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N-3 PUFAs and neuroinflammatory processes in cognitive disorders

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Abstract – With the ageing population and increased cases of neurodegenerative diseases, there is a crucial need for the development of new nutritional approaches to prevent and delay the onset of cognitive decline. Neuroinflammatory processes contribute to neuronal damage that underpins neurodegenerative disorders. Growing evidence sheds light on the use of dietary n-3 long chain polyunsaturated fatty acids to improve cognitive performances and reduce the neuroinflammatory responses occurring with age and neurodegenerative pathologies. This review will summarise the most recent information related to the impact and mechanisms underlying the neuroinflammatory processes in cognitive disorders. We will also discuss the mechanisms underlying n-3 polyunsaturated fatty acids effect on neuroinflammation and memory decline.

Keywords: Neuroinflammation / microglia / n-3 polyunsaturated fatty acids / cognitive disorders / Alzheimer disease

Résumé – Acides gras polyinsaturés de la famille des oméga 3, processus neuroinflammatoires et troubles cognitifs. Le développement d'approches nutritionnelles pertinentes pour prévenir et retarder l'apparition du déclin cognitif est un enjeu important, compte tenu du vieillissement de la population et de l'augmentation de l'incidence des maladies neurodégénératives. Les processus neuro-inflammatoires contribuent aux mécanismes neuropathologiques impliqués dans les troubles neurodégénératifs et de la cognition. Des données récentes indiquent l'importance des acides gras polyinsaturés n-3 alimentaires dans le maintien des performances mnésiques et la régulation de la neuroinflammation liée à l'âge ou à la maladie d'Alzheimer. Dans cette revue, seront présentées des données récentes sur les liens existants entre le statut nutritionnel en acides gras polyinsaturés n-3, les processus neuro-inflammatoires et les troubles cognitifs associés, ainsi que les mécanismes qui pourraient être impliqués dans les effets protecteurs de ces acides gras.

Mots clés : Neuroinflammation / microglie / acides gras polyinsaturés n-3 / désordres cognitifs / maladie d'Alzheimer

1 Introduction

It is estimated that 35.6 million people worldwide are living with dementia which is predicted to increase to 65.7 million by 2030 and 115.4 million by 2050. Neuroinflammation is recognised for its overall role in Alzheimer Disease (AD) pathology, including the acceleration of neuronal loss and amyloid beta (Aβ) and Tau mysfolding and deposition (Krabbe *et al.*, 2013; Krstic *et al.*, 2012). The majority of AD drug treatments (cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists) are poorly efficient and do not delay neuronal death. A new potent strategy will be to target neuroinflammatory processes. In this regard, several approaches that directly or indirectly target inflammation are under development (Glass *et al.*, 2010). Recently, much attention has been given to long chain (LC) n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have potent anti-inflammatory activities, thus interesting for the prevention and treatment of neuroinflammation and cognitive disorders in AD.

2 Cognitifs maladie d'Alzheimer Neuroinflammation in neurodegenerative diseases

Proinflammatory cytokines produced by activated innate immune cells in response to tissue injury, infection or

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inflammation act on the brain through several pathways (humoral, neural and cellular) (Dantzer *et al.*, 2008). Activation of immune-to-brain communication ultimately induces the production of brain cytokines by activated glial cells, particularly microglia (Dinel *et al.*, 2014; Laye *et al.*, 1994). Neuroinflammation describes the brain inflammatory response involving not only peripheral immune cells influx in the brain but also the discrete response of brain innate immune cells so called microglia. Microglia respond to non sterile stimuli (pathogens such as virus, bacteria, etc) and get activated producing pro and/or anti-inflammatory factors, in particular cytokines but also lipid derived products such as prostaglandins (PG). The microglia response promotes the clearance of pathogens, toxic cellular debris and apoptotic cells and therefore protects the brain. Indeed, a complete blockade of microglial activity exacerbates brain damage in adult and several ischemic injury models (Lalancette-Hebert *et al.*, 2007). Microglia is also activated in the brain associated to ageing, obesity, and neurodegenerative diseases. The cause of microglia activation in neurodegenerative diseases such as AD is rather linked to neuropathological processes such as Aβ synthesis or senescence of microglia cells and reactive oxygen products (Heneka *et al.*, 2015; Laye, 2010).

The sustained expression of inflammatory factors such as proinflammatory cytokines can lead to neurodegeneration. The production of proinflammatory response in the brain is therefore a double-edged sword representing a fine balance between protective and detrimental effects and therefore needs to be tightly regulated. Microglia phenotypes could be crucial in the protective or detrimental role of microglia response toward neurons. Accordingly, whilst activated M1 cells have cytotoxic properties, M2a are involved in repair and regeneration (Perry *et al.*, 2010). *In vivo*, microglia express proinflammatory cytokines associated with an M1 response (interleukin (IL)-1β, IL-6, IL-12 and tumor necrosis factor (TNF)α) in response to an immune stimulus (Perry *et al.*, 2010), while the anti-inflammatory cytokines IL-10 and IL-4 deactivate the M1 microglial phenotype (Fenn *et al.*, 2012). Microglia senescence, as observed in the ageing brain, impairs microglial cells number, phagocytic activity and increases a production of low-grade proinflammatory cytokines such as IL-1β, IL-6 and TNFα at the expense of anti-inflammatory factors such as IL-10 and IL-4. This state is called inflammaging at the periphery and in the brain. In addition to producing proinflammatory cytokines, senescent microglia also express lipofuscin granules, higher levels of CD86, major histocompatibility complex II (MHC II), toll-like receptors (TLRs) and complement receptor 3 (CD11b) and display a decreased number and complexity of processes as described in activated microglia (Hanisch and Kettenmann, 2007; Tremblay *et al.*, 2011). They also have reduced phagocytic activities of Aβ as demonstrated in aged transgenic mice (Heneka *et al.*, 2010). The mechanisms involved in increased microglia activation in the ageing brain is not fully understood, although the impaired expression of CD200 and CX3CR1, known to be produced by neurons to maintain microglia in the non-activated state in the healthy brain, might be involved (Dilger and Johnson, 2008). In addition, when challenged with either immune stimuli or a stress, aged animals clearly mount an exaggerated neuroinflammatory response, characterized by the overproduction of proinflammatory cytokines (IL-1β, IL-6, TNFα, iNOS) compared to young congeners with a longer duration of activation (Barrientos *et al.*, 2009; Godbout *et al.*, 2005; Sparkman *et al.*, 2005). This phenomenon, first described in a mice model of prion disease is called microglia priming or sensitization (Cunningham *et al.*, 2005). The failure of aged microglia to polarize from a proinflammatory to an anti-inflammatory phenotype supports the detrimental role of primed microglia in neurodegenerative diseases with a self-sustaining and self-amplifying cycle of neurotoxicity. These new knowledge therefore stimulate research aiming at developing drugs targeting the M1 phenotype. Failure to tightly regulate systemic immune activation and/or brain microglial activation leads to significant and prolonged induction of brain cytokines.

Microglia is also activated by insulin resistance developing in the ageing brain. Indeed, brain insulin resistance causes Tau hyper-phosphorylation, increased β amyloid production and plaque-associated microglial-mediated inflammatory responses (De la Monte, 2012). Upregulation of cytosolic phospholipase A2 (cPLA2), which release free fatty acids such as arachidonic acid (AA), has also been reported in neurodegenerative diseases such as AD (Sundaram *et al.*, 2013). AA metabolisation by cycloxygenases (COX) and lipoxygenases (LOX) into PG, leukotrienes, thromboxanes (TX) and lipoxins further triggers the neuroinflammatory response (Ong *et al.*, 2015).

The underlying mechanisms of neuronal degeneration associated with cognitive decline remain elusive, although it is thought that several cellular and molecular events are involved which are sensitive to oxidative stress and chronic neuroinflammation. Indeed, chronic cytokines production has been proposed to participate in cognitive decline through processes related to neuroinflammation, neurodegeneration, structural remodelling and impaired neurotransmission (Capuron and Miller, 2011; Delpech *et al.*, 2015a; Laye, 2010). In particular, the activation of microglia leads to *de novo* production of proinflammatory cytokines (*i.e.* IL-1β, IL-6 and TNFα), chemokines, nitric oxide (NO), eicosanoids (i.e. PGE2) and reactive oxygen species (ROS) (Barrientos *et al.*, 2015; Vauzour, 2012). For example, increased level of IL-1β elevates the production of ROS, which in turn, activates mitogen-activated protein (MAP) kinases such as c-Jun N-terminal kinase (JNK) and p38, resulting in cell damage and cell death therefore impairing the long-term potentiation (LTP) and leading to cognitive decline. In addition, the excessive production of pro-inflammatory cytokines such as TNFα and IL-1β has been reported to result in glutamate cytotoxicity by directly stimulating NMDA receptors while inhibiting gamma-aminobutyric acid (GABA)-A receptors (Barrientos *et al.*, 2015; Olmos and Llado, 2014).

Another mechanism by which cytokines may impair synaptic plasticity (Delpech *et al.*, 2015b) is their capacity to induce the synthesis of indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme degrading tryptophan along the kynurenine pathway, in activated microglia. Although cytokine-induced activation of IDO is usually beneficial to the host (Harrington *et al.*, 2008), sustained brain IDO activation can also be deleterious by negatively impacting the monoaminergic neurotransmission (*e.g.* serotonin, dopamine)

and neuronal survival (Capuron and Miller, 2011; Dantzer *et al.*, 2008). Indeed, increased brain or cerebrospinal fluid concentrations of kynurenine and its neurotoxic metabolites have been reported in several neurodegenerative and psychiatric disorders (Campbell *et al.*, 2014; Capuron *et al.*, 2011) suggesting that IDO activation may lead to both functional and structural alterations in the brain. Consistent with this statement, activation of the kynurenine pathway has been recently reported to affect human neurogenesis in the hippocampal formation (Zunszain *et al.*, 2012), an important brain structure involved in cognitive functions and an important site for IDO production (Andre *et al.*, 2008; Frenois *et al.*, 2007). In addition, pharmacological or genetic inhibition of IDO activity prevents induction of cognitive impairments (reviewed in (Castanon *et al.*, 2014).

Recently, the role of guanosine triphosphate cyclohydrolase I (GTP-CH1) in the cognitive effect of chronic inflammation has also been revealed in elderly (Capuron and Miller, 2011). GTP-CH1 is the rate-limiting enzyme of GTP conversion into 7,8-dihydroneopterin (BH2), which leads to the production of neopterin at the expense of tetrahydrobiopterin (BH4) (Oxenkrug, 2011). BH4 is a cofactor of aromatic amino acid hydroxylase and therefore plays a fundamental role in dopamine synthesis (Neurauter *et al.*, 2008). Cytokines-induced GTP-CH1 activation, classically assessed by measuring increased production of neopterin, is therefore able to impair the dopaminergic neurotransmission which is known to be involved in mood disorders and cognitive dysfunctions, including in conditions of chronic immune stimulation (Capuron *et al.*, 2011).

3 N-3 PUFAs, neuroinflammation and cognitive disorders

As a result of the lack of effectiveness of current treatments for cognitive disorders, a lot of effort has been invested to enhance the search for new therapeutic targets. Based on the results obtained in patients taking anti-inflammatory drugs, a new possibility has been opened studying the association of inflammatory processes and brain pathophysiology. An important strategy to prevent brain impairment is based on dietary changes and nutritional supplements, functional foods and nutraceuticals. In this regard, a substantial amount of recent evidence suggests that many food components and in particular n-3 PUFA, could be good candidates to modulate inflammation both acutely and chronically. LC n-3 PUFA modulate the inflammatory processes by acting at the immune system level through the regulation of inflammatory gene expression, especially cytokines and chemokines, the decrease of inflammatory PG and eicosanoids and the induction of pro-resolutive factors, resolvins and protectins that are involved in the resolution of inflammation (Calder, 2013; Serhan, 2007; Serhan *et al.*, 2007). LC n-3 PUFA anti-inflammatory effects are thought to require their incorporation into plasma membranes of target tissues, however they have short-term effect as they are rapidly metabolized into bioactive products. In particular, EPA, DHA and their bioactive mediators have potent anti-inflammatory and pro-resolving properties in the periphery (Serhan and Chiang, 2013) and in the brain (Bazinet and Laye, 2014; Laye, 2010; Orr and Bazinet, 2008; Rapoport, 2008). Loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can cause irreparable damage to host tissues, including the brain. EPA is a substrate for the COX, LOX and cytochrome P450 enzymes that produce 3-series eicosanoids (PG and TX) and 5-series leucotrienes that are increased in macrophages or neutrophils enriched in EPA and DHA by dietary means (Calder and Grimble, 2002; Yates *et al.*, 2014). In addition, other anti-inflammatory and pro-resolving derivates so-called resolvins, protectins and maresins are produced from EPA and DHA from the COX and LOX pathways. Resolvin E1 (RvE1), RvE2 and RvE3 are produced from EPA and RvD1, RvD2 and RvD5 are biosynthesized from DHA (reviewed in Serhan, 2007; Serhan *et al.*, 2011). When produced in the brain, protectins are referred to as neuroprotectins (Bazan, 2012).

The cellular concentrations of LC n-3 and n-6 PUFA and their metabolites are determined by their relative dietary intake. Increased dietary intake of LC n-3 PUFA has been shown to significantly alter DHA levels in the brain (Freund Levi *et al.*, 2014) suggesting that DHA and EPA dietary supplementation could be used to directly influence neuroinflammatory pathways (Bazinet and Laye, 2014). DHA entry in the brain is still a matter of debate. Non esterified DHA freely enters the brain (Bazinet and Laye, 2014; Song *et al.*, 2010) and recently, an orphan receptor, the major facilitator superfamily domain-containing protein 2a (Mfsd2a) has been described as important to transport DHA through the BBB (Nguyen *et al.*, 2014). In retinal cells, adiponectin receptor 1 is key for DHA uptake and retention (Rice *et al.*, 2015). Once in the brain, DHA exerts anti-inflammatory/pro-resolutive activities through several action modes briefly described below. We will focus on the effect of LC n-3 PUFA on neuroinflammatory processes, especially DHA as this LC n-3 PUFA accumulates in the brain, while EPA does not.

At the periphery, inflammation is tightly regulated to be quickly resolved. The control and resolution of inflammation is due to the activation of several negative feedback mechanisms: secretion of anti-inflammatory cytokines, inhibition of pro-inflammatory signalling cascades, shedding of receptors acting as decoy targets for inflammatory mediators, glucocorticoids and activation of regulatory cells. More recently, pro-resolving lipid mediators have been identified as novel key regulators of the resolution of inflammation. Resolution is an active mechanisms allowing tissues to return to homeostasis in particular through pushing back invading neutrophils from the inflamed tissue by new produced factors (Serhan, 2007). Indeed, the LC n-3 PUFA modulate the inflammatory processes by acting at the immune system level through the regulation of inflammatory gene expression, especially cytokines and chemokines, the decrease of inflammatory PG and eicosanoids and the induction of proresolutive factors, resolvins and protectins that are involved in the resolution of inflammation (Calder, 2013; Serhan *et al.*, 2007; Serhan and Chiang, 2013). LC n-3 PUFA anti-inflammatory effects are thought to require their incorporation into plasma membranes of target tissues, however they have short term effect as they are metabolized in bioactive products quite quickly. In particular EPA, DHA and their bioactive mediators have potent anti-inflammatory and pro-resolving properties in the periphery

(Serhan and Chiang, 2013) and in the brain (Bazinet and Laye, 2014; Laye, 2010; Orr and Bazinet, 2008; Rapoport, 2008). Loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can cause irreparable damage to host tissues, including the brain. Several reports in humans highlight that higher dietary intake or blood/brain level of EPA and/or DHA are correlated with lower risk of developing brain diseases with an inflammatory component including AD and PD recently reviewed in (Bazinet and Laye, 2014).

EPA is a substrate for the COX, LOX and cytochrome P450 enzymes that produce 3-series eicosanoids (PG and TX) and 5-series leucotrienes (LT) that are increased in macrophages or neutrophils enriched in EPA and DHA by dietary means (Calder and Grimble, 2002; Yates *et al.*, 2014). As the enzymatic pathway used to convert EPA into the 3 and 5 series derivates is the same than the one used to convert arachidonic acid (AA), a n-6 PUFA, into series 2 derivates, the higher level of EPA allow to produce more 3 series derivates that are less proinflammatory. Thus, EPA results in decreased production of proinflammatory eicosanoids from AA and increased production of weaker proinflammatory eicosanoids. In addition, other anti-inflammatory and pro-resolving derivates so-called resolvins, protectins and maresins are produced from EPA and DHA from the COX and LOX pathways. Resolvin E1 (RvE1), RvE2 and RvE3 are produced from EPA and RvD1, RvD2 and RvD5 are biosynthesized from DHA (reviewed in Serhan, 2007; Serhan *et al.*, 2011). When produced in the brain, protectins are referred to as neuroprotectins (Bazan, 2012). Importantly, resolvin synthesis is increased in the blood or peripheral tissues of both humans and laboratory rodent with enriched levels of EPA and DHA by dietary means (Calder, 2015). The anti-inflammatory activity of these compounds is linked to the inhibition of the synthesis of proinflammatory cytokines such as IL-1β and TNFα and the inhibition of trans-endothelial migration of neutrophils into tissues, preventing the infiltration of these cells in inflamed tissues therefore protecting from excessive inflammation (Ariel and Serhan, 2007; Calder, 2015). Some of the biological activities of resolvins are mediated by specific G-protein coupled receptors. Indeed, RvD1 activates lipoxin A4 receptor/formyl peptide receptor 2 (ALX/FPR2) and orphan receptor G protein coupling receptor 32 (GPR32) to limit leukocyte infiltration in tissues and attenuate the production of proinflammatory cytokines (Fredman *et al.*, 2014; Wang *et al.*, 2014). Interestingly, RvD1 promotes the synthesis of pro-resolvin miRNAs and elicits macrophage polarization toward an M2-like phenotype (Pierdomenico *et al.*, 2015).

LC PUFA cannot be synthesized by vertebrates and must be obtained from diet. Therefore, the cellular concentrations of LC n-3 and n-6 PUFA, and their relative derived bioactive products are determined by their relative dietary intake. Increased dietary intake of LC n-3 PUFA has been shown to significantly alter DHA levels in the brain (Freund Levi *et al.*, 2014) suggesting that DHA and EPA dietary supplementation could be used to directly influence neuroinflammatory pathways (Bazinet and Laye, 2014). DHA entry in the brain is still a matter of debate. Non esterified DHA freely entries the brain (Bazinet and Laye, 2014; Song *et al.*, 2010). Recently, an orphan receptor, the major facilitator superfamily domain-containing protein 2a (Mfsd2a) has been described as important to transport DHA through the BBB (Nguyen *et al.*, 2014). Once in the brain, DHA exerts anti-inflammatory/proresolutive activities through several action modes briefly described below. However, poor studies studied in humans the effect of LC n-3 PUFA supplementation on neuroinflammation or microglia activity *in vivo*.

Higher dietary intakes of DHA are correlated with lower risk of developing several neurodegenerative and neuropsychiatric diseases that are associated with inflammatory component (AD, depression, etc.) thus it was hypothesized that one mechanism may be via anti-inflammatory signalling in the brain (Bazinet and Laye, 2014; Laye, 2010) Epidemiological studies have provided more consistent support for n-3 PUFA's anti-inflammatory properties than randomized controlled trials (RCTs) (Sijben and Calder, 2007). Indeed, several epidemiological and observational studies report that a higher level of blood n-3 PUFAs is associated with lower proinflammatory cytokine production (Alfano *et al.*, 2012; Farzaneh-Far *et al.*, 2009; Ferrucci *et al.*, 2006; Kiecolt-Glaser *et al.*, 2007, 2011). In a cohort of elderly subjects, depressive individuals with an elevated plasma n-6/n-3 ratio were found to exhibit higher levels of the proinflammatory cytokine TNFα and of IL-6 (Kiecolt-Glaser *et al.*, 2007). F2-isoprostane, an oxidative marker and telomere length an indicator of immune cell ageing, are decreased in the blood of subjects supplemented with EPA/DHA (Kiecolt-Glaser *et al.*, 2013). Additionally, LC n-3 PUFA supplementation in elderly subjects reduced the levels of inflammatory cytokines produced by blood leukocytes stimulated *in vitro* (Meydani *et al.*, 1991). The production of PGE2 by monocytes is inversely correlated to the EPA content of leukocytes obtained from aged subjects after the consumption of dietary complements containing different doses of EPA (Rees *et al.*, 2006). However, even if most of randomized trials with LC n-3 PUFAs have reported consistent decreased inflammation in groups with high baseline inflammation (stressed students, elderly, diabetics, and hypertriglyceridemic subjects), results are mixed (Fritsche, 2006). Indeed, DHA/EPA dietary supplementation in healthy subjects blunted the endocrine stress response and the increase in body temperature, with or without impact on cytokine production after bacterial endotoxin administration (Ferguson *et al.*, 2014; Michaeli *et al.*, 2007). AD patients supplemented with a DHA-rich diet display reduced release of proinflammatory cytokines (IL-1β, IL-6, GM-CSF) from stimulated peripheral blood mononuclear cells (Vedin *et al.*, 2008). In addition, students with DHA/EPA supplementation show a decreased anxiety and proinflammatory cytokines production only in *ex vivo* stimulated immune cells but not in the plasma (Kiecolt-Glaser *et al.*, 2011). However, decreased plasma cytokines level was observed in students with the higher increase of LC n-3 PUFA after supplementation, reinforcing the necessity in RCT of evaluate both basal level of LC n-3/n-6 PUFA before and after dietary interventions. A potential explanation of conflicting results from randomised controlled trials might be that some condition-specific clinical end points are more sensitive markers to LC n-3 PUFA treatment than immune markers. For instance, a LC n-3 PUFA-enriched diet (Souvenaid® formulation) revealed improved cognitive decline in mild AD patients without taking any AD drug, by influencing synaptic plasticity

along with cognitive tasks (Scheltens *et al.*, 2012). Additionally, as lifestyle habits impact on cognition and the onset of dementia, the efficacy of a LC n-3 PUFA enriched diet on neuroinflammatory markers might be revealed if included in a multidomain intervention trial. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER) study is the first long-term randomised controlled trial showing a beneficial impact on cognition in at-risk older individuals of a multiple intervention (nutritional guidance, exercise, cognitive training and social activity) (Ngandu *et al.*, 2015). The development of such strategies points out the importance of assessing the subject's lifestyle habits in particular from mid-life (Fratiglioni *et al.*, 2004, 2007).

4 How do n-3 PUFA mechanisms control neuroinflammation?

Whether decreased brain DHA level through dietary means is proinflammatory in absence of proinflammatory stimulus has been poorly studied in animal models. *In vivo*, chronic dietary n-3 PUFA deficiency significantly increased the production and release of IL-6 and TNFα in the blood (McNamara *et al.*, 2010) while it was not the case in adult and aged mice brain (Delpech *et al.*, 2015a; Mingam *et al.*, 2008; Moranis *et al.*, 2012). However, DHA decrease in the brain during post-natal period strongly affects microglia activity (Madore *et al.*, 2014). On the opposite, the expression of brain proinflammatory cytokines following systemic LPS administration (Delpech *et al.*, 2015a; Mingam *et al.*, 2008), brain ischemia-reperfusion (Lalancette-Hebert *et al.*, 2011) or spinal cord injury (Huang *et al.*, 2007) is reduced in the brain of rodents with higher level of DHA by genetic or dietary means. Short-term exposure to dietary EPA reduced IL-1-induced spatial memory deficit and anxiolytic behavior (Song *et al.*, 2004, 2008) and improved LPS and Aβ-induced inhibition of LTP in both adult and aged rats (Minogue *et al.*, 2007). Furthermore, DHA and NPD1 infusion in the brain is acutely protective toward brain cytokine production and microglia activation (Lukiw *et al.*, 2005; Orr *et al.*, 2013). In addition, DHA increase in the brain protects from the effect of bacterial endotoxin-induced synaptic plasticity impairment and ageing (Delpech *et al.*, 2015a, 2015c; Labrousse *et al.*, 2012).

Proper neuronal membrane lipid composition is crucial to maintain neuronal signalling. Neuronal membranes, which are highly enriched in DHA (Bazan *et al.*, 2011), are susceptible to oxidative damage and metabolic perturbations. As most receptors are embedded, damage to the membrane would disrupt all forms of neuronal communication (Gomez-Pinilla *et al.*, 2008). With ageing, lipid composition and fat deposition distribution are disturbed in the brain, most likely due to decreased liver peroxisomal β-oxidation (Yang *et al.*, 2014; Zamzow *et al.*, 2014), which is responsible for specific fatty acids synthesis such as DHA (Ferdinandusse *et al.*, 2001). In addition, along with the decreased level and activity of the enzyme delta 6-desaturase (Yehuda *et al.*, 2005), the higher cholesterol content in the ageing neuronal membrane decreases membrane fluidity of the BBB (Yehuda *et al.*, 2002). Both *in vivo* and *in vitro* studies have reported anti-inflammatory activities of DHA in the brain especially in microglia (Laye, 2010; Orr and Bazinet, 2008). At the cellular level, brain DHA modulates several proinflammatory signalling pathways in microglia such as TLR signalling and nucleotide-binding oligomerization domain protein (NOD) signalling (De Smedt-Peyrusse *et al.*, 2008; Liu *et al.*, 2012), inhibits JUNK (Ma *et al.*, 2009), and reduces or blocks NF-kB signalling (De Smedt-Peyrusse *et al.*, 2008; Orr *et al.*, 2013). The inhibitory effect of DHA on proinflammatory signalling pathway could be mediated by both non-genomic and genomic effect. Indeed, DHA influences membrane composition of microglial cells and the TLR4 positioning, decreasing the binding of its ligand LPS (De Smedt-Peyrusse *et al.*, 2008). DHA also impairs the phospholipid raft assembly of EPA and DHA in the plasma membrane (Rockett *et al.*, 2011; Ruth *et al.*, 2009). In addition, genomic effect of DHA has been reported thanks to its effect on specific receptors either located at the membrane such as GPR120 or GPR40 and/or the regulation of the peroxisome proliferator activated receptor (PPARγ) (Calder, 2013). The anti-inflammatory activity of DHA could also derive from its direct effect on invading macrophages or microglia. Both in vitro and in vivo data highlight that DHA blocks invading macrophages and microglia activation and the signalling pathway (NF-kB) in the brain and spinal cord of several inflammatory rodents models (De Smedt-Peyrusse *et al.*, 2008; Figueroa *et al.*, 2012; Lim *et al.*, 2013; Lu *et al.*, 2013). Recent data highlight that *in vitro* DHA has not only anti-inflammatory activity but also promotes microglia to a M2 phenotype with increased Aβ42 phagocytosis (Hjorth *et al.*, 2013).

In the brain, LC n-3 PUFA could also yield protective influence indirectly, through the synthesis of bioactive derivates with pro-resolutive activities. Indeed, several in vitro studies performed on microglia show that several LC n-3 PUFA pro-resolving derivatives have potent effects. As an example, RvD1 triggers anti-inflammatory activities and potentiates IL-4-induced expression of M2 markers in microglial cells and the signaling pathways involved in these processes, in particular the PPARγ signalling pathways (Li *et al.*, 2014; Odusanwo *et al.*, 2012; Wang *et al.*, 2014). In addition, RvD1 inhibits the activation of several proinflammatory signalling pathways, including NFkB and MAPK in microglia cells which express RvD1 receptors ALX (Xu *et al.*, 2013). Another important mediator of anti-inflammatory activity of DHA is NPD1 (Bazan, 2006, 2012). This DHA derivative inhibits leukocyte infiltration, COX-2 expression, and NFκB activation *in vivo* and *in vitro* (Marcheselli *et al.*, 2010). In addition, aspirine-triggered NPD1 (AT-NPD1), recently discovered as a new potent neuroprotective derivative of DHA, could also exert strong anti-inflammatory and pro-resolutive activities (Bazan *et al.*, 2012).

In the ageing brain, microglial activation, production of proinflammatory cytokines such as IL-1β and alterations in hippocampal LTP with age are attenuated by EPA (Lynch *et al.*, 2003, 2007). A 2-month fish-oil dietary supply increases DHA in the brain, prevented proinflammatory cytokines expression and astrocytes morphology changes in the hippocampus and restored spatial memory deficits and Fos-associated activation in the hippocampus of aged mice (Labrousse *et al.*, 2012). To the extent that the level of peripheral cytokines reflects that of cytokines in the brain, these results suggest

that dietary n-3 PUFAs modulate neuroinflammation and associated neurobehavioural effects in elderly individuals. However, the direct effect of DHA on the brain immune system is difficult to ascertain since primary injury in these animal models of neuroinflammation was also improved. Chronic neuroinflammation in the brain of patients with AD could indicate that the resolution of inflammation is dysfunctional. To support this notion, while proinflammatory stimuli such as LPS promoted resolvin pathways activation in microglia, Aβ42 had an opposite or insignificant effect suggesting that pro-resolutive pathways are impaired in AD (Zhu *et al.*, 2015). This is further substantiated by the observation that the lipoxin A4 (LXA4) level is decreased in postmortem brain tissue and cerebrospinal fluid samples from AD patients (Wang *et al.*, 2015b). Very recently, it was shown that upon Aβ40 exposure, peripheral blood mononuclear cells from AD patients secreted less LXA4 and RvD1 together with the disease progression. Importantly, dietary supplementation of DHA prevented this reduction (Wang *et al.*, 2015a), suggesting that long chain n-3 PUFAs protect from the Alzheimer-associated inflammation through the promotion of pro-resolving signaling. Interestingly, LOX and LTB4 expression increases while LXA4 decreases in the brain of aged and AD mice models (Dunn *et al.*, 2015).

Recent data show that 12 and 5-LOX are widely expressed in the brain where it mainly localizes in neuronal cells. *In vivo* overexpression of 5-LOX increases phosphorylation of specific Tau epitopes, and neuronal cells transfected with 5-LOX show a significant increase in tau phosphorylation even when their ability to generate Aβ is completely blocked, suggesting that the effect on tau is independent from Aβ (Chu *et al.*, 2012). Interestingly, Tau-mice treated with zileuton (a potent 5-LOX inhibitor) displayed a significant improvement in memory and synaptic function together with a decreased tau phosphorylation level (Chu and Pratico, 2013; Giannopoulos *et al.*, 2014). The use of PD146176, a specific 12/15 LOX inhibitor, also improved memory deficits and decreased Aβ plaques and neurofibrillary tangles in a genetic mice model of AD (Chu *et al.*, 2015). All together, these data suggest the importance of using DHA and/or its mediator to target neuroinflammatory processes in the management of neurodegenerative diseases. This new therapeutic strategy is of particular importance since the target of proinflammatory pathways with COX-2 inhibitors is puzzling as (1) they poorly cross the BBB, (2) some of AA derivatives dependent on COX-2 are proresolutive and (3) COX-2 inhibitors are poorly efficient in AD (Aid and Bosetti, 2007, 2011; McGeer and McGeer, 2007).

5 Conclusion

Chronic neuroinflammation, demonstrated by the activation of microglia and astrocytes as well as the release of reactive oxygen species and cytokines, has a considerable interest in cognitive disorders, and is a target site for developing for prevention and treatment of neurodegenerative diseases. In this regard, n-3 PUFAs are an interesting dietary strategy to limit dementia. A better understanding of the effects of n-3 PUFAs and their derivatives in microglia are therefore warranted. Nonetheless, it is worth noting that it is not clear whether the n-3 PUFAs derivatives with anti-inflammatory activity access the brain to interact directly with microglia. While it is biologically plausible that peripheral inflammatory modulation may reflect brain health, further human studies are required to elucidate whether dietary n-3 PUFAs target microglia. The use of imaging techniques like positron emission tomography (PET) imaging to measure *in vivo* changes in microglia activation (Cagnin *et al.*, 2007) would be of high benefit to decipher this important question.

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Conflict of interest

The authors declare no financial or personal conflict of interest.

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