Omega-3 PUFA supplementation differentially affects behavior and cognition in the young and aged non-human primate Grey mouse lemur (Microcebus murinus)

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Abstract – Data are divergent about the ability of dietary ω3 fatty acids to prevent age-associated cognitive decline. Most of the clinical trials failed to demonstrate a protective effect of ω3 fatty acids against cognitive decline and methodological issues are still under debate. Conversely to human studies, experiments performed in adult rodents clearly indicate that long chain ω3 fatty acids play a beneficial role in behavioral and cognitive functions. Inconsistent observations between human and rodent studies highlight the importance of the use of non-human primate models. We recently started a series of experiments on Grey mouse lemurs, an emerging non-human primate model of aging in order to assess the impact of ω3 fatty acids dietary supplementation on several brain functions. These experiments started with the determination of the fatty acids composition of target organs (brain, adipose tissue, liver, plasma) of animals fed under control diet. We then explored the impact of ω3 polyunsaturated fatty acids (PUFA) supplementation on cognition and behavior in young and aged grey mouse lemurs. The aim of the present review is to compare the observations made in young and aged grey mouse lemurs and to explore the possibilities of new experiments in order to bridge the gap between rodents and Humans.

Keywords: Grey mouse lemur / non-human primate / PUFA / aging / cognition / behavior

Résumé – Les acides gras omega-3 affectent différemment le comportement et la cognition chez un primate non-humain jeune ou âgé, le Microcèbe (Microcebus murinus). Les données divergent quant à la capacité des acides gras ω3 à prévenir le déclin cognitif associé à l’âge. La plupart des essais cliniques réalisés jusqu’à présent ne permettent pas de démontrer d’effet protecteur des ω3 contre le déclin cognitif, des problèmes méthodologiques étant encore débattus. Contrairement aux études cliniques, des expériences réalisées chez le rongeur adulte indiquent clairement que les ω3 à longue chaîne ont un rôle bénéfique sur les fonctions comportementales et cognitives, y compris au cours du vieillissement. Les observations contradictoires entre les études humaines et celles réalisées chez le rongeur soulignent l’importance de l’utilisation de primates non-humains. Nous avons récemment commencé une série d’expériences chez un primate non-humain, le Microcèbe (Microcebus murinus), un modèle émergent du vieillissement, afin d’évaluer l’impact d’une supplémentation alimentaire en ω3 sur les fonctions cérébrales. Ces expériences ont commencé avec la détermination de la composition en acides gras de certains organes cibles (cerveau, tissu adipeux, foie, plasma) d’animaux nourris sous régime standard. Nous avons ensuite exploré l’impact des ω3 sur la cognition et le comportement chez de jeunes adultes, puis chez des individus âgés. L’objectif de la présente étude est de comparer les observations faites chez les lémuriens jeunes et âgés et d’explorer les possibilités de nouvelles expériences afin de combler le fossé expérimental entre rongeurs et humains.

Mots clés : Microcèbe / primate non-humain / AGPI / vieillissement / cognition / comportement

1 Introduction

In the brain, ω3 polyunsaturated fatty acids (ω3 PUFA) are present in high quantities (up to 50% of total fatty acids in the cellular membranes and retina). One long-chain derivative of the ω3 family is present in very high quantities in the brain: docosahexaenoic acid (DHA). In animals, a decrease in membrane DHA, obtained by dietary deficiency, is accompanied by severe neurosensory disturbances (learning, behavior, vision) (Lavialle et al., 2007). DHA is known to be involved in modulating the activity and expression of membrane proteins such as receptors, transporters, pumps and ion channels at several stages of neurotransmission (Guesnet et al., 2005). The importance of ω3 fatty acids for the aging brain is revealed by epidemiological studies that address the question of a protective effect of fish and DHA against the risk of cognitive decline in the elderly.
of Alzheimer’s disease, a question that remains under debate (reviewed in Bégin et al., 2009, 2010; Barberger-Gateau et al., 2013).

In addition, in both animals and Humans, a low dietary level of DHA has been associated with increased risk of developing neuropsychiatric diseases. Even if large clinical trials are lacking in Humans, a reduced abundance of ω3 PUFA have been reported in patients with anxiety, while supplementation with ω3 PUFA appears to inhibit activation of the hypothalamic-pituitary-adrenal axis and can ameliorate some of the symptoms of anxiety (Ross, 2009). In animals, Larrieu et al. (2012) recently demonstrated that long-term exposure to an ω3 deficient diet decreases the level of DHA in the brain and impairs the cannabinoid receptor signaling pathway in mood-controlling structures. Mathieu et al. (2011) also evidenced such a link, supporting the notion that PUFA-unbalanced diet, together with early maternal stress, may be a determinant risk factor in emotional disorders.

Conversely to anxiety and mood disorders, data in rodents and Humans are divergent about the ability of dietary ω3 fatty acids to prevent age-associated cognitive decline. Indeed, most of the clinical trials failed to demonstrate a protective effect of ω3 fatty acids dietary supplements against cognitive decline and methodological issues are still under debate (Bégin et al., 2009, 2010). While ω3 supplementation studies in rodents demonstrated a general enhancement of cognitive functions (Fedorova and Salem, 2006), studies in humans are more controversial and have so far not shown clear beneficial effects (Bégin et al., 2009, 2010). However, these studies in rodent and Humans used very different experimental approaches and are therefore difficult to compare.

Inconsistent observations between human and rodent studies (in both adult and aged subjects) highlight the importance of the use of non-human primate models. To our knowledge, only one study investigated the impact of ω3 fatty acid supplementation on behavioral and cognitive functions in non-human primate species (Tsukada et al., 2000). In this study aged monkeys were supplemented with DHA for 1 to 4 weeks (a very short term dietary supplementation), leading to increased regional cerebral blood flow, a parameter closely linked to neuronal activation.

Non-human primates are at the crossroad between genetic models (such as Drosophila melanogaster and inbred mouse strains), non-transgenic rodent models, and human beings, and constitute indispensable models for physiological and biochemical research on ageing. For ageing research, non-human primate models are more relevant to human ageing than classical biological models, such as rodents (Lavery, 2000), for two reasons: (i) they share several genetic, physiological, and anatomical similarities (a complex nervous system in particular) with humans, (ii) they mimic the heterogeneity observed in the human population. Moreover, they can be studied under controlled experimental conditions more easily than humans.

The grey mouse lemur (Fig. 1) is a nocturnal prosimian primate originating from Madagascar. This non-human primate has a life expectancy of around 8 years (Languille et al., 2009, 2010; Barberger-Gateau et al., 2013). The grey mouse lemur exhibits biological seasonal rhythms that are phasochronically driven characterized in particular by a winter body mass gain and decreased resting metabolic rate (Perret and Aujard, 2001). The grey mouse lemur constitutes one of the rare non-transgenic primate models of spontaneous development of Alzheimer’s disease, making this species an adequate model to test the possibility of a cognitive improvement after ω3 fatty acids supplementation in non-human primates (Languille et al., 2012). The grey mouse lemur could thus help bridge the gap between rodents and human studies.

In the present study we review our previously published experiments performed in young (Pifferi et al., 2012; Vinot et al., 2011) and aged (Languille et al., 2012b) grey mouse lemurs receiving or not a long-term dietary supplement of ω3 fatty acids (under the form of fish oil, naturally rich in long-chain ω3 fatty acids). In these studies, we evaluated the impact of ω3 fatty acids on behavior and cognition in both adult and aged primates. We postulated that fish oil supplementation may improve behavioral and cognitive parameters which could be of major importance in the perspective of their use as supplemental ingredient in human foods. After a brief description of the fatty acid composition in lipid classes from the main target tissues (brain, retina, liver and adipose tissue) of non-supplemented animals, we will report the impact of fish oil supplementation on plasma total lipids fatty acids composition. The impact of fish oil supplementation on anxiety, measured in an open-field task, and spatial memory, measured in a radial arm maze task, will then be reported and discussed for both young and aged animals.

![Fig. 1. The grey mouse lemur (Microcebus murinus).](image)

2 Fatty acid composition of the main target tissues in non-supplemented animals

In a first study (Pifferi et al., 2012), we reported the fatty acid composition in lipid classes from the main target tissues (brain, retina, liver and adipose tissue) of non-supplemented animals.
Table 1. Fatty acid composition (g/100g) in plasma phospholipids of young and aged control (CTL) and fish oil (FO) supplemented animals.

<table>
<thead>
<tr>
<th>Fatty acids2</th>
<th>Young CTL (n = 6)</th>
<th>Young FO (n = 6)</th>
<th>Aged CTL (n = 6)</th>
<th>Aged FO (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/100g2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:0</td>
<td>24.8 ± 0.6</td>
<td>27.2 ± 0.3*</td>
<td>17.2 ± 0.6</td>
<td>19.5 ± 0.3</td>
</tr>
<tr>
<td>18:0</td>
<td>16.7 ± 0.8</td>
<td>14.4 ± 0.2*</td>
<td>12.0 ± 0.2</td>
<td>11.3 ± 0.5</td>
</tr>
<tr>
<td>Σ Saturated</td>
<td>43.3 ± 0.0</td>
<td>45.0 ± 0.6</td>
<td>30.4 ± 0.2</td>
<td>32.0 ± 1.0</td>
</tr>
<tr>
<td>18:1 n-9</td>
<td>9.0 ± 0.0</td>
<td>6.0 ± 0.2*</td>
<td>14.2 ± 1.7</td>
<td>10.9 ± 0.3</td>
</tr>
<tr>
<td>18:1 n-7</td>
<td>1.8 ± 0.0</td>
<td>1.3 ± 0.0</td>
<td>1.7 ± 0.2</td>
<td>0.6 ± 0.4*</td>
</tr>
<tr>
<td>Σ MUFA</td>
<td>11.6 ± 0.0</td>
<td>8.0 ± 0.3*</td>
<td>18.0 ± 1.7</td>
<td>12.9 ± 0.8*</td>
</tr>
<tr>
<td>18:2 ω6</td>
<td>13.4 ± 1.4</td>
<td>8.9 ± 0.7*</td>
<td>16.9 ± 0.8</td>
<td>12.9 ± 0.9*</td>
</tr>
<tr>
<td>20:4 ω6a</td>
<td>16.3 ± 0.1</td>
<td>9.6 ± 1.2*</td>
<td>24.5 ± 1.5</td>
<td>16.2 ± 2.6*</td>
</tr>
<tr>
<td>22:4 ω6</td>
<td>1.5 ± 0.3</td>
<td>0.2 ± 0.1</td>
<td>0.7 ± 0.0</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>22:5 ω6</td>
<td>1.5 ± 0.2</td>
<td>0.4 ± 0.0</td>
<td>1.2 ± 0.2</td>
<td>0.6 ± 0.1*</td>
</tr>
<tr>
<td>Σω6 PUFA</td>
<td>35.3 ± 0.8</td>
<td>20.5 ± 1.9*</td>
<td>45.3 ± 0.8</td>
<td>31.3 ± 1.5*</td>
</tr>
<tr>
<td>18:3 ω3</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>20:5 ω3b</td>
<td>0.2 ± 0.0</td>
<td>4.0 ± 0.6*</td>
<td>0.6 ± 0.0</td>
<td>3.6 ± 0.5*</td>
</tr>
<tr>
<td>22:5 ω3</td>
<td>1.7 ± 0.3</td>
<td>4.9 ± 0.8*</td>
<td>1.0 ± 0.2</td>
<td>2.0 ± 0.2*</td>
</tr>
<tr>
<td>22:6 ω3</td>
<td>6.0 ± 0.7</td>
<td>15.5 ± 0.9*</td>
<td>3.9 ± 0.6</td>
<td>17.2 ± 1.4*</td>
</tr>
<tr>
<td>Σω3 PUFA</td>
<td>8.1 ± 0.9</td>
<td>24.7 ± 1.1*</td>
<td>6.4 ± 0.8</td>
<td>23.7 ± 1.3*</td>
</tr>
</tbody>
</table>

SFA, saturated fatty acids; MUFA, Monounsaturated fatty acids; PUFA, Polysaturated fatty acids.

1Values are means ±SEM, n = 6. * indicates significant differences between dietary treatments with p < 0.01.

2Minor fatty acids [14:0, 15:0, 17:0, 19:0, 20:0, 22:0, 24:0, 14:1(n-5), 16:1(n-9), 20:1(n-7), 20:1(n-11), 22:1(n-7), 24:1(n-11), 24:1(n-7), 20:3(n-9), and 22:3(n-9)] are not reported because they represented < 0.3% of total fatty acids.

Young animals data were previously published in Vinot et al. (2011). Aged animals data were previously published in Languille et al. (2012a).

The presence of ω6-docosapentaenoic acid (22:5 ω6, DPA), a long-chain end product of the ω6 series, in the hepatic and plasma phospholipids at a substantial level was indicative of an endogenous synthesis, which could be due to a moderate inadequacy of the amount of ω3 PUFA in the diet (only traces of ω6-PUFA were present in the diet). The presence of α-linolenic acid (α-LNA) in the adipose tissue, the metabolic essential precursor of ω3 PUFA, is a marker of dietary α-LNA intake. Consistently to the presence of ω6-DPA, the very low content of α-LNA in the adipose tissue of the grey mouse lemur (0.2 mol% of total fatty acids), compared to that found in rat fed an α-LNA adequate diet (1%) (Guesnet et al., 2011) was also indicative of a relative inadequacy in ω3 in the diet. However, the very low amount of eicosatrienoic acid (20:3 ω9, ETA), a biomarker of ω6 + ω3 PUFA deficiency, indicated that total PUFA intakes are sufficient (Guesnet et al., 2011).

The brain cortex phospholipids were rich in DHA (in brain cortex ethanolamine glycerophospholipid DHA represented 32.0 mol%), although at a lower level than in the retina. It was previously shown in rat submitted to a dose-response effect that the retina and brain phospholipids have their own and specific maximum of DHA incorporation (DHAmax), even though DHA continues to increase in diet (Alessandri et al., 2003). In the rat ethanolamine glycerophospholipid fraction, the DHAmax values were equal to 29% in the frontal cortex and 46% in the retina. The values which we found in the mouse lemur, 29 and 47% respectively, clearly show that the incorporation of DHA into the outer retina is highly similar in the two animal models. It allowed us to conclude that, the mouse lemur raised on the home-made diet efficiently metabolizes the dietary ω3 PUFA for the optimum modeling of his cortical and retinal membranes. Therefore, the relative inadequacy of ω3 supplies in the home-made diet seems to be fully compensated by the very efficient transfer of DHA to the neural tissues, excluding on the contrary ω6-DPA.

3 ω3 supplementation and cognitive performances in young mouse lemur

In the study by Vinot et al. (2011), we investigated the effects of a 5 month long-chain ω3 PUFA supplementation on behavioral, cognitive and locomotor performances in adult mouse lemur. Our results evidenced for the first time in a non-human primate species that ω3 PUFA supplementation was able to lower anxiety and spontaneous locomotor activity and concomitantly improved cognitive performances.

Plasma fatty acids from total phospholipids confirmed that animals receiving the fish oil-supplemented diet had significantly higher levels of circulating long chain ω3 PUFA (including EPA, 22:5 ω3 and DHA) compared to controls (Tab. 1). The brain fatty acid compositions being not accessible without the sacrifice of animals, plasma fatty acids constituted a proper marker of body fatty acid composition. Indeed, it has been demonstrated in several mammal species that an increase in dietary DHA correlates with plasma DHA content which is in turn predictive of internal organ DHA status and is also a useful biomarker of brain DHA status during adulthood (Kuratko and Salem, 2009). The increased level of ω3 PUFA in fish oil supplemented animals occurred at the expense of both ω6 PUFA and monounsaturated fatty acids. These changes contributed to improve the balance between ω3 and ω6 PUFA.
Young CTL
Young FO
Aged CTL
Aged FO

Latency in OF (s)

(a)

Latency to the exit (s)

(b)

Total distance in OF (cm)

(c)

Fig. 2. Performances in an open field (OF) task for young and aged control (CTL) and fish oil (FO) supplemented animals. (a) Latency before first movement (s). (b) Total distance travelled (cm). Values are means ±SEM, n = 6 in each dietary and age group. Data of young animals have been previously published in Vinot et al. (2011). Data of aged animals have been previously published in Languille et al. (2012a).

in the plasma phospholipids of fish oil supplemented animals with a ratio of ω6:ω3 of 0.83:1 compared to 4.35:1 in the control group. It is recommended for human health benefits that the dietary ratio of ω6:ω3 fatty acids should be close to 1:1 (Simopoulos, 2009).

ω3 PUFA-supplemented animals exhibited increased activity during the open field task (increase in traveled distance) (Fig. 2) suggesting a reduction of their anxiety level. As suggested by Prut and Belzung (2003), in this task, anxiolytic treatments (such as ω3 PUFA in our case) do not increase exploration in the open field but decrease the stress-induced inhibition of exploratory behavior. This observation is corroborated by the lowered spontaneous locomotor activity in a familiar environment measured for ω3-supplemented animals (not shown, see Vinot et al. 2011 for details). In this test, performed in their breeding room, animals were habituated during 48 h to their new cage (similar in size and form to their home-cage) previously to the recording of spontaneous locomotor activity during 5 consecutive days. In such conditions, locomotor activity is generally gradually reduced over the testing as the animals are habituated to the cage environment (Fedorova and Salem, 2006). The observation of reduced spontaneous locomotor activity in animals fed the ω3-supplemented diet corroborates the potential reduced level of anxiety, a parameter that could facilitate the habituation process, a simple form of learning.

In the radial arm maze (Fig. 3), animals of the fish oil group exhibited close to 90% of success in finding the correct exit compared to 33% in the control group (p = 0.0078). Moreover, fish oil supplemented animals tended to spend less time to exit from the maze compared to controls (524 s vs. 906 s; p = 0.060), while their exploratory activity (total number of successful trials) was significantly lower than in the control group (p = 0.008). Data of young animals have been previously published in Vinot et al., 2011. Data of aged animals have been previously published in Languille et al., 2012a.
of visits, not shown) was increased (6.8 ± 1.5 vs. 3.2 ± 0.3; p = 0.061). Although these last results did not reach the level of statistical significance, it suggests a tendency to higher exploration for fish oil fed animals. On the other hand, the mean number of errors before finding the correct exit tended to increase in fish oil supplemented animals (5.9 ± 1.5) compared to controls (3.6 ± 0.8), but this difference was not significant (p = 0.2).

Our finding that fish oil-supplemented mouse lemurs exhibited both lower anxiety in the open field task and better performances in the radial arm maze (% of success) suggests that the two outcomes may be directly linked. Indeed, the tendency to higher exploration in the radial arm maze of the fish oil supplemented animals (higher number of visits and lower time spent to find the right exit) may be issued from the lower anxiety, resulting in a higher score in comparison with more anxious and less exploring animals (trend) of the control group. The difference of performance between the two groups might depend more on their anxiety level than on their intrinsic cognitive capacity, what is corroborated by the absence of a significant difference in the number of errors between control and fish oil groups. Similar findings have been made in rodents which exhibited increased level of anxiety upon chronic ω3 PUFA dietary deficiency (Carrié et al., 2000; Takeuchi et al., 2003), and decreased anxiety upon DHA supplementation (Takeuchi et al., 2003). Therefore, it is possible that lowering of anxiety underlies better cognitive performances of mouse lemurs raised on the fish oil-enriched diet.

According to Fedorova and Salem (2006), there is some evidence of an enhanced vulnerability to stress of ω3 fatty acid deficient animals and this factor can influence performance in a variety of tests. Thus, behavioral tasks that involve a higher level of stress may better differentiate behavioral effects related to brain DHA status. They thus emphasize the possible role of non-cognitive factors like emotionality and attention in the impaired performance on different types of learning tasks of ω3 deficient animals. In any case, if brain DHA status affects performance, this is of importance since performance plays a crucial role in adaptation and therefore survival.

In the study by Vinot et al. (2011), we evidenced that dietary ω3 fatty acids positively impact on anxiety and concomitantly on cognitive performances in adult mouse lemurs. The observation of decreased anxiety with ω3 PUFA supplementation is of particular interest in the context of human health. Indeed, even if it exists significant evidence supporting the potential anxiolytic effect of ω3 PUFA in rodents, there is a lack of studies to demonstrate it, more particularly in primates. The present observations are also very encouraging in the context of aging-associated cognitive decline, in which handling of dietary ω3 fatty acids could offer an efficient strategy for sustaining cognitive functions. Further studies are in progress in our laboratory to determine whether the effects on cognition and behavior are attributable to the direct improvement of neuronal functions and/or to lowering of anxiety.

The beneficial effect of the fish oil-supplementation in the grey mouse lemur may a priori suggest an improvement of their cerebral DHA status. However, on the basis of the data in animals placed under standard feeding (Pifferi et al., 2012), which have low levels of ω6-DPA in their brain phospholipids and DHA values close to those of the rat DHAmx, it is likely that the requirements for DHA of the neural tissues are almost fully covered with the standard diet. If this speculation was correct, supplementing the diet of adult animals with fish oil would have resulted in only a modest gain of DHA in the neural tissues. However, in the supplementation study by Vinot (2011) showed that lemurs fed the fish oil-supplemented diet had much higher concentrations of EPA, ω3-DPA and DHA in their blood plasma phospholipids than those fed the control diet. This allows us to suggest that even a modest gain in brain ω3 PUFA may have strong beneficial effects on behavior and cognition in non-human primates.

4 ω3 supplementation and cognitive performances in aged mouse lemurs

In our study by Languille (2012a), we aimed to determine the effect of dietary fish oil supplementation on exploratory activity, emotional status and spatial memory in aged mouse lemur. Our results revealed that, conversely to young animals, fish oil supplementation decreased the exploratory behavior in a novel environment as revealed by the higher latency to move in open-field (Fig. 2). In addition, and conversely to young lemurs, we observed that fish oil supplementation did not significantly improve the spatial memory performance in radial arm maze task (Fig. 3).

During the open-field task the latency of first movement was significantly higher in fish oil supplemented animals compared to controls and they exhibited a tendency to travel less (indicative of increase anxiety related behavior). This observation suggests that the impact of ω3 fatty acids supplementation highly differs according to age. Very few studies have investigated the impact of ω3 fatty acids supplementation on such behaviors in old animals. Carrié et al. (2000) showed that fish oil supplementation starting in the perinatal period tends to decrease the exploratory activity in the 5-min open-field test, and significantly decreased locomotor activity in a 20-min cage test, in 17–19-months-old mice. Conversely, in 1 month old mice, the level of locomotor activity was significantly higher in fish-oil-fed animals than in the control group. This study suggests that fish oil diet affects behavior differently across aging: increasing locomotor activity in adult and decreasing it in old mice.

During the radial arm maze task we observed that fish oil supplementation inclined to increase the ability to find the correct exit (% of success, not significant, Fig. 3). This observation is in agreement with the two clinical trials in cognitively healthy elderly subjects (aged 65 years or older) in which the authors showed no positive effect of ω3 fatty acids supplementation during 6.5 months (van de Rest et al., 2008) and 24 months (Dangour et al., 2010) on cognitive aspects (attention, memory, executive function). In the study using young adult mouse lemurs (Vinot et al., 2011) we reported that fish oil supplementation did not modify the latency to reach the target and the number of errors in the radial arm maze task, but significantly improved the % of successful trials. Taken together, these observations indicate that fish oil supplementation in both adult and aged mouse lemur had no
effect on memory performance in a little stressful task but improved (or tended to improve in aged animals) the rate of success, what can be a sign of lower anxiety or higher arousal and/or motivation.

To our knowledge, only two studies have shown a positive effect of ω3 fatty acids on cognitive functions in aged animals. Supplementation of DHA during 7 weeks reduced the number of errors in a passageway water maze test in 15 months old mice (Jiang et al., 2009). Gamoh et al. (2001) showed that 25 months old rats supplemented with DHA during 5 weeks expressed less reference and working memory errors in radial arm maze. However, the improvement was only observed in the latter phase of learning, after more than 21 days of training with two daily trials. These studies suggested that ω3 fatty acids dietary supplementation is able to limit the apparition of cognitive deficit, even when the administration starts at old age. Conversely, some studies using fish oil supplementation did not reveal improvement of spatial learning or memory in the Morris water maze test in aged rodents (Barceló-Coblijn et al., 2003; Calon et al., 2003; Sergeant et al., 2011). Finally, it is noteworthy that in the study with aged monkeys supplemented with DHA (Tsukada et al., 2000), only 4 weeks of treatment led to increased regional cerebral blood flow, a parameter closely linked to neuronal activation. Our findings in lemurs seem to indicate that ω3 PUFA supplementation is not efficient to counteract the age-related declines in old non-human primate when started at old age.

On the basis of fatty acid composition of brain and retinal tissues (Pifferi et al., 2012), it is likely that the requirements for DHA of the neural tissues are almost fully covered with the control diet. Plasma fatty acids determination in aged animals showed that the fish oil supplemented lemurs exhibited significantly higher levels of plasma long chain ω3 PUFA (including EPA, 22:5 ω3 and DHA) compared to controls (Tab. 1). The increased level of ω3 PUFA in fish oil supplemented animals occurred at the expense of both ω6 PUFA and monounsaturated fatty acids. These changes contributed to improve the balance between ω3 and ω6 PUFA in the plasma of fish oil supplemented animals with a ratio of ω6/ω3 of 1.3:1 compared to 7:1 in the control group. Since these observations were highly comparable to those made in young animals, it allows us to suggest that brain incorporation of ω3 PUFA may be less efficient in aged animals compared to young. This is consistent with observations made in aged animals in which it was reported a significant decrease in the level and turnover of PUFA during aging in rodents (reviewed by Yehuda et al., 2002). In humans no such differences have been evidenced, even if differences in plasma incorporation of long-chain ω3 PUFA between young and aged subjects has been recently described (Fortier et al., 2010), with higher levels for aged healthy subjects. This apparent paradox, that still remains to be fully explained, is indicative of a difference in fatty acids metabolism between young and aged subjects, as revealed by Walker (2013).

5 Conclusions

Structural and functional modifications of the brain during aging could explain that fatty acids act differently on behavior in function of age. Aged animal may differ from young due to age-related changes in ω3 fatty acid metabolism. One beneficial role of ω3 fatty acids in young animals could be driven by enhancement of neurogenesis since this process seems to be age-dependent (Lazic et al., 2012). Neurogenesis, previously thought to occur only in the embryo, is now known to take place in the adult brain, dependent on numerous stimulating and inhibiting factors, including dietary components. Because of classic associations between neurogenesis and the hippocampus, in learning and cognition, this brain region has also been the focus of attention when studying the links between diet and neurogenesis (Yon et al., 2013). The hippocampus represents one of the two areas in the mammalian brain in which adult neurogenesis occur. This process is associated with beneficial effects on cognition. The exposure to ω3 fatty acids enhances adult hippocampal neurogenesis associated with cognitive and behavioral processes, promotes synaptic plasticity and modulates synaptic protein expression, thereby stimulating the dendritic arborization and new spine formation (Crupi et al., 2013). The grey mouse lemur breeding colony of Brunoy (UMR CNRS-MNHN 7179) is in the unique situation to test if the behavioral cognitive improvements observed after ω3 fatty acids supplementation are indeed linked to an enhancement of neurogenesis in a well-established primate model. We hope such studies will help to improve our understanding of the mechanisms of age related impairments in cognitive function that challenge our society in many ways.

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