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Review

Omega-3 fatty acids and brain resistance to ageing and stress: Body of evidence and possible mechanisms

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ABSTRACT

The increasing life expectancy in the populations of rich countries raises the pressing question of how the elderly can maintain their cognitive function. Cognitive decline is characterised by the loss of short-term memory due to a progressive impairment of the underlying brain cell processes. Age-related brain damage has many causes, some of which may be influenced by diet. An optimal diet may therefore be a practical way of delaying the onset of age-related cognitive decline. Nutritional investigations indicate that the ω-3 poyunsaturated fatty acid (PUFA) content of western diets is too low to provide the brain with an optimal supply of docosahexaenoic acid (DHA), the main ω-3 PUFA in cell membranes. Insufficient brain DHA has been associated with memory impairment, emotional disturbances and altered brain processes in rodents. Human studies suggest that an adequate dietary intake of ω-3 PUFA can slow the age-related cognitive decline and may also protect against the risk of senile dementia. However, despite the many studies in this domain, the beneficial impact of ω-3 PUFA on brain function has only recently been linked to specific mechanisms.

This review examines the hypothesis that an optimal brain DHA status, conferred by an adequate ω-3 PUFA intake, limits age-related brain damage by optimizing endogenous brain repair mechanisms. Our analysis of the abundant literature indicates that an adequate amount of DHA in the brain may limit the impact of stress, an important age-aggravating factor, and influences the neuronal and astroglial functions that govern and protect synaptic transmission. This transmission, particularly glutamatergic neurotransmission in the hippocampus, underlies memory formation. The brain DHA status also influences neurogenesis, nested in the hippocampus, which helps maintain cognitive function throughout life.

Although there are still gaps in our knowledge of the way ω-3 PUFA act, the mechanistic studies reviewed here indicate that ω-3 PUFA may be a promising tool for preventing age-related brain deterioration.

1. Introduction

A disturbing feature of western diets is the growing imbalance between ω-6 and ω-3 PUFA that may restrict the availability of ω-3 long-chain polyunsaturated fatty acids (LC-PUFA) (mainly docosahexaenoic acid, DHA) to the tissues and lead to a mild ω-3 PUFA deficiency. Because DHA is more abundant in the brain than in most other tissues, there have been many studies on the effect of an inadequate ω-3 PUFA nutritional intake on brain function (cognition, behaviour) and disorders (psychiatric and neurodegenerative).

Several lines of evidence suggest that an adequate dietary intake of ω-3 PUFA throughout life can preserve cognitive function in the elderly. An increased dietary intake of ω-3 PUFA would therefore be a valuable nutritional strategy for coping with the health concerns in the ageing populations of the developed world. Many of the epidemiological studies questioning the link between the intake of ω-3 PUFA and brain ageing have shown that high ω-3 PUFA intakes are associated with a slower age-related cognitive decline and a lower risk of neurodegenerative dementia, including Alzheimer's disease. However, the many pitfalls associated with human nutritional studies make it almost impossible to clearly demonstrate the benefits of ω-3 PUFA for brain ageing. It is difficult to isolate the ω-3 PUFA intake of subjects from other environmental/cultural factors, and attempts to reduce cognitive decline or dementia with dietary supplements of ω-3 PUFA have so far given differing or inconsistent results.

We need to understand the part played by ω-3 PUFAs in the mechanisms contributing to brain ageing and cognitive decline in order to develop the nutritional guidelines and health claims

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suggested by epidemiological studies. The experimental data accumulated over the past two decades provide a number of clues to the role of ω-3 PUFAs (especially DHA, the main ω-3 PUFA in brain cell membranes) in regulating the glutamatergic synapses that are responsible for memory formation and maintaining their efficacy during ageing. Glutamate is the major excitatory neurotransmitter in the brain. Glutamatergic synapses are particularly abundant in the hippocampus, the brain area mainly involved in memory processes. The plasticity of the glutamatergic synapse is characterised by persistent increase (long-term potentiation, LTP) or decrease (long-term depression, LTD) in synaptic efficacy, which are generally considered to be the major cellular mechanisms that underlie learning and memory. The plasticity of glutamatergic synapses is supported by the concerted action of three cellular partners. These are the pre-synaptic and post-synaptic neuronal compartments and the surrounding astrocyte (the tripartite synapse: for review see Halassa et al., 2007). The homeostasis of the synaptic environment ensures the fine tuning of glutamatergic neurotransmission. Its disruption is an initiating and/or propagating step in age-related brain damage leading to cognitive decline.

This review assesses the numerous and disparate data on the topic to determine how ω-3 PUFA influence the maintenance of the efficient synaptic transmission needed to support memory formation throughout life. We focus on the emerging role of DHA in the neuron–astrocyte cross-talk at the glutamatergic synapse and in the process of hippocampal neurogenesis, both of which are crucial for maintaining proper synaptic function and the associated memory processes during ageing.

Another interesting effect of ω-3 PUFA is their possible ability to regulate the physiological responses to stress and putatively to reduce the deleterious impact of stress on the brain. The long-term consequences of repeated or prolonged stress on brain physiology, and especially on the glutamatergic synapse, may indeed greatly contribute to exacerbate age-related damage to the brain. We therefore also examined data exploring the positive impact of ω-3 PUFA on the resistance to stress, inasmuch as it can explain part of the neuroprotective action of ω-3 PUFA on brain ageing.

2. Nutritional concerns about ω-3 PUFA and the brain

2.1. Imbalance between ω-6 and ω-3 PUFA in western diets

The ω-6 PUFA content of western diets has increased considerably over the past four decades, while the ω-3 PUFA content has remained unchanged. This is due to the increased consumption of vegetable oils rich in linoleic acid (LA, 18:2ω-6) and poor in α-linolenic acid (LNA, 18:3ω-3), such as peanut or sunflower oil, and to the increased ω-6/ω-3 LC-PUFA ratio in meat and dairy products resulting from changes in animal feeding. Therefore, the dietary intakes of ω-3 LC-PUFA (docosahexaenoic acid (DHA, 22:6ω-3) and eicosapentenoic acid (EPA, 20:5ω-3)) are now almost exclusively dependent on fish consumption (sea products contain large amounts of DHA and EPA). These changes have occurred in the USA, Canada, Australia and European countries. The LA/LNA ratio in the diets of French people has increased 4-fold over the past 40 years. It is now about 10–15, far above the guidelines (ω-6/ω-3 ≤ 5) (Legrand et al., 2001; Simopoulos, 2002; Astorg et al., 2004; Ailhaud et al., 2006). The intake of ω-6 LC-PUFA (mainly arachidonic acid, AA, 20:4ω-6) has more than doubled in 40 years (Ailhaud et al., 2006). Data obtained from blood, breast milk and adipose tissue sample indicate that these changes in the intakes of ω-6/ω-3 PUFA have markedly altered the ω-6/ω-3 PUFA status of the western population (Ailhaud et al., 2006). As humans cannot synthesise these PUFA *de novo*, the ratio of the precursors LA/LNA obtained from food determines their ratio in the tissues as well as the ratio of their long-chain derivatives (AA for ω-6 and DHA for ω-3) which compete for the same enzymatic pathway (elongases and desaturases) (for review, see Alessandri et al., 2004). For instance, ω-6 PUFA deprivation has been shown to increase by 25% the conversion of ALA into DHA in rats (Bazinet et al., 2003). The changes in our diet and the poor rate at which LNA is converted into DHA in humans compromise the optimal supply of DHA to the tissues. This is especially a problem for people who do not eat fish. Because PUFA is involved in many aspects of cellular physiology, a lack of dietary ω-3 PUFA contributes to the increasing prevalence of disorders; in particular, it favours the exacerbation of inflammatory processes involving ω-6 PUFA and its derivatives (Calder, 2005). The fact that DHA is more abundant in the brain than in most other tissues raises the question of how an inadequate ω-3 PUFA intake may influence brain function (cognition, behaviour) and disorders (psychiatric and neurodegenerative).

2.2. Influence on brain fatty acid composition

The brain contains large amounts of fatty acids, 50% of which are PUFAs, essentially equal quantities of arachidonic acid (20:4ω-6) and docosahexaenoic acid (22:6ω-3). These PUFAs, which are constituent of cell membranes, are esterified in the Sn2 position of their phospholipids. They confer specific properties on the lipid bilayer because of the length of their carbon chain and the number of double bonds it contains. Thus, DHA is able to make the bilayer dynamic and flexible because of its long carbon chain (22 carbons) and high degree of unsaturation (6 double bounds) (Stillwell and Wassall, 2003). Essentially all the AA and DHA in the brain are provided by plasma stores, albeit astrocytes do seem to synthesise some from ω-3 PUFA precursors (Williard et al., 2001). These plasma stores are provided by the diet and hepatic synthesis from the precursors, linoleic and α-linolenic acids. Most AA and DHA are incorporated into brain structures during the third trimester of prenatal development and the early post-natal period. An adequate dietary supply of ω-6 and ω-3 PUFA during the perinatal period is therefore crucial for the optimal incorporation of DHA and AA into the brain. Thus the limited amounts of ω-3 PUFA in western diets could lead to a relative lack of DHA during brain development. Studies on animal models (review Alessandri et al., 2004) and humans (review Cunnane, 2000) have demonstrated the perinatal decrease in brain DHA due to insufficient dietary ω-3 PUFA. Rats deprived of ω-3 PUFA from the time of their conception have 50% less DHA in their brains than do rats given adequate dietary ω-3 PUFA. The DHA deficit is offset by an increase in the ω-6 PUFA docosapentaenoic acid (22:5 ω-6), only very small amounts of which are usually found in membrane phospholipids (Alessandri et al., 2003, 2004; Champeil-Potokar et al., 2006). Studies in humans have confirmed the crucial need for dietary ω-3 PUFA (and especially DHA) during infancy: babies fed formulas poor in ω-3 PUFA have up to 35% less DHA in their brain than breast-fed babies, and the decrease in DHA is compensated by an increase in 22:5 ω-6 (Farquharson et al., 1995; Makrides et al., 1994).

While the dietary ω-3 PUFA supply largely determines the amount of brain DHA during the perinatal period, it can also have an important impact in adults. Both AA and DHA are continuously released from membrane phospholipids by phospholipases A2 (PLA2) that are activated in response to many signals. The released PUFAs can be converted to signalling molecules (notably eicosanoids and docosanoids) by enzymatic or non-enzymatic oxygenation, metabolised *via* the β-oxidation pathway to energy-producing substrates, re-esterified in membrane phospholipids, or even diffuse back into the plasma. This turn-over of AA and DHA in brain membranes leads to an exchange of the unesterified PUFAs between brain and plasma. This exchange was measured by Rapoport et al. in rats (5 to 8% per day) and in humans (18 mg/day

for AA; 4–5 mg/day for DHA) (Rapoport et al., 2001, 2007; Rapoport, 2003, 2008). Therefore, the dietary ω-3 PUFA supply must compensate for the daily losses of brain DHA throughout life. Adult rats fed a diet lacking ω-3 PUFA for 4 months had 37% less brain DHA than controls (DeMar et al., 2004). Thus, the relative lack of ω-3 PUFA in the western diet may result in insufficient DHA in the brain membranes of many individuals. Fortunately, DHA seems to be so important for the brain that the human body uses efficient sparing mechanisms when the DHA supply is restricted. The brain-plasma turnover of DHA in adult rats fed a diet low in ω-3 PUFA for 4 months was 4-times slower than normal (DeMar et al., 2004). However, the sparing of brain DHA probably alters the signalling cascades involving PLA2 and hence the balance between the bioactive metabolites produced from AA or DHA. This may contribute to the overproduction of AA derivatives that would favour the development of a pro-inflammatory status in the brain. The dietary intake of ω-3 PUFA has been shown to influence the profile of lipid signalling molecules generated by the PLA2/COX axis (eicosanoids and docosanoids) as well as the concentrations of the various PLA2 and COX isoforms (Bazan, 2007; Rao et al., 2007). The activation of the PLA2/COX axis in brain cell membranes (neurons, microglia and astrocytes) is a key element of the response of the brain to homeostasis disruptions leading to glial activation and neuro-inflammatory processes that occur in brain disorders and ageing. The balance between the various isoforms of these enzymes is thought to influence the balance between the good and bad aspects of the neuro-inflammatory processes (Sun et al., 2004).

Therefore, the present lack of ω-3 PUFA in the western diet during infancy and adulthood may gradually result in a chronic DHA deficit in brain membranes. This could result in the emergence of the pro-inflammatory status characteristic of brain ageing in later life (Pizza et al., 2011).

The impact of insufficient ω-3 PUFA dietary supply may be reinforced during ageing by the fact that the ageing brain seems to lose DHA, as shown in rodent models. We and others (Delion et al., 1997; Little et al., 2007) have shown that the brain membranes of old rats (22 month-old) have slightly but significantly less DHA than do those of young rats (4 month-old). The difference is 5% to 20%, depending on the type of membrane phospholipids and is not paralleled by any decrease in AA (Latour et al., 2013). The specific decrease of DHA in aged brain may be due to an age-associated reduction in the activity of the enzymes specifically allowing the incorporation of DHA into brain phospholipids, such as long-chain acyl-CoA synthetase, thought to have specificity for individual PUFA (review Chen et al., 2008). This age-related loss of DHA may be prevented by dietary supplements of DHA, as shown in old rats (Little et al., 2007).

The lack of brain DHA may therefore be crucial for brain ageing and should be of particular concern for the ageing populations of western countries.

3. Possible influence on brain ageing

3.1. Human studies linking ω-3 PUFA to brain ageing

Several lines of evidence suggest that an adequate dietary intake of ω-3 PUFA can prevent cognitive decline and attenuate the physiological disturbances of the brain that are associated with ageing.

There is evidence from several epidemiological studies for an inverse correlation between the ω-3 PUFA intake or fish consumption and the risk of Alzheimer's disease (Kalmijn, 2000; Morris et al., 2003, 2005; Barberger-Gateau et al., 2002, 2005; Schaefer et al., 2006), although others have failed to confirm this link (Engelhart et al., 2005; Devore et al., 2009; Kröger et al., 2009). Studies showing that a high ω-3 PUFA intake can protect cognitive performance or slow a decline in non-pathological ageing are more conclusive (Heude et al., 2003; Whalley et al., 2004; Kotani et al., 2006; van Gelder et al., 2007; Dullemeijer et al., 2007; Dangour et al., 2009) and two recent reviews of the published data (including observational studies and clinical trials) concluded that ω-3 PUFA helped slow down cognitive decline among old people without dementia (Fotuhi et al., 2009) and have a role in preventing the onset of age-related dementia (Solfrizzi et al., 2010). However, the ω-3 PUFA intakes of the subjects in most of these studies depended largely on eating fish or taking food supplements and therefore cannot be truly isolated from confounding factors that also influence cognitive function, such as a high socio-economical status or health concerned habits, and from other healthy nutrients associated with eating fish (Barberger-Gateau et al., 2002). For instance, the French Three-Cities study found that the ω-6/ω-3 PUFA ratio in the diets of poorly-educated people is higher than in that of better-educated people (Feart et al., 2007). Also, the E3N study in France showed that cognitive decline in elderly women was associated with decreased intakes of fish and ω-3 PUFA but also of animal fats and dietary fibres (Vercambre et al., 2009), underlying the global impact of healthy diet which renders difficult the demonstration of a specific protective effect of ω-3 PUFA on cognitive function. Several clinical trials, some of which are still ongoing, are testing the impact of ω-3 PUFA supplementation (oil supplements differing in the combination of DHA with EPA or AA). They do not conclusively show that ω-3 PUFA can protect against the risk of dementia or cognitive decline, except when the cognitive decline is very mild, or on specific cognitive traits (attention, notably) or specifically in non ApoE-ε4 carriers (see exhaustive reviews: Fotuhi et al., 2009; Cunnane et al., 2009; Mazereeuw et al., 2012). Again, many factors explain the weakness of interventional studies to show an effect of dietary ω-3 PUFA on cognitive functions. A better knowledge of the role of ω-3 PUFA in brain ageing is needed to give precise directions for human studies. In particular, more experimental data are needed to determine (1) the effectiveness of the supplementation in terms of dose, type of ω-3 PUFA, duration, and the influence of concurrent ω-6 PUFA in the basal diet, (2) the target of ω-3 PUFA action in brain (neurotransmission pathway, inflammation, neurogenesis. . .) and the specificity of the impacted cognitive traits (memory, attention, emotivity, stress response. . .), (3) the implicated mechanisms in order to select specific responsive populations (genotype, gender, exposure to stress. . .). All these parameters constitute confounding factors that seem to greatly influence the results of the numerous reported studies (Mazereeuw et al., 2012). Therefore, the promising action of ω-3 PUFA to prevent cognitive decline in the elderly needs to be supported by a better understanding of the roles of these PUFA, especially DHA (the main long-chain ω-3 PUFA in cell membranes), in brain physiology.

3.2. Animal studies linking ω-3 PUFA to brain ageing

Animal studies provide several leads as to how ω-3 PUFA may influence physiology of the brain and help it resist age-induced damage. Some of the many experimental studies on rodents showing that an ω-3 PUFA deficiency impairs memory (review Fedorova and Salem, 2006) have confirmed that the ω-3 PUFA status has an impact on age-related cognitive impairment (Umezawa et al., 1995, Kelly et al., 2011) and on several brain physiological parameters that are altered during ageing (review Su, 2010). Since the dietary manipulation of the ω-3 PUFA status can be performed through many ways, we have tried in this review to distinguish results obtained in deficient or supplemented animals and to indicate the type of deficiency or supplementation used. Indeed, different models of deficiency can induce a 35% (4 months of ω-3 deprivation in young adult rats), 50% (first generation deficiency, *i.e.*from conception to death), or even 80% (second or third generation deficiency)

decrease in brain DHA and a compensatory proportional increase in 22:5 ω-6. This late model is probably the less relevant for extrapolation to human. ω-3 PUFA supplementation protocols vary a lot in duration (weeks to months), quality and amount (DHA or/and EPA in various ratio) and generally induce more change in plasma than in brain ω-3 PUFA. In the supplementation models, the peripheral anti-inflammatory action of EPA and DHA takes therefore a significant part in the observed effects.

Some studies have shown altered spatial learning capacities in ω-3 PUFA deficient (first generation deficiency) old mouse (Umezawa et al., 1995; Carrié et al., 2002) or old rats (Yamamoto et al., 1991) as compared to ω-3 PUFA supplied old animals, but some others failed to do so (Moranis et al., 2011). The beneficial effects of short or long-term supplementation with ω-3 LC-PUFA on cognitive improvement have also been documented in old rats (Gamoh et al., 2001 (several weeks of DHA supplementation), Kelly et al., 2011(2-month EPA supplementation)) and in rodent models of Alzheimer disease (Calon et al., 2004; Hashimoto et al., 2005 (several weeks of DHA supplementation)) with some contradictory results (Barcelo-Coblijn et al., 2003; Arendash et al., 2007, (weeks/months of fish oil supplementation)). The beneficial effect of acute (several weeks) fish oil supplementation seems to be, at least partly, attributable to the restoration of synaptic plasticity, notably of LTP, the electrophysiological measure of synaptic plasticity considered to be a support for memory formation, through an anti-oxidative and anti-inflammatory action of ω-3 LC-PUFA (Lynch et al., 2007; Kelly et al., 2011; Dyall et al., 2007; review Boudrault et al., 2009).

Studies by Lynch and collaborators attribute the effect of ω-3 PUFA to the anti-oxidative action of eicosapentaenoic acid (EPA). This ω-3 PUFA does not accumulate in brain membranes but it has anti-oxidative properties that would restore LTP and memory in old rats by reducing the age-related activation of microglia and the associated increase in IL-1β in the hippocampus (Martin et al., 2002; Lynch et al., 2007; Kelly et al., 2011). In support of this, ω-3 PUFA dietary supplementation has been found to reduce the inflammation and oedema that occurs after an experimental brain lesion in young rats. This suggests that ω-3 PUFA have a neuroprotective effect, notably against glutamate excitotoxicity (Valencia et al., 1998; Hogyes et al., 2003 (chronic fish oil supplementation starting from gestation); Mizota et al., 2001 (three bolus of DHA supplementation at three months of age)). Studies by Calon and collaborators have also shown that high DHA dietary intakes protect synaptic components in a transgenic mouse model of Alzheimer's disease (Calon et al., 2004, 2005; Lim et al., 2005).

Therefore, an adequate ω-3 PUFA status seems to help the brain to cope with the various injuries that lead to the progressive age-related impairment of brain function.

4. Possible influence on stress-induced brain alteration

Stress response, which physiologically promotes the adaptation of the body to acute environmental changes, can also induce deleterious processes in the brain in case of chronic exposure. Chronic stress associated alterations are thought to be an aggravating factor in brain ageing. Because ω-3 PUFA seems to temper some features of stress response, one of their major neuroprotective actions may be through their involvement in the stress axis regulation.

4.1. Human studies linking ω-3 PUFA and stress

Stress is a crucial factor that precipitates the pathogenesis of various disorders, from metabolic to cardiovascular and mental diseases. Repeated or chronic exposure to stressful situations is linked to the development of psychological disorders such as anxiety and depression, together with a hyper-responsiveness of the hypothalamic-pituitary-adrenal axis (HPA) (McEwen, 2010 for review). However, individuals differ greatly in their risk of developing disease, partly because they vary in the magnitude and direction of their sensitivity to stress. The intensities of behavioural and neuroendocrine responses to stressful stimuli seem to be inversely related to lifespan. Thus a repeated/sub-chronic stress environment leads to systemic inflammation, which in turn impairs and accelerates cell ageing.

A growing body of evidence now suggests that the status in ω-3 PUFA and/or PUFA metabolism is involved in this individual reactivity and sensitivity to stress (McNamara and Carlson, 2006). Large cross-sectional studies have found inverse relationships between risk of psychological distress and the ω-3 PUFA concentration in the plasma of Cree Indian (Lucas et al., 2009a) and Canadian Inuit populations (Lucas et al., 2009b). Epidemiological studies have revealed a correlation between a reduced DHA concentration in red cell membranes and anxiety and even depression (Liperoti et al., 2009; Ross, 2009). Meta-analyses have demonstrated that an adequate ω-3 PUFA intake affects mood disorders, with significant improvements, particularly in uni- and bipolar depression (Freeman et al., 2006). Further, hostility and anger have also been associated with an insufficient ω-3 PUFA intake, while they were reduced in young subjects faced with the stress of examinations following ω-3 PUFA supplementation in association with an inhibition of the adrenal activation (Delarue et al., 2003; Hamazaki et al., 2005; Hamazaki and Hamazaki, 2008). The few clinical investigations that have tested the effect of fatty acids on anxiety disorders support the apparent anxiolytic effect of ω-3 PUFA (Ross, 2009; Yehuda et al., 2005). A recent prospective, open-label trial of ω-3 PUFA supplementation conducted in patients with accidental injury showed a significant attenuation of post-traumatic stress disorder (PTSD) symptoms (Matsuoka et al., 2010).

4.2. Animal studies linking ω-3 PUFA and stress

It has been suggested that stress alters cell membrane composition and associated functions. Recent studies on monkeys have shown that chronic stress is associated with a higher phosphatidylethanolamine ω-6/ω-3 ratio (Laugero et al., 2011). Chronic exposure of humans to psychological stress or experimental animals to physical stress results in increased lipid peroxidation activity in the brain and results in tissue damage (Zafir and Banu, 2009; Matsumoto et al., 1999; Lucca et al., 2009; Sahin and Gumuslu, 2004). We showed in mice subjected to an unpredictable chronic mild stress (UCMS) procedure that supplementation in ω-3 long-chain PUFA could reverse certain effects of the stress in cerebral structures involved stress-related behaviours, but in the same time, UCMS prevented the incorporation of supplemental-DHA into brain phospholipid membranes (Vancassel et al., 2008). The chemical structure of DHA makes it highly sensitive to oxidation and this could contribute to the lower DHA concentrations in the brain phospholipids of stressed subjects.

We have recently used the paradigm of early maternal separation (MS) as social stressor (Matthews et al., 1996) to show that adult rats that had been separated and kept on a chronic dietary ω-3 PUFA deficiency (2 generations) were more impulsive and reactive to novelty and exhibited changes in reward response as compared to separated rats fed an ω-3 PUFA balanced diet (Mathieu et al., 2008), particularly when coping with stressful situations. We also found the well-known diet-induced DHA loss in brain membranes which was compensated for by an increase in ω-6 PUFA, especially AA. However, this increase in AA was particularly pronounced in rats subjected to the stress of MS, suggesting a pro-inflammatory status. Clarke et al. (2009) also described a pro-inflammatory PUFA profile as a persistent consequence of the

stress of MS in Sprague-Dawley rats, with a concomitant increase in AA and decrease in total ω-3 PUFA in the plasma of stressed rats compared to unstressed rats. In line with this study, we have recently shown that chronic restraint stress induced a slight but significant decrease in the DHA content of brain phospholipids in Wistar rats (Hennebelle et al., 2012). In these rats, we also found that ω-3 PUFA dietary deprivation (first generation) increased some stress-induced behavioural traits (increased grooming and reduced locomotor activity) while Long-chain ω-3 PUFA chronic dietary supplementation (first generation) attenuated some of the stress-responses including elevation of corticosterone, weight loss and reduced locomotor activity (Hennebelle et al., 2012). These data suggest that the stress response is, at least partly, dependent on the n-3 PUFA supply.

We have previously shown that the modifications of the brain lipid composition that occur in ω-3 PUFA deficient rats (two-generation deficiency) are associated with changes in monoaminergic neurotransmission. Thus the frontal cortex and the nucleus accumbens of deficient animals have below-normal dopamine concentrations. This was associated with decreased densities of the vesicle monoamine transporter 2 (VMAT2), suggesting a presynaptic deficit in dopamine storage (Delion et al., 1994; Zimmer et al., 1998). There were also changes in the balance between the spontaneous and stimulated release of neurotransmitters (Aïd et al., 2003, 2005; Kodas et al., 2004; Zimmer et al., 2000, 2002), along with overexpression of dopaminergic 2 (RD2) receptors in mesolimbic and mesocortical structures (Kuperstein et al., 2005, 2008). This very high concentration of D2 receptors has been attributed to hypersensitivity caused by impaired DA production during brain development, corresponding to a compensatory mechanism making targeted synapses able to act even when the DA concentration is low. Others have shown a reduction in the number of dopamine neurons in both the substantia nigra and the tegmental area (Ahmad et al., 2008). The striatum content of DA metabolites (DOPAC and HVA) was increased in deficient animals, indicating active DA metabolism and increased DA use in this cerebral area. Thus, chronic ω-3 PUFA deficient rats suffer from striatal hyperdopaminergia, probably caused by cortical hypodopaminergia, which is consistent with the observed hyperactive locomotion and learning deficits (Vancassel et al., 2005, 2007; Lavialle et al., 2010; Mathieu et al., 2008; Fedorova and Salem, 2006). There are also reports of changes in the vesicular stores of serotonin and the density of serotoninergic 1 and 2 receptors in ω-3 PUFA deficient (two generations) rats (Kodas et al., 2004; Yoshida et al., 1997).

Studies using microdialysis showed that a chronic DHA deficiency (two generations) also modified some cholinergic neurochemical parameters that could be related to cognitive alterations. There were changes in the release of acetylcholine in the hippocampus of adult deficient rats (Aïd et al., 2003) and in ageing rats in response to a DHA-enriched phospholipid diet (Favrelière et al., 2003). All these data suggest that a deficit in ω-3 PUFA in brain membranes, particularly in the early stages of development, may lead to a cascade of suboptimal neurotransmitter system functions and then to altered emotional and cognitive responses to environmental challenges.

4.3. Stress and brain ageing

The cellular changes in the hippocampus and behavioural alterations that occur during ageing are thought to be exacerbated by stressful events during life, as postulated in the "glucocorticoid hypothesis of stress and ageing" (Gilad and Gilad, 1995; Kim and Yoon, 1998; McEwen, 2000, 2001; Sapolsky et al., 1986). Prolonged exposure to stress may lead to exacerbation of inflammatory processes, increased risk of age-related brain disorders (Joëls et al., 2004; Swaab et al., 2005) and aggravation of age-related cognitive deficits (McEwen, 1999; Porter and Landfield, 1998; Sandi and Touyarot, 2006). Chronic stress has been reported to damage hippocampal structures and to affect hippocampal-dependent learning. Stress (and the associated overexposure of the brain to glucocorticoids) inhibits LTP and enables LTD in the CA1 region of the hippocampus, alters the synaptic vesicle exocytosis (Magarinos et al., 1997; Gao et al., 2006; Pavlides et al., 2002) and the astroglial regulation of glutamate (Gilad et al., 1990; Fontella et al., 2004, 2005; Yang et al., 2005; Autry et al., 2006). Stress also depresses neurogenesis in the hippocampus of adults, and this probably contributes to the acceleration of ageing (Kim and Yoon, 1998; Warner-Schmidt and Duman, 2006; Paizanis et al., 2007).

Thus, a combination of stress and an ω-3 PUFA deficit could be a powerfull stimulus of a state of biochemical stress, especially by promoting a pro-inflammatory status, and thus lead to accelerated cell ageing.

This suggests that it would be possible to slow brain ageing processes by reducing perceptions of stress and increasing healthy behaviour. A dietary supplement of ω-3 PUFA could be effective in protecting against premature ageing.

5. Mechanistic leads

The hypothesis that a high brain content of DHA optimises the resistance of the brain to stress and ageing is supported by studies showing that DHA is involved in the mechanisms governing synaptic function and its regulation/protection. We will therefore examine the aspects of neuronal and astroglial activities that are influenced by the brain DHA status and may help maintain cognitive performance during ageing. We will focus on the tripartite synapse supporting glutamatergic transmission (the dominant excitatory system in brain) which is one of the most well documented synaptic regulations related to memory formation, in the pre-frontal cortex and in the hippocampus. The hippocampus is also the site of adult neurogenesis, which also helps maintain cognitive function. We will see that neurogenesis is probably influenced by the brain DHA status.

5.1. Neurotransmission

5.1.1. Age-induced alteration in glutamatergic synaptic transmission

The age-related decline in cognitive capacities, shown in various studies in rodents (see for review Bergado and Almaguer, 2002; Burke and Barnes, 2006), humans (Albert, 1997; Langley and Madden, 2000; Hänninen and Soininen, 1997) and primates (Bachevalier et al., 1991), originates from many physiological alterations. One of them is the deregulation of the glutamatergic synapse in the hippocampus and pre-frontal cortex. The efficacy of the glutamatergic transmission depends on the presynaptic release of glutamate, the activation by glutamate of the post-synaptic 2-amino-3-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, and the elimination of glutamate by astroglial transporters GLAST and GLT-1 (Fig. 1). All of these components are finely regulated and can be altered by ageing (for review see Segovia et al., 2001; Rosenzweig and Barnes, 2003).

LTP and its opposite LTD are respectively defined as a persistent increase or decrease in the strength of glutamate neurotransmission. These two main forms of synaptic plasticity have been described in diverse areas of the brain (cortex, amygdala, cerebellum, *etc.*), but they have been most extensively studied in the hippocampus, where they can be easily induced experimentally in *ex vivo* hippocampal slice preparations, using different patterns of high or low frequency presynaptic stimulation. Synaptic plasticity is now widely considered to be the major cellular

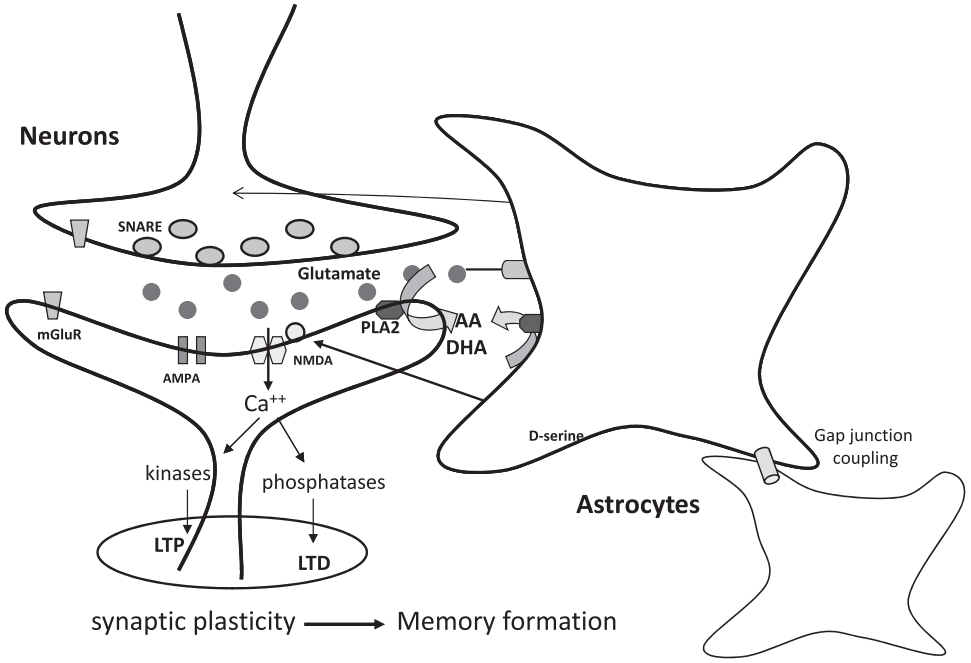

Fig. 1. Neuron–astrocyte cross-talk at the glutamatergic synapse. The fine tuning of glutamatergic neurotransmission, induces diversity in the duration and amplitude of neuron firing, depending on the activities of the neurons and astroglia. Long term potentiation (LTP) and long term depression (LTD) of the synaptic efficacy can be induced experimentally and are considered to be models of memory acquisition. Several neuronal and astroglial mechanisms are involved in regulating synaptic transmission. First, the release of glutamate at the pre-synaptic terminal is induced by intracellular calcium elevation and the resulting exocytosis of synaptic vesicles involving proteins of the SNARE complex. The release is regulated by feedback activation of metabotropic glutamate receptors (mGluR). Second, the post-synaptic reception of glutamate is ensured by 2 types of ionotropic glutamate receptors (AMPA and NMDA). Activation of NMDA receptors triggers the increase in intracellular calcium that activates the protein kinase or phosphatase pathways controlling the number of active AMPA receptors at the synaptic membrane. Third, the concentration of glutamate in the synaptic cleft is regulated by two factors; the extent of the astroglial sheath around the synapse, which controls the extracellular volume and the extra-synaptic leakage of glutamate, and the activity of astroglial glutamate uptake. The astrocytes also release gliotransmitters such as D-serine, which is a co-agonist of the NMDA receptors and is part of the post-synaptic response. Several of the many mechanisms involved in synaptic regulation are affected directly by DHA or by the n-3 PUFA status of brain cell membranes. These include exocytosis, the density of glutamate receptors and the ability of the synapse to exhibit LTP, the signalling pathway involving PLA2 (activated by the post-synaptic reception of glutamate), the activity of astroglial glutamate transporters (EAAT), the morphological plasticity of astrocytes, and their gap junction coupling capacity.

mechanism underlying learning and memory in the hippocampus (Cook and Bliss, 2006; Neves et al., 2008). LTP and LTD are both triggered by activation of the NMDA subtype of postsynaptic glutamate receptors (Morris et al., 1986; see Bliss and Collingridge, 1993), but there is a range of downstream cascades of events that lead to persistent reinforcement or weakening of synaptic strength. LTP is mainly supported by the activation of protein kinases, such as the calcium-calmodulin-dependent protein kinase II (CaMKII, Colbran and Brown, 2004). These then phosphorylate target proteins like the cyclic adenosine monophosphate (AMP) response element binding protein CREB, which ultimately leads to new AMPA receptors being inserted into the synapse, resulting in stronger synaptic transmission (Kessels and Malinow, 2009). Conversely, LTD arises from activation of calcium-dependent phosphatases that dephosphorylate the target proteins. The activation of postsynaptic phosphatases causes internalisation of synaptic AMPA receptors into the postsynaptic cell by clathrin-coated endocytosis thereby reducing sensitivity to glutamate released by the terminals (see for a review Esteban, 2008).

There are numerous indications that LTP deteriorates in the rodent hippocampus with age (Barnes, 1979, 1988; Barnes and McNaughton, 1985; Billard et al., 1997; De Toledo-Morrell et al., 1988; Geinisman et al., 1995). This decline may be attributed to a reduction in the number of glutamate NMDA subtype receptors and the responses they mediate (Kito et al., 1990; Magnusson, 1998; Magnusson and Cotman, 1993; Tamaru et al., 1991; Wenk et al., 1991; Potier et al., 2000; Kollen et al., 2010) associated with a change in their subunit composition (Clayton and Browning, 2001; Clayton et al., 2002; Magnusson et al., 2002). LTD has also been shown to be altered by ageing (Billard, 2010).

Ageing reduces the efficacy of the glutamatergic transmission in the hippocampus, as we showed in the CA1 of aged Sprague-Dawley or Wistar rats (Potier et al., 2000; Kollen et al., 2008) and this decline is partly due to decreased pre-synaptic glutamate release (Latour et al., 2013). Canas et al. (2009) evidenced a decrease in VGlut-1 and VGlut-2, indicative of a diminished glutamatergic neurotransmission in the initial steps of ageing in Wistar rat hippocampus; Minkeviciene et al. (2008) showed a decreased expression of VGlut-1 in the hippocampus of old mice associated to a decrease in KCl-stimulated glutamate release; Stephens et al. (2011) recently examining the age-related alterations in the glutamatergic hippocampal circuitry have shown a loss of glutamate release capacity in CA3 (mossy fibres) and CA1 (Schaffer collaterals) in aged Fischer 344 rats. Earlier studies reported contradictory effects of age on glutamate release in the hippocampus, as well as on the number of AMPA receptors (for review see Segovia et al., 2001). Indeed, compensatory mechanisms probably induce regional variations in the excitatory tri-synaptic circuitry in the ageing hippocampus, contributing to varying results.

5.1.2. Stress-induced alteration in glutamatergic synaptic transmission

Acute stress and corticosteroids have been shown to stimulate glutamatergic transmission, notably in the prefrontal cortex and the hippocampus, by enhancing the pre-synaptic release of glutamate and the density of ionotropic glutamate receptors at the post-synaptic site, resulting in synaptic potentiation (review Popoli et al., 2012). The effects of chronic stress are less clear but seem, on the opposite, to reduce the efficacy of the glutamatergic synapse and the number of active AMPA and NMDA receptors at

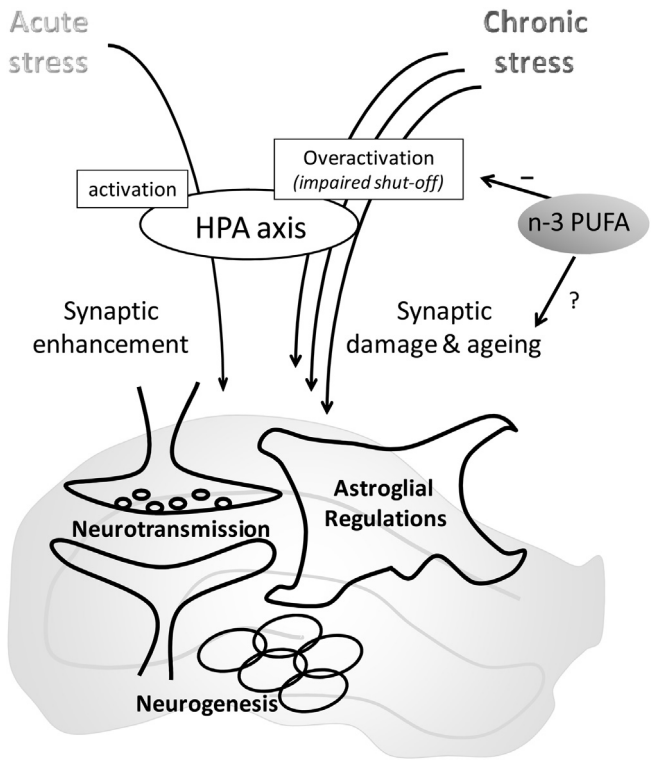

Fig. 2. Influence of stress on brain ageing. Acute stress activates the HPA axis which induces the elevation of circulating corticosteroids and of excitatory amino-acids such as glutamate in the hippocampus. This triggers the reinforcement of certain types of memory by enhancing synaptic function and plasticity. The activation of the corticosteroid receptors present in the hippocampus shuts-off the HPA activation, thereby limiting excessive stimulation. Repeated-chronic stress progressively impairs the mechanism of HPA axis shut-off and leads to a more prolonged HPA response to stressors which contributes to excitotoxicity and the disruption of synaptic homeostasis, notably in the hippocampus. The resulting damages are thought to participate in brain ageing (the "glucocorticoid hypothesis of stress and ageing" (Sapolsky et al., 1986; McEwen, 2010; Popoli et al., 2012)). An adequate n-3 PUFA supply can damper the activation of the HPA axis in stressful condition, and consequently improve neuroprotection and modulate the plasticity of the hippocampus. Therefore, providing enough dietary n-3 PUFAs could be an effective way of protecting against premature ageing.

the post-synaptic sites. Furthermore chronic stress induces morphological changes in the neuronal circuits in the hippocampus. Dendrites shrinkage in the CA3 and loss of dendritic spines in the CA1 in rodents submitted to chronic stress seems to result from excitotoxic processes involving NMDA receptors and decreased neurotrophic factors such as brain derived neurotrophic factor (BDNF) (Magarinos and McEwen, 1995; Magarinos et al., 2011; review Popoli et al., 2012).

The opposite effects of acute and chronic stress on glutamatergic transmission may both explain the deleterious effect of repeated stress throughout life on the ageing process. The increased glutamatergic transmission induced by repeated acute stress may progressively overcome the regulation of glutamate homeostasis and lead to excitotoxic events altering neuronal integrity and damaging glutamatergic transmission (Popoli et al., 2012) (Fig. 2).

5.1.3. *Influence of ω-3 PUFA on glutamatergic synaptic transmission*

5.1.3.1. Influence of ω-3 PUFA on synaptic efficacy and plasticity. ω-3 PUFA seem to regulate the function of the glutamatergic synapse, notably by affecting the expression and function of glutamate receptors and transporters, the machinery of pre-synaptic exocytosis and some components contributing to synaptic plasticity (Su, 2010).

Applying DHA directly onto isolated neurons increases probability of the NMDA-associated channels opening, thereby facilitating NMDA currents (Nishikawa et al., 1994). ω-3 PUFA deficient (first generation) young mice had fewer NR1, NR2A and NR2B NMDA receptor subunits in the hippocampus and LTP was impaired in their hippocampus (Cao et al., 2009). In contrast, LTP was enhanced in the hippocampus of adult rats fed a diet supplemented with EPA, the precursor of DHA (Kawashima et al., 2010 (8-week-EPA supplementation)). Studies on adult rats fed a DHA-enriched diet (for 1 or 2 weeks) showed that DHA acts in synergy with exercise to improve synaptic plasticity and water-maze learning memory performance by increasing the amounts of CaMKII, CREB, BDNF and synapsin-1 (Wu et al., 2008), and GAP-43, syntaxin and NR2B in the hippocampus (Chytrova et al., 2010). Adult normal gerbils given DHA supplement during four weeks had an increase in postsynaptic dendritic spine density in the hippocampus (Sakamoto et al., 2007) and an increase in synaptic proteins (Cansev and Wurtman, 2007). DHA can also promote synaptogenesis and neurite outgrowth by increasing the expression of synaptic genes. Adult fat-1 mice are transgenic mice that can synthesise ω-3 PUFA from ω-6 PUFA. In the hippocampus of these mice, the synaptic genes coding for synapsin-1, GAP-43, post-synaptic density protein-95 (PSD-95) and the GluR1 subunit of the AMPA receptor are all more active and their water-maze learning memory performance is improved (He et al., 2009).

In aged rodents, several studies have shown improved cognitive performance after ω-3PUFA supplementation (especially with DHA and EPA supplementation) (Umezawa et al., 1995; Yamamoto et al., 1991; Carrié et al., 2002; Gamoh et al., 2001; Hashimoto et al., 2005; Calon et al., 2004, 2005) and some of them have correlated the improved learning capacities to a restoration of synaptic plasticity in the hippocampus (Martin et al., 2002; Lynch et al., 2007, Kelly et al., 2011). However synaptic regulation has not been examined in these studies. Only one study, that of Dyall et al. (2007) found that a fish-oil-supplemented diet (given during 12 weeks) restored the concentration of the NR2B and GLUR2 subunits of the glutamate receptors NMDA and AMPA in old rats.

We have recently observed that ω-3 PUFA deficient old rats (first generation) exhibit an aggravation of the age-related alterations of the glutamatergic synapse in the hippocampal CA1 (Latour et al., 2013).

The decrease in glutamatergic transmission (observed by measuring field evoked post-synaptic potentials) was worsened in ω-3 PUFA deficient old rats as compared to ω-3 PUFA balanced old rats. In this study, one pre-eminent impact of ageing and ω-3 PUFA deficiency was the alteration of the pre-synaptic release of glutamate (increased Paired-Pulse Facilitation and decreased expression of VGlut-1 and VGlut-2).

Indeed, we will see in the following section, that among the many mechanisms that determine the efficacy of synaptic transmission, the pre-synaptic release of neurotransmitter may well be an important target of ω-3 PUFA.

5.1.3.2. Influence of ω-3 PUFA on the presynaptic release of neurotransmitter. Our results and those of others have shown alterations in most of the neurotransmission pathways in the brains of ω-3 PUFA-deprived (two generations) rodents. We showed that these changes involve the pre-synaptic storage of neurotransmitters and the dynamics of their release (Lesa et al., 2003; Zimmer et al., 2002).

The release of neurotransmitter is a closely regulated process that involves the recruitment of the SNARE protein complex at the active zone. Upon arrival of action potential, the SNARE proteins provide the driving force to initiate the fusion of secretory vesicles with the plasma membrane that leads to exocytosis (Südhof, 2004).

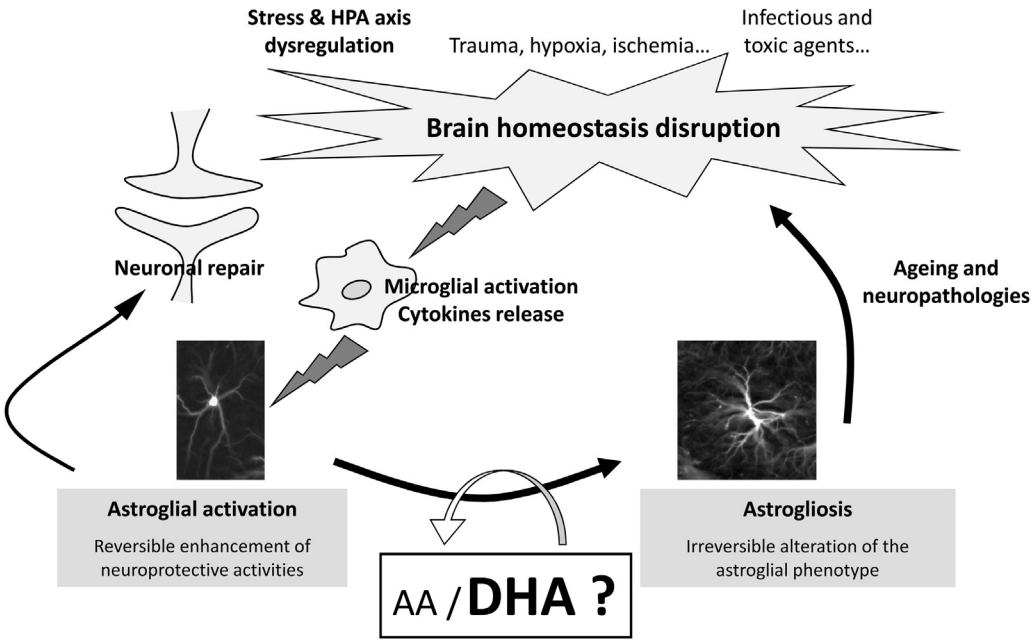

Fig. 3. Astroglial activation: an endogenous brain repair system.
Astrocytes are crucial for enabling the brain to adapt to ageing. The brain suffers aggressive events throughout life (micro-trauma, infections. . .). These events can disrupt the homeostasis of the milieu, such as dysregulation caused by stress (increased glutamate release following activation of the hypothalamus-pituitary-adrenal (HPA) axis). This disturbance activates the microglia, the immune cells of the brain, which then release pro-inflammatory cytokines (IL-1β, IL-6, TNFα) that in turn activate the astrocytes. Activation of the astrocytes reinforces their neuroprotective action. They restore the homeostasis by eliminating toxic molecules like glutamate and K^+ and releasing neurotrophic factors. But when the insults are too intense or too frequent the astrocyte activation turns to astrogliosis, which is an irreversible alteration of the astrocyte phenotype. Diffuse astrogliosis gradually occurs with age, resulting in a progressive loss of the regulatory functions of the astrocytes. Astrogliosis therefore contributes to the impairment of synaptic transmission and the neuron damage associated with ageing. A high DHA/AA ratio in brain cell membranes may temper the exacerbation of AA-signalling cascade involved in these processes. It may also optimise some essential properties of the astrocytes, as suggested by our results. Again, an adequate n-3 PUFA dietary intake that provides sufficient DHA to the brain may limit the astroglial activation developing into astrogliosis and slow down age-induced brain damage.

Latham et al. (2007) have shown that arachidonic acid (AA, 20: 4ω-6) regulates the assembly of the SNARE complex in chromaffin cells. It has also been shown recently that a dietary-induced decrease in DHA in the rat hippocampus leads to changes in the concentration of ternary SNARE complexes (Pongrac et al., 2007).

These data suggest that the PUFA modulates neurotransmitter release *via* a single mechanism, and that exocytosis could be the key target.

The modulation of neurotransmission by ω-3 PUFA was confirmed in neuroblastoma cells (SH-SY5Y). These have neuronal features and contain the proteins needed to regulate secretion (Goodall et al., 1997) and so are a suitable model in which to study exocytosis (Ou et al., 1998). We have shown that the incorporation of DHA into membrane ethanolamine glycerophospholipids (by incubating the cells with DHA for 72 h) is associated with an enhanced spontaneous release of norepinephrine from SH-SY5Y cells (Mathieu et al., 2010). These results suggest that shifting the balance between ω-3 and ω-6 PUFA incorporated into brain membrane towards a low AA/DHA ratio affects neurotransmission by altering the spontaneous efflux of neurotransmitters. SH-SY5Y cells incubated for a short time (3 min) with exogenous DHA also increased norepinephrine release, suggesting that DHA acts directly on the exocytosis pathway (this effect was not observed with AA under similar conditions). We observed no change in the mRNAs and proteins of the SNARE complex when the cells were incubated with PUFA for 72 h. The effects on post-translational steps in the synthesis of SNARE complex proteins remain to be explored.

This highlights the importance of the ω-6/ω-3 ratio in phospholipid membranes for the regulation of neurotransmitter release and hence for neurotransmission.

5.2. Neuroprotection

5.2.1. Regulation/protection of the glutamatergic synapse by astroglia (Fig. 3)

The astrocytes are the main regulators of the homeostasis of the glutamatergic synapse. They maintain a safe concentration of glutamate in the neuronal environment by transporting glutamate and by regulating the volume of the extra-cellular milieu, according to the intensity of the glutamatergic input (Danbolt, 2001; Maragakis and Rothstein, 2004). Disruption of the synaptic homeostasis by overstimulating the glutamatergic input (as produced by exposure to stress) or by decreased regulation by the astrocytes (as in ageing) can lead to glutamate accumulating in the extra-cellular milieu and the death of the neuron due to excitotoxicity. Such disruption is therefore considered to initiate and/or propagate the brain damage associated with ageing and disorders (Yi and Hazell, 2006; Matute et al., 2006; Sheldon and Robinson, 2007). The brain responds to disrupted homeostasis by activating microglial cells (microgliosis). These release pro-inflammatory cytokines that in turn activates astrocytes. Activated astrocytes reversibly become more protective by taking up glutamate and releasing neurotrophic/growth factors, leading to synaptic regulation and neuronal repair. When the insults are too intense or too frequent, the astrocyte activation becomes irreversible and the astrocyte phenotype is altered by the process of astrogliosis (Cotrina and Nedergaard, 2002; Sofroniew and Vinters, 2010). This reinforces the disruption of homeostasis, aggravates neuronal damage and progressively exacerbates the dysfunctions associated with neuropathologies and ageing (Morale et al., 2006).

The switch from a repairing to a deleterious glial reaction is therefore a crucial therapeutic/preventive target for maintaining

brain function in ageing (Sun et al., 2004; Heneka, 2006; Morale et al., 2006). This is particularly true in the hippocampus, which is most sensitive to stress, ageing and neurodegeneration (McEwen, 2000, 2001). Because behavioural stress is one of the factors leading to disruption of the homeostasis of the synapse, notably through overstimulation of the glutamatergic transmission, it is believed to exacerbate the ageing degenerative process (for reviews see McEwen, 1999, 2000, 2001; Zarate et al., 2003). Studies evaluating the impact of stress on astroglial function have generated various results depending on the stress protocol and brain area. However, they suggest that chronic stress alter glutamate clearance by astroglia, a process which contributes to elevate extracellular glutamate concentration in brain and progressively deregulate the homeostasis of glutamatergic synapses (Popoli et al., 2012).

5.2.2. Alteration of astroglial function during ageing

Astrogliosis or astroglial hypertrophy is considered a hallmark of brain ageing, and indeed many studies have shown increased GFAP (Glial fibrillary acidic protein, specific to the astroglial intermediate filaments) expression (mRNA and protein) or immuno-reactivity in the brain of aged rodents (Kaur et al., 2008; Lynch et al., 2010; Weinstock et al., 2011), primates (Haley et al., 2010) and humans (review Middeldorp and Hol, 2011). However, the age-related astrogliosis is found more or less pronounced depending on the rodent strain (Alz models show more age-related astrogliosis than wild mice; Minkeviciene et al., 2008), sex (aged female seems to be more prone to astrogliosis; Mouton et al., 2002), brain region (Bernal and Peterson, 2011), and the method used to measure GFAP (immunohistochemistry is less acurate to characterise GFAP increase; Minkeviciene et al., 2008). In some studies, the age-induced increase in GFAP is associated to a slight increase in the number of astrocytes (review Middeldorp and Hol, 2011). The astrogliosis is associated with microglial activation and the brain low-grade inflammatory state occurring in the ageing brain (Cowley et al., 2012).

Whereas reactive astrocytes characterizing acute astrogliosis seem to increase their neuroprotective functions and therefore acquire increased capacity to eliminate extracellular glutamate, ageing astrocytes exhibit altered regulatory function and diminished glutamate uptake activity. Indeed, several studies have shown a decrease in high affinity glutamate transport and in the expression of corresponding glial glutamate transporters in the brain of ageing rodents. We have observed a 30% reduction in the V_{max} and no change in the K_m of astroglial glutamate uptake measured in hippocampal CA1 cell suspensions from old Wistar rats or Sprague-Dawley rats *versus* young ones, indicating that less glutamate transporters were active (Potier et al., 2010; Latour et al., 2013). Other studies have shown a similar 20–30% decrease in glutamate uptake in the cortex of old rats (review Segovia et al., 2001) and in the cortex of old mice (Saransaari and Oja, 1995).

In aged rats, the combination of increased synaptic astroglial coverage due to astrocyte hypertrophy, and reduced glutamate uptake probably concur to enhance ambient glutamate concentration in the synaptic cleft and in the close peri-synaptic area (Rusakov, 2001; Syková et al., 2002). This may favour the activation of pre-synaptic mGluRs controlling the exocytosis of glutamate and then reduce glutamate release at the pre-synaptic membrane in aged rats.

The reduction of pre-synaptic glutamate release in aged rats, as we identified by the elevated PPF and decreased expression of VGlut-1 and VGlut-2 (Potier et al., 2010; Latour et al., 2013), may therefore be due to an increase in synaptic glutamate concentration resulting from the hypertrophy of astroglial processes and the slower scavenging of glutamate by astrocytes.

Disruption of the synaptic environment homeostasis during ageing can, together with changes in glutamate receptor density, also be deleterious for synaptic plasticity. A reduction in the extracellular volume associated with an increase in tortuosity which can be partly attributed to hypertrophied astrocytes, characterised by an increase in GFAP (O'Callaghan and Miller, 1991; Nichols et al., 1993; Cotrina and Nedergaard, 2002), is closely correlated with poor behavioural performances and altered LTP in the aged rat hippocampus (Syková et al., 1998, 2002).

5.2.3. Influence of ω-3 PUFA on the regulation/protection of the glutamatergic synapse

5.2.3.1. Influence of ω-3 PUFA on astroglia. Astrocytes may be a target cell for the effects of ω-3 PUFA in the brain. They have a high concentration of DHA in their membrane phospholipids, which depends on the amount of ω-3 PUFA dietary intakes (Bourre et al., 1984). Our studies on cultured astrocytes indicate that DHA influences major functions involved in the regulation of brain homeostasis.

Astrocytes cultured in standard condition rapidly become DHA-deficient because the fatty acid composition of the foetal calf serum classically added to the medium contains more AA than DHA. Their membranes have a high AA/DHA ratio, similar to that found in the brain membranes of ω-3 PUFA-deprived animals. Adding DHA to the culture medium restores the physiological high concentration of DHA in the astrocyte membranes (Champeil-Potokar et al., 2004). Such DHA-enrichment favours the gap-junction coupling of the astrocytes by increasing the amount of connexin 43, the main protein of gap junctions in astrocytes, and its location at the cell-to-cell interface (Champeil-Potokar et al., 2006). This effect is specific of DHA as it was not observed in AA-enriched astrocytes. The gap junction coupling capacity of astrocytes actively contributes to the neuroprotective and regulatory actions of these cells. It allows the rapid buffering of the glutamate captured from the extracellular milieu, and takes part in the calcium signalling between connected astrocytes (review Giaume et al., 2007).

Another important property of astrocytes is their ability to spread out thin peripheral processes (PAP, peripheral astrocyte processes) that ensheath the synapses (Derouiche and Frotscher, 2001). We have shown that the DHA-enrichment, but not AA-enrichment, of cultured astrocytes changes their morphology (unpublished data). The density of the GFAP in the main processes is increased and numerous PAP appear. This suggests that membrane-DHA is involved in the mechanisms underlying the morphological plasticity of the astrocytes.

Astrocytes also protect neurons by supplying them with appropriate amount of energy substrates, essentially glucose and lactate (Magistretti, 2006). We have shown that ω-3 PUFA deficient (first generation) rats have a lower glucose transport capacity at the blood brain barrier involving endothelial cells and astroglial end-feet glucose transporters than ω-3 PUFA-replete rats (Ximenes da Silva et al., 2002; Pifferi et al., 2005, 2007).

We have also shown that free DHA, as opposed to membrane-DHA, is a potent effector of two important transport systems in astrocytes. Free DHA can rapidly increase glucose transport (unpublished data) and strongly decrease glutamate transport in cultured astrocytes (Grintal et al., 2009). The rapid action of free DHA, which can be released from membrane phospholipids by PLA2 at the synaptic sites, on glucose and glutamate transports, which are involved in the astroglial regulation of synaptic transmission, suggests that DHA have a direct regulatory role in the glutamatergic synapses (Grintal et al., 2009). Several lipid molecules in the synaptic machinery are also regulators, but their role is poorly understood. More studies have been done on AA than on DHA because of its pro-inflammatory potential in brain injury. AA has been claimed to inhibit glutamate transport in astrocytes (Volterra et al., 1992). But our studies with physiological concentrations of PUFA indicated that DHA only, but not AA, inhibited glutamate

transport by astroglia, suggesting that DHA has a specific role in synaptic signalling in physiological situations. AA is only effective at higher concentrations that may be reached in pathological situations inducing cell membrane lysis such as ischaemia.

In summary, dietary ω-3 PUFA may participate in several important functions of astrocyte by maintaining a high amount of DHA in their membranes. These functions, such as gap-junction coupling and morphological plasticity, are involved in their ability to regulate synaptic transmission and protect neurons. Also, by maintaining a balanced AA/DHA ratio in the synaptic membranes, dietary ω-3 PUFA promote the release of DHA in response to PLA2 activation, which may represent an important signalling pathway at the synapse. An adequate supply of dietary ω-3 PUFA throughout life would therefore help preserve the function of the astroglia during ageing.

This was recently confirmed by our study showing that astrogliosis was worsened in the hippocampal CA1 of ω-3 PUFA deficient (first generation) aged rats as compared to ω-3 PUFA balanced aged rats. The reinforced astrogliosis, characterised by increased GFAP and number of astrocytes, was associated with an aggravation of the age-induced decrease in astroglial glutamate uptake (Latour et al., 2013). Therefore ω-3 PUFA deficiency exacerbates the alteration of astroglial function during ageing.

5.2.3.2. Involvement of lipid signalling pathways in the glutamatergic synapse. The disruption of homeostasis at the glutamatergic synapse leads to extracellular glutamate accumulation that may initiate a vicious spiral by over-stimulating the arachidonic signalling cascade initiated by activation of the calcium dependent isoform of PLA2, cPLA2 (Sun et al., 2004; Haydon and Carmignoto, 2006; Bossetti, 2007). The resulting excitotoxicity and astrogliosis are part of the ageing process in the hippocampus and result in a loss of synaptic plasticity and impaired hippocampus-dependent memory. Lipid signalling pathways are directly involved in these mechanisms (Phillis and O'Regan, 2004). The binding of glutamate to NMDA post-synaptic and astroglial receptors activates cPLA2, which releases AA from membrane phospholipids (Ramadan et al., 2010). Excess glutamate may lead to excessive release of AA, especially when cell membranes have a high AA/DHA ratio and a high cPLA2/iPLA2 ratio such as found in the brains of ω-3 PUFA deficient animals (Rao et al., 2007). The release of excess AA then initiates a pro-inflammatory cascade of events involving the production of eicosanoids *via* the activation of inducible cyclooxigenase (COX2) and lipoxigenases (LOX), and the production of pro-inflammatory cytokines (Bazan, 2007; Farooqui et al., 2007). ω-3 PUFA moderate the onset of the arachidonic acid (AA) signalling cascade by down regulating the pro-inflammatory isoforms (cytoplasmic (cPLA2) and secretory (sPLA2)) of PLA2 and cyclooxygenase (COX2), and by reducing the production of eicosanoids. This counteracting effect of ω-3 PUFA on the AA signalling cascade has been described in peripheral tissues (Calder, 2005) and in the brain (Rao et al., 2007; Rapoport, 2008). Furthermore, DHA is released from astrocyte membranes by the calcium independent isoform of PLA2, iPLA2 (Strokin et al., 2007), which is activated by glutamate and seems to play a role in the replenishment of calcium stores (review Sun et al., 2010). iPLA2, which is down-regulated in ω-3 deficient rats (Rao et al., 2007), also participate in the regulation of post-synaptic AMPA receptors. Its activation seems to be neuroprotective by limiting the phosphorylation of the GluR1 subunit of AMPA receptors that exacerbates excitotoxic responses (Ménard et al., 2007). Therefore, the differential activation of cPLA2 and iPLA2 in the glutamatergic synapse, and the respective release of AA and DHA, albeit not precisely deciphered, support the concept of a protective role of ω-3 PUFA.

DHA has been shown to regulate brain cytokines expression in response to experimentally induced inflammation (De Smedt-Peyrusse et al., 2008; Mingam et al., 2008). The anti-inflammatory properties of ω-3 PUFA and the production of potentially protective docosanoids (DHA derivatives) (Bazan, 2005) may therefore regulate microglial activation (Layé, 2010) and favour the activation of reparative glia in response to the disruption of glutamate homeostasis.

5.3. Neurogenesis

5.3.1. Proliferation/differentiation of neural stem cells in the dentate gyrus

At least three areas of the adult mammalian brain continuously generate new neurons throughout life. One is the dentate gyrus of the hippocampus, another is the subventricular zone (SVZ), and the third is the olfactory epithelium. Neuroblasts generated in the SVZ migrate into the olfactory bulb, and this process is particularly active in the rodents. Some studies suggest that there are other sites of neurogenesis, such as the amygdala, the forebrain or the cerebral cortex and that neurogenesis is a local response to pathological events such as ischaemic injury (Macas et al., 2006).

The adult hippocampus harbours neural stem cells (NSC) that contribute to neural repair by generating daughter cells that then become neurons or glia. The neural progenitors are located in the subgranular zone, between the granule cell layer and the hilus of the dentate gyrus. They undergo several steps of proliferation, differentiation and migration before they enter functional neuronal networks in the pyramidal cell layers CA1 and CA3. Several studies have shown that these new connections help to maintain spatial memory, and there seems to be a correlation between the survival of newborn cells and the performance of spatial memory (Borcel et al., 2008; Trouche et al., 2009).

Neurogenesis is highly sensitive to external positive or negative influences, and some stimuli are specific to the areas, like for instance prolactin, which stimulates the proliferation in the subventricular zone, but has no effect on the hippocampus (Larsen and Grattan, 2010). We will focus here on ageing and uncontrollable stress, which act as associated deleterious elements on the hippocampic neurogenesis.

Although neurogenesis persists in the ageing brain, it is markedly reduced. Monitored mainly by BrdU incorporation, the decline has been observed in several species, with differences in the rate of occurrence, but complete similarity in the end-result. The greatest decline occurs around middle age, and is less pronounced afterwards (Kuhn et al., 1996; Nacher et al., 2003; Leuner et al., 2007)

The probable cause for this decline is a reduction in the proliferation of progenitors. BrdU injections have shown that the number of dividing cells declines by 50–90% (Kuhn et al., 1996). Another factor is the lengthening of the cell cycle with age, and particularly the S phase in progenitors (Hayes and Nowakowski, 2002). Cell survival may also be a cause of reduced cell renewal, but the causes may differ with the structures. It has been recently suggested that in the hippocampus specifically, the stem cell depletion occurring with age was associated with a progressive differentiation of the stem cells pool into astrocytes (Encinas et al., 2011)

Neurogenesis is a process very sensitive to external and endogenous factors, and the list of culprits responsible for its decline in old organisms could be extremely long and not particularly relevant. But the influence of stress and stress hormones could be important, and, again, complex according to the nature of the stressor. Exercise, for instance, is considered a predictable and voluntary stress. Its impact on adult neurogenesis is favourable. On the other hand, unpredictable and uncontrollable stress diminishes neuronal regeneration (Wosiski-Kuhn and Stranahan, 2012). It has been frequently suspected that negative stress contributes to the

age-related decline in neurogenesis, since stress is known to influence cognitive functions.

The stress caused by conditions like sleep deprivation, chronic restraint, and an inescapable shock is consistently said to inhibit the proliferation of progenitors. The NSC isolated from stressed animals and grown in culture proliferate more slowly than controls *in vitro* (Mirescu et al., 2006; Kikuchi et al., 2008; Chigr et al., 2009), which seems to indicate that stress can markedly affect the renewal of neural stem cells in the long term. Glucocorticoids also inhibit the proliferation of neural stem cells *in vivo* and *in vitro* (Murray et al., 2008; Kumamaru et al., 2008), and glucocorticoid receptor antagonists can reverse this effect (Mayer et al., 2006).

There is uncertainty about whether ageing stem cells lose their ability to proliferate, or whether the micro-environment in the ageing brain becomes less favourable. Some have suggested that growth factors and neurotrophins synthesis are reduced while anti-neurogenic factors are increased. Neural stem cells from ageing organisms would not have lost *per se* the ability to divide, but would be prevented from doing so by an unfavourable environment (Drapeau and Nora Abrous, 2008). Recent studies have reported finding quiescent pools of NSC in the hippocampus, and claim that the age-associated loss of neurogenesis could be due to a change in the sizes of quiescent and active NSC pools (Lugert et al., 2010; Mira et al., 2010), or to their terminal differentiation into astrocytes (Encinas et al., 2011).

The micro-environment is therefore very important, and that is where DHA could play a decisive role.

5.3.2. *Effects of ω-3 PUFA on neurogenesis*

We recently demonstrated that the fatty acid composition of phospholipids determines the biophysical properties of cell membranes, and protein function or location of neuronal stem cells in culture (Langelier et al., 2010). Fatty acids are also precursors of signalling derivatives, and ligands for membrane and nuclear receptors (Piomelli et al., 2007).

In vivo and *in vitro* studies on the effect of DHA on adult neurogenesis indicate that the PUFA has a favourable influence on neurogenesis. The *in vitro* proliferation of NSC is increased when the cells are grown in medium supplemented with DHA (Kawakita et al., 2006; Kan et al., 2007). AA, *in vitro* though, shows comparable effects. DHA also improves neuronal differentiation, as shown by enhanced neuritogenesis, even in cells isolated from older animals (Calderon and Kim, 2004; Robson et al., 2010). Therefore, DHA could play a positive role in aged organisms, by maintaining active proliferative pools, and favouring neuronal maturation.

Yet, these *in vitro* studies do not always take into account the possible role of ω-6 PUFA. Therefore, *in vivo* observations may help to distinguish the influence of the two PUFA families. Several studies have concluded that an ω-3 -PUFA supplemented diets has a beneficial effect on adult neurogenesis, with enhanced progenitor proliferation, and more nuclear receptors in older animals (Kawakita et al., 2006; Dyall et al., 2010). ω-3 PUFA may also have an impact on the cell environment, in addition to the direct effect on cell properties. For example, rats deficient in ω-3 PUFA synthesise less BDNF (Rao et al., 2007). It has been shown recently that neurogenesis was increased in transgenic Fat1 mice that can synthesise large amounts of DHA, and that the animals also had enhanced spatial learning abilities (He et al., 2009) Adult neurogenesis is not the only event favoured by ω-3 PUFA supplementation; embryonic neurodevelopment is also improved when the diet contains sufficient ω-3 PUFA (Coti Bertrand et al., 2006; Yavin et al., 2009).

In addition to the molecular events already demonstrated, a new avenue of research has now recently emerged, with still scarce data pointing to a possible epigenetic effect of the PUFA supply (Massiera et al., 2010; Innis, 2011; Kulkarni et al., 2011). Since neural stem cells are prone to epigenetic regulations, the question of the existence of such effects on adult neurogenesis should be addressed.

6. Conclusion

Considering the nutritional imbalance between ω-6 and ω-3 PUFA in western diets, the risk of sub-optimal amounts of DHA in the brains of these populations is far from negligible. Analysis of the data from human and animal studies indicates that such a decrease in brain DHA may lead to the erosion of physiological regulation involved in stress responses and of that occurring in the brain during ageing. The aggravation of the impact of stress and ageing on brain, induced by a low status in ω-3 PUFA may superimpose throughout life and participate in cognitive decline. The many data cited here all point to the involvement of DHA in numerous cerebral mechanisms. We therefore postulate that a high concentration of DHA in the brain optimises the efficiency/plasticity of synaptic transmission and helps maintain synaptic homeostasis, both conditions that sustain efficient cognitive processes throughout life. There are now sufficient data indicating that the amount of DHA in membranes influences several steps of synaptic transmission, notably at the glutamatergic synapses. These steps are neurotransmitter release, transmitter post-synaptic reception, and regulation by astrocytes. DHA may also temper the exacerbation of the glial reaction and the resulting pro-inflammatory events that accelerate brain ageing through its effects on astroglia and the way it antagonises AA in the PLA2/COX signalling pathway. Finally, the emerging picture of the role of DHA in neurogenesis in the adult hippocampus suggests that DHA also promotes the renewal of neural cells and the supply of newly formed neurons to support the memory throughout life. While these findings need to be further investigated and validated, they clearly point to the need to re-balance the ω-3 PUFA in our western diet and so help preserve cognitive function in older people.

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