OCL 2016, 23(1) D103

DOI: 10.1051/ocl/2015064

OCL Oilseeds & fats Crops and Lipids

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www.ocl-journal.org

RESEARCH ARTICLE – DOSSIER OPEN ACCESS

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N-3 PUFAs and neuroinflammatory processes in cognitive disorders

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Received 6 November 2015 – Accepted 16 November 2015

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.

Acknowledgements. QL is a recipient of Paris Ile de France stipend. AN and SL are supported by INRA, Bordeaux University, Région Aquitaine.

Conflict of interest

The authors declare no financial or personal conflict of interest.

References

Aid S, Bosetti F. 2007. Gene expression of cyclooxygenase-1 and Ca^{2+}-independent phospholipase A_2 is altered in rat hippocampus during normal aging. *Brain Res. Bull.* 73: 108–113.

Aid S, Bosetti F. 2011. Targeting cyclooxygenases-1 and -2 in neuroinflammation: Therapeutic implications. *Biochimie* 93: 46–51.

Alfano CM, Imayama I, Neuhouser ML, *et al.* 2012. Fatigue, inflammation, and omega-3 and omega-6 fatty acid intake among breast cancer survivors. *J. Clin. Oncol.* 30: 1280–1287.

Andre C, O'Connor JC, Kelley KW, Lestage J, Dantzer R, Castanon, N. 2008. Spatio-temporal differences in the profile of murine brain expression of proinflammatory cytokines and indoleamine 2,3-dioxygenase in response to peripheral lipopolysaccharide administration. *J. Neuroimmunol.* 200: 90–99.

Ariel A, Serhan CN. 2007. Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol.* 28: 176–183.

Barrientos RM, Frank MG, Hein AM, *et al.* 2009. Time course of hippocampal IL-1 beta and memory consolidation impairments in aging rats following peripheral infection. *Brain Behav. Immun.* 23: 46–54.

Barrientos RM., Kitt MM, Watkins LR., Maier SF. 2015. Neuroinflammation in the normal aging hippocampus. *Neuroscience* 309: 84–99.

Bazan NG. 2006. Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. *Trends Neurosci.* 29: 263–271.

Bazan NG. 2007. Omega-3 fatty acids, pro-inflammatory signaling and neuroprotection. *Curr. Opin. Clin. Nutr. Metab. Care* 10: 136–141.

Bazan NG. 2012. Neuroinflammation and proteostasis are modulated by endogenously biosynthesized neuroprotectin D1. *Mol. Neurobiol.* 46: 221–226.

Bazan NG, Eady TN, Khoutorova L, *et al.* 2012. Novel aspirin-triggered neuroprotectin D1 attenuates cerebral ischemic injury after experimental stroke. *Exp. Neurol* 236: 122–130.

Bazan NG, Molina MF, Gordon WC. 2011. Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. *Annu. Rev. Nutr.* 31: 321–351.

Bazinet RP, Laye S. 2014. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.* 15: 771–785.

Cagnin A, Kassiou M, Meikle SR, Banati RB. 2007. Positron emission tomography imaging of neuroinflammation. *Neurotherapeutics* 4: 443–452.
Calder PC. 2013. n-3 fatty acids, inflammation and immunity: new mechanisms to explain old actions. *Proc. Nutr. Soc.* 72: 326–336.
Calder PC. 2015. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim. Biophys. Acta* 1851: 469–484.
Calder PC, Grimble RF. 2002. Polyunsaturated fatty acids, inflammation and immunity. *Eur. J. Clin. Nutr.* 56: S14–19.
Campbell BM, Charych E, Lee AW, Moller T. 2014. Kynurenines in CNS disease: regulation by inflammatory cytokines. *Front. Neurosci.* 8: 12.
Capuron L, Miller AH. 2011. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol. Ther.* 130: 226–238.
Capuron L, Schroecksnadel S, Feart C, Aubert A, Higueret D, Barberger-Gateau P, Laye S, Fuchs D, 2011. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. *Biol. Psychiatry.* 70: 175–182.
Castanon N, Lasselin J, Capuron L. 2014. Neuropsychiatric comorbidity in obesity: role of inflammatory processes. *Front. Endocrinol.* (Lausanne) 5: 74.
Chu J, Pratico D. 2013. 5-Lipoxygenase pharmacological blockade decreases tau phosphorylation in vivo: involvement of the cyclin-dependent kinase-5. *Neurobiol. Aging.* 34: 1549–1554.
Chu J, Giannopoulos PF, Ceballos-Diaz C, Golde TE, Pratico D. 2012. 5-Lipoxygenase gene transfer worsens memory, amyloid, and tau brain pathologies in a mouse model of Alzheimer disease. *Ann. Neurol.* 72: 442–454.
Chu J, Li JG, Giannopoulos PF, Blass BE, Childers W, Abou-Gharbia M, Pratico D. 2015. Pharmacologic blockade of 12/15-lipoxygenase ameliorates memory deficits, Abeta and tau neuropathology in the triple-transgenic mice. *Mol. Psychiatry.* 20: 1329–38.
Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. 2005. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J. Neurosci.* 25: 9275–9284.
Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9: 46–56.
De la Monte SM. 2012. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Curr. Alzheimer. Res.* 9: 35–66.
De Smedt-Peyrusse V, Sargueil F, Moranis A, Harizi H, *et al.* 2008. Docosahexaenoic acid prevents lipopolysaccharide-induced cytokine production in microglial cells by inhibiting lipopolysaccharide receptor presentation but not its membrane subdomain localization. *J. Neurochem.* 105: 296–307.
Delpech JC, Madore C, Joffre C, *et al.* 2015a. Transgenic increase in n-3/n-6 fatty acid ratio protects against cognitive deficits induced by an immune challenge through decrease of neuroinflammation. *Neuropsychopharmacology* 40: 525–536.
Delpech JC, Saucisse N, Parkes SL, *et al.* 2015b. Microglial activation enhances associative taste memory through purinergic modulation of glutamatergic neurotransmission. *J. Neurosci.* 35: 3022–3033.
Delpech JC, Thomazeau A, Madore C, *et al.* 2015c. Dietary n-3 PUFAs Deficiency Increases Vulnerability to Inflammation-Induced Spatial Memory Impairment. *Neuropsychopharmacology* 40: 2774–87.
Dilger RN, Johnson RW. 2008. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. *J. Leukoc. Biol.* 84: 932–939.
Dinel AL, Andre C, Aubert A, Ferreira G, Laye S, Castanon N. 2014. Lipopolysaccharide-induced brain activation of the indoleamine 2,3-dioxygenase and depressive-like behavior are impaired in a mouse model of metabolic syndrome. *Psychoneuroendocrinology* 40: 48–59.
Dunn HC, Ager RR, Baglietto-Vargas D, *et al.* 2015. Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model. *J. Alzheimers Dis.* 43: 893–903.
Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. 2009. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. *Atherosclerosis* 205: 538–543.
Fenn AM, Henry CJ, Huang Y, Dugan A, Godbout JP. 2012. Lipopolysaccharide-induced interleukin (IL)-4 receptor-alpha expression and corresponding sensitivity to the M2 promoting effects of IL-4 are impaired in microglia of aged mice. *Brain Behav. Immun.* 26: 766–777.
Ferdinandusse S, Denis S, Mooijer PA, *et al.* 2001. Identification of the peroxisomal beta-oxidation enzymes involved in the biosynthesis of docosahexaenoic acid. *J. Lipid. Res.* 42: 1987–1995.
Ferguson JF, Mulvey CK, Patel PN, *et al.* 2014. Omega-3 PUFA supplementation and the response to evoked endotoxemia in healthy volunteers. *Mol. Nutr. Food. Res.* 58: 601–613.
Ferrucci L, Cherubini A, Bandinelli S, *et al.* 2006. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J. Clin. Endocrinol. Metab.* 91: 439–446.
Figueroa JD, Cordero K, Baldeosingh K, *et al.* 2012. Docosahexaenoic acid pretreatment confers protection and functional improvements after acute spinal cord injury in adult rats. *J. Neurotrauma.* 29: 551–566.
Fratiglioni L, Paillard-Borg S, Winbla B. 2004. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol.* 3: 343–5.
Fratiglioni L, Winblad B, von Strauss E. 2007. Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. *Physiol. Behav.* 92: 98–104.
Fredman G, Ozcan L, Spolitu S, Hellmann J, Spite M, Backs J, Tabas I. 2014. Resolvin D1 limits 5-lipoxygenase nuclear localization and leukotriene B4 synthesis by inhibiting a calcium-activated kinase pathway. *Proc. Natl. Acad. Sci. USA* 111: 14530–14535.
Frenois F, Moreau M, O'Connor J, *et al.* 2007. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. *Psychoneuroendocrinology* 32: 516–531.
Freund Levi Y, Vedin I, Cederholm T, *et al.* 2014. Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: the OmegAD study. *J. Intern. Med.* 275: 428–436.
Fritsche K. 2006. Fatty acids as modulators of the immune response. *Annu. Rev. Nutr.* 26: 45–73.
Giannopoulos PF, Chu J, Joshi YB, Sperow M, Li JG, Kirby LG, Pratico D. 2014. Gene knockout of 5-lipoxygenase rescues synaptic dysfunction and improves memory in the triple-transgenic model of Alzheimer's disease. *Mol. Psychiatry* 19: 511–518.
Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. 2010. Mechanisms underlying inflammation in neurodegeneration. *Cell* 140: 918–934.

Godbout JP, Chen J, Abraham J, *et al.* 2005. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *Faseb. J.* 19: 1329–1331.

Gómez-Pinilla F. 2008. Brain foods: the effects of nutrients on brain function. *Nat. Rev. Neurosci.* 9: 568–78.

Hanisch UK, Kettenmann H. 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.* 10: 1387–1394.

Harrington L, Srikanth CV, Antony R, *et al.* 2008. Deficiency of indoleamine 2,3-dioxygenase enhances commensal-induced antibody responses and protects against Citrobacter rodentium-induced colitis. *Infect. Immun.* 76: 3045–3053.

Heneka MT, O'Banion MK, Terwel D, Kummer MP. 2010. Neuroinflammatory processes in Alzheimer's disease. *J. Neural. Transm.* 117: 919–947.

Heneka MT, Carson MJ, El Khoury J, *et al.* 2015. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 14: 388–405.

Hjorth E, Zhu M, Toro VC, *et al.* 2013. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-beta42 by human microglia and decrease inflammatory markers. *J. Alzheimers Dis.* 35: 697–713.

Huang WL, King VR, Curran OE, *et al.* 2007. A combination of intravenous and dietary docosahexaenoic acid significantly improves outcome after spinal cord injury. *Brain* 130: 3004–3019.

Kiecolt-Glaser JK, Belury MA, Porter K, Beversdorf DQ, Lemeshow S, Glaser R. 2007. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. *Psychosom. Med.* 69: 217–224.

Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Glaser R. 2011. Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain Behav. Immun.* 25: 1725–1734.

Kiecolt-Glaser JK, Epel ES, Belury MA, *et al.* 2013. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial. *Brain Behav. Immun.* 28: 16–24.

Krabbe G, Halle A, Matyash V, *et al.* 2013. Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology. *PLoS One* 8: e60921.

Krstic D, Madhusudan A, Doehner J, *et al.* 2012. Systemic immune challenges trigger and drive Alzheimer-like neuropathology in mice. *J. Neuroinflammation* 9: 151.

Labrousse VF, Nadjar A, Joffre C, Costes L, Aubert A, Gregoire S, Bretillon L, Laye S. 2012. Short-term long chain omega3 diet protects from neuroinflammatory processes and memory impairment in aged mice. *PLoS One* 7: e36861.

Lalancette-Hebert M, Gowing G, Simard A, Weng YC, Kriz J. 2007. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. *J. Neurosci.* 27: 2596–2605.

Lalancette-Hebert M, Julien C, Cordeau P, *et al.* 2011. Accumulation of dietary docosahexaenoic acid in the brain attenuates acute immune response and development of postischemic neuronal damage. *Stroke* 42: 2903–2909.

Laye S. 2010. Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins Leukot Essent Fatty Acids* 82: 295–303.

Laye S, Parnet P, Goujon E, Dantzer R. 1994. Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. *Brain Res. Mol. Brain Res.* 27: 157–162.

Li L, Wu Y, Wang Y, Wu J, *et al.* 2014. Resolvin D1 promotes the interleukin-4-induced alternative activation in BV-2 microglial cells. *J. Neuroinflammation* 11: 72.

Lim SN, Huang W, Hall JC, Michael-Titus AT, Priestley JV. 2013. Improved outcome after spinal cord compression injury in mice treated with docosahexaenoic acid. *Exp. Neurol.* 239: 13–27.

Liu Y, Chen F, Odle J, Lin X, Jacobi SK, Zhu H, Wu Z, Hou Y. 2012. Fish oil enhances intestinal integrity and inhibits TLR4 and NOD2 signaling pathways in weaned pigs after LPS challenge. *J. Nutr.* 142: 2017–2024.

Lu Y, Zhao LX, Cao DL, Gao YJ. 2013. Spinal injection of docosahexaenoic acid attenuates carrageenan-induced inflammatory pain through inhibition of microglia-mediated neuroinflammation in the spinal cord. *Neuroscience* 241: 22–31.

Lukiw WJ, Cui JG, Marcheselli VL, *et al.* 2005. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J. Clin. Invest.* 115: 2774–2783.

Lynch AM, Moore M, Craig S, Lonergan PE, Martin DS, Lynch MA. 2003. Analysis of interleukin-1 beta-induced cell signaling activation in rat hippocampus following exposure to gamma irradiation. Protective effect of eicosapentaenoic acid. *J. Biol. Chem.* 278: 51075–51084.

Lynch AM, Loane DJ, Minogue AM, *et al.* 2007. Eicosapentaenoic acid confers neuroprotection in the amyloid-beta challenged aged hippocampus. *Neurobiol. Aging.* 28: 845–855.

Ma QL, Yang F, Rosario ER, *et al.* 2009. Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *J. Neurosci.* 29: 9078–9089.

Madore C, Nadjar A, Delpech JC, *et al.* 2014. Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain Behav. Immun.* 41: 22–31.

Marcheselli VL, Mukherjee PK, Arita M, *et al.* 2010. Neuroprotectin D1/protectin D1 stereoselective and specific binding with human retinal pigment epithelial cells and neutrophils. Prostaglandins Leukot Essent *Fatty. Acids.* 82: 27–34.

McGeer PL, McGeer EG. 2007. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiol. Aging.* 28: 639–647.

McNamara RK, Jandacek R, Rider T, Tso P, Cole-Strauss A, Lipton JW. 2010. Omega-3 fatty acid deficiency increases constitutive pro-inflammatory cytokine production in rats: relationship with central serotonin turnover. *Prostaglandins Leukot Essent Fatty Acids* 83: 185–191.

Meydani SN, Lichtenstein AH, White PJ, *et al.* 1991. Food use and health effects of soybean and sunflower oils. *J. Am. Coll. Nutr.* 10: 406–428.

Michaeli B, Berger MM, Revelly JP, Tappy L, Chiolero R. 2007. Effects of fish oil on the neuro-endocrine responses to an endotoxin challenge in healthy volunteers. *Clin. Nutr.* 26: 70–77.

Mingam R, Moranis A, Bluthe RM, *et al.* 2008. Uncoupling of interleukin-6 from its signalling pathway by dietary n-3-polyunsaturated fatty acid deprivation alters sickness behaviour in mice. *Eur. J. Neurosci.* 28: 1877–1886.

Minogue AM, Lynch AM, Loane DJ, Herron CE, Lynch MA. 2007. Modulation of amyloid-beta-induced and age-associated changes in rat hippocampus by eicosapentaenoic acid. *J. Neurochem.* 103: 914–926.

Moranis A, Delpech JC, De Smedt-Peyrusse V, *et al.* 2012. Long term adequate n-3 polyunsaturated fatty acid diet protects from depressive-like behavior but not from working memory disruption and brain cytokine expression in aged mice. *Brain Behav. Immun.* 26: 721–731.

Neurauter G, Schrocksnadel K, Scholl-Burgi S, *et al.* 2008. Chronic immune stimulation correlates with reduced phenylalanine turnover. *Curr. Drug. Metab.* 9: 622–627.

Ngandu T, Lehtisalo J, Solomon A, *et al.* 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 6: 2255–63.

Nguyen LN, Ma D, Shui G, *et al.* 2014. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature* 509: 503–506.

Odusanwo O, Chinthamani S, McCall A, Duffey ME, Baker OJ. 2012. Resolvin D1 prevents TNF-alpha-mediated disruption of salivary epithelial formation. *Am. J. Physiol. Cell. Physiol.* 302: C1331–1345.

Olmos G, Llado J. 2014. Tumor necrosis factor alpha: a link between neuroinflammation and excitotoxicity. *Mediators. Inflamm.* 2014: 861231.

Ong WY, Farooqui T, Kokotos G, Farooqui AA. 2015. Synthetic and Natural Inhibitors of Phospholipases A: Their Importance for Understanding and Treatment of Neurological Disorders. *ACS Chem. Neurosci.* 6: 814–31.

Orr SK, Bazinet RP. 2008. The emerging role of docosahexaenoic acid in neuroinflammation. *Curr. Opin. Investig. Drugs* 9: 735–743.

Orr SK, Palumbo S, Bosetti F, *et al.* 2013. Unesterified docosahexaenoic acid is protective in neuroinflammation. *J. Neurochem.* 127: 378–393.

Oxenkrug G. 2011. Interferon-gamma-Inducible Inflammation: Contribution to Aging and Aging-Associated Psychiatric Disorders. *Aging. Dis.* 2: 474–486.

Perry VH, Nicoll JA, Holmes C. 2010. Microglia in neurodegenerative disease. *Nat. Rev. Neurol.* 6: 193–201.

Pierdomenico AM, Recchiuti A, Simiele F, *et al.* 2015. MicroRNA-181b regulates ALX/FPR2 receptor expression and proresolution signaling in human macrophages. *J. Biol. Chem.* 290: 3592–3600.

Rapoport SI. 2008. Brain arachidonic and docosahexaenoic acid cascades are selectively altered by drugs, diet and disease. *Prostaglandins Leukot Essent Fatty Acids* 79: 153–156.

Rees D, Miles EA, Banerjee T, *et al.* 2006. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am. J. Clin. Nutr.* 83: 331–342.

Rice DS, Calandria JM, Gordon WC, *et al.* 2015. Adiponectin receptor 1 conserves docosahexaenoic acid and promotes photoreceptor cell survival. *Nat. Commun.* 4: 6:6228.

Rockett BD, Franklin A, Harris M, Teague H, Rockett A, Shaikh SR. 2011. Membrane raft organization is more sensitive to disruption by (n-3) PUFA than nonraft organization in EL4 and B cells. *J. Nutr.* 141: 1041–1048.

Ruth MR, Proctor SD, Field CJ. 2009. Feeding long-chain n-3 polyunsaturated fatty acids to obese leptin receptor-deficient JCR:LA- cp rats modifies immune function and lipid-raft fatty acid composition. *Br. J. Nutr.* 101: 1341–1350.

Scheltens P, Twisk JW, Blesa R, *et al.* 2012. Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. *J. Alzheimers Dis.* 31: 225–36.

Serhan CN. 2007. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Annu. Rev. Immunol.* 25: 101–137.

Serhan CN, Chiang N. 2013. Resolution phase lipid mediators of inflammation: agonists of resolution. *Curr. Opin. Pharmacol.* 13: 632–640.

Serhan CN, Brain SD, Buckley CD, *et al.* 2007. Resolution of inflammation: state of the art, definitions and terms. *Faseb. J.* 21: 325–332.

Serhan CN, Fredman G, Yang R, *et al.* 2011. Novel proresolving aspirin-triggered DHA pathway. *Chem. Biol.* 18: 976–987.

Serhan CN, Dalli J, Colas RA, Winkler JW, Chiang N. 2015. Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. *Biochim. Biophys. Acta* 1851: 397–413.

Sijben JW, Calder PC. 2007. Differential immunomodulation with long-chain n-3 PUFA in health and chronic disease. *Proc. Nutr. Soc.* 66: 237–259.

Song BJ, Elbert A, Rahman T, Orr SK, Chen CT, Febbraio M, Bazinet RP. 2010. Genetic ablation of CD36 does not alter mouse brain polyunsaturated fatty acid concentrations. *Lipids* 45: 291–299.

Song C, Leonard BE, Horrobin DF. 2004. Dietary ethyl-eicosapentaenoic acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. *Stress* 7: 43–54.

Song C, Manku MS, Horrobin DF. 2008. Long-chain polyunsaturated fatty acids modulate interleukin-1beta-induced changes in behavior, monoaminergic neurotransmitters, and brain inflammation in rats. *J. Nutr.* 138: 954–963.

Sparkman NL, Martin LA, Calvert WS, Boehm GW. 2005. Effects of intraperitoneal lipopolysaccharide on Morris maze performance in year-old and 2-month-old female C57BL/6J mice. *Behav. Brain Res.* 159: 145–151.

Sundaram JR, Poore CP, Sulaimee NH, Pareek T, Asad AB, Rajkumar R, Cheong WF, Wenk MR, Dawe GS, Chuang KH, Pant HC, Kesavapany S. 2013. Specific inhibition of p25/Cdk5 activity by the Cdk5 inhibitory peptide reduces neurodegeneration *in vivo*. *J. Neurosci.* 33: 334–343.

Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A. 2011. The role of microglia in the healthy brain. *J. Neurosci.* 31: 16064–16069.

Vauzour D. 2012. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxid. Med. Cell. Longev.* 2012: 914273.

Vedin I, Cederholm T, Freund Levi Y, *et al.* 2008. Effects of docosahexaenoic acid-rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes: the OmegAD study. *Am. J. Clin. Nutr.* 87: 1616–1622.

Wang Q, Zheng X, Cheng Y, *et al.* 2014. Resolvin D1 stimulates alveolar fluid clearance through alveolar epithelial sodium channel, Na,K-ATPase via ALX/cAMP/PI3K pathway in lipopolysaccharide-induced acute lung injury. *J. Immunol.* 192: 3765–3777.

Wang X, Hjorth E, Vedin I, *et al.* 2015a. Effects of n-3 FA supplementation on the release of proresolving lipid mediators by blood mononuclear cells: the OmegAD study. *J. Lipid. Res.* 56: 674–681.

Wang X, Zhu M, Hjorth E, *et al.* 2015b. Resolution of inflammation is altered in Alzheimer's disease. *Alzheimers Dement* 11: 40-50 e41-42.

Xu MX, Tan BC, Zhou W, *et al.* 2013, Resolvin D1, an endogenous lipid mediator for inactivation of inflammation-related signaling pathways in microglial cells, prevents lipopolysaccharide-induced inflammatory responses. *CNS Neurosci. Ther.* 19: 235–243.

Yang L, Zhang Y, Wang S, Zhang W, Shi R. 2014. Decreased liver peroxisomal beta-oxidation accompanied by changes in brain fatty acid composition in aged rats. *Neurol. Sci.* 35: 289−293.

Yates CM, Calder PC, Ed Rainger G. 2014. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol. Ther.* 141: 272−282.

Yehuda S, Rabinovitz S, Carasso RL, Mostofsky DI. 2002. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. *Neurobiol. Aging.* 23: 843−853.

Yehuda S, Rabinovitz S, Mostofsky DI. 2005. Essential fatty acids and the brain: from infancy to aging. *Neurobiol. Aging* 26: 98−102.

Zamzow DR, Elias V, Legette LL, Choi J, Stevens JF, Magnusson KR. 2014. Xanthohumol improved cognitive flexibility in young mice. *Behav. Brain Res.* 275: 1−10.

Zhu M, Wang X, Schultzberg M, Hjorth E. 2015. Differential regulation of resolution in inflammation induced by amyloid-beta42 and lipopolysaccharides in human microglia. *J. Alzheimers Dis.* 43: 1237−1250.

Zunszain PA, Anacker C, Cattaneo A, *et al.* 2012. Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology* 37: 939−949.

Cite this article as: Quentin Leyrolle, Sophie Layé, Agnès Nadjar. N-3 PUFAs and neuroinflammatory processes in cognitive disorders. OCL 2016, 23(1) D103.