parameters may have significant effects on long-term health outcomes. Nonetheless, one thing certain is that LC n-3 PUFA are sensitive to oxidation due to the presence of several double bonds in their chemical structures(Arab-Tehrany et al., 2012, Shahidi & Zhong, 2010). Therefore, the use of formulations that effectively preserve n-3 PUFA bioactivity is likely to be critical. In preclinical studies, protecting DHA molecules from oxidation can be achieved by using microencapsulated n-3 PUFA formulations, like those developed by DSM Nutritional Products. Microencapsulated DHA can then be incorporated in a pelleted rodent diets. The microencapsulation process into gelatin beads is intended to allow incorporation of DHA into ordinary food such as milk or bread and has been designed to preserve DHA for months(Hogan et al., 2003, Kolanowski et al., 2004). It is also crucial in n-3 PUFA nutritional supplements for humans to prevent oxidation. Indeed, LC-FA oxidation leads to the apparition of primary lipid hydroperoxides and secondary oxidation products(Albert et al., 2013, Arab-Tehrany et al., 2012, Shahidi & Zhong, 2010). It has been shown in animals that lipid peroxidation could contribute to the pathophysiology of inflammation-associated diseases, including NDD(Grimm et al., 2016, Maruyama et al., 2014, Pamplona et al., 2005, Yakubenko & Byzova, 2016). Formulation excipients can be useful for preservation purposes and phenolic compounds have been widely shown to be efficient to delay oxidation of n-3 PUFA(Crauste et al., 2016, Hasiewicz-Derkacz et al., 2015). However, these

synthetic components have been criticized and the use of natural antioxidants often favored both by consumers and public health authorities. In a very recent study, Guitard et al. (2016), have shown that natural antioxidants such as myricetin, rosmarinic and carnosic acids are more effective to prevent oxidation in n-3 PUFA oils than α-tocopherol (fat-soluble antioxidants that function as scavengers of lipid peroxyl radicals) and synthetic antioxidants(Guitard et al., 2016).

Conclusion

Scientists, health professionals and the lay public increasingly recognize the potential benefit of nutrition in the prevention of CNS-related diseases. A steep rise in reported consumption of n-3 PUFA supplements was recently reported between 1999 and 2012(Kantor et al., 2016). However, since the diagnosis of NDD is made a long time after disease onset, we may wonder if it is not too late to intervene. Manipulating dietary intake of fatty acids could be a relevant strategy to postpone the appearance of the more severe symptoms of NDD. Animal, epidemiology and non-AD clinical data all suggest cognitive benefits of n-3 PUFA, while animal studies may highlight evidence of disease modifications. Clinical evidence however remains limited to possible benefits in prodromal stages. It could also be interesting to combine n-3 PUFA with other nutrients such as polyphenols, which may also have cognitive benefits. Indeed, with the Neurophenols Consortium, our group has just reported the cognitive benefits of polyphenol extracts in the 3xTg-AD animal model of AD, without clear impact on canonical neuropathological markers(Dal-Pan et al., 2017). It will still be difficult to adopt the best omega-3 PUFA supplementation strategy, as we need a better understanding of mechanisms of NDD. That includes pharmacodynamic and pharmacokinetic studies. A more precise knowledge of AD pathogenesis and PUFA metabolism could lead to the constitution of different subgroups of patients more likely to take benefit of omega-3 PUFA supplementation. Furthermore, larger clinical trials on prevention should be made in order to understand the real impact of omega-3 PUFA on neuroprotection in the population. In summary, literature shows that many nutrients (n-3 PUFA, polyphenols, antioxidants…) have a potential benefit in the prevention of diseases and especially those related to the CNS through direct effect on brain function and not necessarily related to classical pathophysiological cascades. As NDD prevalence will continue to rise in the next decades, prevention strategies based on nutrition needs to be thoroughly investigated now, in the hope of defining an optimal diet for the aging brain.

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Table 1: Effects of omega-3 fatty acids on cognition in animal models of Alzheimer's disease

Rodent species and age	Treatment and duration ***Model***	Outcomes	Study
Rats, 20 weeks	DHA 300mg/Kg/day 7 weeks *Aß infused rats*	↓reference memory error	Hashimoto et al. (2005)
Rats, 20 weeks	DHA 300mg/Kg/day 12 weeks *Aß infused rats*	↓reference and working memory errors	Hashimoto et al. (2005)
Mice, 17 months	DHA 0.6 % 103 ± 5 days *Tg2576*	↑spatial memory	Calon et al (2004)
Mice, 8 months and 15 months	DHA 3.5g/Kg diet 6 or 13 months *APP/PS1*	↑spatial memory in 15-month-old mice	Hooijmans et al (2009)
Mice, 6 months	DHA 0.4% 3-4 months *APP/PS1*	↑exploration activity No change in spatial learning in Morris water maze	Oksman et al (2006)
Mice, 12-14 months	DHA 0.6g/Kg/day 8 to 10 months *3xTg-AD*	↑object recognition	Arsenault et al (2011)
Rats, 17-18 months	DHA 0.6% 4 months *APP/PS1*	↑spatial memory	Teng et al (2015)

Aβ, amyloid beta; APP, amyloid protein precursor; DHA, docosahexaenoic acid

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Table 2: Effects of omega-3 fatty acids on neuropathology in animal models of Alzheimer's disease and Parkinson's disease

Rodent species and age	Treatment and duration ***Model***	Brain regions	Outcomes	Study
Alzheimer's disease				
Rats, 20 weeks	DHA 300 mg/Kg/day 7 weeks *Aβ infused rats*	Cx	↓Aβ ↓cholesterol ↓reference memory error	Hashimoto et al. (2005)
Mice, 17 months	DHA 0.6 % 103 ± 5 days *APP/Tg2576*	FrCx, Cx and hemi brain	↑drebrin ↓oxidation ↓caspase-cleaved actin ↑antiapoptotic BAD phosphorylation	Calon et al (2004)
Mice, 8 months and 15 months	DHA 3.5g/Kg diet 6 or 13 months *APP/PS1*	FrCx, Cx, Hip, Acg	No change in rCBV in 8 months old mice ↓Aβ in 15 months old mice ↑rCBV in 15 months old mice	Hooijmans et al (2009)
Mice, 6 months	DHA 0.4% 3-4 months *APP/PS1*	Hip, FrCx, Cx ,Cer	↓Aβ ↓activated microglia	Oksman et al (2006)
Mice, 12-14 months	DHA 0.6g/Kg/day 8 to 10 months *3xTg-AD*	ECx neurons, FrCx, Cx	↑DHA and ↓AA ↓seizure-like akinetic episodes ↑cell capacitance ↓firing rate versus injected current	Arsenault et al (2011)
Mice, 17 and 19 months	DHA 0.6% *APP/Tg2576*	Cx, Hip, parietal Cx	↓Aβ40 and Aβ42 ↓Aβ plaques ↓α- and β-APP C-terminal fragments	Lim et al (2005)
Mice, 3 months	DHA 0% or 0.6% 3 months *APPswe/PS1 Delta E9*	Cx, HipV, Str, Hip, liver	↑DHA and ↓AA ↓Aβ plaques ↑drebrin	Perez et al (2010)
Mice, 3 months	DHA 1.3g/100g diet and DPA n-6 0.5g/100g diet 3, 6 or 9 months *3xTg-AD*	Whole brain	↓intraneuronal Aβ and Tau ↓PS1	Green et al (2007)
Mice, 12 and 20 months	n-6/n-3 = 25 (4.6Kcalories/g diet) *fat-1* transgene Whole life *fat-1 x 3x-TgAD*	Cx, FrCx	↑n-3/n-6 ratio and DHA at 20 months ↓soluble Aβ42 at 20 months ↓soluble and insoluble phosphorylated tau at 20 months ↓CaMKII and GFAP at 20 months	Lebbadi et al (2011)

Mice, 17 months	DHA 0.6% 3-5 months *3xTg-AD*	Cx, Hip	↑NMDA receptor subunit (NR2A and NR2B) ↑CaMKII ↓caspase/calpain activity	Calon et al (2005)
Rats, 17-18 months	DHA 0.6% 4 months *APP/PS1*	Cx, Hip	↓Aβ plaque ↑soluble fibrillar Aβ oligomers	Teng et al (2015)
Parkinson's disease				
Mice, 2 months	DHA/EPA:425/90 mg/kg 10 months *MPTP*	SN, Str	↑TH+ nigral cells ↑Nurr1 mRNA ↑DAT mRNA ↑DA in striatum	Bousquet et al (2008)
Mice, 2 months	DHA/EPA:425/90 mg/kg 10 months *MPTP*	Str	↑BDNF mRNA ↑TrkB mRNA	Bousquet et al (2009)
Mice, 6 months	n-6/n-3 ratio: 101.79 (3.9kcal/g diet) Whole life *MPTP repeated injections in fat 1 mice*	Str	Correlation between DHA levels and : ↑TH+ nigral cells ↑Nurr1 mRNA ↑DAT mRNA	Bousquet et al (2011)
Mice, 9 weeks	DHA 0.5-1.0 g/kg/day Week 3 to week 9 after 6-OHDA lesion *6-OHDA*	SN, Str	↑TH+ terminals in Str ↑perimeter of DAergic neurons in SN ↑areas of DAergic neuron cell bodies in SN ↑DA turnover in Str	Coulombe et al (2016)
Rats	Fish oil 4.0 mg/kg of (DHA/EPA:180/120mg) 21-90 days of life *6-OHDA*	Str	↑DA turnover ↓apomorphine-induced rotational behavior	Delattre et al (2010)
Cynomolgus female monkey	DHA (100mg/kg SC or 200mg/kg PO) before or after the initiation of L-DOPA treatment. *MPTP*	na	↓L-DOPA induced dyskinesias	Samadi et al (2006)

3xTgAD, triple transgenic model of Alzheimer's disease ; 6-OHDA : 6-hydroxydopamine ; Aβ, amyloid beta; Acg, anterior cingulate gyrus; APP, amyloid protein precursor; BDNF, Brain-derived neurotrophic factor ; CaMKII, calcium/calmodulin-dependent protein kinase II; Cer, cerebellum; Cx, cortex; FrCx, frontal cortex; DA, dopamine ; DAT, dopamine transporter ; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; ECx, enthorinal cortex; EPA, eicosopentaenoic acid; Hip, hippocampus; HipV, ventral hippocampus; GFAP, glial fibrillary acidic protein; L-DOPA, levodopa; MPTP, 1-methyl-4-phenyl-

1,2,3,6-tetrahydropyridine ; na, not applicable; NMDA, N-methyl-D-aspartate; PO, *per* os; PS1, presenilin 1; rCBV, relative cerebral blood volume; SC, subcutaneous; SN, substantia nigra ; Str, striatum ; TrkB, tropomyosine receptor kinase B.

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- Increasing brain DHA concentrations improves rodent performance in memory tests.
- Amyloid, tau, synaptic neuropathologies are improved by DHA in the most studies in animal models.
- N-3 PUFAs induce neuroprotection and partial neurorecovery in animal models of PD.
- N-3 PUFAs may act through neuroinflammatory pathways.
- Specific formulations of N-3 PUFAs from different sources can improve conservation and bioavailability.