Neuroinflammation and aging: influence of dietary n-3 polyunsaturated fatty acid*

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Abstract: *The innate immune system of the brain is principally composed of microglial cells and astrocytes, which, once activated, protect neurons against noxious agents or lesions. Activated glial cells produce inflammatory cytokines that act specifically through receptors expressed in the brain, leading to the development of altered emotional and cognitive behavior. These behavioral alterations cease along with the synthesis of brain cytokines. When the level of expression of these cytokines remains high, they become toxic to neurons possibly leading to neuronal death, as observed in neurodegenerative disorders such as Alzheimer's disease. Omega-3 (n-3) type polyunsaturated fatty acids (PUFAs) are essential nutrients and fundamental components of neuronal and glial cell membranes. Additionally, they have immunomodulatory properties. They accumulate in the brain during the perinatal period in a dietary supply-dependant fashion. Their brain levels diminish with age, but can be corrected by a diet enriched in n-3 PUFAs. The increasing exposure of the population to diets unbalanced in n-3 PUFAs could contribute to the deleterious effect of inflammatory cytokines in the brain.*

Key words: *DHA, EPA, brain, cytokine, diet, depression, cognition, elderly*

The central nervous system (CNS) has long been considered a privileged organ from the point of view of immunity, as the blood brain barrier (BBB), thanks to its tight junctions, limits the entry of immune cells, notably lymphocytes, into the brain. Research in neuroimmunology has shown that the brain possesses its own system of defense, which, in addition to being activated by immune stimuli, is closely linked to the immune system *(figure 1)*. Inflammatory cytokines, which are important mediators of communication within the immune system, also act in the brain, in particular by activating the innate immune cells of the brain that in turn, produce inflammatory cytokines (Dantzer *et al.*, 1998). The synthesis of brain cytokines is finely regulated, allowing them to return to basal levels without leading either to a rupture of the BBB or to cerebral lesion. On the other hand, when these factors are synthesized in large quantities or in a chronic manner by the brain, they have toxic effects on neurons, resulting in substantial neuronal dysfunction that can lead to cell death. The alteration of neuronal function induced by cytokine actions is also seen during aging, where microinflammation, characterized by microglial reactivity and the chronic production of low levels of inflammatory cytokines occurs (Laye, 2010). This microneuroinflammation, which increases the vulnerability of the aging brain to immune stimuli, is characterized by the increased production of brain cytokines and the risk of developing delirium and/or neurodegenerative disorders with an inflammatory component, such as Alzheimer's disease (Perry *et al.*, 2003). Accordingly, clinical and epidemiological studies have shown a correlation between the systemic expression levels of inflammatory cytokines and the incidence of functional/behavioral alterations (cognitive or mood disorders) in elderly subjects. In this context, limiting the development of chronic neuroinflammation represents a key element in the

*Lecture from the symposium ''Lipids and Brain II'' held by The French Society for the Study of Lipids (Sfel) - Paris 28-30 March 2011, cf. OCL 18-4 and 18-5.

doi: 10.1684/ocl.2011.0412

To cite this article: Layé S, Delpech JC, De Smedt-Peyrusse V, Joffre C, Larrieu T, Madore C, Nadjar A, Capuron L. Neuroinflammation and aging: influence of dietary n-3 polyunsaturated fatty acid. *OCL* 2011; 18(6): 301-306. doi : 10.1684/ocl.2011.0412

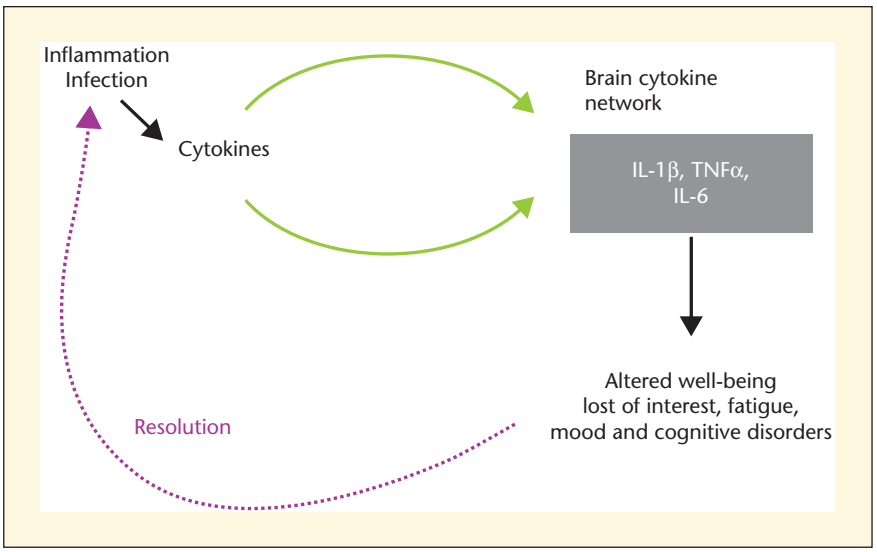

Figure 1. *Inflammation affects the well-being. Cytokines produced by immune cells act into the brain to induce their own synthesis by microglial cells. In turn, brain cytokine interleukin(IL)-1β, IL-6 and tumor necrosis factor (TNF) α trigger the development of mood and cognitive disorders and, as a consequence, disturb well-being.*

protection of the brain against neurodegenerative disorders.

Diet constitutes a strategy of choice for such an approach, since it represents an environmental factor to which individuals are exposed throughout their life. Increasing attention has been paid to omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs), micronutrients that are essential since they cannot be synthesized de novo by the organism. An increasing database attests of the powerful immunomodulatory effects of PUFAs (Calder, 2001). Thus, n-3 PUFAs form the basis of lipid derivatives (neuroprotectins and resolvins) with anti-inflammatory properties, whereas n-6 PUFAs are the precursors of the proinflammatory prostacyclins, and stimulate the production and activity of inflammatory cytokines. The brain is extremely rich in PUFAs and the accumulation of PUFAS in brain tissues takes place during the perinatal period in proportions which are dependent on maternal dietary levels. Conversely, their levels diminish as the individual ages, but can be corrected by appropriate nutritional strategies. During the last few decades, the lifestyle of Western societies has evolved towards a decrease in energy expenditure mainly related to our sedenterization, processes and a changes in our dietary habits towards the consumption of energy-rich foods with high levels of saturated fats, n-6 PUFAs and sugar, and poor in vitamins and micronutrients (Simopoulos, 2001). This dramatic reduction in the dietary supply of n-3 PUFAs and the corresponding increase in n-6 PUFAs, leading to an imbalanced n-6/n-3 ratio currently estimated at 12-20 in developed countries (of note, the current recommended ratio is 5), could therefore contribute to the sensitization of the brain to inflammatory cytokines, and thus to the development of neurodegenerative and/or neurobehavioral disorders.

The innate immune system of the brain

Microglial cells are the resident macrophages of the brain, and constitute the first line of immune defense of the brain (phagocytosis, antigen presentation and secretion of proinflammatory cytokines) (Biber *et al.*, 2007). These cells have a ramified morphology when quiescent and an ameboid morphology when activated and they produce cytokines. Ramified microglia cells generally do not display phagocytic activity and weakly express ligands and receptors involved in macrophage function. Disseminated throughout the brain parenchyma, they use their processes to receive signals such as inflammatory cytokines from their microenvironment, which reveal the existence of a lesion or the presence of a pathogen. In order to do this, microglial cells express several membrane receptors, including those for the inflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6, as well as those that allow the recognition of PAMPs (pathogen-associated molecular patterns), such as the bacterial endotoxin receptors Toll-like receptor (TLR)4 and CD14. Recent evidence indicates that neurons control microglial activity. As a result, neurons release ON or OFF signals to regulate the activation of microglia. OFF signals (CD200, CX3CL1, CD47, CD55 and HMGB1) are produced by healthy neurons to keep microglia in their surveillance mode. On the opposite, damaged neurons express inducible ON signals (chemokines, purine and glutamate) to activate microglia and phagocytosis (Biber *et al.*, 2007). Interestingly, such neuronal-glial interactions are impaired in the aged brain leading to amplified and prolonged microglial activation and production of proinflammatory cytokines (Streit, 2006).

Brain innate immune system in the aging brain

Aging is characterized by a chronic low grade inflammatory state with a higher expression of proinflammatory cytokines IL-1*b*, IL-6 and TNFα to the detriment of anti-inflammatory factors such as IL-10 and IL-4. This state is called *inflammaging* at the periphery and in the brain. Recent clinical and experimental data obtained in our group have shown a strong association between blood proinflammatory cytokines levels, especially IL-6, quality of life and neuropsychiatric symptoms in a cohort of elderly subjects (Capuron *et al.*, 2009; Capuron *et al.*, 2011) and in aged laboratory mice (Moranis *et al.*, 2011). The mechanisms underlying the effect of proinflammatory cytokine on mood and cognitive disorders have been intensively studied in rodents (Yirmiya and Goshen, 2011). In the brain, IL-1β, TNFα and IL-6 are produced by glial cells (microglia and astrocytes) in response to peripheral immune stimuli like the bacterial endotoxin lipopolysaccharide (LPS) (Laye *et al.*, 1994). Studies using minocycline, a tetracycline derivative that inhibits microglial activation and cytokine production, show a link between brain cytokine production and depressive-like symptoms as well as

spatial memory impairment (Dantzer *et al.*, 2008). In addition to impairing the metabolism of serotoninergic and glutamatergic neurotransmission systems, which are well known players in mood and cognition respectively, brain proinflammatory cytokines alter hippocampal synaptic plasticity in adult and aged rodents (Lynch, 1998). Importantly, we recently showed in a population of elderly subjects, that age-related low-grade systemic inflammation was associated with alterations in the activity of two enzymatic pathways, the indoleamine 2,3 dioxygenase (IDO) and guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) pathways, which are involved on in the metabolism of key monoamines (Capuron *et al.*, 2011) *(figure 2)*. Interestingly, increased IDO activity was associated with the depressive symptoms of lassitude, reduced motivation, anorexia, and pessimism in the same population. In contrast, decreased GTP-CH1 activity correlated more with neurovegetative symptoms, including sleep disturbance, digestive symptoms, fatigue, sickness, and motor symptoms.

IL-1 overexpression has been implicated in both the initiation and progression of neuropathological changes (Rothwell and Luheshi, 2000). Accordingly, overexpression of IL-1 in the Alzheimer brain has been linked to an increased microglial activity, frequently associated with amyloid plaques. This specific distribution suggests a role for IL-1 in the initiation and progression of neuritic and neuronal injury in Alzheimer's disease, because of its appearance in early plaque formation and its absence in plaques that are devoid of injured neuritic elements. In addition, brain from Tg2576 mice (a model of Alzheimer disease) exhibited significant increases in IL-1 expression in comparison to healthy animals. Moreover, aged Tg2576 showed mounted and exacerbated cytokine response to LPS, a process that may be responsible for the amplification of degenerative processes. IL-1 administration was found to diminish food intake in a greater extent in aged mice compared to adults.

Age-induced IL-1 overproduction in the brain, and more particularly in the hippocampus, is associated with a decrease in synaptic plasticity measured by long term potentiation (LTP) in the dentate gyrus, which could explain the cognitive impairment observed in the elderly. Receptors for IL-1 are distributed with a high density in the hippocampus, where IL-1 exerts inhibitory effects on the release of calcium. There is also evidence for a role of endogenous brain IL-1 in the normal physiological regulation of hippocampal plasticity and learning processes (Lynch, 1998). Low levels of IL-1 are essential for memory and plasticity, whereas higher levels of IL-1, similar to those achieved during aging and neurodegeneration, can be detrimental.

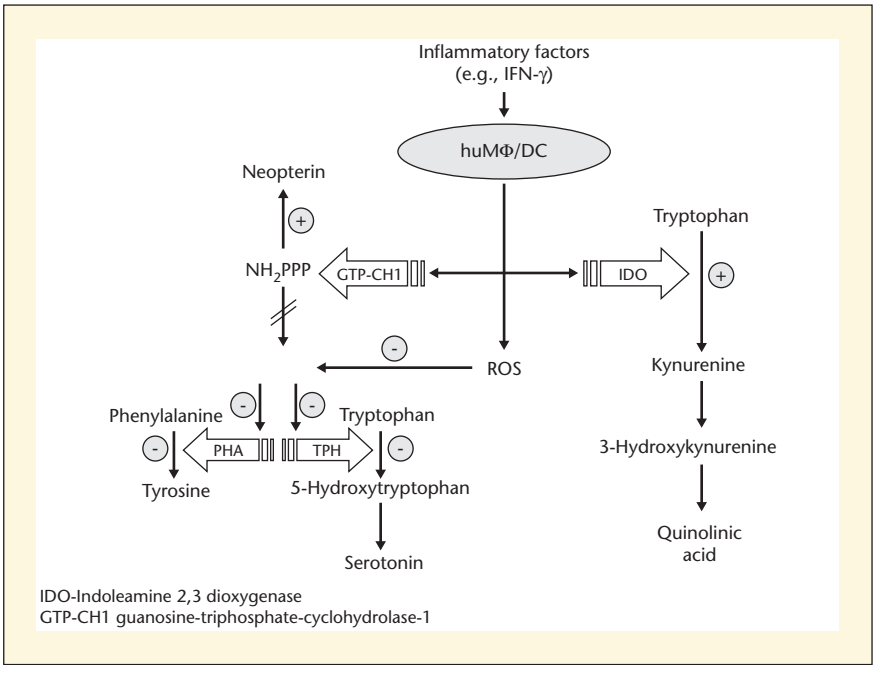

Figure 2. *Inflammation alters amino acid metabolism. Low-grade systemic inflammation in elderly (> 65 years-old) is associated with alterations in the activity of two enzymatic pathways, the indoleamine 2,3 dioxygenase (IDO) and guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) pathways, which are involved on in the metabolism of key monoamines serotonin and (Capuron* et al.*, 2011).*

Polyunsaturated fatty acids and their role in the control of innate cerebral immunity and its behavioral effects

PUFAs of the n-3 or n-6 families are essential nutriments, as they cannot be generated de novo in mammals. In plants, they exist as precursors (linoleic acid (18:2n-6, LA) and α-linolenic acid (18:3n-3, ALA)) that are metabolized by a series of elongation and desaturation steps into arachidonic acid (20:4n-6, AA) in the first case and eicosapentaenoic acid (20:5 n-3, EPA) and docosahexaenoic acid (22:6 n-3, DHA) in the second. These PUFAs are incorporated into cell membranes as phospholipids. The liver is the principal site of conversion of the precursors LA and ALA into long-chain PUFAs, although other organs such as the brain also express the necessary elongases and desaturases. Since the two series of PUFAs compete for the use of the enzymes necessary for their biosynthesis, and because they have distinct physiological properties, the n-6/n-3 ratio in the diet is of particular importance. Foods that were previously consumed by humans were rich in n-3 PUFAs (products of hunting), while those consumed today are poor in these nutrients. Since the industrial revolution, the ratio of n-6/n-3 PUFAs in the diet has increased from 1 to almost 20 in industrialized countries like the United States, leading to a significant deficiency in n-3 PUFAs (Simopoulos, 2006).

The dietary deficiency in n-3 PUFAs is associated with significant decreases in PUFAs intracerebral levels, promoting thus neuroinflammatory processes and

the subsequent development of inflammatory-based CNS disorders (Laye, 2010). Supporting this notion is the low very incidence of inflammatory disorders (e.g., psoriasis, asthma, multiple sclerosis) in populations, such as Greenland Inuits, with a high n-3 PUFAs dietary intake due to elevated fish consumption. The effect of n-3 supplementation is currently subject to debate. While some clinical studies have reported anti-inflammatory effects of n-3 PUFAs administered in the context of chronic and autoimmune inflammatory disorders, other reports fail to reproduce these findings. Conversely, dietary supplementation with fish oil rich in long chain n-3 derivatives, including EPA and DHA, leads to an improvement in symptoms in patients with rheumatoid arthritis, chronic inflammatory intestinal disorders or multiple sclerosis (Calder, 2006).

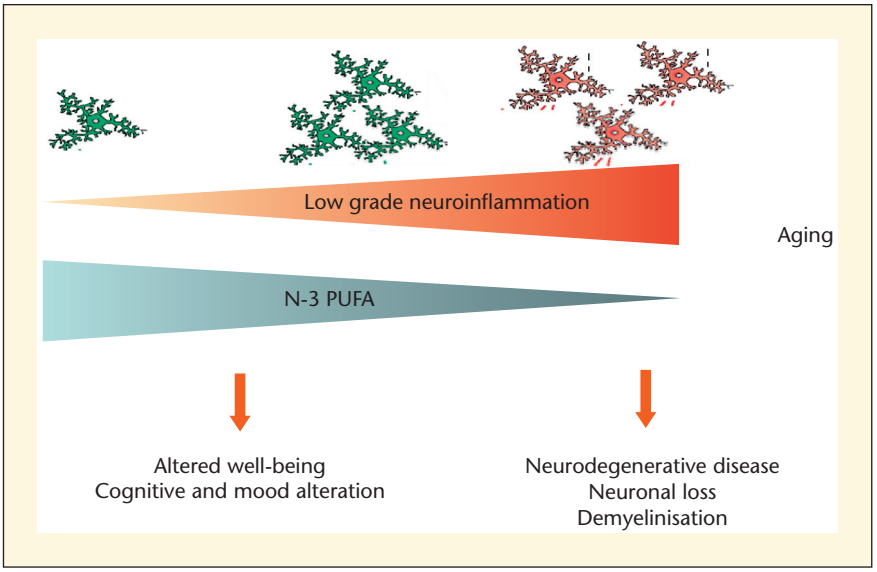

Figure 3. *Neuroinflammation, n-3 PUFAs and aging. Aging is characterized by a chronic low grade inflammatory state with a microglial activation and a higher expression of proinflammatory cytokines to the detriment of anti-inflammatory factors. This state is called* inflammaging *at the periphery and in the brain. Inflammaging could be linked to the decrease in brain n-3 PUFA and involved in altered well-being measured in elderly.*

Consequences of the decrease in n-3 PUFAs on age-related neuroinflammation

Experiments conducted in animals have highlighted brain DHA as a potent mediator of the protective effects of dietary n-3 PUFAs. Because it cannot be synthesized de novo in mammalian cells, brain DHA must be provided in the diet, either in the form of its precursor α-linolenic acid (α-LNA, 18:3n-3) or in the form of DHA. Low dietary intake of n-3 PUFA decreases DHA levels in the animal brain. As a result, emotional behavior (depressive-like symptoms and anxiety) as well as learning and memory are impaired as shown by us and others (Fedorova and Salem, 2006; Lafourcade *et al.*, 2011; Moranis *et al.*, 2011). On the opposite, positive effects of diet enriched in DHA on learning and memory have been demonstrated in laboratory animals (Gamoh *et al.*, 1999; Yehuda *et al.*, 1999; Carrie *et al.*, 2002). During aging, the level and replacement of brain PUFAs decreases, particularly in the hippocampus, cortex, striatum and hypothalamus *(figure 3)*. Brain levels of DHA and AA diminish in aging rats who display alterations in cognition and in LTP in the hippocampus (Favreliere *et al.*, 2003). In transgenic SAMP8 mice, in which aging is accelerated, DHA decreases with age whereas lipid peroxidation increases (Petursdottir *et al.*, 2002). In addition, the conversion of the precursors LA and ALA into their long-chain derivatives becomes less efficient. In fact, the activity of the desaturases responsible for the conversion of LA and ALA into their respective long-chain derivatives, and the activity of the Δ6 desaturase in particular, decreases with age in the liver and the brain. Phospholipid synthesis pathways are also altered with age, thus reducing the incorporation of PUFAs into membranes. The combination and interaction of these different alterations associated with aging contributes to a reduction in the level of DHA, i.e. a reduction in the index of membrane fluidity, in the brain of elderly people. In animals, aging was found to be associated with a decrease in the membrane content of AA in the hippocampus together with an attenuation of long term potentiation (LTP) that can be reestablished by a diet containing AA (McGahon *et al.*, 1999). These data support the idea of the importance of DHA dietary supply in aged subjects *(figure 3)*.

As mentioned above, PUFAs represent potent immunomodulatory agents. We have recently demonstrated *in vitro* that the production of IL-1β and TNFα by murine microglia induced by LPS was strongly inhibited by DHA through its effect on LPS signaling pathway Nuclear Factor κ B (De Smedt-Peyrusse *et al.*, 2008). *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). In addition, mice exposed throughout life to a diet devoid of n-3 PUFAs displayed lower brain DHA level and higher LPS-induced IL-6 in the plasma and in the hippocampus (Mingam *et al.*, 2008). With aging, IL-6 expression was increased in the cortex of both n-3 deficient and n-3 adequate mice while IL-10 expression was decreased with no effect of long term α-LNA deficient or enriched diet (Moranis et al., 2011) *(figure 4)*. On the opposite, short term exposure to dietary EPA reduced IL-1-induced spatial memory deficit and anxiolytic behavior (Song *et al.*, 2004; Song *et al.*, 2008) and improved LPS and Aβ-induced inhibition of long term potentiation (LTP) in both adult and aged rats (Minogue *et al.*, 2007). The expression of markers of microglial activation (CD68, MHCII and CD11b) increases with age in animals, as does the number of microglia in the brain of humans, attesting of the occurrence of age-related neuroinflammation (Godbout *et al.*, 2005). Microglial cell reactivity is involved in the age-dependant increase in the production of inflammatory cytokines, as demonstrated by the inhibition of inflammatory cytokine overexpression by minocycline in aged rats (Griffin

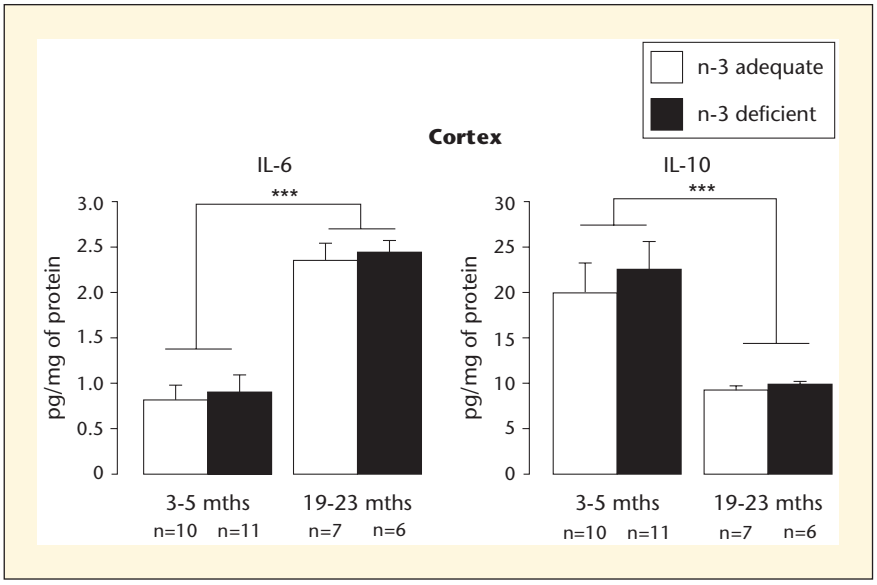

Figure 4. *Long life adequate diet consumption does not protect from age-associated neuroinflammation. After mating, female mice were submitted either to an essential fatty acid adequate diet containing a mixture of rapeseed oil (rich in α-LNA), high-oleic sunflower oil and palm oil resulting in an α-LNA/LA ratio of $^1/_4$ (n-3 adequate diet), or to n-3 PUFA deficient diet (n-3 deficient diet) containing only sunflower oil. Male pups were fed the same diets as their dams. IL-6 and IL-10 were measured by multiplex in the cortex of adult (3-5 month-old) and aged (19-23 month-old) mice fed the n-3 adequate (diet or n-3 deficient diet. Data are expressed as mean ± SEM. Age effect, ***p<0.001. (Moranis* et al.*, 2011)*

et al., 2006). In a cohort of elderly subjects, depressive individuals with an elevated plasma n-6/n-3 ratio were found to exhibit higher levels of TNFα and of IL-6 (Kiecolt-Glaser *et al.*, 2007). Additionally, 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). In rats, microglial activation, production of IL-1β and alterations in hippocampal LTP with age were attenuated by EPA (Lynch *et al.*, 2007). 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 neurobehavioral effects in elderly individuals (Laye, 2010).

Epidemiological studies reveal the importance of n-3 PUFA levels in the development of age-linked neurodegenerative disorders. Thus, decreases in plasma and brain DHA levels have been shown in patients with Alzheimer's disease. These results, however, remain controversial, since other studies have demonstrated an increase or an absence of variation in brain DHA levels in similar populations. Nonetheless, the risk of dementia was found to be augmented in elderly subjects presenting low levels of circulating EPA (Samieri *et al.*, 2011). In addition, regular consumption of diets rich in n-3 PUFA, such as the Mediterranean diet, appears to contribute to a decrease in the risk of depression and/or dementia in the elderly (Feart *et al.*, 2008; Feart *et al.*, 2011). The use of a mouse model of Alzheimer's disease, the Tg2576 mouse, has demonstrated that a dietary supply of DHA leads to a reduction in the formation of amyloid plaques. However, the administration of dietary supplements containing DHA to patients with Alzheimer's disease or mild cognitive impairment has not yielded conclusive results (Calon and Cole, 2007).

Conclusion

There is growing evidence that the expression and action of proinflammatory cytokines in the brain are responsible not only for the development and maintenance of mood and cognitive disorders during the host response to infection, but also during chronic inflammatory states and aging. In addition, neuroinflammation can have detrimental consequences on neuronal viability, especially when maintained over long periods of time and transiently amplified by peripheral infectious episodes. All of this points to the interest of finding new ways of controlling inflammation in the brain. Because of their abundance in the brain and their modulatory effects on inflammation and cell functions, PUFAs definitely play a role in this process. However, this role needs to be better characterized by multidisciplinary studies aimed at assessing the effects of these molecules at different levels, from the molecular level to that of the organism as a whole.

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