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ABSTRACT POSTERS

P.1 Impact of omega-3 fatty acids on brain glucose metabolism and cognitive functions in a non-human primate (Microcebus murinus)

Fabien PIFFERI[1], Olène DORIEUX[1,2], Marie MASSON[1], Nadja VAN CAMP[2], Philippe GUESNET[3], Jean-Marc ALESSANDRI[4], Marc DHENAIN[2], Fabienne AUJARD[1]

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Omega-3 (ω3) fatty acids are major components of brain cells membranes. They are essential nutrients that must be provided by food. ω3-deficient rodents exhibit severe cognitive impairments (learning, memory) that have been linked to changes in neurotransmission processes. Since neurotransmission is highly dependent on energy supply, dietary ω3 fatty acids could play a role in brain glucose utilization. We now propose that ω3 supplementation could improve cognitive performances in primates, and that this effect could be supported by a better brain glucose utilization.

Adult male Grey Mouse Lemurs (Microcebus murinus, Primates) were fed either a control diet (CTL group, n=6) or a diet supplemented with a fish oil naturally rich in long-chain □3 fatty acids (ω3 group, n=6). After 6 months of dietary treatment, cognitive and behavioral performances were tested using a circular platform test (reference spatial memory) and an open field test (anxiety). In parallel to cognitive assessments brain glucose utilisation regional cerebral activity were measured by Positron Emitting Tomography (PET) imaging.

Animals fed the diet supplemented with ω3 fatty acids exhibited better performances in the reference spatial memory task compared to control animas ($p<0.05$), with more than 80% of success in this task for supplemented animals and less than 40% of success for control animals. This increased rate of success was accompanied by a decreased level of anxiety in ω3-fed animals, assessed with the open field test. The decreased anxiety can explain the better performances in the reference spatial memory task since it increases the exploratory behaviour and thus the rate of success. In parallel, PET data revealed a significant increase in brain glucose uptake for ω3-fed animals in the whole brain (no significant variations of glucose uptake were observed within in the 8 brain regions we studied).

These results suggest that the positive impact of dietary ω3 fatty acids on cognitive performances in adult primates could be partly explained by a better emotional status (lowered anxiety). ω3 fatty acids supplementation also enhances brain glucose metabolism, but the causality between lowered anxiety and better brain glucose uptake still needs to be proven.

P.2 Profiling of oxygenated metabolites of arachidonic and docosahexaenoic acids in rat brains

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The two main polyunsaturated fatty acids (PUFA) of the brain are arachidonic (ARA) and docosahexaenoic (DHA) acids, with the latter being predominant. These PUFA are well known to be oxygenated into potent lipid mediators, ARA as a substrate of both cyclooxygenases and lipoxygenases, and DHA of lipoxygenases. However, relatively few data are available on the production of those lipid mediators in the brain, although a recent review has given information on this topic (Bazinet and Layé, Nature Rev Neurosci 2014).

We have been interested by investigating the formation of some stable oxygenated products of ARA and DHA in rat brain homogenates. Brains from adult rats were removed after exsanguination or not. They were homogenized under liquid nitrogen and incubated with or without addition of exogenous 20 μM DHA for 30 minutes at 37°C. PUFA oxygenated derivatives from homogenates were extracted afteracidificationto pH 3 with acetic acid, and successive liquid/liquid (CHCl3:CH3CH2OH, 2:1, v/v) and solid phase (OASIS MAX, Waters) extractions. The oxygenated PUFA were then analyzed by liquid chromatography coupled with tandem mass spectrometry.

A substantial difference in the amount of both ARA and DHA metabolites could be observed by comparing exsanguinated and non-exsanguinated brains, with more products from the latter. Surprisingly enough, we found very small amounts of protectin (P) D1 and DX (from DHA) in non-exsanguinated brain homogenates, and they were even undetectable in exsanguinated ones. A 3-4 fold higher PDX than PD1 were found after adding DHA, but still at low amounts.

These preliminary results deserve further research in different conditions for investigating several metabolic pools. They already provide evidence for a substantial contribution of the blood brain content in the generation of ARA and DHA lipid mediators.

P.3 Multicompartment lipid nanoparticles for neurotrophic protein delivery in neuropsychiatric and neurodegenerative

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We report lipid nanoparticles containing a polyunsaturated fatty acid and amphiphilic building blocks suitable for creation of self-assembled biocompatible nanocarriers for encapsulation of neurotrophic compounds that may induce neurotrophic signaling and synaptic regeneration. This research on lipidic delivery devices is inspired by the compartmentalization in biological systems and the formation of cubic and tubular membrane architectures in diverse cells and organelles, which currently stimulates the preparation of sponge type and mesoporous particles of sophisticated shapes and channel organizations.

We investigate the mechanism of lipid membrane-neurotrophic BDNF (brain-derived neurotrophic factor) protein complexes formation and ordering in nanoparticles, with the purpose of innovation in nanostructure-based neuroprotection and design of future nanomedicines for neuropsychiatric and neurodegenerative disorders.

The neurotrophic protein BDNF loading into lipid membrane nanoassemblies yielded multicompartment nanoparticles with a dense core and a porous periphery of aqueous channels.

Our structural study established that 82 % of the therapeutic protein molecules were entrapped in the lipid membranous nanostructures, which exerted potentiation effect on the BDNF action in a cellular model of neurodegeneration.

P.4 Microalgae and fish oil effects on metabolic syndrome risk factors in rat fed with high fat diet

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Dietary supplementation with long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) can have beneficial effects on a number of risk factors for cardiovascular disease. The principal dietary source of DHA and EPA is fish oil. In an unfavourable economic and environmental context of fish oil production, an alternative and renewable source has to be found: microalgae as *Odontella aurita* that presents high level of EPA, a central fatty acid in the prevention of cardiovascular risks. The aim of this work is to compare the effects of two food supplements rich in n-3 PUFAs (*O. aurita* and fish oil) on risk factors for metabolic syndrome.

Twenty four male Wistar rats were randomly divided into four groups and were fed with the following diets for 8 weeks: the control (C); high fat (HF) ; high-fat supplemented with 0.5% of fish oil (HFFO); high fat diet supplemented with 12% of freeze dried O. aurita (HFOA).

After 8 weeks of diet, rats fed with high fat diet supplemented with *O. aurita* showed a significant lower body weight as compared with the others groups. Moreover, results in relation to different parameters related to metabolic syndrome showed that microalgae as well as fish oil significantly decreased insulinemia and serum lipid levels. However, O. aurita was more effective than fish oil to decrease liver lipid levels and to prevent high fat diet-induced steatosis. On the other hand, *O. aurita* decreased platelet aggregation and oxidative status induced by high fat intake. However, phospholipids fatty acid composition of liver and platelets showed a higher incorporation of EPA and DHA in HFFO group than HFOA one.

In conclusion, *O. aurita* showed similar biological effects, see larger, compared to fish oil, although the incorporation of n-3 PUFAs in HFFO group was higher in HFOA one. This can be explained by a synergistic effect between the n-3 PUFAs and other biological molecules present in the microalga.

P.5 Anti-inflammation activity of some non-enzymatic products of arachidonic and docosahexaenoic acids and N-arachidonoyl dopamine

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Arachidonic and docosahexaenoic acids are the main polyunsaturated fatty acids in the brain and under conditions of oxidative stress form prostanoid-like compounds (iso- and neuroprostanes) via non-enzymatic cyclization and oxidation. Forming locally in rather high molar concentration these compounds can significantly influence cellular function. There are numerous reports demonstrating isoprostanes (IsoP) and neuroprostanes (NeuroP) are the most reliable biomarkers of oxidative stress in vitro and in animal models, as well as in humans. Additionally, several IsoPs have also been shown to be biologically active.

In this study we evaluated ability of 15-epi-15-E2-IsoP, 4(RS)-4-F4t-NeuroP and 10-epi-10-F4t-NeuroP, prepared by total chemical synthesis, to influence inflammation response of mouse macrophage cell line RAW 264.7. The cells were stimulated either by isoprostanoids per se or by the mixture of phorbol ester and bacterial lipopolysaccharide. Inflammation response was registered by measurement of nitrite-ion formed from generated nitric oxide.

No one of tested IsoP nor NeuroPs induced elevation of nitrite level in the cells, while all of them demonstrated marked inhibition of induced inflammation response in RAW 264.7. Thus, at 50 μM 15-epi-15-E2-IsoP, 4(RS)-4-F4t-NeuroP and 10-epi-10-F4t-NeuroP inhibited NO-generation in 90±5%, 55±5% and 75±10%, correspondingly.

One can propose that like free arachidonic acid its natural occurring derivatives e.g. ethanolamide (anandamide) or dopamine amide (AA-DA) can also be prone to non-enzymatic oxidation with formation of corresponding IsoP-derivatives. To check how will change the activity of IsoP after conversion into dopamine derivative we prepared dopamine amide of 15-epi-15-E2-IsoP (15e-E2-IP-DA) and prostaglandin E2 (PGE2-DA) as putative COX-2 product of AA-DA. It was found that 15e-E2-IP-DA was extremely active as anti-inflammatory agent in this test system and evoked 75% inhibition effect at 0.5 μM while its precursor was non-active at this concentration. PGE2-DA was also active in reducing inflammation (IC50 18±2 μM). It should be noted that all dopamine derivatives studied were toxic for RAW 264.7 cells at micromolar concentration. The parent AA-DA was extremely toxic (LD50 5±2 μM) and at concentration of 0.1 μM provoked inflammation response (23±6% from stimulated control). Isoprostane 15e-E2-IP-DA induced 100% cell death at 50 μM, but was non-toxic at 0.5 μM, and PGE2-DA demonstrated only35±2% cell death at 100 μM. However as opposed to AA-DA both prostanoids demonstrated no pro-inflammatory effect.

These data clearly demonstrate that at least some IsoP and NeuroP can act as anti-inflammation agents in standard cellular test system. For the first time it was shown that putative enzymatic and non-enzymatic metabolites of endovanilloid/endocannabinoid N-arachidonoyl dopamine–15e-E2-IP-DA and PGE2-DA were active at low micromolar concentration in blocking of the inflammation response in RAW 264.7 cell line.

P.6 Impact of lipid quality in perinatal period on inflammation and neurogenesis

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The innate immune system of the brain is principally composed of microglial cells, which, once activated, protect neurons against insults. Activated microglial cells produce inflammatory cytokines that act specifically through receptors expressed by the brain. The functional consequences of chronic brain cytokine action are the alteration in cognition, affect and behaviour, a hallmark of altered well-being. Limiting synthesis of inflammatory cytokines in brain could be crucial during perinatal period to prevent cognitive alteration in adulthood.
Polyunsaturated fatty acids of the n-3 family (n-3 PUFA), in particular docosahexaenoïc acid (DHA), are very potent anti inflammatory agents. DHA are highly incorporated in the brain during the developmental period. Microglial phenotype could be modulated by the composition of lipid in the diet.
The present project aimed at evaluating the impact of different dietary fat matrix (vegetable or dairy lipids) on neuroinflammatory (neuroinflammation, neurogenesis and micoglial phenotype) process in early life
Pregnant CD1 mice and their offspring were fed since day 1 of gestation with different diets containing dairy or vegetable lipid supplemented or not in DHA and ARA. At postnatal day (PND) 14, pups were injected intraperitoneally with lipopolysaccharide (LPS, 100µg/kg) from E.coli. 3h after injection, animals were sacrified to evaluate neuroinflammation, microglial phenotype and neurogenesis in dentate gyrus of hippocampus.
Our results showed that dairy lipid diet can modulate microglial phenotype since we observed a decrease of CD86 positive cells in animals fed with dairy lipid. We also observed an increase of hippocampus neurogenesis 3h post-LPS in animals fed with dairy lipids. Moreover in this group, BDNF (neurotrophic factor) activity is decreased in the hippocampus whereas phosphorylation of glucocorticoid receptors is increased.
To conclude, our results showed that consumption of dairy lipids diet could protect from neuroinflammation and its consequences induced by perinatal inflammation.

P.7 Differential effect of an alpha-linolenic acid-rich supplement on ketogenesis and plasma n-3 polyunsaturated fatty acids in young compared to older adults

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Background: As the main alternative fuel to glucose for the brain, increased plasma ketones could potentially help compensate for brain glucose hypometabolism occurring during aging. The precursor long-chain n-3 polyunsaturated fatty acid (PUFA), α-linolenic acid (ALA), is normally mostly β-oxidized and so could potentially be used to stimulate ketogenesis in humans.
Objective: To compare the impact of an ALA-rich supplement on (i) the ketogenic response and (ii) plasma long-chain n-3 PUFA in young and older healthy adults. Design: Ten young (25±0.9 y old) and ten older adults (73.1±2.2 y old) consumed a flaxseed oil supplement providing 2 g/d of ALA for 4 weeks. Plasma ketones, free fatty acids, triglycerides, total cholesterol, glucose and insulin were measured over 6 h during two metabolic study days, one before and one at the end of the supplementation.
Results: ALA supplementation did not significantly modify fasting ketones but postprandial production of β-hydroxybutyrate (β-HB) was increased by 26% ($p=0.0371$) in young adults. At baseline, older adults had 47% higher total plasma fatty acids than young adults ($p=0.007$). After ALA supplementation, plasma ALA doubled in both groups ($p<0.01$), an effect that was associated in older adults with a 24% higher eicosapentaenoic acid (EPA; $p=0.004$), but no difference in docosahexaenoic acid (DHA). The post-supplementation increase in plasma ALA correlated negatively to the change in postprandial β-HB ($r=-0.484$; $p=0.031$) and positively with % total body fat ($r=0.639$; $p=0.002$).
Conclusion: In young adults, ALA supplementation mildly stimulated postprandial ketogenesis, whereas in the elderly, it favoured increased plasma ALA and EPA.

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P.8 Synthesis and evaluations of lipo-phenolic derivatives as anti-carbonyl stressors in retina pathologies

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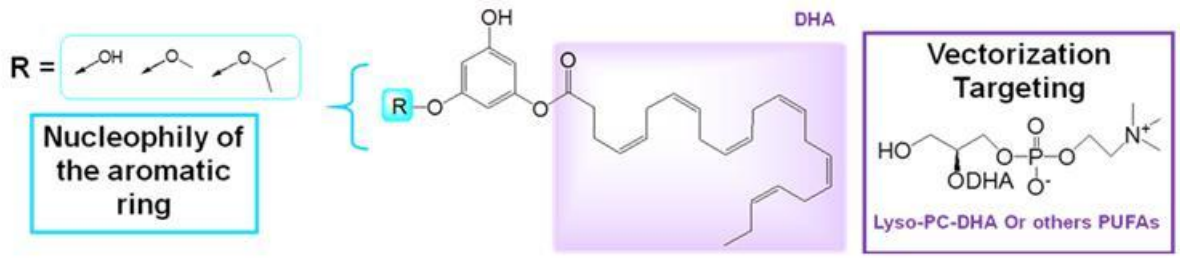
Carbonyl and oxidative stress play a substantial role in various neurodegenerative diseases such as Alzheimer's Disease, Parkinsonism or Age-related Macular Degeneration (AMD). In retinal pathologies, both mechanisms are involved in the transformation of all-trans-retinal (AtR, reactive aldehyde) to bis-retinoid A2E. Since accumulation of trans-retinal and A2E contribute to photoreceptor apoptosis, we designed and synthesized a resorcinol derivatives (phloroglucinol and resveratrol) featuring enhanced anti-carbonyl stress properties. Structural modifications include alkylation to increase nucleophilic and carbonyl trap properties. To improve their bioavailability and to induce a vectorization process to retinal tissue, more lipophilic derivatives have been considered. Regarding the high level of polyunsaturated fatty acids (PUFAs) present in the membrane of photoreceptors, the phenolic moity was linked to polyunsaturated lipid moieties such as docosahexaenoic acid (DHA, C22:6 n-3), or sn2-Lyso-PC-DHA, eicosapentaenoic acid (EPA, C20:5 n-3), alpha-linolenic acid (ALA, C18:3, n-3) and linoleic acid (LA, C18:2, n-6). Biological evaluations in ARPE-19 cell lines pointed out the benefit of isopropyl and PUFA substituents for cell survival in the presence of a carbonyl stressor.



P.9 Omega-3 as a strategy to protect brain development from prenatal infection

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Maternal infection during pregnancy is associated with an increased risk for CNS disorders such as memory deficits in the offspring. Such prenatal immune challenge induces inflammatory response in the fetal brain, which may disturb neurodevelopment of the hippocampus in the embryo. The innate immune response in the brain is mediated by microglia, which also play a critical role during neurodevelopment. Their phagocytic activity is involved in removing unnecessary synapses and neurons, allowing effective neuronal connectivity in the mature brain. Because microglia are important players both in neuroinflammation and neurodevelopment, we propose that they are involved in mechanisms by which maternal immune challenge causes brain maturation impairments in the fetus. One preventative strategy to avoid such impairments is to limit the inflammatory response in the fetal brain, which we believe can be achieved through balanced diet. Omega-3 PUFAs have anti-inflammatory properties, and are also important neuronal components.

In the present study we investigated whether balancing omega-3 levels in the diet can impact microglia function and prevent neuronal deficits in the mature mouse brain after prenatal immune challenge. To address this question, pregnant females fed with a deficient or balanced diet in omega-3 were injected intraperitoneally with bacterial lipoplysaccharide (LPS), at gestational day 17 and spine density and microglia phagocytic activity were analyzed in the offspring at post-natal days 14 (P14) and 28 (P28).

Our data showed that in animals developed under a diet devoid of omega-3, prenatal inflammation leads to a decreased phagocytic activity of microglia regarding exogenous (Quantum dots) and endogenous (PSD-95) elements at P14. We also found that this was paralleled by an increase in dendritic spines and PSD-95 protein levels in the hippocampus at P28. These alterations were not observed in animals developed under a diet balanced in omega-3.

Altogether, our data suggest that a prenatal inflammation decreases microglia-dependent synaptic pruning during the maturation phase of the hippocampus, leading to alterations of neuronal morphology later on. All these alterations are rescued by increasing omega-3 content of maternal diet.

P.10 Resolvins promote resolution of brain inflammation

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The brain innate immune system is mainly composed of microglial cells. Microglia are activated in response to an immune or inflammatory stimuli or a trauma, and then produce pro- and anti-inflammatory factors. These factors drive the innate immune response and can modulate neuronal activity and in fine, learning and memory. Although brain innate immune system defends brain tissue from aggression, chronic activation of microglia can also be deleterious. In the adult brain, chronic production of inflammatory cytokines can contribute to the pathogenesis of neurodegenerative diseases. Limiting the production of pro-inflammatory cytokines and enhancing the production of anti-inflammatory cytokines are crucial for neuron survival. New molecules have recently been identified. Lipidic mediators derived from n-3 polyunsaturated fatty acids (PUFAs), as the resolvins D1 and E1 (RvD1 and RvE1) and from n-6 PUFAs, as the lipoxin A4 (LxA4) are involved in the resolution of inflammation. However their involvement in the resolution of inflammation in microglial cells and the mechanisms by which they influence are unknown.

Herein we studied the effects of lipoxin and resolvins on the resolution of inflammation in microglial cells stimulated with systemic lipopolysaccharide. Our results indicated that resolvins and lipoxins were able to inhibit the production of pro-inflammatory cytokines and enhance the production of anti-inflammatory cytokines. Moreover, the receptor of LxA4 and RvD1 was overexpressed, reinforcing the idea that these molecules are involved in the resolution of inflammation. We also showed that resolvins and lipoxins promoted a phenotypic switch in microglial polarization toward a M2-like phenotype.

These findings illustrate novel mechanisms through which PUFAs conferred anti-inflammatory and proresolving actions in inflamed brain.

P.11 Transgenic increase in n-3/n-6 fatty acid ratio protects against cognitive deficits induced by an immune challenge through decrease of neuroinflammation

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Polyunsaturated fatty acids (PUFAs) display immunomodulatory properties in the brain, n-3 PUFAs being able to reduce inflammation while n-6 PUFAs are pro-inflammatory. It has been extensively demonstrated that exposure to a peripheral immune challenge leads to the production and release of inflammatory mediators in the brain in association with cognitive deficits. The question arises whether n-3 PUFA supplementation could down-regulate the brain inflammatory response and subsequent cognitive alterations.

In this study, we used a genetically modified mouse line carrying the fat-1 gene from the roundworm Caenorhabditis elegans, encoding an n-3 PUFA desaturase that catalyzes conversion of n-6 into n-3 PUFA. Consequently, these mice display endogenously elevated n-3 PUFA tissue contents. Fat-1 mice or WT littermates were injected peripherally with lipopolysaccharide (LPS), a bacterial endotoxin, to induce an inflammatory episode. Our results show that LPS alters differently the phenotype of microglia and the expression of cytokines and chemokines in Fat-1 and WT mice. In Fat-1 mice, pro-inflammatory factors synthesis was lowered compared to WT mice, while anti-inflammatory mechanisms were favored 24h after LPS treatment. Moreover, we were able to show that LPS injection impaired spatial memory in WT mice, while interestingly, the Fat-1 mice showed normal cognitive performances.

All together, these data suggest that the central n-3 PUFA increase observed in Fat-1 mice modulated the brain innate immune system activity, leading to the protection of animals against LPS-induced pro-inflammatory cytokine production and subsequent spatial memory alteration.

P.12 Lipidomics of Omega-3 transgenic mice reveals a panel of anti-inflammatory and proresolving mediators

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Essential fats, such as omega-3 and omega-6 fatty acids, must be obtained through the diet and cannot be synthesized de novo in mammals. In 2004, the fat-1 transgenic mouse model was developed, enabling the mouse to endogenously convert omega-6 to omega-3 fatty acids. Research has demonstrated that the fat-1 mouse is protected against a wide variety of diseases and conditions related to inflammation including colitis, pancreatitis, asthma, hepatitis, liver disease, atherosclerosis, insulin resistance, and several types of cancer (breast, colon, pancreatic, liver).

Although a large number of studies have demonstrated reduced disease risk and health benefits in fat-1 mice, a comprehensive comparison of lipids profiles in fat-1 and wild-type mice has not been previously feasible due to lack of a sensitive and comprehensive analytical technique capable of simultaneously quantifying high-abundance (e.g., phospholipids) and low abundance lipids (e.g., oxylipins).

In this study, we used a state-of-the-art, high-throughput assays for the analysis of bioactive lipid species in plasma and liver samples from fat-1 and wild-type mice, providing new clues to the pathways and mechanisms that may be involved in the health benefits associated with alterations of the omega-6/omega-3 fatty acids ratio.

P.17 Potential effects of polyphenolic diets on mitochondrial and cognitive dysfunction in C57BL/6 mice

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Even though demographic change leads to a constant aging of society around the world, effective diagnosis, therapy and prevention of age-related neurodegenerative disorders have yet to be discovered.

One major point of interest is the nutritional prevention of age-related brain disorders. As some ethnical groups show lower prevalence for developing dementia, regional diets seem to be a possible nutraceutical target. The amount of antioxidants within the ingested food is one of the varying factors between local traditional foods. Antioxidants have proven to work as radical scavengers in the body, reducing mitochondrial dysfunction and therefore offering protection against what has been identified as one of the main reasons for cell-aging. Plants produce antioxidants as secondary metabolites, such as polyphenols that are stored in fruits, leaves and seeds. Even though many studies, in particular regarding a mediterranean diet, have already shown benefits of plant-based nutrition, there is no consensus about the influence and potency of polyphenols on cellular aging-processes.

In a six months-feeding study, 94 male mice of the C57BL/6J strain were tested regarding their cognitive and mitochondrial integrity. Using a young control group as well a group of untreated aged mice as comparison, four different polyphenolic diets were fed. One diet contained a grape extract, one a bilberry extract, hydroxytyrosol as the main metabolite in native olive oil, and one diet combined the grape extract and Hydroxytyrosol mimicking a mediterranean diet. The mice were tested using behavioural trials such as social recognition testing, passive avoidance testing and Y-maze testing. ATP-measurements, determination of mitochondrial membrane potential and bioenergetic measurements were the biochemical methods used to evaluate the functionality of isolated mitochondria and dissociated brain cells of the mice.

Overall, only minor influences of the polyphenols on cognitive and mitochondrial function in the aged C57BL/6 mice could be achieved. Considering the results of the Y-maze testing as well as the comparison of the results using the artificial radical-donor SNP on the dissociated brain cells, some promising protective effects of the grape extract and the hydroxytyrosol were observed. Also taking into account the results of other study groups, polyphenols have been proven to potentially prevent dementia and aging within the brain. Optimising und extending the experiments carried out as well as using different animal models might further verify the obtained results.

P.18 Perinatal high fat exposure through maternal diet protects against the adverse effects of early life stress.

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There are strong links between stress and nutrition. For instance, stress drives choices of food rich in fat or sugar, and consumption of palatable high-fat food attenuates symptoms associated with chronic stress in adults. Early adversity in childhood is a major predisposing factor for mood and anxiety disorders. However, the influence of the present occidental dietary habits on early stress is unknown. Chronic maternal separation (MS) in rodent mimics several alterations induced by early life adversity. Here, we tested the hypothesis that early exposure to high-fat through maternal diet modifies the phenotype induced by MS.

Dams were fed either a standard (SD, 12% of fat) or high-fat (HFD, 39% of fat) diet throughout gestation and lactation. Pups were submitted to MS (3hr per day) from postnatal day (PND) 2 to PND14.

MS resulted in higher anxiety-like behavior and plasma corticosterone levels post-stress, reduced social interaction, spatial memory impairments, decreased hippocampal neurogenesis and visceral hypersensitivity in offspring of standard-fed dams. However, offspring exposed to maternal HFD did not show any of these deleterious effects of MS. In order to better understand the mechanisms underlying the protective effects of maternal HFD, we examined its impact on gene expression in the prefrontal cortex during development. Perinatal HFD abolishes several alterations of gene expression (BDNF, 5HTr1A, REST, REST4) reported in pups exposed to maternal separation. We also demonstrate that maternal HFD intake produces a reduction of anxiety and enhances maternal care in stressed dams. Finally, we report a change in the stomach milk fatty acid composition in pups exposed to HFD. Maternal HFD did not alter the total milk fat content but increased the level of unsaturated fatty acids.

These processes might contribute to the protective effects of HFD in early stressed animals.

P.19 Lipidome changes in development of the human prefrontal cortex

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We performed liquid chromatography-mass spectrometry (LC-MS) measurements of the lipidome composition of prefrontal cortex (PFC) of 120 human, chimpanzee, and rhesus macaque individuals, of ages spanning from newborns to adults. We inspected changes of lipid concentration levels in the PFC from development to adulthood in the three species. We found a predominant number of lipids showing age-related change, over 5-fold more compared to the change in gene expression levels in the same set of individuals as well as compared to lipids in heart, an example of a non-neural tissue. Using additional measurements in corpus callosum from adult human brain, we sorted the observed age-related changes between those, characteristic to white and gray matter. By comparing patterns of change among the three species we also distinguished those showing uniquely human patterns of change. We found that myelination can explain some, though not all of the lipidome changes in the brain. Additionally, lipids showing human-specific patterns of change with age contained known age markers and lipids potentially contributing to unique features of the human PFC.

P.20 The role of altered fat metabolism and nutritional intervention with essential fatty acids in the early-life stress induced cognitive impairments

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Early-life stress (ES) is associated with increased vulnerability to develop psychopathology and cognitive decline in adulthood. Stress during adulthood is known to affect lipid metabolism and cause changes in fat deposition and function, e.g. adipokine secretion. However, it is unknown if stress early in life exerts similar metabolic changes during development and if this influences the lasting effects on brain development and function. Importantly, imbalances in n6:n3 fatty acid (FA) status (especially during development) are known to be associated with cognitive impairments as well as metabolic development. Therefore, we set out to study if chronic ES affects 1) peripheral and central FA profiles, and 2) fat deposition and function throughout life. In addition, to test if these effects are causally related to the ES-induced central effect, we aim to test 3) if the fatty acid composition of the early life diet can influence the ES induced metabolic and cognitive effects.

We used a chronic ES model consisting of exposing C57/BL6 dams to limited nesting/bedding material from P2 to P9. This in turn resulted in cognitive decline in the ES-exposed male adult offspring. Although exposure to ES did not affect body weight in adults at P150, we found long term reductions in both inguinal and gonadal white adipose tissues (WATs) and a higher ratio mesenteric to other WATs, possibly indicating metabolic derangements. The ES-induced changes in fat depositions at P9 were accompanied by reduced leptin and increased resistin levels in plasma. Interestingly, brown adipose tissue (BAT), which is important for thermogenesis, was increased in ES-exposed offspring at P9 but not in adulthood. At P9, ES reduced the n6:n3 FA ratio in the liver, whereas it was increased in the hippocampus. Interestingly, preliminary results indicate increased n6:n3 FA ratio in the liver at P150. To test if a low or high n6:n3 FA ratio in diet early in life can modulate effects of ES is currently ongoing.

These results imply that exposure to ES results in persistent alterations in lipid metabolism and adipose tissue regulation and function, suggesting a profound role of these metabolic processes in the ES-induced cognitive impairments.

P.21 Dairy fat or α-linolenic (ALA)-rich rapeseed diets for dams and mice offspring are similarly protecting against anxiety observed with low-ALA-palm diet

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Omega-3 deficiencies during gestation/lactation could have dramatic impacts on cognition and behaviour. We previously showed in omega-3-deficient-rats that dairy-fat-diet containing naturally low levels of omega-3 (ALA0.8%) was as efficient as ALA-rich-rapeseed-diet (8%) to restore brain DHA levels to normal values and was much more efficient than low-ALA-palm-diet (0.4%).

Objectives: Evaluation of the dairy-fat potential, compared to rapeseed or palm diets on mother and pups behaviour.

Methods: Three groups of dams (Swiss strain) were fed during 6weeks before and during gestation/lactation with: (i) Deficient-ALA-palm (0.4%) diet, (ii) Dairy fat (ALA0.8%) diet, (iii) Protective-ALA-rich (8%) rapeseed diet. Post-weaning pups received diets similar to their mothers until PND40 (Post-Natal-Day40).

Results: There was no change in the behavior of pregnant dams, except in the palm-group which showed a reduced activity in a spatial memory test (Y-maze). Pups belonging to the palm-group showed a reduced time at PND3 in the surface righting reflex test when compared to rapeseed and dairy fat groups. No significant differences were found between the treated groups in the geotaxis test (motor coordination and vestibular function, assessed at PND5, 7, 9, 11), the suspension test (muscular strength, PND9&11) or in the Y-maze (assessing the short term memory post-weaning).

Three weeks after weaning, an increased anxiety was noticed in female mice of the palm-diet group when placed into an open-field (locomotor activity and anxiety). This result was confirmed with an elevated-plus-maze test, while females born from ALA-rich-diet dams (rapeseed) or dairy-fat-diet dams did not differed (reduced anxiety compared to ALA-poor-palm-diet dams)

Conclusions: Females born from dams fed with dairy-fat, despite 10 times less ALA than rapeseed oil (0.8% *vs* 8%), present the same absence of post-weaning anxiogenesis while those born from palm (similar ALA levels to dairy-fat 0.4% *vs* 0.8%) presented an increased level of anxiety. The same low omega-6/omega-3 ratio (2.3) for dairy and rapeseed (while 21 for palm) and dairy-fat-matrix complexity could be part of their protective effect via a better brain DHA status.

P.22 Brain DHA restoration in young-deficient rat is better with pure or blended dairy-fat diets compared to similar α-linolenic (ALA)-content vegetable blends

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Background and aims: Achieving an appropriate Docosahexaenoic Acid (DHA) status in the neonatal brain is an important goal of neonatal nutrition. In an attempt to validate the potential replacement of vegetable fat with dairy-fat in infant formulas, we used the brain DHA level of rats as a nutritional model to compare the effects of blends based on dairy-fat instead of palm oil.

Methods: Six groups of 10 males-rats, born from dams fed low 0.4% ALA-diet over gestation/lactation, received, for 6 weeks after weaning, diets providing either similar 1.5% ALA (from rapeseed) recommended for infant formulas, blended with (i) dairy-fat, (ii) palm oil, or (iii) increased to 2.3% ALA-dairy-fat and were compared to diets containing pure 0.4% ALA-palm, pure 0.8% ALA-dairy-fat and pure 8% ALA-rapeseed

Results: Restoration of brain DHA levels was superior with the 1.5% ALA-dairy-fat compared to 1.5% ALA-palm-blend (+80% *vs* +60% $p<0.001$). Increasing to 2.3% ALA-dairy-fat blend induced a further increase (+90%) and was as efficient as pure 0.8% ALA-dairy-fat or 8% ALA-rapeseed diets, while 0.4% ALA-palm diet was only 30%.

Conclusions:

1/ Brain DHA restoration of young-deficient-rats is more efficient with 1.5%ALA-dairy-fat blend diet compared to similar 1.5% ALA-vegetable blend (specificity/complexity of dairy-fat matrix could be involved).

2/ Brain DHA restoration is even more efficient with a 2.3% ALA-dairy-fat blend diet compared to the previous ones (higher level of ALA and a better n-6/n-3ratio (5 *vs* 10) could be involved).

3/ Brain DHA restoration with a 2.3% ALA-dairy-fat blend diet is comparable to pure 8% ALA-rapeseed diet.

4/ Pure 0.8% ALA-dairy-fat is 3 times better than pure 0.4% ALA-palm despite similar ALA levels (better n-6/n-3ratio 2.3 *vs* 21).

5/ Pure 0.8% ALA-dairy-fat is as efficient as pure 8% ALA-rapeseed despite 10 times less ALA (similar n-6/n-3 ratio 2.3 associated to a lower Delta6-desaturase competition within the n-3 family between ALA and DHA of dairy-fat matrix). Use of dairy-fat for infant formulas should be reconsidered.

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P.23 A multinutrient preparation developed for neurodegenerative disease enhances functional outcome following spinal cord injury

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Spinal cord injury (SCI) leads to major neurological impairment, associated with significant tissue loss. Endogenous repair processes occur following SCI, but they are limited. Recent clinical trials in Alzheimer's disease have demonstrated the efficacy of Fortasyn® Connect (FC), a specific multinutrient combination that was designed to compensate for the loss of neuronal membranes and synapses in dementia patients, and that contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), choline, uridine monophosphate, phospholipids, folate, vitamins B6, B12, C, E and selenium. We tested if this multinutrient combination countered the tissue destruction occurring after SCI and supported regenerative processes, improving the neurological outcome. Adult rats received an injury induced by cord compression at thoracic level, and immediately after SCI they were fed daily with a control diet or a diet supplemented with different doses of the specific FC multinutrient combination (low-dose FC, medium-dose FC, or high-dose FC) for 4 or 9 weeks. At 4 weeks, only 50% of rats that were fed the control diet were able to plantar place their paws, and only 2 rats had recovered gait coordination. In contrast, 6 out of 7 rats fed the diet with the high dose of FC had recovered a coordinated gait. Five of them showed a normal position of the paws and full recovery of toe clearance, and 2 of them showed a gait that was undistinguishable from that of uninjured rats. The BBB score was 17.1 ± 1.6 in this group, in comparison with the BBB score of 8.8 ± 1.3 in rats fed the control diet. This was accompanied by significant protection of oligodendrocytes and myelin in the injured tissue, a decreased microglial neuroinflammatory response, and an increase in pre- and postsynaptic markers. The medium dose of FC did not show efficacy after 4 weeks of treatment, but led to improved motor score, increased neuronal and oligodendrocyte survival, decreased microglial activation, and better axonal preservation after 9 weeks of supplementation. These results suggest that a diet supplemented with this specific multinutrient combination has marked therapeutic potential in SCI.

P.24 Impact of denutrition and lipid quality for rapid restoration of tissue fatty acids and inflammatory FA markers in old rats

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Denutrition, frequently observed in elderly is generally associated to omeg3 deficiency.
Objectives: In an attempt to mimic the denutrition status of elderly, an animal model of old rat was used to evaluate the impact of protein and lipid quality of refeeding diets regarding the plasma, red blood cells (RBC) and brain FA composition and the resulting impact on FA markers of the inflammatory status.
Methods: Control (C) 20month-old-rats were food restricted to 50% during 12 weeks (D). Four groups were refed by 1m-ad-libitum diets: RF1 similar to control diet with lipid as soya oil; RF2 same diet where milk soluble proteins replaced casein; RF3 a casein diet with a blend of dairy fat/rapeseed/DHA; RF4 a full formulae that combines increased level of milk soluble proteins (22vs14%), a blend of dairy fat/rapeseed/DHA and high vitamin D concentration.
Results: 1/Food restriction for three months, despite being only moderately ALA deficient, induced a drastic loss of the anti-inflammatory n-3FA (ALA and Lcn-3) in all tissues, while Arachidonic Acid (AA) considered as pro-inflammatory is more or less stable. This gave rise to the FA pro-inflammatory markers expressed as AA/EPA in plasma (2.5 fold increase) and RBC and AA/DHA increased in RBC and brain (+12%). 2/ Refeeding diets. The four-week-refeeding formulas containing a blend of dairy-fat/rapeseed/DHA associated with casein or milk soluble proteins, restored:
1/ DHA values of the brain not previously restored by the refeeding control soya diet, and reduced the AA/DHA pro-inflammatory marker to normal values, contrarily to the soya diet group still higher (+6%$p<0.009$).
2/ LCn-3 (EPA, DHA) values to levels above those (i) of denutrition group, (ii) of soya restored group and (iii) even higher than those of the control group before denutrition. This increase was associated to an AA reduction (-30%/-15%), leading to a drastic drop in plasma and RBC of AA/EPA or AA/LCn-3 markers of the pro-inflammatory status (-78%compared to C).
Protein quality did not impact the FA modifications, but the increase of the milk soluble proteins quantity at the expense of carbo-hydrates induced a further increase of LCn-6 and n-3 which did not impaired the benefit of the reduced FA pro-inflammatory status observed with the lipid blend alone.
Conclusions: Dairy fat/rapeseed/DHA refeeding diets induced a rapid recovery of the brain compared to soya diet and reduced drastically the pro-inflammatory FA markers in plasma and RBC to much lower levels than control and could offer large benefits against aging associated to or even prior denutrition. *ANR ALIA2010-01306Présage*

P.25 Multi-analytical platform metabolomic approach to study differential changes in brain tissue metabolites

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Metabolomics, the last of the omics sciences, studies the metabolic profiles in biological samples, such as biological fluids or tissues, thanks to the combination of different separation techniques coupled with mass spectrometry and multivariate data analysis [1]. There are previous applications to study brain tissue for different purposes [2].

A non-targeted analysis mass spectrometry-based approach was developed for this study in order to perform the relative quantification of a broad range of metabolites. This will help us to get deeper knowledge of some neurological disorders, including Alzheimer's disease, which can be detected by an abnormal phosphorylation and aggregation of Tau protein. Nowadays, this phenomenon and its causes are not well understood. However, recent studies have found evidence that small mammals, like Syrian hamsters (*Mesocricetus auratus*) can reverse this process [3].

The first step was establishing the methodology. We have worked with right hemispheres of hamster brains and two extraction methods [4,5]. Best results were obtained using MeOH:H_2O 50/50 (v/v) for homogenization and a combination of solvents for extraction:tissue homogenate: MeOH:Methyl tert-butyl ether 100/320/80 (v/v/v). Only 30 mg of brain tissue is required for the global metabolomic approach. Supernatants were analyzed in three techniques, gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS) and capillary electrophoresis-mass spectrometry (CE-MS) in order to obtain the profiles of metabolites in brain tissue. LC-MS and CE-MS were performed both in MS (+) and MS (-) modes.

When comparing brain tissues from old and young animals as a proof of concept, two types of statistical analysis were applied: univariate and multivariate analysis to select statistically significant variables. Untargeted multiplatform metabolomic approaches offer a powerful tool to study the effects of disease by aiding the discovery of biomarkers which may help to identify and treat diseases earlier.

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P.26 DHA improves spatial memory and modulates gene expression in the brain of aged mice

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Brain aging is associated with multiple morphological and biochemical changes leading to cognitive decline. Fatty acids are the main components of the brain membranes and among them docosahexaenoic acid (DHA) is the major n-3 polyunsaturated fatty acid (n-3 PUFAs). Several studies have suggested that n-3 PUFAs and most particularly DHA are critical for the maintenance of cognitive functions during aging. It has been recently reported that unesterified DHA pool contained in plasma decreases with age in rodents and that brain DHA levels are altered during aging. DHA may modulate brain functions by several mechanisms including the regulation of gene transcription. Indeed DHA is the endogenous ligand of nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) and retinoid X receptors (RXRs) which are transcription factors that modulate the expression of genes involved in brain synaptic plasticity. RXR is a master regulator that forms heterodimers with numerous nuclear receptors such as PPAR or the retinoic acid receptor (RAR). Recent data suggest that unesterified DHA (active form) is involved in working memory in mice via RXRγ activation. The objective of the present study was to evaluate in aged mice the effects of intraperitoneal administration of unesterified DHA on memory performances and synaptic plasticity.

In a first experiment, we studied the effect off our doses of DHA injected during four days on the spatial working memory evaluated in a sequential alternation paradigm. Our results showed that DHA (0.1 and 1 mg/kg of body weight) has a beneficial effect on the alternation performances. We then evaluated in aged mice the effects of these efficient doses in a contextual and serial discrimination (CSD) task involving episodic-like memory. Our results showed that DHA improves memory performances of aged mice in the CSD paradigm. In order to understand the molecular mechanisms involved in this beneficial effect we also measured the mRNA expression of nuclear receptors (RARs, RXRs and PPARs) and synaptic plasticity markers (GAP-43, RC3 and PSD95) by qPCR in the hippocampus and the prefrontal cortex. Our results suggest that unesterified DHA plays an important role in the maintenance of memory processes during aging.

P.27 An omega-3 fatty acid as a novel therapeutic agent for acute intervention after traumatic brain injury

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Every 90 seconds someone is admitted to hospital in the UK with acquired traumatic brain injury (TBI), more than a million people a year. This represents an increase of 33.5% compared to the previous decade. Currently, there are no specific therapeutic interventions for TBI and clinical management is limited to reduction of the intracranial pressure and symptomatic relief. TBI is associated with a rapid onset of a neuroinflammatory response (delayed secondary injury events), following a primary mechanical insult. The secondary injury represents a window of opportunity for therapeutic intervention; however, despite extensive efforts to develop neuroprotective therapies, there have been no successful outcomes in human clinical trials to date. Docosahexaenoic acid (DHA) is an omega-3 fatty acid that is the most abundant fatty acid in the brain. Previous studies have shown that acute DHA treatment has neuroprotective effects in several acute central nervous pathologies such as stroke and spinal cord injury.

Our research objective was to examine whether the acute administration of DHA after TBI could reduce the acute inflammatory response, which could improve functional outcome after TBI.

A controlled cortical impact (CCI) model of TBI was used in male adult CD1 mice. Mice received intravenously (i.v.) 500 nmol/kg DHA or vehicle (0.2% v:v ethanol in saline) , half an hour after the injury, and all animals received an intraperitoneal (i.p.) injection of the tracer 5-bromo-2-deoxyuridine (BrdU; 50 mg/kg, twice a day) to label dividing cells. The modified Neurological Severity Score (mNSS) was assessed on day 1, 3, 5 and 7 post-injury. On day 7 the brains were harvested for immunohistochemistry and for assessing the lesion volume.

This study shows modulatory effect of DHA on glial response and neurons as well as on levels of oxidative stress. DHA treated animals developed a considerable smaller brain lesion compared to vehicle. All animals showed moderate impaired neurological function after trauma, but there was an improvement on motor function in treated animals. To conclude, we suggest that DHA could serve as a pharmacological approach to minimize the inflammatory responses and enable a less hostile environment for regenerative growth and recovery.

P.28 High intake of dietary Linoleic Acid, compared to saturated and monounsaturated fatty acids, limits accretion of preformed DHA to the brain of young rats

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Background: Achieving an appropriate DocosaHexaenoic-Acid (DHA) status in the neonatal brain is an important goal of neonatal nutrition. The role of the linoleic (LA)/α-linolenic (ALA) ratio is known to modulate the conversion of ALA to LCn-3 and specifically to DHA which could modify the accretion to the brain. However the impact of dietary fat matrix quality on accretion of added preformed DHA is not known

Aims: In an attempt to evaluate the potential impact of the dietary FA matrix on brain DHA accretion when a supplementation with preformed DHA is proposed, we selected different fat based diet to compare 3 ALA-free oils - a n-6 FA rich diet (Sunflower oil, S), a MUFA rich (High-oleic sunflower oil, H) and a SFA rich (Palm oil, P) diets - to an ALA-rich diet (Rapeseed oil; 9%ALA, R) and to a blend mimicking human diet (Mix of dairy fat/ rapeseed/sunflower/ palm; 2.3% ALA, M).

Methods: Ten groups of 6 male rats, born from control dams fed a chow diet based on soya oil, received, for 6 weeks after weaning, the 5 selected diets (S, H, P, R, M) and 5 similar diets with a DHA-tuna oil supplementation (SD, HD, PD, RD, MD).

Results: Without DHA supplementations the levels of brain DHA were the lowest with Sunflower diet: S<H=P<R=M (12.6 *vs* 13.4 *vs* 14.5%) while a mirror like effect on AA (arachidonic acid) with S>H=P>R=M (10.5 *vs* 10 *vs* 9.6%) was observed. This indicates that within the groups of free-ALA diets (S, H, P) the highest LA-sunflower oil (60%) induced a 10% reduction of DHA compared to SFA-Palm and oleic-sunflower diets, and an increase of AA (+5%). The AA/DHA ratio in the brain (FA marker of inflammation) is the highest for Sunflower (0.85), lower for H and P (0.75) and the lowest for ALA-rich oils (0.65).

The supplementation with preformed DHA induced a DHA increase in all groups (+7% to +15%) and a concomitant reduction of AA only in the free-ALA diets (-5%), while ALA rich or mix diets were unchanged. However, with the LA-rich-Sunflower diet, the DHA levels did not reached those obtained with all the other groups (-7%) and AA was maintained higher (+5%). Similarly, the AA/DHA ratio in the brain (FA marker of inflammation) despite a global reduction in each group compared to the DHA-free diets, showed that the LA-rich-sunflower is still the highest (0.68) compared to all the others (0.62); ratio obtained with the sunflower diet is even higher than the ratio observed with the ALA-rich diet not supplemented (pure rapeseed)

Conclusions: High intake of LA, which is able to limit the bioconversion of ALA to LCn-3 (DHA) is also limiting the accretion to the brain of dietary preformed DHA.

A.50 Analysis of saccharides as dosimetric materials for high energy radiation

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After discovery of radioactivity in the last century, it finds several practical applications in many fields of human life. However, harmful effect of ionizing radiation on the living organisms requires strict control on the processes of high energy irradiation. Much needed control in the industrial enterprises, operating with radioactive materials, and in cases of accidents has resulted in the development of many dosimetric systems. Each of them consists of two parts – radiation sensitive material and instrument reading out the changes in it as a result of irradiation. Two types of dosimeters have been created – physical and chemical. Among chemical systems alanine/EPR spectrometry (EPR = Electron Paramagnetic Resonance) dosimeter has been developed in the last three decades. It is based on the fact that upon irradiation stable free radicals are generated in solid alanine and their quantity is determined by the method of EPR spectrometry. The radiation induced free radicals in solid alanine are stable with time. On the other hand, in the last two decades there is an increased interest in searching for new materials exhibiting equal or higher than alanine radiation sensitivity. Many materials were checked in the last two decades and new properties were discovered in some of them after radiation treatments.

The current study presents the investigation with EPR and UV spectrometry of different kind mono- and disacchrides. Among them the table sugar or sucrose shows the best results. A table sugar is cheap, widespread in the every day practice materials. Moreover, it is important as involved in the DNA structure. In view of this, it was considered as one of the most promising radiation sensitive materials not only for EPR, but also for UV dosimetric systems. The latter is very important, since while EPR is not calibrated, UV spectrometry is a calibrated method. This opens new horizons, using UV spectra of irradiated sugar to calibrate the EPR measurements.

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A.51 Identification of gamma – irradiated meat

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In the last few decades, it was shown that a very fast, efficient, inexpensive, secure and safe method of sterilization is irradiation of the foodstuffs with high-energy radiation. This process, however, is subject to control. In this context the European Standards Institute has adopted several protocols concerning the identification procedure. A particular place in the control of irradiated foodstuffs is the method of Electron Paramagnetic Resonance (EPR) spectroscopy. The irradiation of the food products leads to the formation therein of free radicals, which are detected by EPR. Some protocols, however, have certain weaknesses and therefore worldwide research continues with the aim of supplementing them. The results from investigation of irradiated pork meat and chicken legs are reported. EPR spectroscopy, microbiological Direct Epifluorescent Technique (DEFT) combining total aerobic plate count (APC) and DNA comet assay are used. The DEFT/APC technique and DNA comet assay method are not radiation specific and is utilized only for "screening" purpose. Therefore, it is recommended to confirm positive results using standardized method - EPR or GC/MS. The main Protocol adopted by the European Committee of Standardization for meat containing bone use EPR (EN 1786, 1996). The obtain EPR spectra from irradiated meat containing bone can be used as an unambiguous proof of irradiation independently of applied dose and time of storage.

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