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Relevance of ω-6 GLA Added to ω-3 PUFAs Supplements for ADHD: A Narrative Review

Mr Jelle D'Helft ORCID iD[1], Dr Riccardo Caccialanza ORCID iD[2], Dr Emma Derbyshire ORCID iD[3], Prof. Dr. Michael Maes ORCID iD[4]
[1]Springfield Nutraceuticals BVBV, Heist-op-den-Berg, Belgium. [2]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [3]Nutritional Insight, Epsom, United Kingdom. [4]Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract

The use of polyunsaturated fatty acids in Attention-Deficit/Hyperactivity Disorder (ADHD) and developmental disorders has been gaining interest with preparations containing different dosages and combinations. Gamma-linolenic acid (GLA) is an ω-6 fatty acid of emerging interest with potential roles as an adjuvant anti-inflammatory agent that could be used with ω-3 PUFAs in the treatment of ADHD and associated symptoms. A narrative review was undertaken to examine the potential role(s) of the ω-6 fatty acid GLA. PubMed, Google Scholar, and Scopus were searched to examine the potential role(s) of the ω-6 fatty acid GLA as (1) an antioxidant and anti-inflammatory agent, (2) a synergistic nutrient when combined with ω-3 PUFAs, and (3) a potential etiological factor in ADHD and its treatment. The results show that GLA exerts anti-inflammatory effects by increasing dihomo-gamma-linolenic acid in immune cells. ω-3 PUFAs, such as EPA and DHA, are often co-administered with GLA because these ω-3 PUFAs may prevent the accumulation of serum arachidonic acid in response to GLA administration without limiting the storage of DGLA in immune cells. The administration of ω-3 PUFAs alone might not be sufficient to effectively treat patients with ADHD and developmental disorders. Overall studies point towards a combination of EPA and DHA with GLA in a 9:3:1 ratio appearing to be associated with ADHD symptom improvement. A combination of PUFAs may lead to better outcomes.

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Omega- 3 Eicosapentaenoic (EPA) Polar Lipid Rich Extract from Microalgae Nannochloropsis Decreases Plasma Triglycerides and Cholesterol in Real-World Normolipidemic Supplement Consumer Population

Head of Research Eneko Ganuza PhD[1], Eghogho Etomi MSC.[2]
[1]iwilife, Houston, USA. [2]iwili\fe, Houston, USA

Abstract

Almega®PL is a polar rich oil (>15%) derived from the microalga Nannochloropsis, that contains EPA-only (>25%), without the DHA that is present in all other sources of omega-3. Its supplementation was previously shown to decrease cholesterol in a randomized controlled clinical trial (Rao et. Al., (2020) Nutrients, 12, 1869), to which we now expand with the present post-market cohort study that targets the actual end-users of this supplement. Participants were recruited from the new subscriber database and monitored at baseline, month-3, and month-6 of supplementation with 1-1.1 g/day of Almega®PL capsules. Changes in triglycerides (TG), very low-density-lipoprotein (VLDL), low-density-lipoprotein (LDL), high-density-lipoprotein (HDL), total cholesterol (TC), hs-CRP, glucose and HbA1c using the at-home Baseline Heart Health Testing Kit by Imaware® (Houston, TX, USA). Participants, who had normal triglycerides level at baseline (1.62±0.60 mmol/L), experienced a very significant and progressive decrease in triglycerides in month-3 (8.0%) and month-6 (14.3%) (primary outcome). Total cholesterol and non-HDL-cholesterol also decreased by 5.0% and 5.6 % respectively after 6-month supplementation, primarily driven by the decrease (14.4%) in VLDL. As observed in our previous clinical trial, the decrease in VLDL was not coupled to an increase in LDL, which seems to be a benefit associated with EPA-only based formulations. Collectively, these results show that Almega®PL offers a natural over-the-counter option for EPA-only that appears particularly effective in maintain lipid levels in the generally healthy, normolipidemic population.

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Effects of a walnut-enriched diet for 2 years on serum oxylipins in healthy elders

Dr. Montserrat Cofan[1], Dr. Antonio Checa[2], Dr. Sujatha Rajaram[3], Dr. Joan Sabaté[3], Dr. Emilio Ros[4], Dr. Craig Wheelock[2], Dr. Aleix Sala-Vila[5,6]

[1]August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain. [2]Unit of Integrative Metabolomics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [3]Center for Nutrition, Healthy Lifestyle and Disease Prevention, School of Public Health, Loma Linda University, Loma Linda, USA. [4]Department of Endocrinology and Nutrition, Hospital Clínic & August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain. [5]Cardiovascular Risk and Nutrition, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. [6]Fatty Acid Research Institute (FARI), Sioux Falls, USA

Abstract

BACKGROUND: Oxylipins include biologically active oxidation products derived from dietary polyunsaturated fatty acids (PUFA) that can play a role in cardiovascular disease and aging. There is clinical evidence that fish oil-derived n-3 PUFAs promote the formation of anti-inflammatory and vasodilatory oxylipins, but there are little data on oxylipins derived from alpha-linolenic acid (ALA), the main plant n-3 PUFA. Walnuts are a sustainable source of ALA. In the framework of the Walnuts and Healthy Aging study, we investigated in healthy elders (63-79 years) the effect on serum oxylipins of a diet enriched with walnuts at 15% energy (30-60 g/d) for 2 y compared to a control diet (abstention from walnuts).

MATERIALS AND METHODS: The red blood cell (RBC) proportion of ALA was determined by gas-chromatography as a measure of compliance. UPLC-MS/MS was used to measure serum concentrations of 53 oxylipins in participants randomly assigned to the walnut diet (n=64) or the control diet (n=51), and data were analyzed using MetaboAnalyst 4.0 software. Two-year concentration changes were log-transformed (base log-10) and standardized (mean-centered and divided by the standard deviation of each variable). Volcano plots were then generated (fold change ≥1.5; false discovery rate ≤0.1).

RESULTS: The 2-year change in RBC ALA in the walnut group was significantly higher than that in the control group ($P<0.001$). We observed significant between-group 2-year changes in the concentration of nine oxylipins. Compared to the control diet, the walnut diet resulted in statistically significantly greater increases of ALA-derived oxylipins 9-HOTrE, 13-HOTrE, 9-KOTrE, and 12,13-EpODE and greater reductions of arachidonic acid-derived 5,6-diHETrE, 14,15-diHETrE, 11-dehydro-TxB2, 5-HETE, and 19-HETE.

CONCLUSIONS: Long-term walnut consumption decreased levels of serum arachidonic acid-derived oxylipins with vasoconstrictor and pro-inflammatory properties. This adds novel mechanistic evidence on the cardioprotective effects of walnuts. The clinical relevance of increased ALA-derived oxylipins warrants further investigation.

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Effect of corticosteroid(s) on essential fatty acid (EFAs) metabolism

Dr Undurti Das MD, DSc
Indian Instittue of Technology, Hyderabad, India. UND Life Sciences, Battle Ground, USA. Asha Nutrition Sciences, Palo Alto, USA

Abstract

Background: Corticosteroids reduce prostaglandins (PGs) and leukotrienes (LTs) formation by inhibiting cyclo-oxygenase, lipoxygenase, and phospholipase A2 (PLA2). We examined whether dexamethasone decreases the availability of arachidonic (AA), eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) by inhibiting the desaturases that are needed to convert linoleic (LA) and alpha-linolenic acids to AA, EPA and DHA.

Methods and Materials: (i) EFA deficient but fed with n-3 fatty acid rich linseed oil (LSO) and n6 rich safflower oil (SFO) were treated with daily i.p. injection of 1 mg/rat dexamethasone for 7 consecutive days, and (ii) normal male Wistar-rats treated with dexamethasone 5 mg/kg/day for 10 days and supplemented with fish oil-n-3 rich oil and Arasco oil-rich in AA using both pre-treatment and post-treatment schedules. Plasma and liver phospholipid fatty acids were estimated by gas-liquid chromatography.

Results: Regardless of different oil supplementations, 18:2 n-6 and 20:3n-6 were increased in dexamethasone treated animals. Dexamethasone increased 18:3n-3 and 20:4 n-6 in the liver of LSO-fed animals, and 20:3n-6 and 22:6 n-3 in liver of SFO-fed animals and decreased 20:3n-6 and 20:5n-3, 22:5n-3 and 22:6n-3 in the plasma of LSO group, and 20:4n-6 22:4n-6 and 22:5n-6 in plasma of the SFO group.

Fish oil and Arasco oils-fed and dexamethasone treated rats showed an increase in saturated fatty acids and an increase in 18:2n-6 and a decrease in other n-6 and n-3 fatty acids.

Conclusions: Dexamethasone inhibited delta-6- and delta-5-desaturases, decreased availability of AA (and EPA and DHA). Hence, some of the anti-inflammatory actions of corticosteroids are due to AA and EPA and DHA deficiency.

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Essential fatty acid metabolism in patients with type 2 diabetes mellitus, hypertension, coronary heart disease and diabetic nephropathy

Dr Undurti Das MD, DSc
Indian Institute of Technology, Hyderabad, India

Abstract

Background: Type 2 diabetes mellitus (T2DM), essential hypertension (HTN), coronary heart disease (CHD) and diabetic nephropathy (DN) are common and are considered as low-grade systemic inflammatory conditions. Essential fatty acids (EFAs) and their metabolites play a critical role in inflammation. Hence, we studied the plasma concentrations of EFAs and their metabolites in these diseases.

Materials and Methods: Newly detected patients of type 2 DM, HTN, CHD and DN were recruited for the study. These patients were not on any medicines at the time of the study. Their fasting blood samples were collected and plasma phospholipid concentrations of various EFAs and their metabolites were estimated by gas-liquid chromatography.

Results: The results of this study given in the table clearly indicate that there are substantial chnages in the levels of EFAs and their metabolites. In all the patients studied, there is a significant decrease in arachidonic acid (AA, 20:4 n-6) levels. It is noteworthy that plasma PL fraction content of EPA (eicosapentaenoic acid, 20:5 n-3) was significantly low in those with CHD, whereas DHA (docosahexaenoic acid, 22:6 n-3) was low in those with CHD, T2DM and DN.

Discussion: There are substantial changes in the EFAs and their metabolites in those with HTN, T2DM, CHD and DN. It remains to be seen whether AA is more important than n-3 EPA and DHA in their prevention and management.

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A traditional marine diet affects glucose homeostasis in Greenlandic Inuit: A randomized crossover study

Jack Ivor Lewis[1], Mads Vendelbo Lind[1], Professor Torben Hansen ORCID iD[2], Professor Ken Stark ORCID iD[3], Professor Peter Bjerregaard ORCID iD[4], Professor Marit Eika Jørgensen PhD ORCID iD[5,6], Professor Lotte Lauritzen PhD ORCID iD[1]

[1]Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark. [2]2The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, København, Denmark. [3]Department of Kinesiology and Health Sciences, University of Waterloo, Waterloo, Canada. [4]National Institute of Public Health, University of Southern Denmark, København, Denmark. [5]Steno Diabetes Center Copenhagen, Herlev, Denmark. [6]Ilisimatusarfik, University of Greenland, Nuuk, Greenland

Abstract

The consumption of traditional foods is decreasing during the lifestyle change in Greenland, while the incidence of type 2 diabetes (T2D) is increasing. The risk of developing T2D is highest in homozygous carriers of a TBC1D4 variant, which causes postprandial insulin resistance in skeletal muscle.

We aimed to investigate the effect of a traditional marine diet on glucose homeostasis and cardio-metabolic health in Greenlandic Inuit carriers and non-carriers of the TBC1D4 variant.

We conducted a randomized, crossover trial with two 4-week dietary interventions; Traditional (marine-based, low in carbohydrates) and Western (Danish-like, high in imported meats and carbohydrates). We assessed glucose homeostasis by oral glucose tolerance tests (OGTT) and 14-day continuous glucose monitors as well as traditional cardio-metabolic markers and used complete-case linear mixed models to investigate the effect of diet and genotype.

Both interventions were completed with high compliance by 9 carriers of the variant plus 48 non-carriers (90%). Compared to the Western diet, the Traditional diet reduced mean and maximum daily blood glucose by 0.17 mmol/L [95% CI; 0.05,0.29; P=0.006] and 0.26 mmol/L [0.06,0.46; P=0.010], respectively, in a dose-dependent manner. Furthermore, it gave rise to a reduction in weight of 0.50 kg [0.09,0.90; P=0.016] and 4% [1,9; P=0.018] lower LDL:HDL-cholesterol, which after adjustment for the weight loss appeared to be driven by an increase in HDL (0.09 [0.03,0.15] mmol/L; P=0.006). A diet-gene interaction was indicated on insulin sensitivity in the OGTT (p=0.093), which seemed to reflect a non-significant increase of 1.4 [-0.6,3.5] mmol/L in 2-h glucose among carriers.

Our results showed that a Traditional marine diet marginally improved daily glycemic control and plasma lipid profile compared to a Western diet in Greenlandic Inuit. The suggested adverse effect on glucose tolerance in carriers of the TBC1D4 variant warrants further studies of diet-gene interactions.

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Stress-Eating and Obesity amidst the COVID-19 Pandemic among Filipino Adults

Prof Cherry Ann Durante MSPH ORCID iD[1,2], Dr Estrella San Juan PhD[2], Dr Rufo Jr Calixtro[2], Dr Lino Reynoso PhD[1]
[1]Emilio Aguinaldo College, Manila, Philippines. [2]University of Perpetual Help - Dr. Jose G. Tamayo Medical University, Binan, Philippines

Abstract

There exists a double-burden of malnutrition in the Philippines. In recent years, there has been an increase in the number of overweight and obesity, making it a public health concern. The most recent Philippine National Nutrition Survey revealed that three out of ten Filipinos are overweight or obese. This study was conducted to estimate the prevalence of obesity and presence of stress eating during the COVID-19 lockdown restrictions. This study utilized a cross-sectional quantitative research design with data gathered through an online, adapted version of the Eating and Appraisal Due to Emotions and Stress (EADES) questionnaire. Two hundred fifty-seven adults ages 21-62 from Binan, Laguna, participated in the study. Data collection was during the lockdown restriction implementation in the country from September to December 2020. Among the participants, 63.8% experienced weight gain during the pandemic; with 20% gaining 5-10 kilograms and 8% gaining more than 10 kilograms. Obesity prevalence was 30% among the participants, while underweight prevalence was 17.51%. Prevalence of stress eating was 86.77%, with low (41.25%), moderate (41.25%), and high (4.28%) levels. Furthermore, it was found that stress eating has a positive, moderately strong correlation with external stressors ($r=0.35$, p-value <0.001) and higher coping resources ($r=0.42$, p-value <0.001). Higher external stressors were also positively correlated with higher coping appraisal ($r=0.3990$, p-value <0.001). The prevalence of stress eating was also very high during the COVID-19 lockdown restrictions. There was a significant relationship between stress eating and external stressors and coping skills. The higher the external stressors, the higher the stress eating. Also, the higher the stress eating level, the higher the coping skill utilized by the participants. Many participants (86.77%) used stress-eating as a coping resource during the COVID-19 pandemic, affecting the increase in BMI and obesity prevalence.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Use of oxylipins to determine the dietary α-linolenic acid (ALA) requirement

Anne Manson[1,2], Karanbir Sidhu[1,2], Tanja Winter[1,2], Oleksandra Fedorova[1,2], Noah La[1,2], Elizabeth Magaji[1,2], Le Nguyen[1,2], Harold Aukema[1,2]

[1]University of Manitoba, Winnipeg, Canada. [2]Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, Canada

Abstract

Previous studies have examined ALA requirements based on the level of dietary ALA that is needed to achieve a plateau in DHA levels. However, ALA requirements have not been explored by analyzing oxylipins, which may better reflect fatty acid function. Data from several studies in our laboratory suggested that tissue DHA oxylipin levels are responsive to dietary ALA levels and may plateau at a different level than DHA. To explore the possibility of using oxylipin levels as a biochemical indicator of dietary ALA requirement, rats and mice were provided diets with increasing levels of ALA (0.1, 0.15, 0.2, 0.3, 0.6, 0.9, 1.2, 1.5, 1.9, and 2.5g/100 g diet). The amount of LA was kept constant at 2 g/100g diet among all groups. Free oxylipins in liver, kidney and brain homogenates underwent solid phase extraction and were analyzed by HPLC-MS/MS. The results indicated that DHA oxylipins increased and ARA oxylipins decreased with increasing dietary ALA, so the ratio of ARA/DHA oxylipins produced via the same enzymatic pathways was calculated. These oxylipin ratios initially decreased rapidly with increasing dietary ALA levels and then leveled off in a biphasic manner; thus, breakpoint analysis was used to determine the dietary ALA level at which a plateau was reached. The tissue that required the highest dietary ALA level to reach the plateau level of ARA/DHA oxylipins was the kidney, indicating that the kidney exhibits the highest ALA requirement among the tissues analyzed. This method provides a biochemical indicator of ALA requirement that should be applicable to estimating relative biological potencies of ALA, EPA and DHA, and determining the optimal dietary n-6/n-3 ratio.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not previously published

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Metabolites of omega-3 fatty acids and their effect on cardiovascular disease risk factors: a translational study

Katja T. Michler ORCID iD[1], Casper K. Nielsen[2], Jens J. Holst ORCID iD[1], Filip K. Knop ORCID iD[2], Trisha J. Grevengoed ORCID iD[1]
[1]University of Copenhagen, Copenhagen, Denmark. [2]Gentofte Hospital, Hellerup, Denmark

Abstract

The main target of cardiovascular disease (CVD) risk reduction is low-density lipoprotein cholesterol (LDLc), but many patients with well-controlled LDLc can further reduce CVD risk by decreasing triglyceride (TG) levels. Hypertriglyceridemia is often seen in patients with diabetes or metabolic syndrome and is associated with increased risk of CVD. Omega-3 fatty acid (FA) supplementation decreases plasma and liver TG levels and has previously demonstrated beneficial effects on CVD risk in both mice and humans. Although the mechanism behind is yet to be fully elucidated, recent evidence suggests the TG-lowering effects of omega-3 FA supplementation may be mediated by an understudied class of lipid metabolites, N-acyl taurines (NAT). In mice, omega-3 FA derived NATs decrease plasma and liver TG as well as intestinal lipid absorption (Grevengoed et al., 2021), which makes them interesting in the context of non-communicable diseases associated with hypertriglyceridemia or increased hepatic lipid accumulation.

To elucidate the potential role of omega-3 FA derived NATs in modulating CVD risk factors (such as hypertriglyceridemia), we will study the cardiometabolic effects of increased NAT levels in atherosclerosis-prone *Ldlr*$^{-/-}$ mice. Furthermore, a randomised, double-blind, placebo-controlled, crossover human trial is conducted to determine the effect of omega-3 FA derived NAT on dietary lipid absorption in humans. During a high-fat meal test, we will evaluate the impact of omega-3 FA derived NAT on postprandial triglyceridemia, lipid metabolism and glucagon-like peptide 1 secretion in healthy, young males. We hypothesise that acute administration of omega-3 FA derived NAT will decrease postprandial TG levels while increasing glucagon-like peptide 1 secretion. The project will increase basic and translational knowledge of omega-3 FA metabolism and contribute to the underlying mechanism of NATs in CVD development.

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Effect of plant extracts and DHA on age-related cognitive decline

Marie Martin[1,2], Céline Lucas[3], Adeline Coursan[1], Milan Boulaire[1], Quentin Leyrolle[1], Line Pourtau[2], David Gaudout[2], Anne-Laure Dinel[3], Corinne Joffre[1]
[1]Nutrineuro (INRAE), Bordeaux, France. [2]Activ'Inside, Beychac-et-Caillau, France. [3]Nutribrain, Bordeaux, France

Abstract

Aging is characterized by a slow and progressive alteration of cognitive functions which can lead to the development of neurodegenerative diseases. Age-related cognitive deficits mainly affect hippocampal-dependent memory, which plays a crucial role in learning and memory consolidation. Aging is also associated with microbiota dysbiosis, DHA deficit in brain membranes, deregulation of the immune system leading to a low-grade chronic inflammation, as well as neurofunctional alterations and increased oxidative stress. All these alterations contribute to the diminution of cognitive performance. Nutrition represents an innovative strategy to prevent or slow down age-related cognitive decline because it can be modulated. Several supplementations including n-3 PUFAs, polyphenols or carotenoids have shown beneficial effects on inflammation, neuroprotection and oxidative stress. Therefore, these nutrients are good candidates for the prevention of age-related cognitive decline. The objective of this study is to demonstrate the effect of a combination of DHA and vegetal extracts, containing grape and blueberries polyphenols and saffron carotenoids, on cognitive function and to understand the biological mechanisms involved. 17 months-old mice were fed with a balanced diet, with or without DHA and/or vegetal extracts supplementations for 2 months. Our main results showed that groups supplemented with DHA, vegetal extracts or both don’t have short and long-term age-related memory deficits unlike control group. These effects were associated with a modulation of inflammatory, neuroprotective and oxidative markers in hippocampus, changes in fatty acids, oxylipins and microbiota composition. These results demonstrated that supplementations prevent cognitive disorders by modulating different pathways and showed the interest to combine them.

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C2-hydroxylated fatty acids in health, pathology and therapy

Prof. Pablo Escriba Ph.D. ORCID iD[1], Dr. Victoria LLado Ph.D. ORCID iD[2], Dr. Paula Fernandez-Garcia Ph.D. ORCID iD[3], Dr. Roberto Beteta-Gobel Ph.D. ORCID iD[3], Dr. Raquel Rodriguez-Lorca Ph.D. ORCID iD[3], Dr. Gema Malet-Engra Ph.D. ORCID iD[3], Dr. Ramon Roman Ph.D. ORCID iD[3], Dr. Marta Salvador-Castell Ph.D. ORCID iD[3], Dr. Manuel Torres Ph.D. ORCID iD[1]
[1]University of the Balearic Islands, Palma, Spain. [2]Laminar Pharma, Boston, USA. [3]Laminar Pharma, Palma, Spain

Abstract

Fatty acids are biological molecules with relevant activities that include energy storage and production, membrane structure, cell signaling, protein localization, etc. The functions of C2 (alpha-carbon)-hydroxylated fatty acids are less known, mainly due to their lower abundance in cells. Mounting evidence indicates their relevance in physiology, pathology, and therapy. They can be incorporated through our diet or be produced in our body by the enzyme Fatty Acid 2-Hydroxylase (FA2H). Mutations on the FA2H gene highlight the relevance of 2-hydroxy fatty acids. Thus, mutations of this enzyme have been associated with spastic paraparesis, leukodystrophy, iron accumulation, and other disorders. In this context, 2-hydroxyoleic acid indices marked reductions in neuropathic pain caused by nervous lesions and tumor regression, which highlights the relevance of monounsaturated C2-hydroxylated fatty acids in the treatment of CNS pathologies.

Similarly, 2-hydroxylinoleic acid and 2-hydroxidocosahexaenoic acid showed efficacy against various types of cancer. In addition, 2-hydroxyarachidonic acid is a potent nonsteroid anti-inflammatory compound, which acts via the inhibition of COX1 and COX2. The 2-hydroxylated DHA analogue, 2-hydroxydocosahexaenoic acid, has been investigated in animal models of human Alzheimer's disease. In this model, it prevents molecular and cellular alterations derived from this neurodegenerative pathology. This induces recovery of neuroregenerative activity and neuronal density in the brains of rats followed by normalization of cognitive scores. Other conditions than neurological disorders, such as obesity or hypertension, can also benefit from therapeutic interventions with this type of fatty acids. In summary, 2-hydroxylated fatty acids are relevant in health, disease, and therapy.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Oral supplementation with oleic acid reduces inflammatory response, attenuating the local effects of Imiquimode in psoriasis mouse model.

Beatriz Burger[1], Natalie Ramos[1], Isabela Baccarin[1], Roberta Sagiorato[1], Jessica Silva[1], Lais Pral[2], Professor Marco Aurelio Vinolo[2], Prof Hosana Rodrigues Associated Professor ORCID iD[1]

[1]Universidade Estadual de Campinas, Limeira, Brazil. [2]Universidade Estadual de Campinas, Campinas, Brazil

Abstract

Thousands of people worldwide suffer with psoriasis, a disease caused by dysregulated immune reactions in skin. Fatty acids have been a successful strategy for the treatment of inflammatory diseases. However, there are few studies that have investigated the effects of oleic acid (OA) on psoriasis. The aim of this study was to evaluate the effects of OA on imiquimode (IMQ)-induced psoriasis mouse model. To psoriasis induction, 60 mg of Ixium® (5% of IMQ) was applied on shaved back skin of C57BL/6 mice from day 1 to day 5. Supplementation with OA occurred from day 1 to day 10. Supplemented mice reduced the percentage of skin thickness (13%) on 3rd day until the 7th day compared to IMQ. OA supplementation did not change body weight, food or water intake. Serum incorporation of oleic acid was increased two-fold in IMQ+OA group in relation to IMQ, as expected. After that, we collected skin on 3rd day. By RT-qPCR we observed that IMQ increased IL-23 and IL-22 expressions (three-fold) in comparison to control mice and, administration of OA reduced IL-23 (39%) in comparison to IMQ group. By flow cytometry, IMQ group increased the percentage of neutrophils (two-fold), monocytes and Langerhans cells (three times) in comparison to control group. On the other hand, OA supplementation reduced neutrophils (34%), monocytes (62%) and Langerhans cells (50%) compared to IMQ group. Moreover, cells isolated from bone marrow were stimulated by granulocyte-macrophage colony stimulating factor (GM-CSF, 10 ng/mL) for 7 days and treated for 24 hours with 10 µM of OA and LPS (1µg/mL). By ELISA, we observed that OA decreased IL-23 and IL-12 concentrations but not altered IL-1β, TNFα, IL-22. In conclusion, oral supplementation with oleic acid reduces inflammatory response, attenuating the local effects of IMQ in psoriasis mouse model.

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Synergistic antidepressant effect of n-3 PUFA and probiotics through brain-gut axis in depressed rats exposed to chronic mild stress

Ms. Hyunji Cho ORCID iD[1], Ms. Miyea Jo ORCID iD[1], Ms. Haemin Oh ORCID iD[1], Ms. Yunjung Lee[1], Dr. Younsoo Cha[2], Dr. Yongsoon Park[1]
[1]Hanyang University, Seoul, Korea, Republic of. [2]Jeonbuk National University, Jeonju, Korea, Republic of

Abstract

N-3 polyunsaturated fatty acids (PUFA) and probiotics have antidepressant-like effects, but the underlying mechanisms are unclear. We hypothesized that n-3 PUFA combined with live and dead probiotics synergistically improves depression by modulating the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic pathways through the brain-gut axis. Rats were randomly divided into seven groups (n = 8/group): non-chronic mild stress (CMS) with n-6 PUFA, CMS with n-3 PUFA, n-6 PUFA, live probiotics, dead probiotics, n-3 PUFA and live probiotics, and n-3 PUFA and dead probiotics. Diets of n-6 and n-3 PUFA and oral supplementation of live and dead probiotics were provided for 12 weeks, and CMS was performed for the last 5 weeks. N-3 PUFA and probiotics improved depressive behaviors and modulated the brain and gut HPA axis by synergistically increasing glucocorticoid receptor expression and decreasing corticotropin-releasing factor expression and blood levels of adrenocorticotropic hormone and corticosterone. N-3 PUFA and probiotics upregulated the brain serotonergic pathway through serotonin levels and expression of brain-derived neurotrophic factor, phosphorylated cAMP response binding protein, and 5-hydroxytrptamine 1A receptor while downregulating the gut serotonergic pathway. Furthermore, n-3 PUFA and probiotics increased the abundance of Ruminococcaceae, brain and gut short chain fatty acid levels, and occludin expression while decreasing the expression of tumor necrosis factor-α, interleukin-1β, and prostaglandin E2 and blood lipopolysaccharides levels. There was no significant difference between the live and dead probiotics. In conclusion, n-3 PUFA and probiotics had synergistic antidepressant-like effects on the HPA axis and serotonergic pathways of the brain and gut through the brain-gut axis.

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Synergistic effect of n-3 PUFA and probiotics on bone loss through brain-gut-bone axis in rats exposed to chronic mild stress

Ms. Hyunji Cho ORCID iD[1], Ms. Miyea Jo ORCID iD[1], Ms. Haemin Oh ORCID iD[1], Ms. Yunjung Lee[1], Dr. Younghee Kang[2], Dr. Yongsoon Park[1]
[1]Hanyang University, Seoul, Korea, Republic of. [2]Hallym University, Chuncheon, Korea, Republic of

Abstract

N-3 polyunsaturated fatty acids (PUFA) and probiotics are known to have helpful effects on bone loss, but bone-protecting mechanism has been uncertain. Therefore, the hypothesis of the present study was to investigate that supplementation of n-3 PUFA and probiotics had synergistic effect on depression induced bone loss through brain-gut-bone axis. Rats were fed with a diet contained 0 % or 1 % n-3 PUFA relative to energy intake, and live or dead probiotics were administered orally for 12 weeks. Chronic mild stress was performed to induce bone loss for 5 weeks. N-3 PUFA with both live and dead probiotics improved bone mass, calcium, and osteoprotegerin, and decreased N-telopeptide of type 1 collagen, receptor activator of nuclear factor kappa-B ligand, and cytokines. N-3 PUFA and probiotics increased brain-derived serotonin, and modulated the hypothalamic-pituitary-adrenal axis by decreasing adrenocorticotropic hormone and corticosterone, which decreased bone expression of beta 2 adrenergic receptor and activating transcription factor 4, while increased runt-related factor 2. On the other hand, n-3 PUFA and probiotics decreased gut-derived serotonin, which downregulated bone expression of 5-hydroxytryptamine receptor 1B and increased cyclic adenosine monophosphate. N-3 PUFA with probiotics had synergistic effect on ameliorated bone loss. This was the first study to show synergistic bone-protective effects of n-3 PUFA and probiotics through brain-gut-bone axis in depressed rats. Further studies are warranted to prove the synergistic effects of n-3 PUFA and probiotics on bone loss in depressed patients.

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Inverse Association between Omega-3 Index and Hyperglycemia among Adults in the United States Depending on Body Mass Index

Ms. Soomin Baik ORCID iD[1], Ms. Sunyoung Jo[1,2], Dr. William S. Harris ORCID iD[3,4], Dr. Nathan L. Tintle[4,5], Dr. Yongsoon Park[1,4]
[1]Hanyang University, Seoul, Korea, Republic of. [2]National Evidence Based Healthcare Collaborating Agency, Seoul, Korea, Republic of. [3]Sanford School of Medicine, University of South Dakota, Sioux Falls, USA. [4]Fatty Acid Research Institute, Sioux Falls, USA. [5]Department of Population Health Nursing Science, College of Nursing, University of Illinois-Chicago, Chicago, USA

Abstract

Type 2 diabetes (T2D) is characterized by a chronic state of hyperglycemia due to relative insulin deficiency and insulin resistance and diet is an important modifiable factor to prevent and manage T2D. There is inconsistency regarding the association between long-chain n-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA; 20:5n3) and docosahexaenoic acid (DHA; 22:6n3) and the risk of type 2 diabetes. The present study aimed to investigate the association between the Omega-3 Index (erythrocyte EPA + DHA) and glycemic status as a function of body mass index (BMI). Cross-sectional data from routine clinical laboratory testing from Health Diagnostic Laboratory, Inc. between 2011 and 2012 with a total of 100,572 people aged over 18 years and BMI ≥ 18.5 kg/m² were included. Of the patients, 10% were hyperglycemic (fasting plasma glucose levels ≥ 126 mg/dL) and 24.7% were of normal weight, 35.0% were overweight, and 40.3% were obese. Odds ratios (ORs) of being hyperglycemic were inversely associated with the Omega-3 Index, but weakened as BMI increased. Thus, ORs (95% CI) comparing quintile 5 with quintile 1 were 0.54 (0.44–0.66) in the normal weight group, 0.70 (0.61–0.79) in the overweight group, and 0.74 (0.67–0.81) in the obese group. Similar patterns were seen for EPA and DHA separately. The present study suggested that a greater risk of disordered glucose metabolism is inversely associated with the Omega-3 Index and this relationship is independent of BMI. Further study is needed to be investigated in large, population-based longitudinal studies with homogeneous samples of diverse geographical regions.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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18

An inflammation-regulated metabolite, arachidonoyl-taurine, protects from diet-induced hepatic fibrosis and steatosis in mice

Katja Michler MS, Samuel Trammell PhD, Trisha Grevengoed PhD
University of Copenhagen, Copenhagen, Denmark

Abstract

N-acyl taurines (NATs) are biologically-active conjugates of a fatty acid and taurine and are conserved from crayfish to mice and humans. The biological functions of NATs have only begun to be studied, but already have yielded promising results in stimulating GLP-1 secretion and lowering lipid absorption and fatty liver development.

Arachidonic acid (ARA) is a precursor for inflammation-regulating molecules, but the roles of ARA-NAT in metabolic disease have not been studied. Using liquid chromatography-mass spectrometry (LC-MS), we showed that plasma ARA-NAT increases with ARA supplementation and inflammation in both mice and humans, and with genetic disruption of its degradation by FAAH (FAAH S268D) in mice. Importantly, in human plasma, ARA-NAT correlated with hepatic steatosis score.

To investigate effects of elevating ARA-NAT in metabolic fatty liver disease development, wildtype and FAAH S268D mice were fed a high fat, high fructose diet +/- ARA for 28 wk. ARA feeding caused biliary ARA-NAT to rise to nearly 100 mM in the FAAH S268D mice, a value exceeding that of traditional bile acids, showing conversion into ARA-NAT may be an important part of ARA metabolism and transport in times of excess. Importantly, the ARA-fed FAAH S268D mice were protected from hepatic steatosis and fibrosis, liver damage, and systemic inflammation. Lipid uptake was higher in these livers, but accumulated triacylglycerol and VLDL secretion were lower, indicating altered hepatic lipid metabolism. This works reveals ARA-NAT as a novel regulator of lipid metabolism and inflammation with potential as a target for treatment or prevention of fatty liver disease.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Loss of an inflammation resolution receptor increases pulmonary PUFA-derived oxylipins and inflammation in mice that are glucose-intolerant

Dr. Saame Shaikh PhD ORCID iD[1], Dr. Kymberly Gowdy PhD[2], Michael Yaeger[2], Rafia Virk[1]
[1]UNC Chapel Hill, Chapel Hill, USA. [2]Ohio State University, Columbus, USA

Abstract

Chronic inflammation contributes toward pulmonary complications in obesity and type 2 diabetes. We recently reported that obese glucose intolerant mice, prior to and after lung injury, display an increase in the concentration of pulmonary polyunsaturated fatty acid-derived oxylipins that drive inflammation. Given that metabolic diseases of overnutrition are characterized by unresolved inflammation, we dissected the mechanistic role of the inflammation resolution receptor known as formyl peptide receptor 2 (ALX/FPR2) on pulmonary oxylipin levels and accompanying inflammation. Metabolically, ALX/FPR2 knockout mice (KO) were glucose intolerant relative to littermate controls despite normal weight gain and food intake. Indirect calorimetry measurements further revealed impaired glucose and lipid metabolism of ALX/FPR2 KO mice. Molecular level studies using targeted mass spectrometry showed that the loss of ALX/FPR2 led to an increase in the concentration of pulmonary oxylipins that control inflammation. Notably, total prostaglandin and hydroxydocosahexaenoic acids were increased in the lungs of ALX/FPR2 KO mice compared to wild type controls. In a model of acute lung injury induced by lipopolysaccharide (LPS), IL-1b secretion was increased with the loss ALX/FPR2. Administration of resolvin D1, an agonist of ALX/FPR2, lowered pulmonary injury and IL-1b secretion in response to LPS in wild type but not ALX/FPR2 KO mice. Taken together, these results show that the loss of an inflammation resolution receptor in mice that are glucose intolerant impairs pulmonary inflammatory status. Thus, therapeutic strategies targeting ALX/FPR2 may improve aspects of pulmonary inflammation, particularly in metabolic diseases in which the resolution of inflammation is dysfunctional.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Ethyl esters of eicosapentaenoic acid improve glucose homeostasis in a host genome and sex-dependent manner through oxylipin and gut microbiome mediated mechanisms

Dr. Saame Shaikh PhD ORCID iD, Dr. Anandita Pal PhD, Dr. Ian Carroll PhD
UNC Chapel Hill, Chapel Hill, USA

Abstract

There is strong epidemiological evidence suggesting that eicosapentaenoic acid (EPA) can prevent dysregulation of glucose homeostasis associated with type 2 diabetes. However, results from randomized clinical trials with EPA-containing marine oils are highly inconclusive, which may be due to a poor understanding of underlying genetic and sex differences in the metabolism of EPA. We have discovered that pure EPA ethyl esters prevent impairments to glucose homeostasis of C57BL/6J male mice fed a high fat diet. At a molecular level, the effects of EPA are dependent on the host genome and are mediated by a hepatic oxylipin-ChemR23 mechanism. EPA ethyl esters also prevent impairments to glucose homeostasis of female C57BL/6J mice consuming a high fat diet, although in a manner that is distinct from males. Mechanistically, female obese mice consuming EPA ethyl esters display a strong increase in the abundance of the Gram-negative microbe Akkermancia muciniphila. This effect is not observed in male mice consuming EPA. Supporting in vitro studies show that EPA, compared to controls, directly increases the growth rate of A. muciniphila. Furthermore, EPA restores changes in gut permeability induced by a high fat diet. Taken together, EPA ethyl esters exert beneficial effects on differing aspects of glucose homeostasis in a sex-dependent and genome-dependent manner through oxylipin production and via targeting of the gut microbiota. These findings have strong implications for the design of future precision clinical trials with EPA ethyl esters in the prevention of type 2 diabetes and its associated complications.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Omega-3 fatty acid biomarkers and incident atrial fibrillation: an individual participant-level, pooled analysis of 17 international prospective studies

Dr. Frank Qian MD, PhD[1], Dr. Nathan Tintle PhD[2], Dr Dariush Mozaffarian MD, DsC[3], Dr David Siscovick MD, MPH[4], Dr Rozenn Lemaitre PhD[5], DR William Harris PhD[6]

[1]Harvard University, Boston, USA. [2]Fatty Acid Research Institute, Sioux Falls, USA. [3]Tufts University, Boston, USA. [4]New York Academy of Medicine, New York, USA. [5]University of Washington, Seattle, USA. [6]Fatty Acid Research Institute, SIOUX FALLS, USA

Abstract

While observational studies of self-reported fish and omega-3 fatty acid intake suggest benefits in the prevention of atrial fibrillation (AF), recent randomized controlled trials (RCTs) of omega-3 treatments suggest harm. Understanding the relationship between blood/tissue omega-3 fatty acid levels and risk for AF can help clarify this issue. We prospectively evaluated circulating and adipose tissue levels of EPA, DPA, DHA and EPA+DHA with respect to incident AF in individuals without prevalent or a history of AF. Participant-level data from 17 prospective cohort studies from 21 nations were used. Participating studies conducted de novo analyses using a prespecified analytical plan with harmonized definitions for exposures, outcome, covariates, and subgroups. Among 54,799 participants, 7,720 incident cases of AF were ascertained, with a weighted median follow-up of 13.3 years. In multivariable analysis (adjusting for age; sex; race/ethnicity; education; smoking; alcohol use; BMI; beta blocker use; and linoleic and arachidonic acid levels; prevalent hypertension; dyslipidemia; diabetes mellitus; atherosclerotic cardiovascular disease; and heart failure) per interquintile range (difference between the 10th and 90th fatty acid percentiles), DPA, DHA, and EPA+DHA were associated with lower incidence of AF, with RR (95%CI) of 0.89 (0.83, 0.95), 0.90 (0.85, 0.96), and 0.93 (0.87, 0.99), respectively. EPA levels were not associated with incident AF, 1.00 (0.95, 1.05). Thus, biomarkers of omega-3 status (except EPA) were inversely associated with incident AF suggesting that within the spectrum of omega-3 fatty acid levels resulting dietary intake (instead of pharmaceutical treatment) these fatty acids are protective against the development of AF.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Association between Blood N-3 Fatty Acid Levels and Risk for COVID-19 in the UK biobank

Dr William Harris PhD[1], Dr Nathan Tintle PhD[1], Dr Swaminathan Sathyanarayanan MD[2], Mr Jason Westra MS[1]
[1]Fatty Acid Research Institute, Sioux Falls, USA. [2]University of South Dakota School of Medicine, Sioux Falls, USA

Abstract

Background: The role of nutritional status and risk for contracting and/or suffering adverse outcomes from SARS-CoV-2 infection is unclear. Preliminary studies suggest that higher n-3 PUFA intakes may be protective. Objectives: The purpose of this study was to compare risk for three COVID-19 outcomes (testing positive for SARS-CoV-2, hospitalization, and death) as a function of baseline plasma DHA levels. Methods: DHA levels (% of total fatty acids) were measured by nuclear magnetic resonance. The three outcomes and relevant covariates were available for 110,584 subjects (hospitalization and death) and for 26,595 ever-tested subjects (positive for SARS-CoV-2) in the UK Biobank prospective cohort study. Outcome data between January 1, 2020 and March 23, 2021 were included. Omega-3 Index (red blood cell EPA+DHA%) values across DHA% quintiles were estimated. Multi-variable Cox-proportional hazards models were constructed and linear (per 1-SD) relations with risk for each outcome were computed as hazard ratios (HRs). Results: In the fully adjusted models, comparing the fifth to the first DHA% quintiles, the HR for testing positive (95% CI) was 0.79 (0.71, 0.89; $p<0.001$), for being hospitalized was 0.74 (0.58, 0.94; $P<0.05$), and for dying with COVID-19 was 1.04 (0.69, 1.57; NS). On a per 1-SD increase in DHA% basis, the HRs were: for testing positive, 0.92 (0.89,0.96; $p<0.001$); for hospitalization, 0.89 (0.83, 0.97; $p<0.01$); and for death, 0.95 (0.83,1.09). Estimated Omega-3 Index values across DHA quintiles ranged from 3.5% (quintile 1) to 8% (quintile 5). Conclusions: These findings suggest that nutritional strategies to increase circulating n-3 PUFA levels, such as increased consumption of oily fish and/or use of n-3 fatty acid supplements, may reduce risk for adverse COVID-19 outcomes.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

https://www.medrxiv.org/content/10.1101/2022.08.19.22278992v2.full.pdf

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Omega-6 fatty acid, eicosadienoic acid, is related to lower risk of peripheral vascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA)

Natalie Weir M.S.[1], Sarah Nomura Ph.D.[1], Amy Karger MD/Ph.D.[1], Weihua Guan Ph.D.[1], Parveen Garg MD[2], Michael Tsai Ph.D.[3]
[1]University of Minnesota, Minneapolis, USA. [2]University of Southern California, Los Angeles, USA. [3]University of Minneosta, Minneapolis, USA

Abstract

Peripheral vascular disease (PVD) is a major comorbidity of type 1 and type 2 diabetes. Previous studies indicate omega-6 polyunsaturated fatty acids (PUFAs) play a role in PVD. While the omega-6 PUFA eicosadienoic acid (EDA) has been previously shown to be inversely related to type 2 diabetes, little is known about the relationship between EDA and PVD. Thus, we aimed to determine if EDA is related to PVD and if the relationship is independent of diabetes status.

This study was conducted in the Multi-Ethnic Study of Atherosclerosis (MESA) prospective cohort (n=6,460). EDA was measured at baseline as part of a phospholipid fatty acid profile by GC-FID. PVD was defined as physician diagnoses with symptoms or ultrasound evidence of obstruction, exercise test positive for claudication, revascularization procedure for PVD, amputation due to ischemia, ankle-arm ratio <0.8, imaging of aortic aneurysm, and/or vascular procedure for aortic aneurysm (N incident cases =104). Cox proportional hazards regression analysis was used to estimate EDA-related risks of incident PVD, including models with diabetes status and insulin levels as covariates.

A 53% lower risk of PVD incidence (Q4 vs Q1 HR=0.47, 95% CI: 0.25, 0.89) was observed in a minimally adjusted model for age and sex over the 13.9 year median follow-up period. Associations remained in a multivariate model (Q4 vs Q1 HR=0.46, 95% CI: 0.24, 0.89) and when additionally adjusted for insulin (Q4 vs Q1 HR=0.45, 95% CI: 0.23, 0.88) or type 2 diabetes (Q4 vs Q1 HR=0.50, 95% CI: 0.27, 0.99).

EDA is associated with lower risk of PVD and appears to be independent of insulin and diabetes status. Coupled with recent evidence of lower risk of diabetes, these results suggest a beneficial effect of EDA on the vascular system. Further research is required to confirm findings and elucidate the mechanism.

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Inhalation of nebulized omega-3 fatty acids mitigates LPS-induced acute lung inflammation in rats: Implications for the treatment of chronic and acute lung disorders

Dr Kumar Kothapalli PhD[1], Chandrashekhar Kocherlakota[2], Nagaraju Banda[2], Arjun Narala[2], Srinath Akula[2], Prof James Thomas Brenna PhD[1]

[1]University of Texas at Austin, Austin, USA. [2]Leiutis Pharmaceuticals LLP, Hyderabad, India

Abstract

Introduction. Many present treatment options for lung inflammation and thrombosis come with unwanted side effects. The omega-3 fatty acids (O3FA) are natural, generally anti-inflammatory and antithrombotic. O3FA are always administered orally and occasionally by intravenous (IV) infusion. Bioactivity/efficacy of O3FA against pathologies depend on their concentrations in target tissue. For instance, efficacy against lung pathology depends on the specific concentration of O3FA in lung tissue.

Hypothesis. The delivery of O3FA by inhalation would be efficacious against inflammatory sequelae.

Aim. The main aim is to determine if O3FA administered by inhalation of a nebulized formulation mitigates LPS-induced acute lung inflammation and is safe in male Wistar rats.

Methods. Intraperitoneal injection of LPS once a day for 14 days was used to trigger inflammation. After one-hour post-injection, rats received nebulized treatments consisting of egg lecithin emulsified O3FA or Budesonide and Montelukast, and blends of O3FA and Melatonin or Montelukast or Cannabidiol; O3FA was in the form of free fatty acids for all groups except one group with ethyl esters. Lung histology and cytokines were determined in n = 3 rats per group at day 8 and day 15.

Results. All groups had alveolar histiocytosis severity scores half or less than that of the disease control (Cd) treated with LPS and saline only inhalation. IL-6, TNF-α, TGF-β, and IL-10 were attenuated in all O3FA groups. IL-1β was attenuated in most but not all O3FA groups.

Conclusions. The ethyl ester form of O3FA administration was overall most effective in mitigating LPS effects. No evidence of lipid pneumonia or other chronic distress was observed. These preclinical data suggest that O3FA formulations should be further investigated as treatments in lung inflammation and thrombosis related chronic and acute lung disorders, including asthma, chronic obstructive pulmonary disease, lung cancer and acute respiratory distress such as COVID-19.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Dihomo-isofurans and F4-neuroprostanes derived from oxidation of AdA and DHA : Promising Biomarkers in Alzheimer’s Disease

Dr Ivana Milic PhD ORCID iD[1], Dr Camille Oger PhD ORCID iD[2], Dr Jean-Marie Galano PhD ORCID iD[2], Dr Thierry Durand PhD ORCID iD[2], Dr Andrew Dewitt PhD ORCID iD[1], Dr Helen Griffiths PhD ORCID iD[3], Dr Irundika Dias PhD ORCID iD[1]
[1]School of Life and Health Sciences, Aston University, Birmingham, United Kingdom. [2]Institut des Biomolécules Max Mousseron, UMR 5247, CNRS, UM, ENSCM, Montpellier, France. [3]Swansea University Medical School, Swansea University, Swansea, United Kingdom

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease with complex aetiology. Due to high content of polyunsaturated fatty acids (PUFA), brain is highly susceptible to free radical-mediated oxidative damage. Isoprostanes (IsoP) and neuroprostanes (NeuroP) are commonly observed lipid peroxidation products in brain. However, due to low abundance, these metabolites are difficult to measure using traditional analytical tools. The aim of this work is to develop a highly sensitive and robust multiple reaction monitoring based LC-MS/MS method for the quantification of 24 different non-enzymatic isoprostanoids and to utilise this method to analyse post-mortem brain samples from patients with AD.

This study analysed ten patients with AD and matched control frozen brain tissue samples (0.1 mg) received from Brains for Dementia, UK. Samples were homogenised in 100% methanol and spiked with internal standards (d4-4(RS)-4-F4t-NeuroP, d4-10-F4t-NeuroP and d4-10-epi-10-F4t-NeuroP). Metabolites were enriched using two-step solid phase extraction (SPE) using a polymeric SPE column (HLB PRiME, Waters) and further separation was achieved by LC-MS/MS.

This assay has a linear dynamic range (R2 > 0.93) between 0.04ng/ml-20ng/ml for the 24 IsoPs and NeuroPs. High intra- and inter-day precision (CV < 11%) was observed from the QC samples. Overall, IsoPs and NeuroPs were present in higher levels in AD patient brain tissue compared to healthy subjects. dihomo-Isofurans and NeuroPs were significantly higher in AD patients compared to healthy subjects (P<0.01). This data with suggest that analysis of different classes of IsoP and NeuroP will provide new opportunities to study lipid peroxidation in the neurodegenerative diseases such as AD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NO

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FADS2 Function at the 11q13 Major Cancer Hotspot Region Alters Fatty Acid Metabolism in Human Cancers

Dr Kumar Kothapalli PhD, Dr Hui Gyu Park PhD, Prof James Thomas Brenna PhD
University of Texas at Austin, Austin, USA

Abstract

Introduction. The 11q13 human chromosome genomic region is a major cancer hotspot and has been established as the most frequently altered by amplification in a variety of human cancers. The fatty acid desaturase genes (FADS1, FADS2 and FADS3) localize to the 11q12-13.1 region. FADS2 activity is promiscuous, catalyzing biosynthesis of polyunsaturated and monounsaturated fatty acids, including unsaturated branched chain fatty acids (BCFA) by Δ6, Δ8, and Δ4 desaturation toward at least 16 substrates.

Aim. Our main aim is to review known and putative consequences of FADS2 dysregulation due to the genomic alterations at the 11q13 locus in various cancer types.

Methods. We searched PubMed and Google Scholar databases for articles reporting 11q13 alterations and FADS2 function in various cancer types.

Results. FADS2 silencing causes synthesis of sciadonic acid (ScA, 5Z,11Z,14Z-20:3) in MCF7 cells and breast cancer in vivo. Melanoma, prostate, liver and lung cancer cells insensitive to SCD inhibition show increased FADS2 activity leading to sapienic acid (16:1n-10) biosynthesis from 16:0. Elevated serum mead acid (20:3n-9) levels were found in more than a third of hepatocellular carcinoma patients, indicative of an unsatisfied demand for arachidonic acid (5Z,8Z,11Z,14Z–20:4), likely as a substrate for eicosanoids. The FADS2 circular RNAs hsa_circ_022382 and circFADS2 are highly expressed in colorectal and lung cancer tissues, respectively.

Conclusions. 20:2n-6 is a common substrate for FADS1 and FADS2, whereas, palmitic acid (16:0) is a common substrate for SCD and FADS2. 5Z,11Z,14Z-20:3 is structurally identical to the eicosanoid precursor 5Z,8Z,11Z,14Z–20:4 except it lacks the internal Δ8 double bond required for prostaglandin and leukotriene synthesis, among other eicosanoids. FADS2 circular RNAs are at high levels in colorectal and lung cancer tissues. The evidence thusfar supports an effort for future research on the role of FADS2 as a tumor suppressor in a range of neoplastic conditions.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Abstract is published as a preprint <https://www.preprints.org/manuscript/202210.0206/v1>, not peer-reviewed.

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Blood and tissue DHA synthesis and turnover rates in mice fed Ahiflower® oil compared to flaxseed and DHA oil using compound-specific isotopic analysis

Adam Metherel[1], Brinley Klievik[1], Giulia Cisbani[1], Mackenzie Smith[1], Greg Cumberford[2], Richard Bazinet[1]
[1]University of Toronto, Toronto, Canada. [2]Natures Crops International, Kensington, Canada

Abstract

Ahiflower® oil is high in alpha-linolenic acid (ALA, 18:3n-3) and stearidonic acid (SDA, 18:4n-3), however, tissue/blood docosahexaenoic acid (DHA, 22:6n-3) turnover from dietary Ahiflower oil compared to other oils has not been investigated. In this study, we use compound-specific isotope analysis to determine tissue DHA turnover from Ahiflower, flaxseed and DHA oils. Pregnant BALBc mice (13-17 days) were placed on a 2% algal DHA diet of high carbon-13 content (delta^{13}C) and pups (n=132) were maintained on the diet until 6 weeks old. Mice were then randomly allocated to a low d13C-n-3 PUFA diet of either: 1) 4% Ahiflower oil (1.9% ALA + 0.8% SDA), 2) 4.35% flaxseed oil (2.7% ALA) or 3) 1% fish-source DHA oil for 1, 3, 7, 14, 30, 60 or 120 days (n=6). Plasma, livers and brains were collected and DHA levels and delta^{13}C determined. DHA concentrations were highest ($p<0.05$) in the liver of DHA-fed animals with no differences between diets in plasma or brain ($p>0.05$). However, DHA half-lives for plasma were 13.8 (12.5, 15.2, 95% C.I.), 11.4 (10.2, 12.9) and 8.6 (7.3, 10.1) days, for liver were 14.0 (12.8, 15.4), 12.2 (10.8, 118) and 10.1 (8.7, 11.9) days and for brain were 250 (137, 1380), 128 (92.3, 208) and 86.8 (68.3, 11.9) days in the flaxseed, Ahiflower and DHA diets, respectively. Based on the presence (not significant) or absence (significant) of overlapping 95% C.I.'s, DHA half-lives and synthesis/turnover rates were not different between Ahiflower and DHA diets in the liver or brain. DHA half-lives from flaxseed oil was significantly longer than from the DHA diet in all tissues. These findings suggest that the distinct Ahiflower oil n-3 PUFA composition could support tissue DHA needs at a similar rate to dietary DHA, making it a unique plant-based dietary option for maintaining DHA levels.

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FADS1 main function is modular of arachidonic acid / dihomo-gamma-linolenic acid (20:4n-6/20:3n-6) balance

Prof James Thomas Brenna PhD, Dr Hui Gyu Park PhD, Dr Kumar Kothapalli PhD
University of Texas at Austin, Austin, USA

Abstract

Introduction. Endogenous synthesis of the highly unsaturated fatty acids (HUFA) is mediated by FADS gene cluster (11q12-13.1) and elongation of very long-chain fatty acids 2 (ELOVL2) and ELOVL5. Molecular studies have also clarified the roles of the acyl-coenzyme A synthase long-chain isoforms (ACSLx) requirement for the entry into HUFA biosynthetic pathways. Regulatory genetic polymorphisms within FADS and ELOVLx are now known to limit HUFA product accumulation at any step of the HUFA biosynthetic pathway. Evolutionarily conserved non-catalytic alternative transcripts (AT) of FADS mediate the enzymatic activity and alters PUFA levels in specific ways.

Results. FADS1 and FADS2 but not FADS3 are active toward PUFA. FADS1 is a Δ5-desaturase operating on five C20 PUFA, and is strongly regulated by a 22 bp Indel polymorphism, modulating circulating arachidonic acid (20:4n-6; ARA) levels by about 84%. In contrast, FADS2 operates on at least 16 substrates and catalyzes Δ6, Δ4, and Δ8 desaturation. FADS2 silencing in cancer cells leads to FADS1 synthesis of unusual unsaturated FA. ACSL6 and ACSL4 are required to maintain tissue 22:6n-3 and 20:4n-6, respectively. The FADS1AT1 enhance desaturation of FADS2, leading to more than 2-fold production of 18:3n-6 and 20:3n-6 FA. FADS2AT2, is the first transcript to differentially inhibit desaturation, attenuating 18:3n-3 but not 18:2n-6 desaturation. The PUFA elongases ELOVL5, 2, and 4 are implicated in cancer, age-related methylation, and retinal degeneration, respectively.

Summary. The FA substrates available to FADS2 in any tissue defines the product mixture available for further synthesis of membrane lipids and signaling molecules and may be relevant in many clinical conditions including cancer. Genetic polymorphisms within FADS and ELOVL and/or non-catalytic FADSAT can limit HUFA product accumulation at any step of the biosynthetic pathway. Functional genetic variants define the levels of circulating AA via FADS1 regulation; genotypes that drive high AA may predispose to disease.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Development of plant-based long-chain omega-3 oils

Dr Xue-Rong Zhou Ph.D. ORCID iD, Dr Surinder Singh Ph.D.
CSIRO Agriculture and Food, Canberra, Australia

Abstract

Omega-3 long chain polyunsaturated fatty acids (ω3 LC-PUFA), in particular EPA (eicosapentaenoic acid, 20:5ω3) and DHA (docosahexaenoic acid, 22:6ω3), play a critical physiological role in health, and they are nutritionally important for both humans and animals. Dominant resources of ω3 LC-PUFAs especially from wild-caught marine fish are declining. Other factors such as heavy metal contamination in marine fish and vegetarians not being able to eat fish, lead to insufficient intake of ω3 LC-PUFA in many countries. These have resulted in a widely recognised need for new sustainable and vegetarian sources of ω3 LC-PUFA. We have developed oilseed crops producing ω3 LC-PUFAs. Genetic engineering of ω3 LC-PUFAs into oilseed crops involved microalgae survey, gene discovery, multiple-gene ω3 LC-PUFA synthesis pathway design, crop transformation and elite event selection resulted in a canola crop with fish oil-like levels of DHA. The canola crop rich in DHA oil is approved by multiple regulators in Australia, USA and Canada for large scale cultivation and the DHA-rich oil is approved for food and feed applications. First commercial sale of Aquaterra®oil for use in aquafeeds occurred in 2020. DHA-rich canola is now also available for human nutrition markets as Nutriterra®. Other plant-based long-chain omega-3 oils with different fatty acid profiles are also being developed. These genetically engineered oilseed crops can and will help meet the increasing market demand for ω3 LC-PUFAs in aquaculture and human nutrition. The land-based source of ω3 LC-PUFAs offers a safe, cost effective, scalable and sustainable solution, which can have critical and positive health, economic and environmental impacts.

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Exercise training rescues the reduced Mfsd2a expression in the blood-brain barrier of hypertensive rats

Sany Pérego MSc ORCID iD, Hiviny Raquel PhD ORCID iD, Gustavo Masson PhD, Mariana Martins ORCID iD, Vanessa Candido PhD ORCID iD, Alexandre Ceroni PhD ORCID iD, Lisete Michelini PhD ORCID iD, Alison Colquhoun DPhil ORCID iD
University of São Paulo, São Paulo, Brazil

Abstract

Background: Chronic hypertension was accompanied by augmented vesicle trafficking (transcytosis) across the blood-brain barrier (BBB) within preautonomic brain areas and autonomic imbalance. We showed previously that aerobic training corrected both increased BBB permeability and autonomic dysfunction. Knowing that Mfsd2a is the main transporter of docosahexaenoic acid (DHA) and that Mfsd2a knockout mice exhibited leaky BBB with increased transcytosis, we sought to identify its possible involvement in hypertension- and exercise-induced transcytosis across the BBB.

Methods: Spontaneously hypertensive rats (SHR) and normotensive controls (Wistar) were submitted to moderate treadmill training (T) or kept sedentary (S) for 4 weeks. Baseline values of arterial pressure (AP), heart rate (HR), and autonomic parameters (power spectral analysis) were recorded in conscious chronically canulated rats. In anesthetized rats, BBB permeability within the hypothalamic paraventricular nucleus (PVN, important preautonomic nucleus) was evaluated. Brains were harvested for Mfsd2a and caveolin-1 (an essential protein for vesicle formation) expression.

Results: SHR-S vs. Wistar-S exhibited elevated MAP and HR, increased vasomotor sympathetic activity, reduced cardiac parasympathetic activity, and intense hormonal modulation, which caused greater pressure variability, reduced HR variability, and depressed baroreflex control. SHR-S also showed increased BBB leakage accompanied by reduced Mfsd2a and increased caveolin-1 expression. SHR-T vs. SHR-S exhibited resting bradycardia, partial drop in MAP, reduced sympathetic activity, normalized cardiac parasympathetic activity, mild HR variability, and reduced pressure variability. These effects occurred simultaneously with the normalization of BBB permeability, accompanied by increased Mfsd2a density and reduced caveolin-1 protein expression within the PVN of the SHR-T. No changes were observed in Wistar-T vs. Wistar-S.

Conclusions: T is an efficient tool to rescue Mfsd2a expression, which by transporting DHA into the endothelial cell reduces caveolin-1 availability and vesicle formation. The exercise-induced Mfsd2a normalization is an important mechanism to correct both BBB function and autonomic control in hypertension.

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If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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The bioactive lipid, 2OHOA, inhibits Notch signaling pathway by downregulation of furin activity

Dr. Raquel Rodríguez Lorca PhD in Biotechnology, Genetic and Cell Biology ORCID iD[1,2], Dr. Ramón Román PhD in Biotechnology[1,2], Dr. Roberto Beteta Göbel PhD in Biotechnology, Genetic and Cell Biology[1,2], Dr. Manuel Torres[1], Dr. Victoria Lladó[1,2], Dr. Pablo V. Escribá[1,2], Dr. Paula Fernández García[1,2]

[1]Laboratory of Molecular Cell Biomedicine, Department of Biology, University of the Balearic Islands, Palma de Mallorca, Spain. [2]R&D Department, Laminar Pharmaceuticals, Palma de Mallorca, Spain

Abstract

Gliomas are the most common and aggressive cancer tumors of the central nervous system, showing resistance to current therapies. 2OHOA, which is currently running a phase IIB/III clinical trial for newly diagnosed GBM patients, was developed in the context of melitherapy, a novel therapeutic platform based on the regulation of the membrane's structure and organization with the consequent modulation of certain cell signals to revert the pathological state in several disorders. These alterations trigger modifications in membrane-associated proteins, as Ras, inducing its translocation from the plasma membrane to the cytoplasm, followed by differentiation and autophagy cell death. Notch signaling pathway is abnormally activated in gliomas and has been highly related to tumorigenesis and cell survival driving to the pathogenesis of GBM. This transmembrane protein is processed by several enzymes, such as furin, in the different cellular compartments to initiate the cascade of signaling. The present study shows the inhibition of this pathway by 2OHOA in U-118 MG and U-87 MG GBM cell lines. The mechanism of action is induced through the inactivation of furin activity by direct physical association, characterizing a novel target of this bioactive lipid. Consequently, Notch processing is impaired downregulating the cascade of signaling, and repressing NICD-dependent transcription genes. Finally, the relevance of this pathway was highlighted not only by the overexpression of the main target of this pathway, HES1, which partially inhibited 2OHOA's antiproliferative effect but also the reduction of its expression by the drug that correlated positively with their sensitivity to the molecule.

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Effects of Fish Oil-Derived N-3 Polyunsaturated Fatty Acids on the Generation and Thrombogenic Activity of Circulating Extracellular Vesicles

Dr Ruihan Zhou, Dr Esra Bozbas, Dr Keith Allen-Redpath, Professor Parveen Yaqoob
University of Reading, Reading, United Kingdom

Abstract

Background: Extracellular vesicles (EVs) are submicron membrane-bound vesicles released from almost all cells, which affect many pathophysiological processes involved in cardiovascular diseases (CVDs) and therefore have potential as novel markers for CVDs. N-3 polyunsaturated fatty acids (PUFA) have been suggested to play a role in cardiovascular health. However, there is little information about the effect of n-3 PUFA on circulating EV numbers, composition and thrombogenic activity in the context of CVDs.

Objective: This study investigated the chronic effects of fish oil-derived n-3 PUFA on the numbers, fatty acid composition and thrombogenic activity of circulating EVs.

Design: Subjects (n=40) aged 40-70y with moderate risk of CVDs were recruited into a double-blind, randomised crossover trial of fish oil (1.8 g/d n-3 PUFA) or control oil (high-oleic safflower oil) for 12 weeks with a 12-week washout. EVs were enumerated and characterised by Nanoparticle Tracking Analysis (NTA) and flow cytometry (FCM). Total lipid fatty acid composition and thrombogenic activity of circulating EVs were analysed by gas chromatography and a thrombin generation assay respectively.

Results: Fish oil supplementation significantly decreased the numbers of circulating EVs detected by both NTA and FCM and resulted in an increase in the proportions of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in circulating EV lipids at the expense of arachidonic acid and oleic acid. The ability of circulating EVs to activate tissue factor-dependent thrombin generation was decreased after intervention with fish oil.

Conclusion: Dietary n-3 PUFA modifies the number, fatty acid composition and thrombogenicity of circulating EVs, suggesting that the anti-thrombogenic effects of n-3 PUFA may be mediated at least partly through EVs.

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The association between calisthenics combined with long-chain polyunsaturated fatty acid intake and cognitive function among older Japanese individuals: A longitudinal analysis

Mrs. CHIKA HORIKAWA[1,2], Dr. Yukiko Nishita[2], Dr. Chikako Tange[2], Mr. Hidenori Obata[1], Dr. Tomohiro Rogi[1], Dr. Takayuki Izumo[1], Dr. Masaaki Nakai[1], Dr. Hiroshi Shimokata[3], Dr. Rei Otsuka[2]

[1]Institute for Health Care Science, Suntory Wellness Ltd., Kyoto, Japan. [2]Department of Epidemiology of Aging, National Center for Geriatrics and Gerontology, Aichi, Japan. [3]Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan

Abstract

The trend of adopting a variety of lifestyle habits to prevent cognitive decline has been increasing. A combination of habits that can be easily modified and is suitable for older people is ideal. Particular attention was paid to the combination of leisure time activities and dietary lifestyle habit. We investigated the association between cognitive decline and calisthenics combined with the intake of long-chain polyunsaturated fatty acid (LCPUFA). The calisthenics in this study included muscle stretching exercises, physical conditioning, and dance.

Baseline data including calisthenics, fatty acid intake, and potential confounders (sex, age, baseline Mini-Mental State Examination: MMSE, etc.) was provided from participants in the fifth examination of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). Cognitive function was assessed by the MMSE. We defined cognitive decline as a MMSE score ≤ 27 after four years. The subjects aged 60−84 (n = 517) had an MMSE score ≥28 at baseline. The participants were divided into two groups (high and low) according to the frequency of calisthenics and the sex-stratified median intake of LCPUFA. The interaction between calisthenics and LCPUFA as well as the main effect of each individual exposure on cognitive decline was investigated using multiple logistic analysis. Using low level combinations as the reference, the odds ratios (OR) for cognitive decline was calculated in the group with both or either of the higher combinations.

The adoption of calisthenics showed a significant interaction on cognitive decline, when combined with LCPUFA intake (Estimate: -2.167, SE: 0.89). The LCPUFA alone also showed a significant main effect. The OR for cognitive decline of the combination of high frequency of calisthenics and high LCPUFA intake was significantly smaller than the both low combinations. The combination of calisthenics and LCPUFA intake might be associated with reduced risk of cognitive decline in older Japanese individuals.

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New insights into LDLR regulation and trafficking: the interplay of MHC-I like molecules with PCSK9

PhD candidate Sepideh Mikaeeli Msc[1,2], Post doctoral fellow Ali Ben Djoudi Ouadda PhD[2], Research associate Alexandra Evagelidis MSc[2], Principal investigator Nabil G. Seidah PhD[2]

[1]McGill University, Montreal, Canada. [2]Institut de recherches cliniques de Montral (IRCM), Montreal, Canada

Abstract

PCSK9 linked to familial hypercholesterolemia via degradation of LDLR. Recently it has been demonstrated that PCSK9 interacts with an RxE motif of an MHC-class-I protein and sends it to lysosomal degradation. This finding elucidates the importance of the RxE motif in partner proteins that might interact with M2 domain of PCSK9. As a result, we hypothesized that MHC-I or other MHC-I proteins with RxE motif, such as HFE or HLA-C, might interact with PCSK9 and regulate its function.

Our preliminary data in hepatocytes, revealed that while HFE inhibits the function of PCSK9, HLA-C enhances PCSK9's activity towards LDLR degradation. Interestingly, HFE is also degraded by extracellular PCSK9 like HLA-C. Interestingly, our co-immunoprecipitation data suggested that HFE interacts with PCSK9 via the same RxE motif that is critical for HLA-C binding to PCSK9. To probe the molecular details of MHC-I RxE and M2 interactions, we Ala-mutated the predicted interaction sites on both PCSK9 (PCSK9-R549A-E567A) and HFE (HFE-R67A-E69A) or HLA-C (HLA-C-R68A-E70A). Our data show that the extracellular PCSK9-R549A-E567A no longer affects LDLR, HFE and HLA-C levels. Furthermore, we showed that the HLA-C-R68A-E70A blocks the function of PCSK9 on LDLR in contrast with WT HLA-C.

Indeed, the PCSK9 effect on HFE is dependent on Caveolin, in contrast to HLA-C that is Clathrin dependent. Thus, in the presence of HFE, the complex internalizes via Caveolin-coated vesicles and LDLR recycles back to the cell surface. On the other hand, with HLA-C the complex is internalized into Clathrin-coated vesicles and LDLR is co-targeted to the lysosomal degradation pathways. Altogether, these data imply that HFE and HLA-C interact with PCSK9 via same motif and can balance its function by taking different regulatory pathways. Further analyses are needed to confirm these results and to better define the unexpected puzzling opposite roles of HFE and HLA-C on PCSK9.

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Novel fat taste receptor agonists decrease obesity in mice

Dr Naim Khan PhD ORCID iD[1], Dr Amira Khan PhD[1], Dr Aziz Hichami PhD[1], Dr Sylvain Jugé PhD[2]
[1]INSERM 1231, Dijon, France. [2]ICMUB, Dijon, France

Abstract

BACKGROUND & AIMS: The spontaneous preference for dietary lipids is, principally, regulated by two lingual fat taste receptors, i.e., CD36 and GPR120. Obese animals and most of human subjects exhibit low oro-sensory perception of dietary fat because of malfunctioning of these taste receptors. Our aim was to target the two fat taste receptors by newly synthesized high affinity fatty acid agonists to decrease fat-rich food intake and obesity.

METHODS: We synthesized two fat taste receptor agonists (FTA), i.e., NKS-3 (CD36 agonist) and NKS-5 (CD36 & GPR120 agonist). In C57Bl/6 male mice, we assessed their gustatory perception and effects of their lingual application on activation of tongue-gut loop. We elucidated their effects on obesity and its related parameters in male mice, fed a high-fat diet.

RESULTS: The two FTA, NKS-3 and NKS-5, triggered higher Ca2+ signaling than a dietary long-chain fatty acid in human and mouse TBC. Mice exhibited a gustatory attraction for these compounds. In conscious mice, the application of FTA onto the tongue papillae induced activation of tongue-gut loop, marked by the release of pancreato-bile juice into collecting duct, and cholecystokinin and peptide-YY into blood stream. Daily intake of NKS-3 or NKS-5 via feeding bottles decreased food intake and progressive weight gain in obese, but not in control, mice.

CONCLUSIONS: Our results show that targeting fat sensors in the tongue by novel chemical fat taste agonists might represent a new strategy to reduce obesity.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Khan AS et al. Novel Fat Taste Receptor Agonists Curtail Progressive Weight Gain in Obese Male Mice. Cell Mol Gastroenterol Hepatol. 2022 Nov 19:S2352-345X(22)00236-3. doi: 10.1016/j.jcmgh.2022.11.003. Epub ahead of print. PMID: 36410709.

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Lipophenols: Synthesis and Applications as Both Analytical Standards and Therapeutics Derivatives

Jordan Lehoux ORCID iD[1], Sandra Rochel[1], Dr Céline Crauste[1], Dr Thierry Durand[1], Dr Sonia Medina[2], Dr Angel Gil-Izquierdo[2], Dr Jetty Lee[3], Dr Maxime Vincent[4], Dr Sylvie Begu[4], Dr Philippe Brabet[5]
[1]IBMM, Montpellier, France. [2]University of Murcia, Murcia, Spain. [3]University of Hong-Kong, Hong-Kong, Hong Kong. [4]INM, Montpellier, France. [5]ICGM, Montpellier, France

Abstract

Lipophenols, polyphenolic compounds acylated by a fatty acid (saturated, mono or polyunsaturated), have recently been identified in food matrices naturally rich in both polyphenols and fatty acids, making them natural derivatives present in human diet. The identification of natural lipophenols is particularly relevant to understand their pharmacological actions, metabolism or to use them as analytical standards.

As an example, hydroxytyrosol (HT) linked to polyunsaturated fatty acids (PUFA) is naturally present in extra virgin olive oil (EVOO) and should participate to its antioxidant properties. In the present work, chemical synthesis of HT lipophenols will be presented to access HT-PUFA standards. UHPLC-MS/MS quantitative study in EVOO was realised during a 12 months period, mimicking both commercial and inappropriate conditions of storage. The results highlighted HT-OA as a relevant marker for the monitoring of oil storage conditions and quality.

The chemical synthesis of biomimetic lipophenols is also of interest to enhance the interesting properties of polyphenols (antioxidants, anticarbonyl stress action) and improve their pharmacological profile, particularly their bioavailability. Moreover, combining both therapeutic aspects of omega-3, and natural polyphenols in a single lipophenolic molecule is also a pharmacological strategy to obtain synergistic potency. Recently, we demonstrated that flavonoids-PUFA derivatives lead to the protection of retinal cells against carbonyl and oxidative stresses, both toxic mechanisms involved in macular degeneration. We also showed that a proper alkyl substituent allowed to dramatically increase their anti-carbonyl stress capacity leading to strong interest on quercetin derivative bearing both an isopropyl and a PUFA part (Q-iP-DHA). In the present work,the chemical synthesis of Q-iP-DHA on gram scale will be presented, allowing the validation of in vivo evaluation of this lipophenol, formulated with Lipid NanoCapsule, in a light induced photoreceptors degeneration mouse model, using both IV and oral administration.

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Nutritional medicine against long COVID: The interplay between inflammation and omega-3 fatty acids in depression

Professor Kuan-Pin Su MD, PhD ORCID iD
China Medical University, Taichung, Taiwan. An-Nan Hospital, Tainan, Taiwan

Abstract

Long COVID is referred to the condition characterized by long-term health problems after the typical recovery period in up to 30% of patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Depressive syndromes have been reported as a prominent feature of long COVID. The mechanisms are multifactorial, from long-term systemic and CNS inflammation to unresolved systemic inflammation. In fact, long COVID might be the largest clinical observation of inflammation theory for depression.

The increasing global burden calls for the development of novel approaches to tackle unmet needs in prevention and treatment of depression underlying biological, psychological and social dysregulations. Depressed patients with chronic low-grade inflammation might be classified as a subgroup of major depressive disorder (MDD); therefore, looking for antidepressant therapies from anti-inflammatory pathways could improve treatment effectiveness for this subgroup of patients. Omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) are anti-inflammatory both in peripheral organs and central nervous systems and have clinically applied in the treatment and prevention of depression, cardiovascular diseases, dyslipidaemia, diabetes and arthritis. Anthropological studies suggest that human beings evolved to a modern diet with less than one-tenth of omega-3 to omega-6 PUFAs intake ratio, which leads to a constitutional bias toward chronic systemic inflammatory status to explain dramatically increasing of depression and chronic medical illnesses in modern world. The presentation is to provide our recent clinical and pre-clinical studies and an overview about the role of inflammation in “mind-body” comorbidity and present anti-inflammatory mechanisms by which n-3 PUFAs may orchestrate the molecular and cellular functions and facilitate the therapeutic pathways in chronic mental and medical illnesses in Long COVID.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

1. Yang CP et al. Long COVID and long chain fatty acids (LCFAs): Psychoneuroimmunity implication of omega-3 LCFAs in delayed consequences of COVID-19. Brain Behavior Immunity 2022;103:19-27.

2. Liu ST et al. The Clinical Observation of Inflammation Theory for Depression: The FOCuS Study. Clinical Psychopharmacology and Neuroscience, in Press

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Different Levels and Pattern of Lipid-Derived Gut Microbial Metabolites after Fermentation of Different Lipid-rich Foods

Zongyao Huyan ORCID iD[1], Dr. Nicoletta Pellegrini ORCID iD[2], Dr. Wilma Steegenga[1], Dr. Edoardo Capuano ORCID iD[1]
[1]Wageningen University & Research, Wageningen, Netherlands. [2]University of Udine, Udine, Italy

Abstract

Next to dietary fiber and proteins, undigested dietary lipids also enter the colon and can be used by human gut microbiota. Although the pathways through which lipids are metabolized by the gut microbiota is partly known, how the nature of the specific lipid-rich matrix modulates lipid metabolism is poorly explored. Here, the differences in the levels and patterns of lipid microbial metabolites produced from different food matrixes, sunflower seed, soybean, and walnut were investigated. Food samples were subjected to a simulated in vitro digestion, after which the undigested material was subjected to an in vitro colonic fermentation using faecal samples from three healthy donors for 48h. Several known linoleic acid (LA) metabolites were quantified by a targeted approach, whereas several other LAs metabolites were identified or putatively annotated by the untargeted lipidomics approach using high-resolution liquid-chromatography mass spectrometry. Results showed that digested walnut produced the highest levels of FFAs and conjugated LAs (CLAs) after fermentation. To further explore the matrix effect, the same amount of defatted digested foods, as well as of fibre and polyphenol extracted from the digested materials were prepared and fermented with sunflower oil. The addition of defatted digested walnut to sunflower oil also produced the higher levels of FFAs and detected CLAs. This is ascribed to its fibre and polyphenols which addition produced the higher increase in CLAs than sunflower and soybean. Several LA metabolites, such as di- or tri-hydroxy-C18FAs, were putatively annotated by the untargeted lipidomics approach. Multivariate analysis of the profile of microbial lipid metabolites showed that the lipid profiles produced with sunflower seeds and walnuts were similar but distinct to soybean. In conclusion, foods with different compositions can modulate the microbial production of lipid metabolites and the fatty acid composition after fermentation is more affected by the type of food matrices than oils.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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The polychaete *Platynereis dumerilii* has complete enzymatic activities required for the biosynthesis of omega-3 long-chain polyunsaturated fatty acids

Marc Ramos-Llorens ORCID iD, Francisco Hontoria ORCID iD, Juan Carlos Navarro ORCID iD, Óscar Monroig ORCID iD
Instituto de Acuicultura Torre de la Sal, Cabanes, Spain

Abstract

Primary production of omega-3 long-chain polyunsaturated fatty acids (LC-PUFA) in marine ecosystems has long been believed to derive almost exclusively from microorganisms. A paradigm-shifting study revealed that many invertebrates inhabiting aquatic ecosystems possess methyl-end desaturases enabling the de novo biosynthesis of polyunsaturated fatty acids (PUFA), an enzymatic capacity believed to be largely absent in animals. The marine polychaete Platynereis dumerilii, a well-established model in evo-devo research, was demonstrated to have two distinct methyl-end desaturases with Δ12 and ω3 (Δ15/17/19) substrate selectivities. In this study, we aimed to characterize both molecularly and functionally, further LC-PUFA biosynthesizing enzymes, namely front-end desaturases and elongation of very long-chain fatty acid (Elovl) enzymes (elongases). The newly characterized *P. dumerilii* front-end desaturases encode enzymes with Δ5 and Δ6/Δ8 activities when expressed in yeast. Moreover, *P. dumerilii* has two Elovl with demonstrated roles in LC-PUFA biosynthesis. Phylogenetic analyses showed that one of the *P. dumerilii* elongases is an ancestral form of the vertebrate Elovl5 and Elovl2, and is hence termed Elovl2/5; the second elongase is an ortholog of Elovl4. Functional assays confirmed that the *P. dumerilii* Elovl2/5 and Elovl4 can elongate C_{18} and C_{20} PUFA substrates to C_{22} and C_{24} products. Collectively, functions of the previously reported two methyl-end desaturases, along with the two front-end desaturases and two elongases studied here, demonstrate that *P. dumerilii* has the endogenous capacity to perform all the reactions required for the synthesis of physiologically relevant LC-PUFA such as eicosapentaenoic acid and arachidonic acid. Given their abundance, these results help to clarify that many invertebrates, including polychaetes, can remarkably contribute to the omega-3 LC-PUFA produced in the ocean.

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Associations between perinatal biomarkers of maternal dairy product consumption and child cognitive development: Results from the EDEN cohort study

Dr Wen Lun YUAN PhD ORCID iD[1,2], Dr Martine Armand PhD[3], Dr Hugo Peyre PhD[4], Mrs Catherine Sarté[3], Dr Marie Aline Charles PhD[1], Dr Jonathan Bernard PhD[1], Dr Barbara Heude PhD[1]

[1]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, INRAE, CRESS, Paris, France. [2]Singapore Institute for Clinical Sciences, Agency for Science, Technology, and Research (A*STAR), Singapore, Singapore. [3]Aix Marseille Univ, CNRS, CRMBM, Marseille, France. [4]Neurodiderot, INSERM UMR 1141, Paris Diderot University, Paris, France

Abstract

Introduction: A lower linoleic acid (LA) level in breastmilk has been associated with poorer cognitive outcomes in childhood. Evidence suggests that maternal high-fat content dairy product (DP) consumption is related to a lower LA level in breastmilk.

Objective: To examine the associations between maternal DP consumption during pregnancy, measured using known biomarkers of dairy fat consumption (pentadecanoic acid (C15:0) and heptadecanoic acid (C17:0)) in several perinatal biofluids and child cognitive development.

Methods: Participants were mother-child pairs from the EDEN cohort study, whose fatty acids levels were assessed in maternal red blood cells membrane (RBC) at 24 weeks' gestation (n≈1200), cord RBC membrane (n≈900) and colostrum (n≈600) and child cognitive development outcomes from 2 to 5-6y. Associations between DP biomarkers levels in perinatal biofluids and child cognitive development were analyzed by multiple linear regression models. Interaction of breastfeeding duration on the studied associations was tested and analyses were stratified when appropriate.

Results: C15:0 level in colostrum was associated positively with the language score at 3y in children breastfed for ≥3 months, and with the verbal IQ and full-scale at 5-6y in children breastfed for ≥6 months. C17:0 level in cord RBC membrane was positively associated with language scores at 2 and 3y. All observed associations remained unchanged after accounting for n-6/n-3 LC-PUFA ratio.

Conclusion: Higher C15:0 level in colostrum and C17:0 level in cord RBC membrane, and hence potentially higher maternal high-fat content DP consumption during pregnancy, were related to better language abilities, independently of n-6/n-3 LC-PUFA ratio.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Incorporation of DHA into neuronal membranes by ACSL6 is critical for protection against age-related neuroinflammation and neurological disease

Dr. Jessica Ellis PhD ORCID iD
East Carolina University, Greenville, USA

Abstract

Brain membrane acyl-chain profiles are highly diverse across cell types and brain regions, yet the regulatory mechanisms governing the composition of these acyl-chains and subsequent influence on neurological health remains incompletely understood. We recently discovered that neuronal enrichment of the neuroprotective fatty acid, docosahexaenoic acid (DHA), requires the enzyme long-chain acyl-CoA synthetase 6 (ACSL6). ACSL6 is an enzyme that initiates cellular fatty acid metabolism, prefers DHA, and is enriched in the brain. Genetic deletion of ACSL6 in mice resulted in large and specific reductions (35-72%) in neuronal DHA-containing phospholipids. This neuron-specific depletion of membrane DHA in mice disrupts motor and memory function and leads to early-onset age-related neuroinflammation. These data demonstrate the importance of ACSL6 mediated lipid metabolism in neurological health and aging. Using this model of neuronal membrane DHA deficit, we have now linked ACSL6 metabolism with the biology of alpha-synuclein – a mediator of age-related neurodegenerative diseases such as Parkinson's disease, dementias, and other synucleinopathies. Alpha-synuclein is well known to interact with DHA, yet how these interactions are regulated and the influence of these interactions on alpha-synuclein-related diseases remain unknown. By combining ACSL6 deficient mice with a model of synucleinopathy, we found a ~3-fold increase in brain alpha-synuclein oligomerization and an early lethality phenotype. Together, these data suggest a critical role for ACSL6-mediated lipid metabolism in synucleinopathies, neurological health, and aging.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Important to consider the lipids in understanding cystic fibrosis pathophysiology

Professor emer Birgitta Strandvik PhD, MD ORCID iD
Dept of Biosciences and Nutrition. Karolinska Institutet, Stockholm, Sweden

Abstract

The gene coding for Cystic Fibrosis (CF), the CF Transmembrane conductance Regulator (CFTR) was identified 1989, concentrating the research on proteomics, studying the function and regulation of this channel transporting chloride and bicarbonate and influencing other proteins. Identification of more than 2000 mutations have not simplified the research for a cure since only about 300 are associated with clinical disease. Recent animal research has also shown that a clinical CF like phenotype is found in animals deficient of the transcription factor LXRβ or deficient of the epithelial sodium channel ENaC.

Already 1962 were lipid abnormalities reported, mostly a deficiency of linoleic acid and increased ratio of arachidonic acid to docosahexaenoic acid, confirmed in many tissues and many studies. In livers of CF patients, the ratio of arachidonic to docosahexaenoic acid is increased and levels of cardiolipin and phosphatidylcholine are low. The typical lipid profile is present in newborn CF pigs and ferrets, incl the livers of the piglets, before feeding. An increased release of arachidonic acid in human CF cells, which would be associated to decreased levels of annexin 1, was suggested to explain this deficiency, associated with increased release of prostanoids. Animal studies have confirmed upregulation of transforming enzymes. Inflammation preceding infection is a problem also with modern therapy by CFTR modulators. Lipid abnormalities have now come to new interest when the modulators have been shown to influence the lipid profile, especially glycerophosphatidylcholine and ceramides. Stereochemistry might explore binding between different amino acids in CFTR and the membrane lipids.

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Not published

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Phospholipid profile of the lateral ventricle choroid plexus in ApoE4 mice during aging

Professional Annick Vachon M.SC, Student Jessica Avila Lopez M.SC, Professor Benoit Laurent PH.D, Professor Mélanie Plourde PH.D
Université de Sherbrooke, Sherbrooke, Canada

Abstract

Carrying the epsilon 4 allele of the apolipoprotein E (APOE4) gene and aging are the two major risk factors for developing late onset Alzheimer's disease (AD). These two risk factors also modify the fatty acid profile of brain membranes. Our team recently reported that the phospholipid (PL) profile of the choroid plexus (CP), a tissue producing the cerebrospinal fluid (CSF), is modified during aging. The objective of this study was to investigate the PL profile of CP in young and old mice knock-in for the human APOE4 or APOE3 gene (control). Our hypothesis was that APOE4 mice would have lower PL containing omega-3 fatty acid, mainly docosahexaenoic acid (DHA), than that of CP of APOE3. Using HILIC LC-ESI-MS/MS analysis, we carried out the lipidomic profile of polar lipids on 7-8 CP of APOE3 and APOE4 mice aged 4-, 6-, and 19-months old. There was no difference in the relative abundance of phospholipid classes in the APOE4 carriers in comparison to APOE3. However, there was 71 lipids with a genotype by age interaction, including 8 PL containing arachidonic acid (AA) and 2 PL containing DHA. Like some results we obtained in the brain of APOE4, these results support that the fatty acid profile of PL in the CP are modified by the APOE4 genotype during aging. Whether this is related to their higher risk of developing AD require further confirmation.

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Evaluating an Omega-3 Test-and-Treat Program, as Part of Routine Pregnancy Care, to Prevent Preterm Birth.

Professor Maria Makrides PhD[1], Ms Vanessa Anfiteatro[1], Ms Celine Northcott[1], Dr Karen Best[1], Professor Philippa Middleton[1], Dr Lisa Yelland[1], Dr Penelope Coates[2], Mr Khoa Lam[2], Dr Carol Siu[2], Emeritus Professor Robert Gibson[1]
[1]South Australian Health and Medical Research Institute, Adelaide, Australia. [2]SA Pathology, Adelaide, Australia

Abstract

Background: The 2020 Australian Pregnancy Care Guidelines include an evidence-based recommendation advising omega-3 long chain polyunsaturated fatty acid (LCPUFA) supplementation to reduce the risk of prematurity for women who are low in omega-3. Implementation of this recommendation requires omega-3 status testing and targeted advice linked to the omega-3 result as part of routine pregnancy care. We report our progress in assessing feasibility, adoption and effectiveness of this approach in South Australia (SA).

Methods: In partnership with the SA government pathology service, ability to order, measure and report serum omega-3 status was added to the routine antenatal serum screening program. This makes omega-3 testing available to all women with singleton pregnancies between 9 and 20 weeks 6 days of gestation. Serum omega-3 cut offs to determine low status were derived and validated from established cut offs in whole blood. Health professional and consumer reference groups co-designed information resources. Health professional seminars and academic detailing with family doctors were undertaken and a consumer awareness campaign was recently added.

Results: To Jan 2023, >8000 omega-3 tests have been ordered and reported since the program began 18 months ago. Characteristics of women who have engaged with the omega-3 program are typical of pregnant women in SA. Numbers have steadily risen, and we are currently reporting >100 omega-3 tests per week, covering about 35% of pregnancies in SA, with >70% of tests ordered and managed through family doctors. About 15% of women report low omega-3 status consistent with our ORIP trial, highlighting the cogency of our test-and-treat approach.

Conclusions: We have shown that embedding an omega-3 test-and-treat program into existing pregnancy health services is feasible and acceptable. Further work will assess the effectiveness of this program in reducing rates of preterm birth.

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APOE 4, BMI, and sex modify the EPA plasma phospholipids response to an omega-3 fatty acid supplementation : a secondary analysis

Insaf Loukil[1,2], Ester Cisneros Aguilera[1,2], Annick Vachon[1,2], Pauline Léveillé[1,2], Mélanie Plourde[1,2]
[1]Department de Medicine, Faculty of Medicine and health sciences, University of Sherbrooke, Sherbrooke, QC J1H 5N4, Canada., Quebec, Canada. [2]Research Center on Aging, Health, and Social Sciences Center – Sherbrooke University Geriatrics Institute, Department of Medicine, University of Sherbrooke, Sherbrooke, QC J1G 1B1, Canada., Quebec, Canada

Abstract

To reach the brain, plasma Omega-3 fatty acids (ω3 FAs), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), must either be esterified in phospholipids (PL) or be non-esterified (NEFA), but these plasma pools can be modified by age, sex, and carrying the apolipoprotein E epsilon 4 (*APOE4*) genotype, the main genetic risk factor of late onset Alzheimer's disease. Our hypothesis was that the increase in ω3 FAs in plasma PL and NEFA after an ω3 FAs supplementation is modified by these factors.

Here, we performed a pharmacodynamic study. Participants were supplemented with either 1.7g EPA and 0.8 g/d of DHA or a placebo for six months. Plasma FAs were extracted with chloroform/methanol (2:1). Solid phase extraction was used to separate PL and NEFA, and gas chromatography was performed to quantify EPA and DHA in PL and NEFA.

A total of 189 participants were included in this study, 92 received the ω3 FAs supplement. Irrespective of age, sex, BMI, or carrying the *APOE4*, EPA, and DHA levels increased respectively by 42% and 31% in the NEFAs after one month taking the ω3 FAs supplementation whereas it increases respectively by 82% and 71% after six months of supplementation. In the PL, EPA was 28% higher in *APOE4* carriers, 26% higher in females and 15% higher in those with a BMI ≤ 25 kg/m², compared to their respective groups. *APOE4*, sex, and BMI should be considered when designing clinical trials involving ω3 FAs supplementation with regards to EPA response.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

not published yet but we are finalising the article

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4(*RS*)-4-F_{4t}-neuroprostane, oxygenated metabolite of DHA: Promising oxylipin for targeting prostate cancer

Dr Thierry Durand PhD ORCID iD[1], Ariana Abawi PhD student[2], Dr Emma PETIOT PhD[2], Dr Giovanna Lollo PhD[2], Pr Thierry Granjon PhD[2], Pr Agnes Girard-Egrot PhD[2], Dr Camille Oger PhD ORCID iD[1], Dr Valérie Bultel-Poncé PhD[1], Dr Ofelia Maniti PhD[2], Dr Jean-Marie Galano PhD ORCID iD[1]

[1]Institut des Biomolécules Max Mousseron, (IBMM), Pôle Chimie Balard Recherche, UMR 5247, Université de Montpellier, CNRS, ENSCM, Montpellier, France. [2]Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, ICBMS UMR 5246, Univ Lyon, Université Lyon 1, CNRS, Lyon, France

Abstract

Docosahexaenoic acid (DHA, C22:6 n-3) is a fatty acid highly abundant among acyl chains of membrane phospholipids. Upon release from phospholipids, DHA undergoes enzymatic reactions resulting in synthesis of bioactive docosanoids and prostanoids, but also non-enzymatic reactions leading to a more complex pattern of metabolites (isoprostanoids), all of them termed oxylipins. In this study, 12 isoprostanoids which include F1-phytoprostanes, F2-isoprostanes, F3-neuroprostanesDPAn-3 and F4-neuroprostanesDHA derived from ALA (C18:3 n-3), AA (C20:4 n-6), DPA (C22:5 n-3) and DHA respectively were evaluated for their cytotoxic activities using PC-3 cell line from a bone metastasis of grade IV prostatic adenocarcinoma and a control cell line fibroblast. They all show an effect on the PC-3 viability compared to the control cells. Among the tested compounds, the non-enzymatic oxidized metabolite of DHA (NEO-DHA), 4(RS)-4-F4t-neuroprostane (4-F4t-NeuroP), had the most important effect on PC-3 cell viability. To increase the molecule selectivity we encapsulated 4-F4t-NeuroP in liposomes. By modulating the liposome composition, we designed a set of particles characterized by different membrane fluidities as a key parameter to obtain selective uptake from fibroblast or prostate tumor cells.

In summary, these findings demonstrated that 4-F4t-NeuroP has an anti-tumor activity, affecting the viability of highly aggressive PC-3 cell line, and this activity can be increased by encapsulation in liposomes. Lipid nanoparticles which encapsulate 4-F4t-NeuroP, are an interesting example of drug carriers, as they can be easily designed to promote the fusion of liposomes with their target membrane and ensure drug selectivity.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Omega-3 fatty acids are not associated with increased risk of peripheral artery disease in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort

Natalie Weir M.S.[1], Dr. Sarah Nomura Ph.D.[1], Dr. Amy Karger MD[1], Dr. Weihua Guan Ph.D.[1], Dr. Parveen Garg MD[2], Dr. Matthew Allison MD[3], Dr. Michael Tsai Ph.D.[1]

[1]University of Minnesota, Minneapolis, USA. [2]University of Southern California, Los Angeles, USA. [3]University of California San Diego, San Diego, USA

Abstract

Clinical peripheral artery disease (PAD) is characterized by the presence of symptomatic atherosclerotic obstruction of the major conduit arteries in the legs and is associated with high morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD). Accumulating evidence suggests omega-3 PUFAs exert favorable preventive effects on several biological processes involved in the development and progression of ASCVD. However, studies examining the prospective relationship between omega-3 PUFAs and PAD are scarce. We determined the relationship between omega-3 fatty acids, specifically EPA and DHA, and incident PAD using a multi-ethnic cohort.

We conducted an analysis of prospective data from the Multi-Ethnic Study of Atherosclerosis (MESA, n=6,460). EPA and DHA were measured at baseline as part of a phospholipid fatty acid profile. Incident PAD was adjudicated and defined as a physician diagnosis with symptoms or ultrasound evidence of obstruction, claudication, revascularization procedure, and/or amputation due to ischemia over a mean follow-up time of 12 years (n=108). Cox proportional hazards regression analysis was used to estimate omega-3-related risks of incident PAD, adjusting for age, sex, race/ethnicity, education, smoking status, alcohol consumption, blood pressure or blood pressure medication, total cholesterol, HDL-C, triglycerides, lipid lower medication, BMI, and diabetes status.

There was no significant association between EPA and/or DHA and the risk of developing PAD (EPA: Q4 vs Q1 hazard ratio (HR)=0.76; 95% confidence interval (CI): 0.41, 1.39; p=0.37; DHA: Q4 vs Q1 HR=0.89; 95% CI: 0.47, 1.70; combined EPA+DHA Q4 vs Q1 HR=0.82; 95% CI: 0.44, 1.53). Repeating analyses using omega-3s as continuous variables did not significantly change the results.

Neither EPA nor DHA were associated with a lower risk of developing PAD in a multi-ethnic cohort. Further studies are needed to determine whether, and at what level, omega-3 PUFAs may play a role in the prevention of PAD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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Relationships between diet, fatty acids and oxylipins in healthy individuals : new insights from two independent cohort studies.

Cécile Gladine[1], John Newman[2], Mathilde Touvier[3], Andrzej Suba[4], Nils Schebb[5], Mads Hjorth[6], Arne Astrup[6], Philp Calder[7], Justine Bertrand-Michel[8], Céline Dalle[1]

[1]INRAE, Saint-Genès-Champanelle, France. [2]USDA, Davis, USA. [3]INSERM, Paris, France. [4]Wroclaw Medical University, Wroclaw, Poland. [5]Wuppertal University, Wuppertal, Germany. [6]Novo Nordisk Foundation, Hellerup, Denmark. [7]University of Southampton, Southampton, United Kingdom. [8]INSERM, Toulouse, France

Abstract

Eicosanoids and other oxylipins represent a superfamily of bioactive lipids involved in the regulation of crucial biological processes such as inflammation, blood clotting or endothelial reactivity. Oxylipins are generated from polyunsaturated fatty acids (PUFAs) through various enzymatic and free-radical mediated reactions. Interestingly, each metabolic steps (PUFAs availability, enzyme activity, oxidative stress) can be influenced by diet. Oxylipins could therefore be important mediators of the effects of diet on human health. To provide new insights into the relationships between oxylipins, fatty acids (FAs) and diet, we conducted two independent cohort studies respectively nested in the Polish branch of the PURE international cohort and in the French Nutrinet-Santé cohort. Selected participants (n= 318) were healthy and fully characterized for their dietary intake. Our first objective was to determine if a healthy diet was associated with a specific oxylipin signature. Our secondary objective was to comprehensively investigate the relationships between diet, FAs and oxylipins. Participants were distributed into two groups according to the quality of their diet (based on the Alternative Healthy Eating Index (AHEI). Targeted lipidomics was performed to comprehensively quantify plasma oxylipins and FAs. The association between oxylipins, FAs and the quality of diet was modelled using conditional logistic regression. The relationships between oxylipins, FAs and diet were investigated using unsupervised multiblock analysis (MFA, Multiblock Factorial Analysis). We have generated a unique database revealing unsuspected associations between diet, FAs and oxylipins. Validation studies are now required to further explore the potential of oxylipins to monitor the health effects of diet.

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Impairment of carotenoids intestinal secretion in primary hypobetalipoproteinemias: from bench to bed

Dr Claire Bordat PhD[1,2], Dr Charlotte Cuerq PhD[3], Mr Donato Vairo[1], Ms Charlotte Halimi[1], Dr Pierre Poinsot[4], Dr Rémi Duclaux-Loras[4], Pr Noël Peretti[2,4], Dr Emmanuelle Reboul[1]

[1]Aix-Marseille Université, INRA, INSERM, C2VN, Marseille, France. [2]Univ-Lyon, CarMeN laboratory, INSERM U1060, INRAE 1397, Université Claude Bernard Lyon-1, Pierre Benite, France. [3]Biochemistry Department, Hospices Civils de Lyon,, Pierre Benite, France. [4]Pediatric Hepato-Gastroenterology and Nutrition Unit, Hôpital Femme Mère Enfant de Lyon HFME, Hospices Civils de Lyon HCL, Bron, France

Abstract

Abetalipoproteinemia FHBL-SD2, and Chylomicron Retention Disease FHBL-SD3, caused by mutations in the MTTP and SARA2 genes respectively, are rare monogenic diseases characterized by very low LDL cholesterol. Both disorders result in malabsorption of lipids, lipid-soluble vitamins, and nutrients. Carotenoids have a pivotal role in ophthalmic function. Despite early supplementations with high doses of vitamins A and E, ophthalmic protection appears sometimes insufficient and serum vitamin E level remains collapsed. Thus, we hypothesize that carotenoids chronic deficiency might worsen the atypical retinitis pigmentosa with macula lutea atrophy, regularly observed in adulthood Our aims are (1) to characterize the absorption and secretion of intestinal carotenoids using our Caco-2/TC7 cells lacking MTP or Sar1b mimicking these diseases; and (2) to quantify carotenoids plasma levels in patients with FHBL to quantify deficiencies.

The results show 1) a significant decrease in carotenoids secretion in vitro: -92% for α-carotene, -88% for β-carotene, -95% for lutein, -82% for zeaxanthin compared to control cells ($p<0.05$). 2) a dramatic decrease of plasmatic carotenoids for patients (n=8) compared to healthy controls (n=4): lutein (0.004 ± 0.002 µmol/L vs 0.220 ± 0.01 µmol/L, p = 0.0014), zeaxanthin (0.003 ± 0.001 µmol/L vs 0.029 ± 0.004 µmol/L, p = 0.0028), β-cryptoxanthin, 0.013 ± 0.004 µmol/L (vs 0.191 ± 0.11 µmol/L, p = 0.0091), α-carotene , (0.009 ± 0.005 µmol/L vs 0.431 ± 0.19 µmol/L, p = 0.0014), β-carotene , (0.030 ± 0.02 µmol/L vs 0.764 ± 0.27 µmol/L, p = 0.0098), and lycopene (0.003 ± 0.001 µmol/L vs 0.094 ± 0.01 µmol/L, p = 0.0024).

In conclusion, this work highlights the altered secretion of the major carotenoids in cellular models of FHBL, along with deep carotenoids deficiencies in FHBL patients. Carotenoid supplementation should thus be considered for these patients to improve their visual health.

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Sterol-induced LXR activation mediates *15-LOX* expression and formation of 15-LOX derived oxylipins in M2-like macrophages

Dr. Rei-ichi Ohno, Dr. Malwina Mainka, Rebecca Pfaff, Dr. Nicole M Hartung, Prof. Nils Helge Schebb
University of Wuppertal, Wuppertal, Germany

Abstract

The crucial role of the liver X receptor (LXR) in macrophage regulation during inflammation is emerging in the recent years. The LXR belongs to a family of nuclear receptors involved in the regulation of inflammation and metabolic homeostases such as cholesterol efflux, fatty acid synthesis and clearance of apoptotic cells. Besides, lipid mediators, cytokines and chemokines play a key role in the regulation of these processes. Recently, we showed that the synthetic LXR agonist T09 increases together with interleukin 4 (IL-4) the gene expression of 15-lipoxygenase (15-LOX) in M2-like human macrophages. The enzyme 15-LOX catalyzes oxylipin formations derived from polyunsaturated fatty acids in anti-inflammatory process. Here, we investigated whether LXR-agonists effect macrophage differentiation and investigated the regulation of 15-LOX expression and 15-LOX-catalyzed oxylipin formation by sterol derivatives. For this, primary human monocyte cells were isolated from buffy coats and differentiated: (i) M1 or M2-like primary macrophages were incubated with CSF-2 or CSF-1 for 8 days and treated with interferon gamma or IL-4 for the final 48 h; (ii) No cytokines were added to generate M0-like macrophages. The potent LXR-agonist T09 was used as positive control and specifically increased 15-LOX abundance in M2 macrophages up to 3-fold and 15-LOX-related oxylipins 15-fold, both in a time- and dose-dependent manner. The LXR-activation T09 had no or only moderate effects on the polarization of macrophages based on abundance of phenotype-specific proteins (TLR2, TLR4, PPARγ and IL-1RII) and surface markers (CD14, CD86 and CD163). The sterol derivatives desmosterol, 24(S),25-epoxy cholesterol and 22(R)-hydroxy cholesterol were identified as potent endogenous LXR-activating ligands, yielding strong induction of 15-LOX. With the LXR-mediated 15-LOX regulation, we describe a new link between the two lipid mediator classes sterols and oxylipins, suggesting that cholesterol precurosers play a role in the regulation of inflammation.

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Development of an n-3 PUFA supplementation strategy in primary macrophages

Rebecca Pfaff, Carina Rothweiler, Nils Helge Schebb
Chair of Food Chemistry, Faculty of Mathematics and Natural Sciences, University of Wuppertal, Wuppertal, Germany

Abstract

Increased dietary intake of long-chain n-3 polyunsaturated fatty acids (n-3 PUFA) has been associated with beneficial health effects such as anti-inflammatory effects. Inside the human body n-3 PUFA undergo enzymatic and non-enzymatic oxidation giving rise to multiple oxylipins. Several of those are potent bioactive lipid mediators involved in the regulation of biological processes such as pain and inflammation. It is believed that these oxylipins are part of the anti-inflammatory mode of action of n-3 PUFA. However, the underlying mechanisms of actions are not yet fully understood.

For a detailed investigation of the effects of n-3 PUFA and arising oxylipins on human immune cells, an *ex-vivo* supplementation strategy was developed in human macrophages. Primary human macrophages derived from blood monocytes were supplemented with different concentrations of n-3 PUFA for different time periods.

In order to achieve a reliable and reproducible supplementation, all steps of the supplementation strategy were investigated in detail: FA profiles of the cells from different human subjects before and after supplementation, purity of n-3 PUFA standards, oxylipin levels in plasma used for cell culture medium and cell culture supernatants as well as stability of supplementation medium during supplementation were analyzed by LC-MS/MS.

All results taken together show that supplementation of cells with n-3 PUFA involves plenty pitfalls complicating interpretation of results. However, the supplementation strategy developed points out not only the challenges of supplementation experiments but also shows how to overcome them. We show, how the cellular FA pattern of monocytes derived from human subjects following a typical Western diet is changed to macrophages with a FA pattern comparable to subjects having a high n-3 PUFA intake. Thus, this supplementation strategy is a helpful tool for mechanistic investigation of n-3 PUFA effects on human immune cells under strictly controlled conditions without carrying out intervention studies in humans.

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Nutrient intake in adults with familial hypercholesterolemia: time to think about dietary interventions

Dr Anastasia Blokhina ORCID iD, Dr Alexandra Ershova ORCID iD, Dr Oxana Kopylova ORCID iD, MD Alena Limonova ORCID iD, Dr Natalia Karamnova ORCID iD, MD Olga Shvabskaia, Dr Anna Kiseleva ORCID iD, Dr Alexey Meshkov ORCID iD, Dr., Prof Oksana Drapkina ORCID iD
National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russian Federation

Abstract

Background: Familial hypercholesterolemia (FH) is a highly atherogenic genetically based lipid disorder. For patients with FH, dietary modification is the cornerstone of complex lipid-lowering therapy. Data on the nutritional status of patients with FH are limited.

Aim: To assess the nutrient intake in adults with FH, including gender comparison.

Methods: The study included 100 patients (≥18 y.o.; 46% men) with “probable” or “definite” FH according to the DLCN criteria from the GENMOTIV-FH study (ClinicalTrials: NCT04656028). Nutrient intake was assessed using the 24-hour dietary recall method. The daily main macronutrient intake (the percentage of the daily energy intake or absolute values) was analyzed. Statistical analyses were done using R 4.1. The data are presented as the median [Q25; Q75].

Results: The study showed the excess consumption of protein (19.3 [16.7; 24.0] % in men and 18.6 [13.6; 24.3] % in women, p = 0.592), total fat (35.1 [29.4; 41.0] % in men vs. 39.2 [33.2; 47.5] % in women, p = 0.018), including saturated fatty acids (9.6 [4.7; 13.0] % vs. 10.4 [7.5; 14.2] %, respectively, p = 0.151), and cholesterol (265.8 [188.8; 521.9] mg/day in men vs. 282.1 [147.2; 542.8] mg/day in women, p = 0.936). Consumption of carbohydrates (44.3 [37.2; 50.0] % vs. 39.6 [30.1; 48.8] %, respectively, p = 0.1) and fiber (10.7 [7.3; 13.3] g/day in men vs. 11.5 [7.9; 13.9] g/day in women, p = 0.372) was insufficient.

Conclusions: The nutrient intake in adults with familial hypercholesterolemia does not match international guidelines.

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Multi-omics profile of the choroid plexus in mice carrying the APOE4 allele and supplemented with LPC-omega-3 for four months: a pilot study

Bijou Andriambelo[1,2,3], Annick Vachon[1,2,3], Benoît Laurent[1,2], Mélanie Plourde[1,2,3]

[1]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Canada. [2]Centre de Recherche sur le Vieillissement, CIUSSS de l'Estrie-CHUS, Sherbrooke, Canada. [3]Institut de la nutrition et des aliments fonctionnels, Université Laval, Sherbrooke, Canada

Abstract

Previously, our lab showed that DHA uptake by the brain is lower in APOE4 mice compared to APOE3 mice. Lipid can enter the brain by crossing throughout the blood-brain barrier or the choroid plexus (CP), a tissue located within the brain ventricles and producing the cerebrospinal fluid. Whether the CP lipid profile is modulated by both dietary omega-3 intake and APOE genotype was investigated. We hypothesized that an interaction between APOE genotype and supplementation would occur in CP phospholipids, especially those containing eicosapentaenoic or docosahexaenoic acid.

APOE3 and APOE4 mice were given omega-3 fatty acids or sunflower oil (control) for two or four months (n = 5-8/genotype/diet/duration). At the end of the supplementation, they were sacrificed, and choroid plexuses were collected. Lipid profiles were analysed with liquid chromatography coupled with mass spectrometry targeted towards phospholipids and sphingomyelins. Whole transcriptome of the CP was analyzed by RNA-sequencing.

Four months of supplementation were required to significantly change the levels of 15 lipids containing long-chain polyunsaturated fatty acids. Regarding genotype*supplementation interaction, it was significant for 24 lipid species following four months of supplementation compared to only three lipids after two months. Most of these lipid species contained arachidonic, eicosapentaenoic, or docosahexaenoic acids. Regarding transcriptomics, analyses are currently underway.

These results indicate that four months of supplementation are required to detect a genotype-dependent effect of omega-3 supplementation on the lipid profile of choroid plexuses in mice. An upcoming study will investigate how these changes in membrane lipids change gene transcription and potentially memory performance.

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New perspectives on randomized controlled trials with omega-3 fatty acid supplements and cognition: a scoping review

Bijou Andriambelo[1,2,3], Michaël Stiffel[1,2], Kaitlin Roke[4], Mélanie Plourde[1,2,3]
[1]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Canada. [2]Centre de Recherche sur le Vieillissement, CIUSSS de l'Estrie-CHUS, Sherbrooke, Canada. [3]Institut de la nutrition et des aliments fonctionnels, Sherbrooke, Canada. [4]GOED - Global Organization for EPA and DHA Omega-3, Utah, USA

Abstract

Epidemiological studies support the relationship between consumption of fish or long chain polyunsaturated omega-3 fatty acid (n-3 FA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and lower risk of cognitive decline. However, results from randomized controlled trials (RCTs) are less consistent. In this review, we depict an overall view of published RCTs dealing with n-3 FA supplementation and cognition, so recommendations regarding future trials in this field are brought to light.

RCTs on n-3 supplementation published before April 2022 were searched through GOED Clinical Study Database, PubMed, CENTRAL and Embase. Inclusion criteria included a clear indication of n-3 FA dosage and use of an objective cognitive score as an outcome.

A total of 78 studies met the inclusion criteria. These were classified in 5 categories according to participants' cognitive status: non-cognitively impaired older adults (n = 24), non-cognitively impaired middle-aged adults (n = 24), adults with subjective memory complaints (n = 14), adults with mild cognitive impairments (MCI, n = 9) and people with dementia or other cognitive changes. Overall, 34 studies showed a positive outcome. When focusing separately on each category, the highest proportion of positive outcomes was observed for RCTs conducted on MCI adults (66.7%). Doses of n-3 FA in supplements and cognitive tests varied considerably between studies.

This review highlights the heterogeneity of RCTs in terms of studied population, type of supplementation, study duration and cognitive outcomes. Considering the elements presented here, justification of the rationale and research design are needed in future trials.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Developing an *In Silico* Model of the Keratinocyte Lipidome in Dandruff

Ms Grace Horne ORCID iD[1], Dr Megan Uttley[1], Dr Amy Saunders[1], Dr David Messenger[2], Dr Ranjit Bhogal[2], Professor Rainer Breitling[1], Professor Anna Nicolaou[1]

[1]University of Manchester, Manchester, United Kingdom. [2]Unilever, Sharnbrook, United Kingdom

Abstract

Dandruff occurs in 10–50% of the population worldwide and is characterised by scalp flaking, pruritus, hyperkeratosis, and parakeratosis. However, there is no clear agreement about its status as an inflammatory skin condition. Dandruff-affected scalps exhibit a mild inflammatory environment with a mixed Th2 and Th17 response (e.g., IL-6, IL-8, IL-17, IL-23, TNF-α, CCL17), and changes to the cutaneous lipidome (e.g., ceramides, N-acyl ethanolamines). *In silico* models of keratinocyte lipid mediators which reflect the changes in dandruff-affected skin, could provide an alternative to animal models in understanding the condition and developing potential treatments.

Here we show the development of an *in silico* metabolic model of the lipid mediators produced by primary epidermal keratinocytes, following dandruff-associated inflammatory stimulation.

To obtain necessary model parameter data, epidermal keratinocytes were stimulated *in vitro* with dandruff-associated cytokines (IL-6, IL-8, IL-17A, IL-17F, IL-23, TNF-α, CCL17), singly or in combinations, for 0–72 h. Ultra-performance electrospray ionisation tandem mass spectrometry (UPLC-ESI-MS/MS) was used to analyse eicosanoids, N-acyl ethanolamines, and sphingolipids (e.g., ceramides, phosphorylated sphingoid bases). Flow cytometry was utilised to assess cellular markers of proliferation, differentiation, and senescence (e.g., Ki67; keratins 1, 10; filaggrin, loricrin; β-galactosidase).

Sphingolipid species were decreased in both proliferating and differentiating keratinocytes following single cytokine stimulation (e.g., IL-17A; 24h). The *in vitro* lipid profiles and cell state protein expression data were then used to develop an ensemble computational model. Metabolic reaction networks were recreated with systems of ordinary differential equations describing expected enzyme kinetics in MATLAB. The resulting *in silico* model can account for the uncertainty of predictions and can be adaptable towards specific lipid changes in keratinocytes arising from treatments with pro-inflammatory stimuli (e.g., by cytokines).

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not published.

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Untargeted lipidomics of oxidized phospholipids by LC-ESI-HRMS/MS – Optimization of chromatographic separation

Laura Carpanedo, Susanne Reif, Dr. Katharina Rund, Prof. Dr. Nils Helge Schebb
Bergische Universität Wuppertal, Wuppertal, Germany

Abstract

Oxylipins and other eicosanoids are oxygenated polyunsaturated fatty acids (PUFA) generated either enzymatically by lipoxygenase, cyclooxygenase and cytochrome P450 enzymes or non-enzymatically by reactive oxygen species. Oxidized PUFA are present in biological samples in non-esterified form but most of them, especially hydroxy-PUFA, are esterified to phospholipids in cell membranes or lipoproteins. Esterified oxylipins are commonly quantified following alkaline hydrolysis of the lipids (Prostag Oth Lipid M, 2020, 146, 106384). However, this indirect analysis using targeted LC-MS/MS does not allow drawing conclusions to which lipids oxylipins are bound.

The analysis of oxidized phospholipids by means of an untargeted approach represents a challenge. Phospholipids bearing hydroxy-PUFA positional isomers (e.g. 5-HETE, 12-HETE and 15-HETE) have the same exact mass and can only be distinguished based on their fragmentation spectra. Therefore, chromatographic separation is key enabling their characterization.

Here, the chromatographic separation of the oxidized phospholipids was optimized starting from an established untargeted LC-ESI-HRMS/MS method for the analysis of phospholipids. The optimization was done with a human serum sample and standards generated using enzymatic or non-enzymatic oxidation of phospholipids (Nat. Prot., 2010, 5, 1919). The ionisation was carried out by a heated electrospray HESI-II probe analysing in positive and negative mode within two separate runs. Mass spectrometric detection was performed using Full MS/data dependent MS2 enabling acquisition of fragment spectra of regioisomeric oxidized lipids by means of high-resolution hybrid quadrupole-Orbitrap (Thermo Scientific Q Exactive HF).

The optimized chromatographic separation allowed to characterize hydroxy-PUFA positional isomers esterified to phosphatidylcholine in human serum.

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Investigating oxylipins as oxidative stress markers in cell culture models

Lilli Zinnert, Katharina Rund, Nadja Kampschulte, Nils Helge Schebb
Chair of Food Chemistry, Faculty of Mathematics and Natrual Sciences, University of Wuppertal, Wuppertal, Germany

Abstract

Almost all diseases including the leading causes of death in western societies such as cardiovascular disease, chronic inflammation and cancer are associated with oxidative stress. Oxidative stress means the imbalance between the production of reactive oxygen and nitrogen species and their degradation by cellular protective mechanisms. Misregulation leads to a massive increase in reactive oxygen species which cause damage to biomolecules like DNA, proteins and membrane lipids. The oxidation of lipids by lipid peroxidation leads among other products to the formation of a multitude of oxylipins. Due to the stereo random reaction mode of autoxidative lipid peroxidation, a vast spectrum of oxylipins is formed. Isoprostanes are established biomarkers and we recently suggested the *trans*- versus *cis*-epoxy fatty acid ratio as new marker for oxidative stress *in vitro* and *in vivo* (Prostag Oth Lipid M, 2019, 144, 106334). However, there are several other oxylipins which have the potential to reflect autoxidative processes.

In the present work, we comprehensively investigate the formation of oxylipins during oxidative stress in cell cultures. In different cell lines e.g. the liver cancer cell line HepG2, autoxidation is elicited by oxidative stress-inducing stimuli such as the radical generating tert-butyl hydroperoxide and H_2O_2. The pattern of non-esterified as well as esterified oxylipins is quantitatively measured by state-of-the-art targeted metabolomics. Following alkaline hydrolysis of esterified oxylipins (Prostag Oth Lipid M, 2020, 146, 106384), oxylipins are extracted by means of solid phase extraction and analyzed by liquid chromatography-tandem mass spectrometry (Anal Chim Acta, 2018, 1037, 63-74).

On the poster, the change in the pattern of oxylipins caused by oxidative stress is shown. Particularly, the quantification of selected oxylipins enables the characterization of the oxidative stress status and to gain insights in the formation routes of the oxidized lipids.

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Therapeutic and analytical interests of lipophenols: from synthesis to quantification and in vivo evaluation.

Céline Crauste ORCID iD[1], Jordan Lehoux[1], Sandra Rochel[1], Sonia Medina[2], Angel Gil-Izquierdo[2], Maxime Vincent[3], Sylvie Begu[3], Philippe Brabet[4], Jetty Lee[5], Thierry Durand[1]

[1]IBMM, Montpellier, France. [2]CEBAS-CSIC, Murcia, Spain. [3]ICGM, Montpellier, France. [4]INM, Montpellier, France. [5]The University of Hong Kong, Hong-Kong, Hong Kong

Abstract

Interest in lipophilization of phenolic structures, named lipophenols or phenolipids, is various and depends on the domain of interest: in the food and cosmetic industries, the development of lipophilic antioxidants could be performed to protect lipid formulations from oxidation. Whereas, on pharmaceutical purpose, increasing the lipophilicity of polar phenolic drugs could be envisaged to improve their pharmacological profile. Moreover, combining both therapeutic aspects of specific lipids such as polyunsaturated fatty acid (PUFA) and natural polyphenols in a single lipophenolic molecule is also a pharmacologic strategy.

Development of polyphenol-PUFA derivatives were recently developed to reduce carbonyl and oxidative stress in retina dystrophy such as macular degeneration, in in vitro (ARPE-19 cells) and in vivo (ABCA4KO mouse) experiments. Results leads to the discovery of two alkyl-phloroglucinol and quercetin lipophenols linked to docosahexaenoic acid (DHA), efficient to reduce photoreceptor degeneration in light induced photoreceptor degeneration model, after IV or oral administration using lipidic formulation systems (LNC, SNEEDS).

The chemical bonding of polyphenols to fatty acids (lipophenols) through an ester link has also evidenced a new family of hybrid lipophenolic molecule “naturally” present in vegetable oils. Thus, lipophenols of hydroxytyrosol (HT), link to OA, LA and ALA have been detected in olive oils using UHPLC-MSMS methodologies, and where supposed to reduce lipid peroxidation in mousse fed with EVOO. Looking at enriched oil in HT, additional work also highlighted the spontaneous generation of lipophenols by transesterification reactions when the oily matrix is enriched with HT. More recently increase in concentration of HT-lipophenol was observed in olive oil that suffer from inappropriate conditions of storage. HT-OA was selected as a relevant marker for the monitoring of oil storage conditions and quality. Already present in our diet further studies on bioavailability, metabolisation and bioactivity of lipophenols needs to be pursued to deeply study those new hybrid molecules.

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Adolescent Female Rats Benefit the Most in Hippocampal-dependent Memory with DHA-Supplementation that is Reflected in the Hippocampal and Erythrocyte Lipidome

Daniel Lamontagne-Kam[1], Saeideh Davari[1], Juan Aristizabal-Henao[2], Seungjae Cho[1], Dan Chalil[1], John Mielke[1], Ken Stark ORCID iD[1]
[1]University of Waterloo, Waterloo, ON, Canada. [2]BPGbio, Framingham, MA, USA

Abstract

The effects of DHA supplementation on human memory may differ between females and males, but the underlying mechanisms are unknown. The spatial memory and hippocampal lipidomic profiles of female and male adolescent rats raised with or without a DHA-enriched diet that began perinatally with their dams were examined. Spatial learning and memory were analyzed using the Morris Water Maze starting at 6 weeks of age and animals were sacrificed at 7 weeks of age. Behavioural testing showed a significant diet x sex interaction for the distance to the correct zone and the time spent in the correct quadrant during the probe test, with female rats benefiting the most from DHA supplementation. Lipidomic analyses indicated arachidonic acid (ARA) and n-6 docosapentaenoic acid (DPA) containing phospholipid species were lower in the hippocampus of DHA supplemented compared with control animals. Females fed DHA had slightly more hippocampal PE P-16:0_22:6, and PE P-18:0_22:6 that was reflected in the erythrocytes. The females fed DHA also maintained levels of PE 18:0_20:4 in the hippocampus better than males fed DHA. Understanding how DHA supplementation during the perinatal and adolescent periods changes cognitive function in a sex-specific manner has important implications for determining the dietary requirements of DHA. This study also identifies potential lipidomic blood biomarkers that may be related to DHA status and spatial memory performance.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

A manuscript related to this abstract will be submitted to PLEFA between this abstract conference submission and the ISSFAL Congress.

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Inhibition of eicosapentaenoic acid (EPA) elongation by docosahexaenoic acid increases EPA levels, not retroconversion

Adam Metherel[1], Rodrigo Valenzuela[2], Brinley Klievik[1], Giulia Cisbani[1], Ruxandra Rotarescu[1], Melissa Gonzalez-Soto[3], Celine Cruciani-Guglielmacci[4], Christophe Magnan[4], David Mutch[3], Richard Bazinet[1]

[1]University of Toronto, Toronto, Canada. [2]University of Chile, Santiago, Chile. [3]University of Guelph, Guelph, Canada. [4]University of Paris, Paris, France

Abstract

Dietary docosahexaenoic acid (DHA, 22:6n-3) increases blood and tissue eicosapentaenoic acid (EPA, 20:5n-3), and was long thought to result from the peroxisomal β-oxidation of DHA – or retroconversion. However, we have shown this EPA increase to more likely be from slowed EPA metabolism. The objective of this study was to identify the potential mechanism for this slowed EPA metabolism by employing 1) mouse dietary (a-linolenic acid [ALA, 18:3n-3], DHA or ALA+DHA) and ^{13}C tracer studies in wild-type, control and liver-specific *Elovl2* (elongation of EPA to docosapentaenoic acid [DPAn-3, 22:5n-3]) knockout mice to measure fatty acid levels, ^{13}C signatures, gene expression, protein levels and enzyme activities, 2) microsomal isolations to test if DHA inhibits EPA elongation, and 3) secondary analysis from DHA supplemented men and women to identify the role of single nucleotide polymorphisms of *ELOVL2* on increases in plasma EPA. Dietary ALA combined with DHA was necessary to induce an increase ($p < 0.05$) in liver and plasma EPA, and the ^{13}C signatures of EPA were not different ($p > 0.05$) between the ALA and ALA+DHA fed animals, indicating the source of the increased EPA was solely ALA. Furthermore, there was no interaction (genotype x diet) or genotype effect ($p > 0.05$) on ^{13}C-EPA signatures in plasma or liver, indicating that the increase in EPA in control and Elovl2 KO animals is driven by a similar mechanism. An enzyme competition assay for EPA elongation to DPAn-3 suggests both uncompetitive and noncompetitive inhibition by DHA depending on DHA levels. Finally, the level of increase in plasma EPA varied depending on a single nucleotide polymorphism in *ELOVL2* (rs953413) of women and men supplemented with 3 g/d DHA for 12 weeks ($p < 0.05$). Taken together, these results indicate that DHA supplementation increases EPA *via* inhibition of EPA elongation to DPAn-3.

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Role of linoleic acid in the inflammatory response of bovine endometrial cells.

Noemi Gutierrez, Alejandra Hidalgo DVM, PhD., Rafael Burgos DVM, MSc, Maria A. Hidalgo PhD
Institute of Pharmacology, University Austral of Chile, Valdivia, Chile

Abstract

Endometrial cells are exposed to damage-associated molecular patterns (DAMPs), and especially in cows, they are exposed to pathogen-associated molecular patterns (PAMPs) after calving. Thus, endometrial cells play a key role in the inflammatory response, in addition to their physiological reproductive function. Bovine endometrial cells express free fatty acids (FFA) receptors, such as FFA1 and FFA4 receptors, and are responsive to the polyunsaturated fatty acid docosahexaenoic acid, however the effect of other fatty acids have not been studied. The aim of this study was to determine the inflammatory response-associated effects of linoleic acid on endometrial cells.

Bovine endometrial (BEND) cells were stimulated with linoleic acid (Lino), lipopolysaccharide (LPS) or LPS plus Lino (LPS/Lino), and extracellular adenosine triphosphate (ATP) was measured with a luminescent assay. The effect of linoleic acid on interleukin-8 (IL-8) and IL-6 was determined by ELISA assay. In addition, the effect of linoleic acid on intracellular calcium mobilization was assessed by spectrofluorimetry.

We observed an increase in ATP release in BEND cells treated with linoleic acid or LPS/Lino for 15 s. Production of IL-8 and IL-6 was increased in LPS-treated BEND cells, and Lino reduced these responses. Interestingly, ATP induced high levels of IL-8 and IL-6 production. Lino did not stimulate intracellular calcium mobilization; but ATP induced a rapid increase in intracellular calcium.

In conclusion, Lino increased ATP release in BEND cells; however, these ATP levels would not be sufficient to stimulate the production of IL-8 and IL-6. In contrast, Lino reduced LPS-induced IL-8 and IL-6 production. This effect could occur through mechanisms other than FFA1 receptor/calcium pathway because Lino did not induce intracellular calcium release.

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Fatty acid composition in phospholipid fractions of white matter tracts in the human brain: a study of age and early life adversity

Kelly Perlman[1], Dr. Chuck Chen[2], Mackenzie Smith[2], Dr. Massimiliano Orri[1], Dr. Gustavo Turecki[2], Dr. Richard Bazinet[2], Dr. Naguib Mechawar[1]
[1]McGill University, Montreal, Canada. [2]University of Toronto, Toronto, Canada

Abstract

Introduction: Child abuse (CA) is the primary preventable risk factor for the development of mental illness. Severe CA has been specifically linked with long lasting disruptions of oligodendrocyte and myelin function. The myelin sheath is highly enriched in lipids and CA-related findings may represent alterations of the myelin lipid profile, especially given that the composition of fatty acids (FA) in myelin phospholipids (PL) influence its compactness, stability, and permeability. Notably, there is a paucity of information on FA composition in cortical white matter (WM) compared to long-range fiber bundles. Therefore, the objective of this study is to quantify FA concentrations in the postmortem human uncinate fasciculus (UF), a major association white matter tract, and characterize the relationships with CA and age.

Methods: FA concentrations in all major PL pools were compared between depressed suicides with a history of CA, depressed suicides without CA, and non-psychiatric controls. Group-matched brain samples were provided by the Douglas-Bell Canada Brain Bank. Total lipids were extracted according to the Folch method and separated into respective PL fractions using thin-layer chromatography. Fatty acid methyl esters (FAMEs) from each fraction were quantified using gas chromatography-flame ionization detection.

Results: PL fractions revealed divergent patterns of FA composition (both in concentration and relative percentage) with respect to CA and show differences as compared to cortical white matter. The FA composition of each PL fraction each varied with age in different patterns, albeit with some overlap in FAs including arachidonic acid, adrenic acid, other polyunsaturates.

Conclusion: We present the first ever characterization of FA in the UF and describe their relationships with CA and age. This data will be supplemented with cholesterol quantification as well as myelin ultrastructure metrics in order to more comprehensively understand their biological relevance.

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Short chain fatty acids (SCFAs): Important mediators for the Gut-Brain communication?

Marrium Liaquat ORCID iD, Gwenaelle Le Gall ORCID iD, Matthew G. Pontifex, Michael Müller ORCID iD, Anne-Marie Minihane ORCID iD, David Vauzour ORCID iD
Norwich Medical School, University of East Anglia, Norwich, United Kingdom

Abstract

There is clear evidence that select food bioactives and healthy dietary patterns promote cognition, and that the gut-brain communication and gut microbiota plays an important role in this crosstalk (Chakrabarti *et al.*,2022; *Cell. Mol. Life Sci.*). Gut microbiota participate mainly through their metabolites, with SCFAs emerging as key cognition mediators (Connell *et al.*,2019; *Mol. Neurodegener.*).

We hypothesised that modulation of the gut microbiota by purified dietary fibres (microbial substrates) may affect serum concentrations of SCFAs and their transporters in the brain as well as blood brain barrier (BBB) integrity.

C57 BL/6J male mice aged 12 weeks were fed either a chow diet (rich in fibres), a refined purified diet (low in fibres) or a refined purified diet supplemented with purified fibres (inulin, psyllium, and pectin; 75 g/kg); either in isolation or in combination as described by (Pontifex *et al.*,2021;*Nutrients*). Liquid Chromatography Tandem Mass Spectrometry (LCMS/MS) based method was developed to quantify all straight and branched SCFAs. No significant difference in serum concentrations of SCFAs was evident, despite significant changes in faeces ($p \leq 0.05$), following dietary fibre interventions. However, a trend was observed for straight SCFAs with lower acetic (C2), propionic (C3), and butyric (C4) acids in psyllium-fed groups; and lower valeric (C5) and caproic (C6) acids in inulin-fed groups. Real-time RT-qPCR analysis revealed significant downregulation of genes involved in SCFA transport (e.g., Mct1, Mct4 and Smct1; $p \leq 0.05$) and BBB integrity (e.g., Ocln, Cldn1 and Zo1; $p \leq 0.05$) in the brain cortical tissue. Pairwise comparison showed a negative association between these SCFA transporters and BBB integrity markers, with the effects being significant ($p = 0.031$) for both inulin and psyllium combination groups. These initial findings support further investigation into the role of SCFAs as mediators of BBB function.

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Red blood cell docosahexaenoic acid relates to preserved brain glucose uptake in cognitively unimpaired individuals at risk of Alzheimer's disease

Iolanda Lázaro[1,2], Eider Arenaza-Urquijo[1,2,3], Oriol Grau[1,2,3], Carolina Minguillon[1,2,3], Mahnaz Shekari[1,2,3], Carles Falcón[1,2,4], Marina Garcia-Prat[1], Jordi Huguet[1], Juan-Domingo Gispert[1,2,4], Aleix Sala-Vila[1,2,5]

[1]Barcelonabeta Brain Research Center - Pasqual Maragall Foundation, Barcelona, Spain. [2]IMIM - Hospital del Mar Medical Research Institute, Barcelona, Spain. [3]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBER-FES), Instituto de Salud Carlos III, Madrid, Spain. [4]Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III, Madrid, Spain. [5]Fatty Acid Research Institute, Sioux Falls, USA

Abstract

BACKGROUND: Brain glucose hypometabolism is observed in Alzheimer's disease (AD) before clinical symptoms. Basic research found that dietary docosahexaenoic acid (DHA) promotes brain glucose uptake. We hypothesized that in a middle-aged cognitively unimpaired population at risk of AD, increasing red blood cell (RBC) proportion of DHA (an objective biomarker of DHA intake) relates to preserved brain glucose metabolism in a predefined set of AD-vulnerable regions of interest (ROIs).

MATERIALS AND METHODS: Cross-sectional study in 321 participants (200 women; age 61.0±4.7 years) from the Alzheimer and Families (ALFA) cohort, enriched for family history of AD and AD genetic risk factors. We determined RBC-DHA by gas-chromatography. We used ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography to assess FDG uptake relative to a vermis reference region. Besides ROIs relative to tau deposition (Braak stage I+II; III+IV; and V+VI), we calculated the composite of five ROIs (right and left angular gyri and middle/inferior temporal regions, and bilateral posterior cingulate cortex) known to undergo glucose hypometabolism at preclinical stages of AD (AD-signature ROIs). We constructed multivariate regression models, adjusting for age, gender, years of education, and *APOLIPOPROTEIN-ε4* allele carriership.

RESULTS: We observed a direct association between RBC-DHA and glucose uptake in ROIs of Braak stage I+II ($p=0.028$). When stratifying for AD risk factors, stronger associations were observed in men (Figure 1A) and *APOLIPOPROTEIN-ε4* carriers (Figure 1B). A direct association was also observed for the AD-signature ROIs ($p=0.040$), with stronger associations in *APOLIPOPROTEIN-ε4* carriers (Figure 1C). No significant associations were observed in other examined ROIs.

CONCLUSIONS: In cognitively unimpaired individuals at increased risk of AD, increasing RBC DHA relates to preserved glucose consumption in AD-vulnerable brain regions, in particular for individuals at increased genetic risk. This finding is aligned with the brain benefits of DHA supplementation in the preclinical stage of AD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Antitumor agent incorporated *in vivo* into glycerophospholipids: biophysical implications.

Marta Salvador-Castell ORCID iD[1,2], Doralicia Casares ORCID iD[2], Joan Cabot[2,3], Marc Miralles[2,3], Victoria Lladó[2,4], Paula Fernández-García ORCID iD[2], Pablo V. Escribá ORCID iD[2,3]

[1]Fundación Marathon, Palma, Spain. [2]Laminar Pharmaceuticals, Palma, Spain. [3]Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands, Palma, Spain. [4]Laminar Inc., Boston, USA

Abstract

Alterations in membrane lipid composition are involved in cancer progression. Thus, manipulating cell membrane lipid composition and membrane physicochemical properties is presented as a good alternative to treat this condition. This is the principle of an innovative therapeutic approach: Membrane Lipid Therapy, or melitherapy, which may bring therapeutic tools to still underserved conditions, such as several types of cancer.

2-Hydroxyoleic acid, a natural analogue of oleic acid, is a melitherapeutic compound which presents an antiproliferative effect by changing the membrane lipid composition and structure of cancer cells. This molecule has showed pharmacological efficacy and safety in cellular and animal models, and it is currently in advanced clinical trials.

Interestingly, 2-hydroxyoleic acid is incorporated into certain glycerophospholipids, thus changing the biophysical properties of lipid membranes, such as membrane structure and hydration, which leads to changes in cell signaling pathways. This study explores these effects using several physicochemical techniques, including X-ray diffraction, differential scanning calorimetry and membrane fusion assays. All the findings suggest that membranes incorporating 2-hydroxyoleic acid have higher degree of mobility and hydration, which could partly explain changes in the localization and activity of signaling membrane proteins and ensuing antiproliferative effect.

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Link between metabolic syndrome, blood lipid markers, dietary lipids and survival in breast cancer women

Dr Christine Bobin Dr ORCID iD
Nantes University, Nantes, France. Institut de Cancérologie de l'Ouest, St Herblain, France

Abstract

It is well known that an inadequate diet, with a high fat content for example, could explain more than 10% of cancers, breast cancer (BC) being the most frequent localization in females. Inadequate diet may lead to several metabolic abnormalities, including metabolic syndrome (MS). The goal of our study is to evaluate the link between survival after BC and MS, as well as diet lipids and circulating lipids.

This study has been performed in an early stage BC cohort (EUDRACT 2008-007652-10 n=140, ICO, France). MS, lipid dietary and circulating biological parameters, including expression of cholesterol carrier (ABCA1, ABCG1) genes in circulating leucocytes have been evaluated before any medication intervention. The data of each patient have been analyzed by univariate logistic regression and expressed by HR- 95%CI [5th-95th]. All these parameters have been explored with survival parameters by Cox regression analyses.

Overall suvival (OS) and in invasive disease free survival (iDFS) are significantly longer for the women without metabolic syndrome with HR 4.7-[1.11-19.92], p=0.03 and 3.58|1.23-10.44], p=0.03, respectively. The expression of ABCG1 in peripheral leucocytes, an ATB-binding cassette transporter involved in cholesterol and phospholipid trafficking, is significantly associated with PFS (1.4-[1.1-1.9], p=0.05]. A higher ratio of dietary PUFA ω3/ ω6 is correlated to a higher ABCG1 expression.

MS is associated with more pejorative survival parameters in early stage breast cancer. A link with dietary fatty acids, lipid metabolism and PFS has also been suggested. A mechanistic approach and larger clinical studies are considered to confirm these data.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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The association between maternal dietary intake of polyunsaturated fatty acids in pregnancy, related maternal gene variants, and ADHD in Dutch children.

MSc Student Tosca Van Hoorde MSc Epidemiology[1], Dr. Carel Thijs MSc Epidemiology[1], Dr. Monique Mommers MSc Epidemiology[1], Carolina Moltó MSc Pharmaceutical sciences[1], Prof.Dr. Petra Hurks MSc Neuropsychology[2]
[1]Maastricht University, Maastricht, Netherlands. [2]2Maastricht University Medical Centre+, Care and Public Health Research Institute CAPHRI, Department of Epidemiology, Maastricht, Netherlands

Abstract

Introduction – Attention Deficit Hyperactivity Disorder (ADHD) has a pronounced genetic component, yet epidemiological studies also show the influence of environmental factors (Banaschewski et al., 2017).The long-chain PUFAs (LC-PUFAs) n-3 docosahexaenoic acid (DHA) but also n-6 arachidonic acid (AA) are necessary for the growth and development of our brains (Haggarty, 2010). Humans can obtain DHA and AA from diet and synthesize them endogenously from the essential polyunsaturated fatty acids (PUFAs) alpha-linolenic acid (ALA) and linoleic acid (LA), respectively. Multiple genes have been related to the endogenous synthesis of LC-PUFAs, such as fatty acid desaturases and elongases (Conway et al., 2020). In addition, PUFA intake has been hypothesized to be modified with genotypic variability (Conway et al., 2020). The above has not yet been studied for ADHD in children.

Aim - To evaluate whether maternal dietary intakes of fatty acids are associated with ADHD in children and whether this is modified by variants in maternal genes. Methods – In the KOALA Birth Cohort Study, maternal dietary fatty acids intake around 34 weeks of pregnancy was assessed by a Food Frequency Questionnaire. Gene scores for n-3 and n-6 LC-PUFA synthesis were constructed from selected maternal SNPs in the FADS1-FADS2-FADS3 gene cluster and ELOVs, predicting plasma phospholipid levels of DHA and AA measured in blood collected around 36 weeks of pregnancy. Children's ADHD was assessed at age eight based on parents' (n = 1833) and children's general practitioners' reports (n = 954). Multivariable logistic regression was used, controlling for potential confounders.

Results - We found positive associations of ALA(OR 1.17) and LA(OR 1.23) with ADHD, but not of DHA and AA, nor gene-diet interactions.

Discussion - Our study population has a high intake of essential PUFAs, which might inhibit the synthesis of LC-PUFAs, and possibly explain the positive associations of ALA and LA.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not published yet.

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9-D1t-phytoprostane an oxylipin derived from ALA, present in Gracilaria longissima activates platelet adhesion to leukocytes and endothelial cell migration through EP3 prostanoid receptor.

Dr Thierry Durand PhD ORCID iD[1], Silvia Montoro-García[2], Dr Sara Martínez-Sánchez PhD[2], Dr Miguel Carmena-Bargueño PhD[3], Dr Horacio Pérez-Sánchez PhD[3], Maria Campillo[2], Dr Camille Oger PhD ORCID iD[1], Dr Jean-Marie Galano PhD ORCID iD[1], Dr Angel Gil-Izquierdo PhD ORCID iD[4], Dr Jose Antonio Gabaldón PhD[5]

[1]Institut des Biomolécules Max Mousseron (IBMM), Pôle Chimie Recherche Balard, UMR 5247, Université de Montpellier, CNRS, ENSCM, Montpellier, France. [2]Izpisua Lab, HiTech, Health Sciences Department, Universidad Católica de Murcia (UCAM), Campus de los Jerónimos, Guadalupe, Spain. [3]Structural Bioinformatics and High-Performance Computing Research Group (BIO-HPC), Computer Engineering Department, Universidad Católica de Murcia (UCAM), Campus de los Jerónimos, Guadalupe, Spain. [4]Research Group on Quality, Safety and Bioactivity of Plant Foods, Department of Food Science and Technology, CEBAS-CSIC, University Campus of Espinardo, Espinardo, Spain. [5]Molecular Recognition and Encapsulation Research Group (REM), Health Sciences Department, Universidad Católica de Murcia (UCAM), Campus de los Jerónimos, Guadalupe, Spain

Abstract

Plant phytoprostanes (PhytoPs) are lipid oxidative stress mediators that share structural similarities with mammal prostaglandins (PGs). They have been demonstrated to modulate inflammatory processes mediated by prostaglandins. The present study aims to test the effects of the most abundant oxylipin from Gracilaria longissima, ent-9-D1t-Phytoprostane (9-D1t-PhytoP), on platelet activation and vascular cells as well as clarify possible interactions with platelets and the endothelial EP3 receptor. Platelet and monocyte activation was assessed by flow cytometry in the presence of purified 9-D1t-PhytoP. Cell migration was studied using the human Ea.hy926 cell line by performing a scratch wound healing assay. The RNA expression of inflammatory markers was evaluated by RT-PCR under inflammatory conditions. Blind docking consensus was applied to the study of the interactions of selected ligands against the EP3 receptor protein. The 9-D1t-PhytoP exerts several pharmacological effects; these include prothrombotic and wound-healing properties. In endothelial cells, 9-D1t-PhytP mimics the migration stimulus of PGE2. Computational analysis revealed that 9-D1t-PhytP forms a stable complex with the hydrophobic pocket of the EP3 receptor by interaction with the same residues as misoprostol and prostaglandin E2 (PGE2), thus supporting its potential as an EP3 agonist. The potential to form procoagulant platelets and the higher endothelial migration rate of the 9-D1t-PhytoP, together with its capability to interact with PGE2 main target receptor in platelets suggest herein that this oxylipin could be a strong candidate for pharmaceutical research from a multitarget perspective.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Plasma PUFA levels in UK Biobank participants: Relationship with dietary and supplement omega-3 PUFA intake

Miss Joanna Aldoori MBChB, MRCS ORCID iD[1,2], Dr Alex Coleman PhD ORCID iD[3], Dr Michael Zulyniak PhD ORCID iD[4], Professor Giles Toogood MD, FRCS ORCID iD[2], Professor Mark Hull PhD, FRCP ORCID iD[1]

[1]Leeds Institute of Medical Research, Leeds, United Kingdom. [2]St James's University Hospital, Leeds, United Kingdom. [3]Research Computing Team, Leeds, United Kingdom. [4]School of Food Science and Nutrition, Leeds, United Kingdom

Abstract

Background: The UK Biobank (UKBB) includes comprehensive dietary and nutritional supplement data. In 2021, the UKBB released NMR data on plasma PUFA levels for approximately one third of UKBB participants. We investigated the relationship between dietary and supplement omega-3 PUFA intake and plasma omega-3 PUFA levels.

Methods: Plasma omega-3 PUFA levels (total omega-3 PUFAs and DHA [as mmol/L and % total fatty acids) were examined against dietary (FFQ oily fish intake) and supplement marine omega-3 PUFA intake, using ordinal logistic regression to predict the highest quartile of plasma omega-3 PUFA levels. Models were adjusted for clinical and lifestyle factors.

Results: Plasma PUFA levels were measured at least once in 121,650 participants (24.5% UKBB population). 38% (n=46,030) reported eating oily fish once a week and 31% (n=38,036) used a fish oil (including cod liver oil) supplement (FOS). Higher oily fish intake was associated with increasing likelihood of FOS use (P<0.001). The mean (standard deviation [range]) omega-3 PUFA level in the lowest quartile of plasma omega-3 PUFA levels was 0.29 (0.06 [0.02-0.37]) mmol/L versus0.82 (0.18 [0.64-3.69]) mmol/L in the highest quartile. Oily fish intake was the strongest predictor of total omega-3 PUFA levels (odds ratio [OR] 6.7 [95% confidence interval 6.3-7.1] for oily fish intake ≥twice a week). FOS use was an independent predictor of higher plasma omega-3 PUFA levels, with the OR in FOS users (2.0 [2.0-2.1]) similar to that for oily fish intake <once a week (1.9 [1.8-2.0]). Similar data were obtained for plasma DHA levels.

Conclusions: Oily fish intake is the strongest predictor of plasma omega-3 PUFA levels in the UKBB. FOS use is more common in individuals who eat oily fish and is independently associated with higher omega-3 PUFA levels. FOS use should be considered when examining the relationship between omega-3 PUFA intake and health outcomes.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Abrupt decrease of arachidonic acid in the lateral ventricle choroid plexus during aging at the root of brain inflammation?

Prof Melanie Plourde PhD ORCID iD[1,2], Mrs Annick Vachon MSc[1,2], Mrs Jessica Avila Lopez MSc[1], M Yunping Qiu PhD[3], Prof Irwin Kurland MD PhD[3], Prof Benoit Laurent PhD[1]

[1]Université de Sherbrooke and Centre de recherche sur le vieillissement, Sherbrooke, Canada. [2]Institut de la nutrition et des aliments fonctionnels, Québec, Canada. [3]Albert Einstein College of Medicine Michael F. Price Center, Bronx, USA

Abstract

The choroid plexus (CP), a secretory tissue found in each brain ventricle, produces the cerebrospinal fluid (CSF). As we age, the morphology and lipid composition of the brain and CP change. The brain generally has lower docosahexaenoic acid (DHA) levels, an omega-3 fatty acid that is a precursor of anti-inflammatory mediators. Our hypothesis was that, like in the brain, phospholipids containing DHA in the CP would be decreased during aging with a concomitant increase in the transcription of genes involved in inflammation and their respective oxylipins/eicosanoids. The CP of C57/BL6 male and female mice aged 6-, 12-, 18-, and 24-months (n = 5/sex/age) were dissected. Lipids were extracted and analyzed by a targeted semi-quantitative lipidomic approach. Whole transcriptome of the CP was analyzed by RNA-seq. Oxylipins were analysed by LS-MS/MS. There was no difference in the relative abundance of polar lipids in the CP during aging. However, in the phosphatidylcholine and phosphatidylethanolamine, PC and PE, there were species abruptly decreased between 18- and 24-months old. These species were not those with DHA but with arachidonic acid (ARA), a long chain omega-6 fatty acid. In the transcriptomics of CP, there was an abrupt upregulation in the expression of genes involved in inflammation and an abrupt downregulation of genes involved in chromatin and neurotransmitter receptor complex between 18- and 24-months of age. A pilot test confirmed that 63 oxylipids/eicosanoids mediators were detected with less than 30% variation in the mouse CP and analyses by sex and age are currently underway. This study provides another mechanistic explanation of brain inflammation by showing that ARA in the membranes of aging CP is consumed at a higher rate than its renewal to generate pro-oxidative mediators in response to upregulation of the transcription of genes involved in inflammation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

no

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Gestational diabetes mellitus affects offspring brain fatty acid composition in a mouse model

Lidewij Schipper[1], Noela Schaap[1], Yixian Liu[2], Hongyu Li[3], Weiping Han[3], Louise Harvey[1]
[1]Danone Nutricia Research, Utrecht, Netherlands. [2]Danone Nutricia Research, Singapore, Singapore. [3]Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

Abstract

Accumulation of n3 and n6 PUFAs in the brain, such as C22:6n3, during foetal and early postnatal life is critical for neurodevelopment. Evidence suggests that pregnancies affected by gestational diabetes mellitus (GDM), a maternal condition characterized by spontaneous hyperglycaemia and altered lipid metabolism, may increase the risk for suboptimal neurocognitive development in infants, but the underlying mechanisms are not fully understood.

We used a mouse model of GDM to explore (pilot study), if there were changes in offspring brain fatty acid (FA) composition as a result of GDM. Female C57BL/6J mice were exposed to short-term high-fat diet and low-dose streptozotocin treatments before pregnancy to induce GDM. Maternal blood glucose was determined at gestational day 16. At postnatal day (PN)2 and 21, female offspring brain FA composition was analysed.

Maternal blood glucose levels positively correlated with offspring brain n6/n3PUFA ratio at PN2 and 21. Specifically, at PN21, brain total n6PUFA content, including C20:4n6; C22:4n6 and C22:5n6, was increased in offspring born to GDM dams compared to offspring born to non-diabetic dams. However, C22:6n3 and total n3PUFA remained unaffected.

The results of the current study suggest that altered brain FA profile may be one of the mechanisms underlying impaired neurodevelopmental outcomes that are observed in infants born after GDM pregnancies. As infant brain FA status is responsive to dietary supply of (preformed) PUFAs during postnatal life, these results advocate for studying the therapeutic potential of specific postnatal dietary interventions targeting n3 and n6 FA status in infants born after GDM exposure.

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Lactiplantibacillus Plantarum WJL : oral administration in mice induces deep modifications in blood and liver lipidome.

Dr Karim Chikh Assistant professor ORCID iD[1,2,3], Vincent Verdier[1], Anais Ehret[1], Oriane Vitalis[2], Dr Marie-Caroline Michalski ORCID iD[1], Dr Hubert Vidal ORCID iD[1,3], Pr Laetitia Koppe ORCID iD[1,2,3]
[1]CarMeN laboratory, Pierre Benite, France. [2]Hospices Civils de Lyon, Pierre Benite, France. [3]Université Claude Bernard Lyon 1, Lyon, France

Abstract

Context : Previous studies have demonstrated that *Lactiplantibacillus Plantarum WJL* (*LP*^{wjl}), a gut bacteria, was able to sustain both weight gain and longitudinal growth in mice fed a depleted diet by means of an interaction with the somatotropic hormone axis (Schwarzer et al., Science 2016). We have tested an oral administration of *LP*^{wjl} in a mouse model of chronic kidney disease. In a complementary study, we have carried out a lipidomic analysis of blood and liver to explore the impact of this Lactobacilli strain on lipid metabolism.

Material and methods : Six groups of mice were designed according to renal function, regimen and oral gavage with *LP*^{wjl} (3×10^8 UFC administered daily by oral gavage) or placebo and here, we will focused on Sham group fed a standard diet and *LP*^{wjl} (n=5) or placebo (n=4). Blood samples and liver tissues were analyzed with the MxP 500 Quant ® (Biocrates) kit by LC-MS/MS. Metaboanalyst 5.0® was used for univariate and multivariate statistical analysis.

Results : the most striking impact of *LP*^{wjl} on lipid metabolism was observed in the sham group. In plasma, we observed a decrease in deoxycholic acid, DG(18:1/20:1), some phosphatidylcholine (PC) and lysoPC species and an increase in total sphingomyelins, total ceramides, DG(16:1/18:2), PC ae C36:0, lysoPC a C18:0. In liver, we observed a decrease in the ratio PC/TG, the ratio PC acyl-alkyl/ total PC, lysoPC a C20:3, CE (18:3) and an increase in total TG, total DG, cholic acid, PC aa C40:6, PC aa C38:4 and in some ceramides species.

Conclusion : *LP*^{wjl}, a potential probiotic, is associated with a deep impact on lipid metabolism in mice. Further studies are needed to better understand the underlying mechanisms.

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Dairy fat intake during early life improves cognitive and psychomotor performances in a primate model, the grey mouse lemur (*Microcebus murinus*)

Yohann Chaudron[1], Constance Boyer[2], Corinne Marmonier[2], Mélanie Plourde[3,4], Annick Vachon[3,4], Bernadette Delplanque[5], Mohammed Taouis[5], Fabien Pifferi[1]

[1]UMR 7179 CNRS MNHN, Brunoy, France. [2]Centre National Interprofessionnel de l'Economie Laitière, Paris, France. [3]Centre de Recherche sur le Vieillissement, CIUSSS de l'Estrie – CHUS, Sherbrooke, Canada. [4]Département de Médecine, Université de Sherbrooke, Sherbrooke, Canada. [5]Institut NeuroPSI - UMR 9197 CNRS Université Paris-Saclay, Saclay, France

Abstract

Milk is the first dietary intake of the new-born and remains the only one until weaning. Especially, its lipid profile - its richness in short and medium saturated fatty acids and its beneficial ω6/ω3 ratio - may enable the cognitive development in the early life. We present here the first results of the *MiCo program,* a study testing the impact of dairy fat on cognitive functions during development in a non-human primate, the grey mouse lemur (*Microcebus murinus*). It is an omnivorous, easy to breed, lemuriform primate, sharing a high phylogenetic proximity with humans, and is consequently a useful model for perinatal nutritional studies.

We designed two experimental diets: a dairy fat-based diet (DF, n=25) and a vegetal fat-based diet (VF, n=25) that have been implemented in 2 cohorts of new-born mouse lemurs. Different cognitive functions have been assessed, such as learning, working and long-term memory, balance performance and exploration, at different stages of life (8, 15, 22 and 30 days old, and 3, 9 and 15 months old). In order to specifically test psychomotor performances in new-borns, we developed a whole new battery of tests based on Fox's tasks.

We showed that DF positively impacted the psychomotor performances in new-borns 8 days after birth, compared to VF. Learning and long-term memory were also improved at 3 months old and after. Strong differences in some plasmatic fatty acids reflect well the differences between diets composition. Ongoing imaging studies (PET-scan, MRI and EEG) may give some physiological support to explain the behavioural differences observed. Finally, differential expression of epigenetic markers, such as miRNA, will allow us to suggest mechanistic hypotheses about regulation of peripheral and central pathways.

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Fatty acid status of children with ADHD - First learnings from the world’s largest ADHD intervention study

Dr. Judeson Royle Joseph MD ORCID iD[1], Alice Marie Pedersen PhD ORCID iD[2]
[1]University Hospital of North-Norway, Tromsø, Norway. [2]Zooca, Tromsø, Norway

Abstract

The term ADHD (attention deficit hyperactivity disorder) is a neurodevelopmental disorder affecting children from an early age and persisting into adulthood. The cause is thought to be multifactorial although the knowledge within the field of dietary impact on neural development is rapidly growing.

Nutritional interventions such as polyunsaturated fatty acids (PUFAs) supplementation, also with its safety profile and anti-inflammatory effects, have been of great interest as a potential treatment for ADHD. PUFAs are shown to affect through several directions such as neurodevelopment, inflammation and emerging data revolving gut-brain axis.

Here we present the early findings of an ongoing double-blinded randomized clinical trial on children with ADHD and their functioning compared to dietary intake and blood fatty acid status. This ADHD study is applying a novel lipid extract from the zooplankton Calanus finmarchicus. This marine oil holds a plethora of monounsaturated fatty acids (MUFAs) and PUFAs in an unusual lipid form (wax esters). Recent studies have also shown that MUFAs may augment the biosynthesis of long chain PUFAs from the shorter fatty acids. 300 children are recruited to take part in the study. Prior to a six-month intervention with zooplankton lipids, a series of baseline tests and observations were performed. The findings we are presenting are based on a three-day diet record, erythrocyte membrane concentration, and a computer-based concentration test. A good interpretation of baseline status can be used as a valuable tool to find patients likely to respond better to dietary interventions.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not yet published

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Metabolic modulation by avocado-derived lipids improves cancer outcome

Paul Spagnuolo PhD, Matthew Tcheng PhD
University of Guelph, Guelph, Canada

Abstract

Acute myeloid leukemia (AML) is a devastating disease characterized by dysregulated cell metabolism, poor patient outcomes, and suboptimal chemotherapeutics. New drugs are desperately needed.

Avocadyne (AYNE) is a food-derived lipid with potent anti-AML activity (EC50: 2.5 µM) that suppresses clonogenic growth of patient-derived AML cells with no effect on normal hematopoietic cells. AYNE (100mg/kg twice weekly for 5 weeks) reduced patient-derived AML cell engraftment in the bone marrow of immune-deficient mice by inhibiting fatty acid oxidation (FAO), a key metabolic process, as demonstrated using radiolabeled studies and high resolution respirometry.

Mechanistically, immunoblotting and LC/MS analysis confirmed that AYNE co-eluted with very long acyl-CoA dehydrogenase (VLCAD), an intramitochondrial enzyme involved in FAO, but not with other key FAO enzymes. Moreover, AYNE inhibited VLCAD activity, as demonstrated using high resolution respirometry and enzymatic assays, confirming a direct physical interaction between AYNE, VLCAD and VLCAD activity.

To expand these findings and increase target validation, mice were injected with patient-derived AML cells and after 8 weeks treated with AYNE. Human AML cells were then extracted from bone marrow and purified by magnetic bead separation. In human cells, VLCAD activity was reduced, as measured by respirometry, and the melting point of VLCAD protein was shifted, an indirect measured of drug-binding, as measured by immunoblotting. This demonstrates that AYNE binds to and inhibits VLCAD in vivo.

In summary, these results highlight VLCAD as a novel anti-AML target and further suggest the clinical utility of a novel food-derived lipid as a potential anti-AML agent.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

77

Considering omega-3 fatty acids and vitamin D across the food system for health: the Om3D consortium

Dr Sebastien Marze PhD
INRAE, Nantes, France

Abstract

We introduce Om3D, an interdisciplinary consortium composed of research scientists interested in studying omega-3 fatty acids and vitamin D in the food system context. The goals are to identify what dimensions of the food system limit their intakes (which are insufficient worldwide) and what sources could optimize both their sustainability and health aspects (for humans, animals, and Earth). To this end, quantitative data are collected in agricultural, food, nutrition, health, social, and environmental sciences. These data are then integrated both qualitatively and quantitatively across disciplines to evaluate the influence of various factors at the levels of sources, ingredients, foods, and diets. Available factors are currently related to plant/animal production, product transformation, food/nutrient composition, structure, consumption, digestion and metabolism, as well as to economic and environmental impacts. This structured data analysis helps identifying knowledge gaps related to omega-3 fatty acids and vitamin D that must be filled towards dietary recommendations optimizing food quantities, qualities, and multiple impacts. Many traditional sources were already evaluated using our multidimensional approach. This will also be used to assess the potential of emerging sources that could develop in the near future.

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Serum and milk PUFA, but not milk volume, are dependent on serum ferritin concentrations in in a study of low milk supply in humans

Rachel Walker ORCID iD[1], Laurie Nommsen-Rivers[2], Lois Oviawe[1], Elizabeth Soucy[1], Kevin Harvatine[3], Erin Wagner[2], Sarah Riddle[4], Alison Gernand[1]

[1]The Pennsylvania State University, Department of Nutritional Sciences, University Park, USA. [2]University of Cincinnati, College of Allied Health Sciences, Cincinnati, USA. [3]The Pennsylvania State University, Department of Animal Science, University Park, USA. [4]Cincinnati Children's Hospital Medical Center, Cincinnati, USA

Abstract

Synthesis and incorporation of long-chain PUFA into human milk are critical for infant growth and development, and require iron-dependent delta-5 and delta-6 desaturase enzymes. Therefore, we hypothesize that iron status, measured as serum ferritin, will predict concentrations of long-chain PUFA, including arachidonic acid (AA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) and facilitate adequate milk production and fat synthesis. In a low milk supply study, mothers were categorized as very low (LOW, milk output <300 mL/d, n=23) or moderate/normal milk supply (MODERATE, milk output ≥300 mL/d, n=20). An exclusively breastfeeding comparison group was separately enrolled (CONTROL, milk output ≥699 mL/d, n=18). Serum ferritin was analyzed by Cobas e411 clinical analyzer and fatty acids by gas chromatography with flame ionization detection. Group differences were assessed by ANOVA or Kruskal Wallis rank sum tests. Continuous associations used linear regression models adjusted by production group. There were no significant differences between milk production groups in serum ferritin (Median[IQR]: LOW, 40[26,75]; MODERATE, 44[32,73]; CONTROL, 50[24,73] ng/mL; p=0.84), and serum ferritin was also not associated with total milk fat % (β=0.39, p=0.30). However, serum ferritin was positively correlated with serum EPA (β=0.077, p=0.01) and serum DHA (β=0.14) although the correlation with DHA was not statistically significant (p=0.06). Serum ferritin predicted milk EPA (β=0.021, p=0.02), milk n-3 DPA (β=0.029, p=0.003), and milk AA (β=0.075, p=0.001), with a positive but not statistically significant correlation with milk DHA (β=0.068, p=0.06). After adjusting for the corresponding serum fatty acid, ferritin predicted both milk DPA (β=0.029, p=0.004) and milk AA (β=0.048, p=0.01) independent of serum concentrations. Although serum ferritin was not associated with milk production or total milk fat, these results suggest that adequate iron status may facilitate adequate long-chain PUFA concentrations in human milk.

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Dietary VLC-PUFA are Rapidly Retroconverted to EPA, DPA, and DHA in Mice

Prof Robert Anderson MD, PhD ORCID iD[1,2], Dr Daniel Stein PhD ORCID iD[3], Mr. Richard Brush BS, MBA ORCID iD[1], Ms Madison Tytanic BS ORCID iD[1], Ms Vicki Ea BS ORCID iD[1], Dr Neeraj Chauhan PhD ORCID iD[1], Dr Lea Bennett PhD ORCID iD[1], Dr Brian Rohrs PhD ORCID iD[3], Dr Martin-Paul Agbaga PhD ORCID iD[1,2]

[1]University of Oklahoma Health Sciences Center, Oklahoma City, USA. [2]Dean McGee Eye Institute, Oklahoma City, USA. [3]Bausch & Lomb Americas, Inc, Bridgewater, USA

Abstract

Purpose: Very long chain polyunsaturated fatty acids (VLC-PUFA; ≥ 28 carbons) are found in the retina. Mutations in the fatty acid elongase-4 (ELOVL4) that is essential for their biosynthesis cause AD Stargardt-like macular dystrophy (STGD3), a juvenile form of macular degeneration. VLC-PUFA are also decreased in donor retinas from age-related macular degeneration (AMD) patients. To assess whether oral supplementation could increase retinal VLC-PUFA levels and improve retinal function, we fed a labeled VLC-PUFA to mice for up to 17 weeks.

Methods: C57Bl/6J mice were started on an AIN-93G diet containing 0.1% (w/w) labeled VLC-PUFA. Liver, plasma, and retina were collected at various ages and fatty acid analyses performed. Feces were collected to determine intestinal absorption. Electroretinograms (ERG) were performed prior to starting the diet and just before tissues were collected.

Results: The VLC-PUFA were >90% absorbed in the intestine. However, there was no detectable uptake of dietary VLC-PUFA into the retina. Surprisingly, after just 1 week of supplementation, there was a significant amount of labeled EPA, DPA, and DHA in the liver, plasma, and retina, indicating that the VLC-PUFA had been retro-converted to these shorter chain PUFAs. Labeled VLC-PUFAs were eventually observed in the retina after 5 weeks of dosing and attributed to elongated shorter chain species. ERG analysis revealed no observable improvement in retinal function.

Conclusion: Dietary VLC-PUFA experiences significant first-pass metabolism in the liver when provided orally to mice. There is no evidence that dietary VLC-PUFA are incorporated directly into in the retina from the blood.

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New insight into the absorption of milk sphingomyelin by enterocytes in vitro

Nina Ritsch MSci[1], Dr Catherine Calzada PhD[1], Annie Durand[1], Dr Magali Pettazzoni PhD[2], Dr David Cheillan PhD[1,2], Dr Marie-Caroline Michalski PhD[1], Dr Armelle Penhoat PhD ORCID iD[1]

[1]CarMeN Laboratory, Inserm U1060, INRAE U1397, Univ-Lyon, Université Claude Bernard Lyon-1, Pierre Bénite, France. [2]Biologie Moléculaire, Centre de Biologie et de Pathologie Est, Hospices Civils de Lyon, Bron, France

Abstract

Milk polar lipids including sphingomyelin (SM) can modulate postprandial lipemia. The intestinal absorption of SM involves its sequential hydrolysis to ceramides (Cer), and further to sphingosine and fatty acids. However, the mechanisms underlying the uptake of dietary sphingolipids (SL) by enterocytes remain poorly understood. Our objective was to investigate the metabolism of milk SM and of its hydrolysis products, in Caco-2/TC7 intestinal cells cultured on permeable inserts, a validated model of the intestinal barrier.

Mixed lipid micelles consisting of oleic acid, 2-oleoylglycerol, phosphatidylcholine, lysophosphatidylcholine, cholesterol and taurocholate were prepared in culture medium: either without (control) or with bovine milk SM (0.4mM), or with sphingosine (0.05mM)+C23:0 (0.05mM), a particular milk fatty acid. After 16h incubation of such micelles on the apical side of the cells, triglycerides (TG) were quantified in basolateral media and SL were analyzed by tandem mass spectrometry in cells.

TG secretion increased at least 10-fold in all conditions with mixed micelles compared with medium devoid of lipids (3±1µM), thereby showing that SL did not alter TG secretion. Regarding SL incorporation within cells, SM-enriched micelles led to increased concentrations of SM (113±18µmol/g protein) and Cer (23±3µmol/g protein) compared to cells loaded with control micelles (19±4µmol/g protein and 8±0.5µmol/g protein, respectively). Micelles enriched with sphingosine+C23:0 also resulted in increased Cer concentrations in cells (23±4µmol/g protein). Analysis of Cer molecular species revealed that increased Cer in cells arise from both uptake and de novo synthesis.

In conclusion, enrichment of mixed lipid micelles with SM or sphingosine+C23:0 applied to the apical side of enterocytes modified the intracellular SM and Cer without impacting TG secretion. Further work should elucidate whether the SL composition of TG-rich lipoproteins is modified in order to decipher the impact of milk SM on cardiometabolic health.

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The impact of an unsaturated fat-rich Mediterranean diet versus a saturated fat-rich Western diet on mood, anxiety and cognitive performance: MediMood randomised controlled trial protocol

Miss Latife Esgunoglu MSc ORCID iD[1], Miss Marrium Liaquat MSc ORCID iD[1], Miss Rachel Gillings MSc[1], Dr Alpar Lazar PhD ORCID iD[1], Professor Michael Hornberger PhD ORCID iD[1], Dr Amy Jennings PhD[1], Professor Anne Marie Minihane PhD ORCID iD[1,2]
[1]University of East Anglia, Norwich, United Kingdom. [2]Norwich Institute of Health Ageing, Norwich, United Kingdom

Abstract

Introduction

The long-term impact of a Mediterranean-style diet (MD) rich in mono- and poly-unsaturated fatty acids (MUFA and PUFA) on cognitive and overall mental health has been repeatedly described (1,2). However, the research into the acute or short-term impact of a MD on brain health is in its infancy.

Methods

MediMood is an efficacy crossover randomised controlled trial (RCT), informed by the research gaps identified by our systematic review (3). Individuals (n=25) over 18 years with mild to moderate level anxiety and/or depression will be recruited. Participants will complete 5-day MD and 5-day Western Diet (WD) interventions with a 4-week wash-out period, with foods, meal plans and instructions provided. The primary outcomes are mood and anxiety. Secondary outcomes include cognitive functions including attention, brain perfusion using MRI, select cardiometabolic and inflammatory biomarkers, ketones, brain-derived neurotrophic factor, several hormones (i.e. catecholamines, serotonin), gut microbiome speciation, sleep quality and behaviour change. The assessment time points during each arm are baseline, postprandial, 24-h and day 6.

Diets are designed using the MD Adherence Screener (MEDAS) and isocaloric, with a 14-points score for the MD and 0-points MEDAS score for the WD. The total energy and lipid profiles of both interventions are presented in Table 1.

Discussion

MediMood will be the first well-controlled RCT examining the acute and short-term (up to 5 days) effects of a MD and a WD, (with special attention to the fatty acid profile) on mental wellbeing and cognition in a targeted risk group. It will identify the potential of a MD to improve daily symptoms and quality of life in those with existing mood and anxiety disorders.

Funding

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1. Petersson *et al.*,2016, Adv Nutr

2. Perica *et al.*,2011, Nutr Clin Pract

3. Esgunoglu *et al.*,2021, Br J Nutr

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NA

Supplemental materials (photos, articles or reports)

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α-Hydroxy-Docosahexaenoic Acid exerts neuroprotection against Alzheimer's disease and restores brain long-chain fatty acid profile, possibly via its metabolic derivative Heneicosapentaenoic Acid

Joan Cabot[1,2], Sebastià Parets[2], Marc Miralles[1,2], Marta Salvador-Castell[3,1], Maria Antonia Fiol-de Roque[2], Paula Fernandez-Garcia[1], Victoria Llado[4], Xavier Busquets[2], Pablo V Escriba[5], Manuel Torres[2]

[1]Laminar Pharmaceuticals S.A., Palma, Spain. [2]Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands, Palma, Spain. [3]Fundación Marathon, Palma, Spain. [4]Laminar Inc., Boston, USA. [5]Laminar Phamaceuticals S.A., Palma, Spain

Abstract

α-Hydroxy-Docosahexaenoic Acid (DHA-H) is a molecule under development for Alzheimer's disease (AD) therapy, based on the concept of the membrane lipid therapy (melitherapy). DHA-H has widely demonstrated neuroprotective effects against this disease in animal and cell models whereas regulatory toxicology studies revealed an excellent safety profile in rodents. Chronic oral administration for 4 months of DHA-H to 5xFAD mice, a transgenic mouse model of AD, prevents cognitive decline as well as synaptic and neuron degeneration. This neuroprotection is also mediated by restoration of neuronal proliferation up to healthy levels in the hippocampus. At molecular level, DHA-H reduces both β-amyloid accumulation and tau protein phosphorylation as compared to untreated 5xFAD controls.

DHA-H administration in mice resulted in increased brain levels of Phosphatidylethanolamines (PE) harboring long-chain Polyunsaturated Fatty Acids (lcPUFAs). Interestingly, DHA-H is converted into Heneicosapentaenoic Acid (HPA, C21:5 n-3) via α-oxidation. Results obtained in animal and cell models point toward HPA as an effector molecule of DHA-H. In this context, both DHA-H and HPA showed a neuroprotective effect against NMDA-induced excitotoxicity. When such an effect is mediated by DHA-H, this can be prevented by oxythiamine, an inhibitor of DHA-H conversion into HPA by α-oxidation. Moreover, although not yet fully understood, the accumulation of HPA after DHA-H treatment leads to a wide variety of species enriched in lcPUFAs in the brain.

In conclusion, our results demonstrate efficacy and safety for DHA-H in AD therapy and point towards restoration of brain lcPUFAs profile as plausible a mechanism of action. Being this mechanism likely promoted by HPA in the neuroprotection observed after treatment with DHA-H, although this hypothesis is still under research.

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Association between the combination of cognitively stimulating leisure activities with arachidonic acid or docosahexaenoic acid intake and cognitive decline among community-dwelling Japanese older people

Hisanori Tokuda Ph.D[1,2], Chika Horikawa[1,2], Yukiko Nishita Ph.D[1], Yoshihisa Kaneda Ph.D[2], Hidenori Obata[2], Tomohiro Rogi Ph.D[2], Takayuki Izumo Ph.D[2], Masaaki Nakai Ph.D[2], Prof. Hiroshi Shimokata Ph.D[1,3], Rei Otsuka Ph.D[1]

[1]Department of Epidemiology of Aging, National Center for Geriatrics and Gerontology, Aichi, Japan. [2]Institute for Health Care Science, Suntory Wellness Ltd., Kyoto, Japan. [3]Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan

Abstract

Multifactorial lifestyle approaches could be more effective than a single factor for maintaining cognitive function. This study investigated the association of combining cognitively stimulating leisure activities (CSLA), such as number/word puzzles, with intake of long-chain polyunsaturated fatty acids (LCPUFA), such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and arachidonic acid (ARA), on cognitive function in the older population.

Participants were community-dwelling Japanese people without self-reported history of dementia (n=903, aged 60–89 years) from datasets of a 2-year longitudinal study. CSLA engagement and LCPUFA intake were divided into high and low groups according to frequency (≥once/week and <once/week) for CSLA engagement and median intake level for LCPUFA intake according to sex, then categorized into four groups. The associations of multivariate-adjusted risk for cognitive decline, shown as the odds ratio (OR) for a decrease in the Mini-Mental State Examination score of ≥2 points, and the combination of CSLA engagement with LCPUFA intake were assessed using a multiple logistic regression model. Subgroup analysis was performed by restricting the participants with low DHA and EPA intakes (n=302; median, 333 mg/d), which was similar to those of North Americans.

The high-CSLA/high-ARA group cumulatively yielded a lower OR for cognitive decline (0.42; 95% CI, 0.25–0.71) than the low-CSLA/low-ARA group (p for trend = 0.001). In the subgroup analysis, compared with the low-CSLA/low-DHA group, the OR in the high-CSLA/high-DHA group was lower (0.36; 95% CI, 0.13–0.99; p for trend = 0.049).

These data suggest that high-frequency engagement in CSLA combined with high ARA intake may cumulatively reduce the risk of cognitive decline among older Japanese people. The combination of high-frequency engagement in CSLA with high DHA intake could have a positive association with maintaining cognitive function among older people with low DHA and EPA intake.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Analytical considerations for the use of dried spot technology for fatty acid profiling

Dr Chang Gao[1,2], Prof. Maria Makrides[1], Prof. Robert Gibson[1]
[1]SAHMRI Women and Kids Theme, Adelaide, Australia. [2]Division of Birth Cohort Study, Guangzhou Women and Children''s Medical Center, Guangzhou, China

Abstract

Analyzing bodily fluids collected as dried spot for various biological markers is a valuable tool for medical research and clinical investigations, owing to its simplified procedures in sample storage and transportation, as well as analytical process. Given the distinctive properties for varying biological samples, careful considerations must be taken when developing dried spot method to best preserve the targeted substances. Here, we will discuss the selection of cellulose paper, necessities and options for pre- and post-collection treatment, as well as extraction methods (where applicable) and describe a logistic workflow aiming to develop novel dried spot method, specifically for fatty acids analysis. For example, in human blood samples, antioxidant cocktails are often used for pre-treating the filter paper to prevent oxidation of polyunsaturated fatty acid due to the presence of hemoglobin and iron. Nevertheless, in human breast milk samples, the major concern is the endogenous natural lipase that causes instability of the triglycerides, but the total fatty acid pool remains undisturbed, a pre- or post-collection treatment to inactive lipase might be necessary. Lastly, we will have a specific discussion around the limitations of current dried milk spot method for profiling free fatty acids in human milk and how it might be improved.

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Charaterization of margarine enriched with long-chain omega 3 fatty acids

MRS Maureen Gerlei PhDStudent[1], Dr Cyril Kahn PhD ORCID iD[1], MRS Marion Feeser R&D Engineer[2], MRS Eulalie Prévot R&D Engineer[2], MRS Béatrice Lemois R&D Engineer[2], Pr Michel Linder Professor ORCID iD[1]
[1]Université de Lorraine - LIbio, Vandœuvre-lès-Nancy, France. [2]SAS St Hubert, Ludres, France

Abstract

French margarine market in France arouses particularly the interest of consumers belonging to the bracket of the seniors for their texture and their sought-after health allegations. Indeed, the prevention of certain chronic diseases, multifactorial and multivariate such as cardiovascular and neurogenerative diseases has been assessed.

In France, the margarine consumption (3,3 kg/per household (AgriFrance, 2019)) remains lower than the butter consumption (8,3 Kg/inhabitant (CNIEL, 2021)). Thus, French people remain the biggest consumers of butter in the world with the New Zealanders.

However, margarine present certain advantages concerning its spreadability and the formulation of its composition in lipids. The latter is obtained from a mixture of oils and concrete fats, added with emulsifiers and vitamins, contrary to butter which is exclusively made of milk fat and produced by mechanical processes.

Indeed, this margarine takes into account the daily needs in essential fatty acids (ALA and LA) and essential like DHA, for people consuming very little amount fish and preserve a claim "food-health" of this type of product, elaborated for the seniors.

This was made possible thanks to a formulation of oils and concrete fats associated with an algal oil. This study presents a comparison between different margarine with health claims. The physicochemical characteristics (fatty acid composition, lipid classes, oil quality indices), mechanical properties (texture, rheology) and structural properties (DSC, OIT, FTIR) will be presented.

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Characterization of expression response in postprandial situation of food detection in rainbow trout fed with plant-based diet : focus to free-fatty-acid-receptor and their signaling

Elodie Baranek, Karine Dias, Cécile Héraud, Anne Surget, Anthony Lanuque, Frédéric Terrier, Sandrine Skiba-Cassy, Jérôme Roy
INRAE, Université de Pau et des Pays de l'Adour, E2S UPPA, UMR1419 Nutrition Metabolism and Aquaculture, Aquapôle, F-64310, Saint-pée-sur-Nivelle, France

Abstract

In vertebrates, taste provides critical information about the quality and nature of nutrients, leading to specific eating responses (consumption or avoidance), fundamental to their growth and survival. Taste perception is one of the first sensing system involved in oro-sensory detection of nutrients that play key role in the regulation of feeding behavior. Previous studies revealed that the concomitant replacement of traditional ingredients of aquafeed, fish meal and fish oil by plant ingredients (totally devoid of omega-3 long chain polyunsaturated fatty acid, ω-3 LC-PUFA) from first feeding of rainbow trout (RT, Oncorhynchus mykiss) led to a reduction of growth and survival rates (Lazzarotto et al., 2018), mainly related to altered feeding behavior. In fish, the impact of ω-3 LC-PUFA in the modulation of food detection and its involvement in the regulation of feeding behavior is largely unknown.

In this study, we assessed the impact of feeding of alternative plant ingredient (without ω-3 LC-PUFA) vs commercial-like diet on the mechanism of food detection in the oro-sensory system in RT. After unique meal, we characterized by post prandial kinetics experiment (before meal, 20mns, 2 hours, 6 hours, 10 hours and 24 hours after meal) the expression pattern of appetite regulating neuropeptides in hypothalamus, free fatty acids receptor family (FFAR), the calcium signaling pathways and indolamine pathways in tongue. Overall findings show that RT displayed the fundamental mechanisms for oro-gustatory perception of nutrients related to different diet composition. The data obtained also indicated that taste receptors for fatty acids (such as the ffar receptor) and pathways involved in nutrients detection (such as calcium or monoaminergic pathways) are involved in the post-prandial regulation of food intake in fish, and their differential regulation according to the proposed diet could suggest a role in the regulation of appetite.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No publication

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MUCOSAL AND PLASMA PUFAS, OXYLIPINS AND ENDOCANNABINOIDS PROFILES IN CROHN'S DISEASE

Mrs Yamina Ben Mustapha MS ORCID iD, Dr Sameh Hadj-Taieb MD, Dr Mohamed Kacem Ben Fradj PhD ORCID iD, Dr Meriem Serghini MD, Dr Moncef Feki MD, Dr Jalel Boubaker MD, Dr Mohamed Bassem Hammami MD
Rabta Hospital, Tunis, Tunisia

Abstract

Introduction and aims. Crohn's disease (CD) is an inflammatory bowel disease characterized by severe intestinal and extra intestinal injuries. The pathogenesis of CD is poorly understood and current treatments result in adverse effects and lose response to the drugs over time. PUFAs and their bioactive derivatives are proven to modulate inflammation and wound repair. However, the role of these bioactive lipids in CD remains unclear. The study aimed to examine selected PUFAs, oxylipins and endocannabinoids in mucosa and plasma of patients with active CD.

Methods. Twenty-eight patients with active CD and thirty-nine controls with normal colonic mucosa were included. Fasting blood and colonic biopsies were collected in all participants, during CD flare for patients. Selected PUFAs, oxylipins and endocannabinoids were assessed in plasma and in colonic mucosa by a targeted LC-MS/MS method. Volcano plot analysis was performed to identify the mediators discriminating CD patients. A multivariate ROC curve-based exploratory analysis was applied to determine a lipidomic signature for CD.

Results. The pattern of lipid mediators in CD patients was characterized by overexpression of ARA-derived proinflammatory (PGE2, TXB2, LTB4, LTC4, LTD4, LTE4) and pro-resolving (6-epi-LXA) oxylipins and endocannabinoids (AEA, 2-AG) and under expression of n-3 PUFAs (ALA, EPA, DPA, DHA) and related oxylipins (18-HEPE) and endocannabinoids (DHEA). A model combining low DPA and high LTB4 and 2-AG in plasma showed good discrimination of patients from controls and would represent a lipidomic signature for CD flare.

Conclusions. The profile of lipid mediators in CD is characterized by unbalanced n-6 to n-3 PUFAs and related oxylipins and endocannabinoids. These bioactive lipids are likely involved in pathophysiology and may serve as biomarkers for CD. Targeting the metabolic and signaling pathways of bioactive lipids might be an effective therapeutic alternative in CD.

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ALTERED EXPRESSION OF OXYLIPINS AND RELATED METABOLIC AND SIGNALING PATHWAYS IN COLONIC MUCOSA IN INFLAMMATORY BOWEL DISEASES.

Mrs Yamina Ben Mustapha MS, Dr Mohamed Kacem Ben Fradj PhD, Dr Khalil Jmal MD, Dr Meriem Serghini MD, Dr Jalel Boubaker MD, Dr Moncef Feki MD, Dr Sameh Hadj-Taieb MD
Rabta Hospital, Tunis, Tunisia

Abstract

Background. As chronic inflammatory disorders, inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC) are thought to be linked to a failure in resolving pathways. Oxylipins are PUFAs derivatives that exert either proinflammatory or pro-resolving actions. This study investigated selected oxylipins together with their precursors, synthetizing enzymes, and receptors in colonic mucosa in patients with IBD.

Methods. Forty-two patients with active IBD; twenty-nine patients with CD and fifteen patients with UC, and thirty-nine patients with normal colonic mucosa were included. mRNA expression of LOX5, LOX12, LOX15, ANXA1, FPR2/ALX, FFAR4/GPR120, and IL-10 were analyzed using qRT-PCR. Selected PUFAs and oxylipins were quantified using a targeted LC-MS/MS method. Volcano plot analyses were performed to identify the compounds that discriminate CD and UC.

Results. FPR2 and ANXA1 were overexpressed in both UC and CD patients. Proinflammatory oxylipins including PGE2, TXB2, LTB4, LTC4, LTC4 and LTE4 and the pro-resolving mediator LXB4 were increased in mucosa in both UC and CD patients, at a higher extent in UC. EPA and its derivative 18-HEPE were decreased in CD patients, only. No significant changes were found for DHA and related resolvins D1, D2 and D5 and PDX in both CD and UC. There were no significant differences for all compounds between CD and UC patients.

Conclusions. The study showed altered lipoxins metabolic and signaling pathways in both CD and UC patients. These findings suggest that these bioactive lipids engage in pathophysiology of IBD. Given the frequent adverse effects and high rate of therapeutic effects loose of IBD treatments, targeting oxylipins metabolic and signaling pathways would represent an alternative or an adjuvant therapy to current treatment of IBD.

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ANXA1-FPR2/ALX SIGNALING AXIS IS UPREGULATED IN COLONIC MUCOSA IN INFLAMMATORY BOWEL DISEASES.

Mrs Yamina Ben Mustapha MS, Dr Sameh Hadj-Taieb MD, Dr Mohamed Kacem Ben Fradj PhD, Dr Meriem Serghini MD, Dr Haifa Sanhaji MD, Dr Jalel Boubaker MD, Dr Moncef Feki MD
Rabta Hospital, Tunis, Tunisia

Abstract

Background an objective. FPR2/ALX is a G-protein-coupled receptor responsive to several ligands including lipoxins (LX) and annexin A-1 (ANXA1). The ANXA1-FPR2 signaling axis is involved in resolution of inflammation in several inflammatory conditions including animal-induced colitis. However, its role in inflammatory bowel diseases (IBD) is unclear. This study aimed to evaluate mucosal FPR2, ANXA1, and selected lipoxins expression in IBD patients.

Methods. Patients with active Crohn's disease (CD, n=29) and active ulcerative colitis (UC, n=15), and controls with normal colonic mucosa (n=39) were included. Mucosal FPR2 and ANXA1 mRNA was analyzed using qRT-PCR and mucosal lipoxins A4 (LXA4), B4 (LXB4), 5R,6R6-epi-LXA4, and 14-epi-LXA4 were quantified using LC-MS/MS.

Results. Compared to controls, patients with UC and with CD showed significantly higher (P<0.001) mucosal mRNA expression of FPR2 [median (IQR), 3.74 (2.01-6.12) and 3.03 (0.94-15.9) vs. 0.034 (0.019-0.062) arbitrary unit] and of ANXA1 [5.11 (4.19-7.96) and 3.54 (1.87-7.68) vs. 0.085(0.063-0.115) arbitrary unit]. Mucosal LXB4 [7.41 (3.15-10.8) and 4.21 (2.48-15.8) vs. 1.58 (0.81-4.82) pg/mL], and 14-epi-LXA4 [5.60 (3.58-7.97) and 3.75 (1.94-13.7) vs. 1.69 (0.69-5.66) pg/mL] were significantly higher (P<0.01) in UC and CD patients than controls. FPR2 levels were significantly correlated with ANXA1 (r=0.821; P<0.001), LXB4 (r=0.431; P<0.001), 14-epi-LXA4 (r=0.350; P=0.001), and CRP (r=0.360; P=0.002) levels in IBD patients, and with Mayo score (r=0.705; P=0.005) in UC patients.

Conclusions. The ANXA1-FPR2 signaling axis is upregulated in both UC and CD and positively correlated with inflammation degree and disease activity. Upregulation of this pro-resolving pathway likely occurs as a normal but unsuccessful attempt to resolve inflammation and restore homeostasis during IBD flare.

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ARE INFLAMMATION RESOLUTION PATHWAYS DEFECTIVE IN ISCHEMIC STROKE?

Dr Mohamed Kacem Ben Fradj PhD[1], Dr Mohamed Bassem Hammami MD[1], Dr Jihene Ben Sassi MD[2], Dr Zakaria Saied MD[2], Dr Samia Ben Sassi MD[2], Dr Moncef Feki MD[1], Dr Sameh Hadj-Taieb MD[1]
[1]Rabta Hospital, Tunis, Tunisia. [2]National Institute of Neurology, Tunis, Tunisia

Abstract

Introduction and aim. Ischemic stroke (IS) is a severe neurological disorder involving disturbances in inflammatory mechanisms. Oxylipins are bioactive lipid mediators (LMs) involved in initiation, progress, and resolution of inflammation. The characterization of oxylipins can be relevant to the pathophysiology and diagnosis of IS. The study aimed to investigate plasma oxylipins and theirs PUFAs precursors in patients with IS.

Methods. Forty-one patients with proved IS and 41 age- and sex-matched controls were included. Patients underwent clinical evaluation, CT-scan, and calculation of NIH Stroke Scale (NHISS). IS was considered severe for patients with an NHISS score > 15. Twenty-three LMs, oxylipins (n=18) and non-esterified PUFAs (n=5) were quantified in plasma using targeted LC-MS/MS method. PLS-DA and multivariate ROC curve-based exploratory analyses were performed to determine discriminatory LMs and identify a lipidomic signature for IS.

Results. PLS-DA analysis identified eight LMs with a VIP score >1, which statistically underpinned the separation between the two groups. There were substantially higher levels of PUFAs (ARA, EPA, DPA, and DHA), pro-inflammatory mediator PGD2, and pro-resolving mediator PDX. Pro-resolving mediators LXB4 and RVD1 levels were lower in patients. Four LMs, increased EPA, PDX and PGE2, and decreased RVD1 were selected as a combinational biomarker panel for IS discrimination with a very good classification performance (AUC, 0.958). The model would be a reliable lipidomic signature for IS. Patients with severe IS showed decreased pro-resolving mediators 15-epi-LXA4 and 7,17-dihydroxy-DPA.

Conclusions. The study revealed high circulating non-esterified PUFAs in IS, which might be secondary to an activation of phospholipase A2. Lower levels in pro-resolving LMS in IS patients and in those with severe form suggests that defective resolution pathways may contribute to the pathophysiology of IS. Further research is needed to test whether the improvement of resolution capacities could contribute to prevent IS occurrence and severity.

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PLASMA OXYLIPINS PROFILE IS A PROMISING PROGNOSTIC BIOMARKER IN ISCHEMIC STROKE

Dr Mohamed Kacem Ben Fradj PhD[1], Dr Jihene Ben Sassi MD[2], Dr Zakaria Saied MD[2], Dr Haifa Sanhaji MD[1], Dr Moncef Feki MD[1], Dr Samia Ben Sassi MD[2], Dr Mohamed Bassem Hammami MD[1]
[1]Rabta Hospital, Tunis, Tunisia. [2]National Institute of Neurology, Tunis, Tunisia

Abstract

Introduction and aims. Ischemic stroke (IS) is a devastating brain injury. Regulation of cerebral post-ischemic inflammation could attenuate neuronal injury and enhance neural repair. Oxylipins have major roles in inflammation, anti-inflammation, and neuroprotection. In this study, we tested whether plasma oxylipins are relevant for short-term outcome in IS patients.

Methods. Forty-one patients with IS were followed for 7 days. NIH Stroke Scale (NHISS) score was calculated at admission and 72 hours after and data on within-one-week mortality was collected. Early neurologic recovery (ENR) was defined as ≤ 2 points decrease in NHISS score at 72 hours. Selected proinflammatory and pro-resolving oxylipins were quantified in plasma using a targeted LC-MS/MS method. Volcano plot analyses were applied to determine which oxylipins are associated with ENR or intra-hospital mortality. For the metabolites identified by volcano plot analysis, ROC curve analysis and multivariate Cox-hazard model were applied to test their association with intra-hospital mortality.

Results. Volcano plot analysis [fold change (FC)>1.5] identified 3 metabolites associated with ENR and 2 metabolites associated with intra-hospital mortality. Patients with ENR had lower PGE2 (FC= 0.28) and TXB2 (FC= 0.50) and higher 7,17-dihydroxy-DPA (FC= 2) levels. Patients who died within one week showed lower LXB4 (FC= 0.62) and higher LTE4 (FC=1.55). ROC curve analyses repaired cut-off values for mortality at 1.15 ng/mL for LXB4 and 10 ng/mL for LTE4. Based on these thresholds, only low plasma LXB4 levels were associated with intra-hospital mortality [multi-adjusted HR (95% CI), 7.51 (1.41-40.7)].

Conclusions: Lower levels of the pro-resolving oxylipins; 7,17-dihydroxy-DPA and LXB4 are associated with poor outcome in IS patients. This data suggest that defective resolution pathways increase the risk of aggravation in IS patients. Future research should verify whether enhancing resolution capacities contribute to improve the outcome in IS patients

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DISRUPTED METABOLISM OF BIOACTIVE LIPID MEDIATORS IN FIRST EPISODE PSYCHOSIS.

Mrs Khouloud Hkimi MS[1], Dr Rania Lansari MD[2], Mrs Amani Riahi MS[1], Dr Mohamed Kacem Ben Fradj PhD[1], Dr Emna Bergaoui MD[2], Dr Moncef Feki MD[1], Dr Wahid Melki MD[2], Dr Khalil Jmal MD[1]
[1]Rabta Hospital, Tunis, Tunisia. [2]Razi Hospital, Mannouba, Tunisia

Abstract

Background and aim. Schizophrenia (SCZ) is a chronic and disabling psychiatric disorder of enigmatic pathogenesis. No reliable biomarker for SCZ diagnosis and therapy monitoring is available. The characterization of the lipidomic would be relevant to the pathophysiology and monitoring of the disease. However, comprehensive lipidomic analysis in SCZ is rare. In this study, we investigated a panel of bioactive lipid mediators in first episode psychosis (FEP).

Methods. Fifty-three patients with FEP who were antipsychotic-naïve/free and 32 healthy controls were included. Clinical, psychological, and biochemical evaluations were performed during the acute phase and during recovery phase, after 3 months of antipsychotic therapy for 20 patients. Selected LCPUFAs (n=5) and deriving oxylipins (n=19) and endocannabinoids (eCBs) (n=7) were analyzed using targeted LC-MS/MS method. Volcano plot and multivariate ROC based exploratory analyses were applied to determine the discriminatory metabolites and identify lipidomic signature for PEP.

Results. During acute phase, n-6-derived proinflammatory oxylipins (PGD2, 6-keto-PGF1-a, LTB4, LTC4, N-acetyl-LTE4) and pro-resolving oxylipins (LXA4, 6-epi-LXA4) were increased in patients, as well as n-6-derived eCBs (2-AG and AEA). Both n-6 (ARA) and n-3 (ALA, EPA, DPA, DHA) LCPUFAs were decreased, but no changes were found in n-3 oxylipins and eCBs derivatives. In multivariate analysis, a model combining decreased ALA and EPA with increased AEA had an excellent discriminatory power (AUC, 0.958) and might be used as a reliable lipidomic signature for active FEP. During recovery, LCPUFAs levels normalized, but proinflammatory (PGD2, TXB2, LTB4, LTC4) and pro-resolving (6-epi-LXA4) oxylipins remained elevated in PEP patients.

Conclusions. The study findings suggest that bioactive lipids including LCPUFAs, oxylipins and eCBs are involved in PEP pathophysiology and can serve as potential biomarkers for monitoring FEP. Further research is needed to examine the potential of these bioactive lipids for psychiatric disorders treatment.

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Should omega-3 polyunsaturated fatty acid - nutrient interactions be considered a missing link in ageing research?

Dr Simon Dyall PhD ORCID iD
University of Roehamptonm, London, United Kingdom

Abstract

Epidemiological evidence strongly suggests that an elevated intake of omega-3 polyunsaturated fatty acids (PUFAs) decreases the risk of developing neurodegenerative conditions, such as dementia. However, these observations have so far failed to translate into consistent positive results in randomised controlled trials (RCTs). One potential explanation for this apparent dissonance may be that omega-3 PUFAs work in conjunction with allied supporting nutrients, which are not traditionally considered in the reductionist design of single nutrient intervention RCTs. For example, a number of studies have identified links between homocysteine and omega-3 PUFA metabolism. Elevated homocysteine is associated with more than 100 diseases, including cardiovascular diseases and diseases of the central nervous system, and the most common cause of elevated homocysteine is insufficient intake or impaired function of B vitamins, such as folic acid, B6 and B12. Consequently, sufficient availability of both omega-3 PUFAs and B vitamins may be required to maximise their therapeutic effects. We have previously shown that providing a combination of omega-3 PUFAs and B vitamins as part of a multi-nutrient formula benefits cognition in older adults. This presentation explores the nature of the interaction between homocysteine and omega-3 PUFAs and discusses the evidence indicating that omega-3 PUFA-based interventions aimed at benefiting cognition in older adults requires consideration of allied nutrients, such as B vitamins.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Long-chain omega-3 polyunsaturated fatty acids are reduced in neonates with substantial brain injury undergoing therapeutic hypothermia after hypoxic-ischemic encephalopathy

Dr Simon Dyall ORCID iD[1], Dr Isabell Nessel[2], Jennine Sharpe[1], Dr Ping Yip[2], Dr Adina Michael-Titus[2], Dr Divyen Shah[2,3]
[1]University of Roehampton, London, United Kingdom. [2]Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom. [3]Royal London Hospital, Barts Health NHS Trust, London, United Kingdom

Abstract

Background & Aims

Hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal morbidity and mortality. Although therapeutic hypothermia (TH) is an effective treatment, there is substantial chronic neurological impairment. Long-chain omega-3 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids, offer therapeutic potential in the post-acute phase. However, to develop effective strategies it is important to understand how PUFAs are affected by HIE and TH. We therefore quantified for the first time the effects of HIE and TH on blood PUFA levels and markers of lipid peroxidation.

Methods

In a cross-sectional approach, blood samples from newborns with moderate to severe HIE, who underwent TH (sHIE group) were compared to samples from newborns with mild HIE, who did not receive TH, and controls. Within the sHIE group, 10 had cerebral MRI predictive of good outcomes and 10 predictive of poor outcome; nine of whom went on to develop cerebral palsy. Cell pellet samples were analysed for fatty acid content, and plasma for lipid peroxidation products, thiobarbituric acid reactive substances and 4-hydroxy-2-nonenal.

Results

Omega-3 Index (% DHA and EPA) did not initially differ between groups; however, there were significantly lower levels in the poor vs. good prognosis sHIE groups on cerebral MRI over the TH phase. Estimated Δ-6-desaturase (D6D) activity was significantly lower in sHIE groups compared to mild HIE and control groups, and linoleic acid significantly increased in the sHIE group with good prognosis.

Conclusion

Long-chain omega-3 PUFAs are reduced in neonates with substantial brain injury associated with poor outcome after HIE and TH, potentially due to decreased D6D activity and elevated linoleic acid levels, which may further limit biosynthesis and complete for tissue incorporation. We speculate that there may be a role for long-chain omega-3 PUFA interventions in addition to existing treatments to improve neurologic outcomes.

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High prevalence of vitamin D deficiency among young healthy female students from Palestine

Janina Susann Lenz[1], Dr. Nathan Tintle PhD ORCID iD[2], Felix Kerlikowsky[1], Dr. Manal Badrasawi[3], Dr. Rana Zahdeh[4], Prof. Dr. Andreas Hahn ORCID iD[1], Prof. Dr. Jan Philipp Schuchardt Jan Philipp Schuchardt ORCID iD[1]

[1]Institute of Food Science and Human Nutrition, Leibniz University Hannover, Hannover, Germany. [2]Department of Population Health Nursing Science, College of Nursing, University of Illinois – Chicago, Chicago, Il, USA. [3]Department of Nutrition and Food technology, Faculty of Agriculture and Veterinary medicine, An-Najah National University, Nablus, West Bank, Palestine. [4]Department of Chemistry and Applied Sciences, College of Applied Sciences, Palestine Polytechnic University, Hebron, West Bank, Palestine

Abstract

Vitamin D requirements are mainly met by endogenous synthesis in the skin, as long as there is adequate sunlight exposure. Palestine is geographically located in a region with abundant sunlight throughout the year, potentially providing enough sunlight to allow for sufficient endogenous synthesis of vitamin-D. However, the vitamin-D status of healthy individuals in Palestine is unknown. The aim of this cross-sectional study was to assess vitamin-D status based on serum concentrations of 25-hydroxycholecalciferol [25-(OH)D] in young healthy Palestinian students (18-27 years, mean±SD age: 20.2±1.54 years) and to evaluate associations between 25-(OH)D concentrations and several predictors. Serum 25-(OH)D concentrations were measured by chemiluminescent microparticle immunoassay (CMIA). Dietary assessment was assessed by questionnaires and three 24-hour recalls. The mean±SD 25-(OH)D concentration in the entire study population was 35.2±19.8 nmol/L. Men (n=52) had significantly higher concentrations (58.3±14.5 nmol/L) than women (n=151; 27.2±14.5 nmol/L). 61.6% of the women were vitamin-D deficient (25-(OH)D<25 nmol/L), while 31.1% had an insufficient vitamin-D status (25-(OH)D 25-< 50 nmol/L). Less than 10% reported a regular fish consumption of ≥2 servings/wk. Only about one-fifth of the subjects reported taking supplements irregularly. 98% of the women wore a hijab. Linear regression analyses showed that sex, dietary vitamin-D, and supplement intake were significantly associated with 25-(OH)D concentrations, even after adjustment for several variables. This cross-sectional study shows that the vitamin-D status of female Palestinian students is alarmingly poor. The vitamin-D status in women is most likely the result of an inadequate sunlight exposure due to skin veiling by wearing a hijab in combination with leg and arm covering clothing’s. This work was supported by the German Federal Ministry of Education and Research (BMBF, FKZ: 01DH19003).

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Evaluating the relationship between dietary PUFA and heavy metal contaminant intake of lactating women and their breast milk nutritional profile: A systematic review and meta-analysis

Coralie Falize, Matthew Savage, Christos Kelaiditis, Dr Yvonne Jeanes, Dr Simon Dyall
University of Roehampton, London, United Kingdom

Abstract

Maternal diet influences breast milk nutritional profile; however, when developing nutritional recommendations, it is important to understand the effects of short-term changes in intake. This study systematically reviewed the literature on the effects of maternal PUFA and heavy metal intake on breast milk content.

PubMed, CENTRAL, Web of Science and CINALH were systematically searched until 6/11/22 on healthy non-micronutrient deficient lactating women. Cochrane RoB2 and Newcastle-Ottawa Scale tools evaluated quality and risk of bias. A random effect meta-analysis was performed where appropriate (PROSPERO, CRD42020221577).

18 publications on fatty acids were considered. The meta-analyses of DHA and EPA revealed positive relationships between maternal intake and breast milk concentration (mean difference = 0.28%, 95% CI [-0.08-0.65], P<0.00001, and mean difference = 0.03%, 95% CI [0.02-0.04], P=0.35, respectively). ALA showed evidence of response to maternal intakes, whereas, ARA did not; however, more evidence is required. The effects of vegan, vegetarian or omnivore diet patterns on PUFA composition were also explored. Four observational studies were considered on contaminants, and although positive relationships were identified between exposure to polychlorinated biphenyls and the heavy metals (arsenic, boron, cadmium, lithium, lead) and breast milk content, which were related to environmental factors in addition to dietary intake, a negative relationship was identified between fresh water fish consumption and breast milk mercury content.

Overall, DHA, EPA, combination of ALA/LA and saturated fatty acids, are responsive to short-term changes in maternal diet; however, research was generally scarce or poor quality, with further studies needed, particularly for ARA and contaminants.

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Very low Omega-3 Index in young healthy students from Palestine

Dr. Theresa Greupner[1], Feras Almasri[1], Dr. Manal Badrasawi[2], Dr. Rana Zahdeh[3], Prof. Dr. Andreas Hahn ORCID iD[1], Prof. Dr. Jan Philipp Schuchardt ORCID iD[1]

[1]Institute of Food Science and Human Nutrition, Leibniz University Hannover, Hannover, Germany. [2]Department of Nutrition and Food technology, Faculty of Agriculture and Veterinary medicine, An-Najah National University, Nablus, West Bank, Palestine. [3]Department of Chemistry and Applied Sciences, College of Applied Sciences, Palestine Polytechnic University, Hebron, West Bank, Palestine

Abstract

Long-chain omega-3 polyunsaturated fatty acids (n3 PUFA) play an important role in maintaining health. The long-term supply status of EPA and DHA is reflected by the Omega-3 Index (O3I) – defined as the sum of EPA+DHA in relation to the total fatty acid content of erythrocytes. In Middle Eastern countries, only a few studies have examined the status of n3 PUFA in blood. In Palestine, the n3 PUFA status of healthy individuals is unknown. This cross-sectional study aimed to determine the O3I and fish intake in a group of young students from Palestine. The O3I was measured using a dry blood spot method combined with GC analysis in a certified laboratory (OmegaQuant Analytics, Sioux Falls, SD, USA). Fish consumption was recorded using a questionnaire. The mean±SD O3I in the entire study population (age: 20.1±0.74 years) was 2.56±0.57% (min: 1.41%, max: 4.17%) with no difference between women (n=99, 2.52±0.50%) and men (n=50, 2.65±0.69%). The majority (97.9%) of the participants had an O3I below 4% which can be classified as “very low”. None of the participants had an O3I that could be classified as “moderate” (> 6% to 8%) or “desirable” (> 8%). Only 8% of the study participants consumed ≥ 2 servings of fish per week. The data show an low intake of fish, which explains the very low O3I. Further studies with a wider age range and balanced gender balance are needed in order to confirm the results. This work was supported by the German Federal Ministry of Education and Research (BMBF, FKZ: 01DH19003).

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Effect of different marine oil sources (calanus oil, fish oil and krill oil) on the omega-3 status after 12 weeks of intervention

Prof. Dr. Andreas Hahn ORCID iD, Franziska Vosskötter, Milena Burhop, Prof. Dr. Jan Philipp Schuchardt ORCID iD
Institute of Food Science and Human Nutrition, Leibniz University Hannover, Hannover, Germany

Abstract

In addition to fish, krill and algae as the conventional marine sources of omega-3 polyunsaturated fatty acids (n3 PUFA), Calanus finmarchicus - a lipid-rich copepod from the North Atlantic Ocean - is a novel source of n3 PUFA for human consumption. Calanus oil (CO) is fundamentally different from conventional n3 oils in that the fatty acids contained in CO are mainly bound as wax esters (WE). The aim of the randomized study with 62 healthy participants (mean±SD age: 29.7±8.3y) was to investigate the influence of a 12-week supplementation with CO (n=21, 4 capsules/d, EPA+DHA dose: 242 mg/d) compared to fish oil (FO, n=22, 1 capsule/d, EPA+DHA dose: 232 mg/d) and krill oil (KO, n=19, 2 capsules/d, EPA+DHA dose: 287 mg/d) on the Omega-3 Index (O3I). The O3I, defined as erythrocyte EPA+DHA content as a percentage of total identified fatty acids, was analyzed by GC at OmegaQuant Analytics (Sioux Falls, SD, USA). Mean±SD baseline O3I levels were similar among the three groups (CO-group: 5.13±1.12%, FO-group: 4.90±0.57%, KO-group: 4.87±0.77%). After 12 weeks, the O3I increased significantly to a similar extent in all three groups (delta change): CO-group: 1.09±0.55%, FO-group: 1.0±0.53%, KO-group: 1.15±0.65% (all $p<0.001$). However, the increase in O3I was identical in relation to the dose of EPA/DHA administered. Our results show that the long-term effect of CO on the O3I increase is comparable to that of FO and KO and could serve as a new bioavailable source of cardioprotective EPA and DHA.

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Effect of omega-3 fatty acid supplementation on blood cell physical phenotypes in healthy young volunteers – an exploratory study

Prof. Dr. Jan Philipp Schuchardt ORCID iD[1,2], Dr. Nathan Tintle PhD ORCID iD[1,3], Prof. Dr. Andreas Hahn ORCID iD[2], Dr. Martin Kräter ORCID iD[4], Prof. Dr. William S. Harris William S. Harris PhD ORCID iD[1,5]

[1]The Fatty Acid Research Institute, Sioux Falls, SD, USA. [2]Institute of Food Science and Human Nutrition, Leibniz University Hannover, Hannover, Germany. [3]Department of Population Health Nursing Science, College of Nursing, University of Illinois – Chicago, Chicago, IL, USA. [4]Max Planck Institute for the Science of Light & Max-Planck-Zentrum für Physik und Medizin, Erlangen, Germany. [5]Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Sioux Falls, SD, USA

Abstract

Omega-3 polyunsaturated fatty acids (n3 PUFA) possess pleiotropic health benefits such as cardio-protective or anti-inflammatory effects, although the mechanisms involved are only partially characterized. In an exploratory study with 31 healthy subjects (16 male, 15 female, mean±SD age: 28±8y), we investigated the effects of 12 weeks of n3 PUFA supplementation (1500mg EPA+DHA/day) on the physical properties of the major blood cell types using real-time deformability cytometry (RT-DC). We correlated changes in blood cell physical properties with changes in the Omega-3 Index (O3I, relative EPA+DHA content of total fatty acids in erythrocytes). The mean±SD O3I increased significantly ($p<0.001$) from 5.3±1.5% to 8.4±1.2%. We observed statistically significant increases in deformability in erythrocytes, lymphocytes, granulocytes and monocytes under physical load (i.e., hydrodynamic force). Deformability is crucial for erythrocytes to pass the microcapillaries of the organs and allow for gas exchange. In addition to increased deformability, leucocytes appeared to be “softer” based on a decrease in Young's modulus (a measure of “cell stiffness”). Similar changes were found in individuals with chronic inflammation, where leukocytes are constantly activated. Softer leukocytes can more easily demarginate, circulate, migrate, and respond more quickly to inflammation or infection. In conclusion, n3 PUFA supplementation alters the physical properties of not only erythrocytes but also white blood cells, theoretically improving their biological function. Placebo-controlled studies should be conducted to investigate the effects of n3 PUFAs on blood cell biology, especially when deranged in various disease states. Moreover, studies are needed to define the mechanisms through by which n3-PUFAs act.

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Omega-3 status and it’s predictors in the Great Britain – results of the UK Biobank

Prof. Dr. Jan Philipp Schuchardt ORCID iD[1,2], Dr. Nathan Tintle PhD ORCID iD[1,3], Jason Westra[1], Prof. Dr. William S. Harris PhD ORCID iD[1,4]
[1]The Fatty Acid Research Institute, Sioux Falls, SD, USA. [2]Institute of Food Science and Human Nutrition, Leibniz University Hannover, Hannover, Germany. [3]Department of Population Health Nursing Science, College of Nursing, University of Illinois – Chicago, Chicago, IL, USA. [4]Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Sioux Falls, USA

Abstract

Data on the status of long-chain omega-3 PUFA in the United Kingdom (UK) are now available from a subset of subjects in the UK Biobank – a prospective, population-based cohort aged 40-70 years recruited between 2007 and 2010. Plasma DHA and total n3 PUFA levels (each expressed as a percentage of total FAs) were measured using nuclear magnetic resonance (NMR). In order to assess n3 PUFA status with a more common metric, the aim of our study was to create an equation to estimate the O3I (eO3I, an erythrocyte-based biomarker) from the plasma data. In an interlaboratory experiment 250 random routine blood samples were analyzed for the O3I by GC at OmegaQuant-Analytics (Sioux Falls, SD, USA), while plasma aliquots from the same subjects were analyzed for plasma DHA and total n3 PUFA by NMR at the Nightingale laboratory (Nightingale Health Plc, Helsinki, Finland). The best predictor of eO3I included both DHA% and a derived metric, the total n3%-DHA%. Together these explained 65% of the variability ($r=0.832$, $p<0.0001$). From this equation, the mean±SD eO3I of the 117,108 UKBB subjects for whom NMR n3 plasma data were available was 5.58±2.35%. In addition, the eO3I was correlated with available anthropometric, demographic, and lifestyle variables in multivariable adjusted models. Oily-fish consumption, fish oil supplement use, female sex, older age, and alcohol consumption were positively associated with eO3I, whereas smoking, larger waist circumference, lower socioeconomic status and less education were negatively associated with eO3I. The results of this study provide the first estimate of the average O3I in the UK.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Adipose tissue inflammation in human obesity and response to chronic marine omega-3 fatty acid supplementation.

Dr Helena Fisk PhD ORCID iD[1], Rob Ayres[1], Dr Caroline Childs PhD[1], Dr Ondrej Kuda PhD[2], Prof Jan Kopecky PhD[3], Dr Elie Antoun PhD[4], Professor Karen Lillycrop PhD[1], Professor Philip Calder PhD[1]
[1]University of Southampton, Southampton, United Kingdom. [2]Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. [3]Institute for Clinical and Experimental Medicine,, Prague, Czech Republic. [4]University of Oxford, Oxford, United Kingdom

Abstract

Obesity is an excess of adipose tissue (AT) and is linked with increased inflammation that enhances risk of type-2 diabetes and cardiovascular disease. The BIOCLAIMS Study assessed AT inflammation in obesity, and responses to chronic omega-3 fatty acid (FA) supplementation.

AT biopsies were collected pre- and post-12 week supplementation with 1.1g EPA + 0.8g DHA/day or corn oil. AT FA composition, lipid mediator profile, whole transcriptome expression, morphology, and immune cell infiltration were assessed by gas chromatography, coupled UPLC-mass spectrometry, RNA-Sequencing, and immuno-histochemical staining respectively.

Obesity was associated with dysregulated FA and lipid mediator profiles exhibiting higher concentrations of arachidonic acid (AA) and respective oxylipins, lower concentrations of DHA oxylipins, and alteration of the endocannabinoid system (ECS) ($P < 0.05$), as well as altered transcriptome expression suggestive of enhanced inflammation, immune response, tissue remodelling, and expansion. Dysregulated Wnt signalling, tissue expansion and inflammation was concordant with tissue morphology in which obesity was associated with adipocyte hypertrophy and immune cell infiltration; however, fibrosis, which was positively correlated with HOMA 2-IR ($P < 0.05$), did not differ.

Chronic supplementation with EPA+DHA increased concentrations of AT omega-3 FAs ($P < 0.01$) and derived oxylipins, and decreased AA oxylipins, with particular effect on the ECS predominantly in normal weight individuals ($P < 0.05$). EPA+DHA modulated AT transcriptome suggesting promotion of tissue remodelling and downregulation of cell differentiation and chronic inflammatory response ($P < 0.05$).

These data suggest enhanced AT inflammation in the context of tissue expansion and remodelling associated with obesity. AT of metabolically healthy obese individuals is sensitive to dietary lipid manipulation but exhibits differences in the handling of these lipids which may link to altered transcriptome. EPA+DHA are able to modulate synthesis of EPA, DHA and AA derived oxylipins and transcriptome expression but obesity may involve resistance to these effects particularly on the ECS.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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COMBINATION OF FATTY ACIDS AND VINCRISTINE FOR THE TREATMENT OF BRAIN TUMOR

Janaína Silva ORCID iD, Alison Colquhoun Professor ORCID iD
University of São Paulo, São Paulo, Brazil

Abstract

Background. Current therapeutic strategies for glioblastoma (GBM) are ineffective. This happens mainly due to the increased activity of multidrug resistance proteins (MRPs). Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Gamma-linonenic acid (GLA) can modulate these mechanisms. Aims. to investigated the effects of polyunsaturated fatty acids (PUFA's) on cellular responses to Vincristine in U87MG cells and VCR-resistant (VCR-R) cells derived from U87MG, verifying the effects upon tumor growth, incorporation, and chemotherapeutic action of Vincristine (VCR). Methods. Drug resistant U87MG-derived cell lines were produced with 0.4 nM VCR. Cell growth assays were performed using DHA, GLA and EPA in U87MG and VCR-R cells. Incorporation, MRP activity and gene expression were evaluated in cells after PUFAs treatments, through GCMS, Rhodamine 123 efflux assay and RT-qPCR, respectively. The Nile Red staining showed LD accumulation after EPA, DHA and GLA treatments. For statistical analysis ANOVA with Tukey post-test or t-test were used to evaluate the statistical relevance. Results. In U87MG cells, VCR + GLA [100 µM] decreased the cell number. In VCR-R cells, VCR + EPA [100 µM] decreased cell growth. VCR-R cells seem to have a decreased MRPs efflux activity after treatments compared to U87MG cells. ABCB1, ABCC1, ABCC3 and ABCC4 genes had a decreased expression in U87MG cells with VCR + PUFAs, mainly with EPA. DHA modifies ABCB1 expression in VCR-R in concomitant treatment. Conclusion. Co-treatment with omega-3 or omega-6 and chemotherapies was more effective in reducing cell number and MRPs gene expression in non-resistant and resistant GBM cells. Further analysis must be done to understand the association between the resistance phenotype and response to these treatments. There is no conflict of interest.

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Combine effects of Ketogenic Diet and GDNF injection on the Schwann cells in a mouse model of Krabbe's disease.

Dr Catherine Mounier PhD ORCID iD, Mr Gaetan Ravaut PhD student, Dr Gregoire Bonnamour PhD, Dr Rodolphe Soret PhD, Dr Nicolas Pilon PhD
universite du Quebec a Montreal, Montreal, Canada

Abstract

Background: Krabbe disease mainly affects children and is characterized by the loss of function of the galactosylceramidase enzyme (GALC). This dysfunctional lysosomal protein cannot recycle myelin inducing accumulation of cytotoxic psychosine. In Twitcher mice (Twi), a model of Krabbe disease, this accumulation occurs in Schwann cells inducing cell death and neuroinflammation. It was recently observed that ketogenic diet (KDiet) increases the lifespan of children and rescues some of their physiological functions.

Methods: Twi mice have been exposed to KDiet or control diet 20 days post-weaning (P20) with or without Glial cell line-Derived Neurotrophic Factor (GDNF) injection, known to induce Schwann cells differentiation. Proteomic analyses were performed at P42 in sciatic nerve and brain tissue. Neuroinflammation and the presence of functional Schwann cells were evaluated in sciatic nerves at P25, P35 and P42.

Results: Compared to control diet, Twi mice increased lifespan when fed with KDiet. The brain proteomic analysis revealed that KDiet-fed Twi mice show an attenuation of the neuroinflammatory pathways. This was confirmed by our analyses showing that Twi mice present an inflammatory profile (evaluation of IL-6 and TNF-a) which is improved when mice were fed with KDiet. In sciatic nerve, the proteomic analysis revealed that in Twi mice, ApoD recruitment is strongly increased compared to WT mice. ApoD is an important player in neuroinflammation resorption. In sciatic nerves of Twi mice, we were almost unable to detect functional Schwann cells (as seen by the expression of SOX10). SOX10 expression is partially rescued when mice were fed with KDiet (25% of recovery at P35 and 50% of recovery at P42). Interestingly, this effect is potentialized by GDNF injection.

Conclusions: Our study shows that KDiet, increases Twi mice lifespan. This is associated with partial restauration of neuronal integrity and neuroinflammation. These effects are potentialized by GDNF injection.

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Antioxidant effect of edible oils on hypertension: Systematic Review.

Sandra Soto MSc, PhD (c)[1], Ailynne Sepulveda MSc[1], Christin Kreindl MSc, PhD (c)[2], Miltha Hidalgo MSc, PhD (c)[1], Omar Porras PhD[1]
[1]University of Chile, Santiago, Chile. [2]Universidad Autonoma de Chile, Santiago, Chile

Abstract

Introduction: Cardiovascular diseases (CVD) are a complex group of heart and blood vessels alterations, hypertension is one of the most prevalent, affecting 27.6% of Chilean population. Oxidative stress is one of the key elements in the pathogenesis of CVD and diet is one of the factors that can contribute to diminish this condition through compounds like phytochemicals, in this sense the consumption of edible oils rich in phytochemicals may have an impact on oxidative stress and clinical outcomes.

Objective: To compare the antioxidant and clinical effects of three edible oils with different composition (lipidids and phytochemical) on hypertension patients.

Methods: Randomized control trials-systematic review of adults with hypertension and oral consumption of extra virgin olive oil (EVOO), sunflower oil, or a mix of n3-PUFA. The search was conducted by two independent authors using MESH words (e.g., sunflower oil, olive oil, oxidative stress, hypertension) in different databases (e.g., PubMed, Medline, Scielo).

Results: 788 reports were identified, only 8 met the inclusion criteria and were included. 1 article reported effects of sunflower oil, 4 of EVOO and 3 of n3-PUFA. The articles included indicated that the oral consumption of 30-35 g/d of sunflower oil decreased lipoperoxidation and blood pressure, however these subjects had been taken nifedipine. The consumption of EVOO as a supplementation of Mediterranean diet show a decreased in lipoperoxidation, as well as the oral consumption of 50-60 ml/day, also with a decreased in blood pressure. The consumption of 1-4 g/day of DHA and EPA on the other hand decreased lipoperoxidation without clinical impact.

Conclusion: The consumption of edible oils can have an impact on oxidative stress and clinical outcomes in humans and apparently EVOO rich in phytochemicals is the one that has the most important effect, however more studies are required to elucidate the precise effect.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Extra virgin olive oil INFOGEST digesta on cell viability with propidium iodide.

Sandra Soto MSc, PhD (c)[1], Ailynne Sepulveda MSc[1], Christine Kreindl MSc, PhD (c)[2], Miltha Hidalgo MSc, PhD (c)[1], Igor Pacheco PhD[1], Omar Porras PhD[1]
[1]University of Chile, Santiago, Chile. [2]Universidad Autonoma de Chile, Santiago, Chile

Abstract

Introduction: Extra virgin olive oil (EVOO), is a highly consume food in Mediterranean countries and has shown to improve human health, however the effect on the gastrointestinal tract has been less study. INFOGEST protocol is a static in vitro digestion method, that can help us understand the physiological response to specific food or food components in Caco-2 cells as an absorption model. However, the evaluation of cell survival to the digesta of INFOGEST, has shown to produce technical difficulties due to the aggressiveness of bile salts and the excess of fatty acids.

Objective: To evaluate the effect of EVOO digesta on caco-2 cells viability using a propidium iodide (PI).

Methods: Chilean Arbequina-EVOO was summited to the INFOGEST protocol, the digesta was frozen at -80°C until use. Caco-2 cells p20-25 cultured in Minimun Essential Medium supplemented with 10% fetal bovine serum, were exposed to filter and un-filter 10%, 20% and 50% v/v of digesta in medium for 15, 30, 60, 90 and 120 minutes. Viability was evaluated using PI, a nuclei acid stain, at a 5 ug/ml concentration, and measure at 533/617 nm, which negative correlated witch cell survival.

Results: EVOO digesta affected Caco-2 cell viability. 0,22-um filter was able to significantly improve cell viability, which diminish with time exposure and with the increased concentration of the filter digesta, reaching at 2 hours of exposure a significant increase in the signal with 50% v/v digesta, with no significant changes with 10 and 20% v/v digesta, compared to control with medium.

Conclusion: EVOO digesta affects cell viability, 10% and 20% v/v have low impact on cell death. At the same time, PI is a save and fast method to evaluate cell viability in study designs where cell attachment is altered by treatment exposure hindering analysis.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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PLA2G4A mutation impairs oxylipin formation during blood coagulation

Nadja Kampschulte[1], Miriam Schmidts[2], Karsten Häffner[3], Nils Helge Schebb[1]

[1]Chair of Food Chemistry, School of Mathematics and Natural Sciences, University of Wuppertal, Wuppertal, Germany. [2]Pediatric Genetics Division, Center for Pediatrics and Adolescent Medicine, University Hospital Freiburg, Freiburg University Faculty of Medicine, Freiburg, Germany. [3]Department of Internal Medicine IV, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Abstract

The cytosolic phospholipase A2 (group IVA) is a key enzyme for the release of fatty acids from *sn*-2 position of phospholipids upon stimuli that occur e.g. during inflammation or blood coagulation. The released polyunsaturated fatty acids (PUFA) are substrates of the enzymes of the arachidonic acid cascade [cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450 monooxygenases]. These enzymes catalyze the formation of prostaglandins, leukotrienes and other oxylipins which mediate the cellular response to the initial stimulus.

We describe the oxylipin levels in plasma and their changes during blood coagulation of a large consanguineous family in which both parents carry a c494dupT, p-Arg166Lysfs*13 mutation in the *PLA2G4A Gene* on one allele. The mutation leads to a premature sequence termination in the phospholipid binding domain. Three of seven children carry the mutation homozygously, two are heterozygous carriers and two do not bear the mutation. The homozygous children show clinical symptoms similar to a prostaglandin deficiency or resemble chronic NSAID nephropathy, such as chronic renal failure and decreased platelet aggregation.

The non-esterified and total oxylipin concentrations in plasma of healthy, heterozygous or homozygous deficient individuals were similar suggesting that enzymes other than PLA2G4A can also release PUFA for the enzymes of the arachidonic acid cascade yielding circulating oxylipins in blood under basal conditions. In contrast, changes in the oxylipin pattern during blood coagulation differ remarkably: While healthy, and with comparable extent also heterozygous-deficient subjects, show a massive increase of COX- and 12-LOX-derived oxylipins such as TxB2, 12-HHT and 12-HETE, the oxylipin concentrations in serum of the subjects with the homozygous defect remain almost unchanged upon the coagulation stimuli.

Taken together, with our targeted metabolomics methodology we could demonstrate that *PLA2G4A* deficiency divergently affects the downstream oxylipin formation, which may contribute to a better understanding of the pathophysiology and therapeutic approaches of this rare disease.

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Addition of dairy lipids and probiotic in infant formulas modulates gut microbiota and intestinal physiology with long-term consequences: a preclinical study in a minipig model

Marion Lemaire[1], Mahendra Mariadassou[2], Laurence Le Normand[1], Gwénaëlle Randuineau[1], Véronique Romé[1], Amandine Ligneul[3], Mathilde Guerville[3], Gaëlle Boudry[1], Sophie Blat[1], Isabelle Le Huërou-Luron[1]
[1]NUMECAN, INRAE INSERM Univ Rennes, Saint-Gilles, France. [2]MAIAGE, INRAE, Jouy-en-Josas, France. [3]Lactalis R&D, Retiers, France

Abstract

Whereas breast milk is the gold standard, most infants are at least partly formula-fed.The aim of the present study was to investigate the short and long-term effects of the addition of dairy lipids (DL), as an alternative to plant lipid in infant formulas, on gut microbiota and on intestinal immune and barrier functions, and of a probiotic, Lactobacillus fermentum (Lf), on the same parameters.

Piglets received from postnatal day (PND) 2 to 28 a balanced formula containing either only plant lipids (PL), a half-half mixture of PL and DL (DL), or a half-half mixture of PL and DL supplemented with Lf (DL+Lf). Pigs were subsequently fed a standard diet for 1 month and then challenged with a high-fat high-sucrose diet for 3 months until PDN140. Dietary-induced changes in gut microbiota composition were observed at both PDN28 and PDN140, mainly within Firmicutes (Lachnospiraceae, Ruminococcaceae and Lactobacillaceae families) and Bacteroidetes (Prevotellaceae, Bacteroidaceae and Bacteroidales S24-7 group families) phyla. At PND28, twenty fecal metabolites (such as valerate, butyrate, amino acids, glucose) discriminated the three groups. DL and DL+Lf reinforced tight junction protein expressions in colon, with moderate changes in epithelial barrier permeability. At PND140, DL+Lf decreased the inflammation risk through decreased ileal pro-inflammatory cytokine secretion and increased ileal expression of genes encoding tight junction proteins. A slight but persisting and coherent effect of probiotic Lf on gut microbiota composition was observed between PND28 and PND140, even after discontinuation of its intake. Correlations between gut microbiota composition and intestinal physiology confirmed the involvement of gut microbiota in such processes.

In conclusion, the addition of DL in infant formula changed the microbial signature and gut physiology in infants. The addition of Lf enhanced the beneficial effects observed in the long term. The addition of DL ± Lf appears to be safe.

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Human Plasma and Erythrocyte Lipidomic Profiles After Controlled Intakes of 0.25, 0.5, and 1 g/d of EPA+DHA from Fish Oil

Ken Stark ORCID iD[1], Juan Aristizabal-Henao[2], Ashley Patterson[3], Michael Kiebish[2]
[1]University of Waterloo, Waterloo, ON, Canada. [2]BPGbio, Inc., Framingham, MA, USA. [3]Reckitt|Mead Johnson, Evansville, IN, USA

Abstract

Lipidomic profiling can provide novel insights into the metabolic pathways impacted during dietary interventions. The response of specific fatty acyl lipids species in plasma and erythrocytes to specific doses of fish oil is not well documented. Blood samples were collected from participants at baseline and after consuming fish oil to achieve intakes of 0.25, 0.5 and 1.0g/d of EPA + DHA over four-week successive stepwise periods. Plasma and erythrocyte lipidomic profiles were determined by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (quadrupole Orbitrap) in positive and negative mode. Lipids were identified using LipidMatch Flow (Innovative Omics) and semi-quantitated using the EquiSPLASH Lipidomix internal standard (Avanti Polar Lipids). In plasma after 1.0g/d intakes, there were 122 lipids containing DHA and 82 lipids containing EPA with CE 20:5 (309 ± 154 nmol/mL), CE 22:6 (254 ± 95) and PC 16:0_22:6 (41 ± 11) being the most abundant. In erythrocytes after 1.0g/d intakes, there were 70 DHA-containing and 48 EPA-containing lipids with PS 18:0_22:6 (48.5 ± 7.0 nmol/mL), PE P-18:0/22:6 (17.5 ± 2.0) and PE 16:0_22:6 (17.1 ± 2.3) being the most abundant. Statistical analysis by one-way ANOVA identified 62 lipids in plasma (34 glycerolipids and 28 glycerophospholipids) and 162 lipids in erythrocytes (158 glycerophospholipids with 86 being oxygenated) that were different across the interventions. In plasma, fish oil intake resulted mainly in increases in the number and amount of EPA and/or DHA-containing lipids. In erythrocytes, increases in EPA and/or DHA-containing lipids coincided with decreases in oxygenated glycerophospholipids. Based on the lipid whisker model, oxidized fatty acyls move to the aqueous exterior of the cell. The present results suggest EPA and DHA intake “trims membrane whiskers”. Additional studies are needed, but lipidomic profiling is a useful approach for enhancing our understanding of the dietary impact of EPA + DHA intake.

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OMEGA-3 POLYUNSATURATED FATTY ACIDS ALTER CAVEOLIN EXPRESSION AND MIGRATORY CAPACITY OF GLIOBLASTOMA CELLS IN VITRO

Dr Alison Colquhoun DPhil ORCID iD, Gustavo Lopes
University of São Paulo, São Paulo, Brazil

Abstract

Background. The prognosis for patients with glioblastoma is poor and current treatment options result in low survival rates. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can modulate several aspects of glioblastoma cell biology. Caveolae are membrane invaginations rich in cholesterol and glycosphingolipids, with important protein components including caveolins (CAVs) and cavins. CAV-1 is overexpressed in glioblastoma and is correlated with migratory processes and poor prognosis. Aims. To investigate the effects of EPA and DHA on caveolae biology and cell migration in human glioblastoma cells. Methods. U87MG and T98G human glioblastoma cells were grown in the presence of 100µM EPA , DHA or fatty acid-free albumin (ALB) vehicle for 24-72 hours. Oil red staining identified lipid droplets; qPCR and Western blotting measured mRNA and protein expression, respectively, of CAV-1; wound healing assay measured monolayer cell migration; Boyden chamber migration measured transmigration through 8µm pores. Results. Incubation of the cells with EPA or DHA resulted in significant increases in lipid droplet accumulation in comparison with ALB. qPCR showed significant decreases in CAV-1 mRNA expression in U87MG and T98G cells. In contrast, EPA and DHA did not alter CAV-1 protein expression in U87MG cells, but DHA significantly increased CAV-1 protein expression in T98G cells. EPA and DHA did not alter monolayer cell migration in U87MG cells, however, T98G cells had significantly increased migration rates. In contrast, neither fatty acid altered transmigration rates in the two cell lines. Conclusion. Exposure to EPA or DHA resulted in significant lipid droplet accumulation which was accompanied by significant changes in CAV-1 expression. These changes were reflected in an altered migratory capacity of the T98G cells. Further studies are underway to identify the mechanisms by which PUFAs can alter CAV-1 expression and whether these changes directly affect cell migration.

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Invertebrates as primary producers of omega-3s in aquatic ecosystems

Dr Oscar Monroig ORCID iD[1], Dr Francisco Hontoria ORCID iD[1], Dr Naoki Kabeya ORCID iD[2], Prof Juan C. Navarro ORCID iD[1]
[1]Agencia Estatal Consejo Superior de Investigaciones Científicas, Ribera de Cabanes, Spain. [2]Tokyo University of Marine Science and Technology, Tokyo, Japan

Abstract

The physiologically essential “omega-3” (or n-3) long-chain (≥C20) polyunsaturated fatty acids (LC-PUFA) have been long believed to be almost exclusively produced in the ocean by microbes, being subsequently transferred through the food web to upper trophic organisms like fish. While being primary sources of n-3 LC-PUFA for humans, fish themselves can only make LC-PUFA via conversions from C18 polyunsaturated fatty acid (PUFA) precursors acquired through the diet. Surprisingly, the capability of marine invertebrates for n-3 LC-PUFA biosynthesis has remained largely unexplored, despite their key position in marine food webs between microorganisms and fish. High throughput sequencing databases have become available from multiple invertebrate species thus providing a unique opportunity to clarify the occurrence of genes involved in n-3 LC-PUFA biosynthesis in these animals. Examination of such genomic resources has unequivocally established that numerous aquatic invertebrates have the enzyme machinery necessary for the de novo biosynthesis of C18 PUFA and, from them, LC-PUFA. A major breakthrough in this area has been the identification in invertebrates of methyl-end desaturases, enzymes that mediate, among other reactions, the biosynthesis of PUFA from monounsaturated fatty acids, and believed to be mostly absent in animals. Moreover, other enzymes with pivotal roles in LC-PUFA biosynthesis, including front-end desaturases and elongation of very long-chain fatty acids proteins, have been molecularly and functionally characterized in several invertebrates. This paper aims to provide an overview of the complement and functions of these gene/protein families in aquatic invertebrates to illustrate their potential contribution to the n-3 LC-PUFA production in the ocean.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Validation of a novel in vivo oxidative status (IVOS) biosensor to quantify ischemia by utilizing isoprostanes as biomarker in an equine model – a pilot study

Associate Professor Erik Noschka MedVet, MS, PhD ORCID iD[1,2,3], Mrs Abby Morgan BSc(Hons)[1], Associate Professor Kiro Petrovski DVM, MVSc, PGDipVCSc, PhD ORCID iD[1], Professor Thierry Durand PhD ORCID iD[4], Dr Tomas Rozek PhD[5], Dr Emilie Mas PharmD, PhD ORCID iD[5,6], Dr Roman Kostecki BSc(Hons), PhD ORCID iD[7,2]

[1]University of Adelaide, School of Animal and Veterinary Sciences, Adelaide, Australia. [2]University of Adelaide, Centre for Nanoscale BioPhotonics, Adelaide, Australia. [3]South Australian Health and Medical Research Institute, Adelaide, Australia. [4]Institut des Biomolécules Max Mousseron (IBMM), Pôle Recherche Chimie Balard, UMR 5247, University of Montpellier, Montpellier, France. [5]SA Pathology - Genetics and Molecular Pathology, Women's and Children's Hospital Adelaide, Adelaide, Australia. [6]Adelaide Medical School, The University of Adelaide Faculty of Health and Medical Sciences, Adelaide, Australia. [7]School of Physical Sciences, University of Adelaide, Adelaide, Australia

Abstract

In human and animal populations, many conditions and causes of death involve ischaemic events, including stroke and myocardial infarction. Accurate detection and quantification of ischaemia is imperative for early diagnosis, treatment, and prognosis of these disorders. Currently used detection methods are time consuming, expensive and may lack accuracy. This study utilised an equine limb tourniquet model to assess the viability of a newly developed in vivo oxidative status biosensor to instantly measure ischaemia by comparing the IVOS biosensor correlation to isoprostane biomarkers associated with ischaemic events.

Six clinically healthy horses' forelimb cephalic veins were catheterised to collect blood samples, with one forelimb acting as internal control and the other as treatment limb. IVOS biosensors was placed subcutaneously to simultaneously measure oxidative status in both limbs. A pneumatic tourniquet was inflated on a randomly selected forelimb proximal to the catheter and implanted IVOS biosensor for 30 minutes to induce ischaemia. Serial blood samples for isoprostane quantification were collected from both limbs during and after tourniquet release. Samples were centrifuged, plasma was aliquoted, stored at -800C for isoprostane quantification using liquid chromatography-tandem mass spectrometry and ex vivo oxidative status of plasma also using the IVOS biosensor.

IVOS biosensor and isoprostane measurements showed correlation and increased in a time-dependent manner. Considerable movement in tourniqueted limbs of some horses coincided with a temporary drop in both quantifications of the tourniqueted limbs.

This study provides preliminary evidence that instant dynamic IVOS measurements can be successfully conducted in animals to quantify ischaemia utilising the IVOS biosensor.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Isoprostanes as a diagnostic tool for subclinical mastitis and potential predictor of mastitis in dairy cows

Associate Professor Erik Noschka MedVet, MS, PhD ORCID iD[1], Dr Roman Kostecki BSc(Hons), PhD ORCID iD[2,3], Mr Thomas Arthur Rowe BSc[1], Mr James Barrie Martin BSc[1], Professor Thierry Durand PhD ORCID iD[4], Dr Tomas Rozek PhD[5], Dr Emilie Mas PharmD, PhD ORCID iD[5,6], Associate Professor Kiro Petrovski DVM, MVSc, PGDipVCSc, PhD ORCID iD[1]

[1]School of Animal and Veterinary Sciences, University of Adelaide, Adelaide, Australia. [2]School of Physical Sciences, University of Adelaide, Adelaide, Australia. [3]University of Adelaide, Centre for Nanoscale BioPhotonics, Adelaide, Australia. [4]Institut des Biomolécules Max Mousseron (IBMM), Pôle Recherche Chimie Balard, UMR 5247, University of Montpellier, Montpellier, France. [5]SA Pathology - Genetics and Molecular Pathology, Women's and Children's Hospital Adelaide, Adelaide, Australia. [6]Adelaide Medical School, The University of Adelaide, Faculty of Health and Medical Sciences, Adelaide, Australia

Abstract

Sub-clinical mastitis (SCM) is one of the largest drivers of economic losses within the dairy industry. It is an inflammatory response within the mammary gland, commonly due to physical damage or bacterial invasion. This leads to increased somatic cell counts (SCC) within milk, which is associated with reduced production and quality of milk. SCM is a challenge for farmers as they are unlikely to notice the condition to intervene prior to the onset of clinical signs. The current gold standard diagnostic test for SCM is a somatic cell count (SCC), however it has its limitations as the SCC doesn't increase appreciably until after inflammation has already occurred. This study measured isoprostanes concentrations in frozen milk samples from dairy cows with known SCC. Milk samples (104) were stored at -80^{o}C for isoprostane quantification using liquid chromatography-tandem mass spectrometry. Output files were analysed for relative isoprostane correlation with SCC and quantitative differences. Differences in detection of SCM were assessed by linear regression. A significant correlation was observed between several isoprostanes and the SCC. Cows with high SCC had average values of all indicative isoprostanes higher than cows with a low SCC. Therefore, isoprostanes may be used as an indicator of inflammatory processes within the mammary gland. Future studies with repeated sampling are required to establish if isoprostanes detect subclinical or even clinical mastitis prior to the rise in SCC. Isoprostane profiling in women experiencing mastitis or undergoing cessation of breast feeding is a prospective translational area of interest.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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The interactive impact of sex and APOE genotype on post-mortem brain fatty acids profile in Alzheimer's Disease, Results from the UK BrainBank.

Dr Rasha Saleh MD, Prof Anne Marie Minihane PhD
Norwich Medical School, University of East Anglia, Norwich, United Kingdom

Abstract

Background: Two-thirds of Alzheimer’s Disease (AD) patients are women, with the risk becoming higher if carrying the APOE4 genotype. Omega-3 fatty acids status is associated with a reduced risk of AD. Little is known about the interactive impact of sex and APOE genotype on brain fatty acids status. In this study, fatty acids were measured in post-mortem brain tissue of AD patients and stratified according to sex and APOE genotype.

Method: Fatty acids were extracted from the hippocampus and frontal cortex of AD cases (n=25, 11 are women) and controls (n=25, 12 are women) using Folch method (from total lipids). Fatty acids were analysed using gas chromatography and flame ionization detection (GC-FID). Samples were requested and granted by the UK Brain Bank. Adjustment for age and post-mortem delay was done.

Result: Arachidonic acid (ARA) and n-6DPA were higher in APOE4 women with AD compared to control (P-Disease*sex*APOE= 0.01 and <0.001 respectively). These results were more evident in the hippocampus than in the frontal cortex. n-3DPA/ARA ratio (an indicator of inflammatory status) was significantly higher in APOE4 women control compared to AD in both the hippocampus and frontal cortex (P-disease*sex*APOE = 0.028 and <0.001 respectively). Similar trends were observed for EPA/ARA ratio. There was no impact of sex or APOE on BRAAK stage.

Conclusion: APOE4 women with AD show a pro-inflammatory brain fatty acid profile compared to controls, with increased n-6 PUFAs (ARA and DPA) and reduced n-3DPA/ARA ratios. Further extraction and analysis of fatty acids-derived oxylipins and SPMs will be carried out.

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Physicochemical stability and in vitro digestibility of vegan ketogenic oil-in-water emulsions stabilized with commercial protein isolates

Melissa Mosselman, Julia Keppler, Silvie Timmers, Jaap Keijer, Marie Hennebelle
Wageningen University & Research, Wageningen, Netherlands

Abstract

Shifting your body to an energy state of mild ketosis has been linked to several health benefits such as brain health, and improved mitochondrial function. Ketosis can be induced by the supplementation of e.g. tricaprylin in the form of oil-in-water emulsions. However, supplements that could be included in a plant-based diet are so far scarce. Additionally, supplementing tricaprylin together with other ingredients such as omega-3 polyunsaturated fatty acids should be considered, as they might have a synergistic effect on cellular health by lowering inflammation.

In this study, we aim to develop a novel plant-based ketogenic supplement in the form of an oil-in-water emulsion using commercial plant protein isolates as emulsifier. During the development of the supplement, the following factors are considered: 1/ Physical and chemical stability of the supplement to ensure sufficient shelf-life, and 2/ Digestibility of the added lipids to determine the bioavailability of the molecules of interest. The supplement formulations contain 16 w/w% tricaprylin oil, 4 w/w% microalgae oil, and 2 w/w% commercial pea- and/or potato protein isolate. The supplements are prepared at different pH (3-7) and heated to prevent microbiological spoilage. Particle size analysis using static light scattering and ^{1}H NMR will be used to determine the physical and chemical stability, respectively. Gastric and intestinal in vitro digestion is performed using a static model as described by INFOGEST. It is hypothesized that not only the commercial protein source, but also the pH of the emulsion and heat treatment will influence physical, chemical stability and digestibility. This study gives us more insight in the applicability of commercial plant protein isolates as emulsifier for the development of novel plant-based food supplements.

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Omega-3 PUFAs and polyphenols interaction on brain function: are we barking up the right tree?

Dr David Vauzour PhD ORCID iD
University of East Anglia, Norwich Medical School, Norwich, United Kingdom

Abstract

Much of the scientific interest and efforts on the effects of nutrition on brain function have focused on increasing understanding of the role of individual food bioactives, such as long-chain omega-3 polyunsaturated fatty acids (PUFA), B vitamins, and polyphenols. Nonetheless, interventional studies, in which individuals are supplemented with one of these bioactives, often fail to show a clear positive effect of the component on brain function. Although there may be several reasons for this, such as differences in statistical power and timescales, one important factor, considered here, is that synergistic and antagonistic interactions can occur between nutrients and food, making the 'whole' very different from the sum of its parts. For example, the clinical evidence for the beneficial effects of DHA supplementation on cognitive decline is mixed, suggesting that long-chain omega-3 PUFA may need to be given in combination with additional nutrients such as B-vitamins to synergistically produce an effect at the cellular and systems level. This presentation will explore the interaction between food bioactives and their impact on brain function with a particular focus given to the interaction between polyphenols/flavonoids and omega-3 PUFAs.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

not published

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Short-chain fatty acids (SCFA) in infant plasma – relation to levels in breast milk and maternal plasma and subsequent atopic disease and sensitization in the infants

Mrs Malin Barman Associate Professor ORCID iD[1], Miss Monica Gio-Batta M.Sc.[2], Miss Léna Andrieux M.Sc.[3], Mrs Mia Stråvik M.Sc.[1], Mr Robert Saalman MD, Professor[2], Mr Rikard Fristedt Ph.D.[1], Mrs Hardis Rabe Ph.D.[2], Mrs Anna Sandin MD, Associate Professor[4], Mrs Agnes Wold MD, Professor[2], Mrs Ann-Sofie Sandberg Professor[1]

[1]Chalmers University of Technology, Gothenburg, Sweden. [2]University of Gothenburg, Gothenburg, Sweden. [3]Université de Lyon, Lyon, France. [4]Umeå University, Umeå, Sweden

Abstract

Short-chain fatty acids (SCFAs) modulate the immune system and have been associated with allergy development. Most analyses have been focused on SCFA in feces, while their levels in blood and associations to allergy have not been studied.

Here we measured SCFAs in infants' and mothers' plasma and mothers' breast milk, all collected four months postpartum (N=148), using Ultra Performance Liquid-Chromatography Mass-Spectrometry. Maternal diet was assessed by semi-quantitative food frequency questionnaires. Food allergy, atopic eczema, and asthma were diagnosed by a pediatrician, and sensitization to a panel of common allergens was measured with a skin prick test at 12 months of age.

The total SCFA levels were highest in infant plasma, but butyrate, isobutyrate, and caproate were strongly enriched in breast milk. SCFAs in the infant's plasma correlated strongly (rho>0.5, propionate, valerate, succinate, caproate) or moderately (rho=0.3-0.45, formate, isovalerate, isobutyrate) with SCFAs in maternal plasma but not with SCFAs in breast milk. Lower levels of acetate and succinate at four months characterized infants who were diagnosed with food allergy (N=14) or atopic eczema (N=19) at 12 months, and infants developing atopic eczema also had lower levels of isobutyrate than non-allergic non-sensitized infants (N=109). Infants who were sensitized (N=11) had lower levels of formate, isobutyrate, succinate, valerate, caproate, and total SCFAs at four months than infants who were non-allergic and non-sensitized (N=109).

Our findings show that SCFA levels in the plasma of mother and infant are correlated, suggesting hereditary influence. Butyrate and caproate are enriched in breast milk, either due to local production in the milk gland or through selective transfer to serving the nutritious needs of the infant. Low levels of SCFAs in plasma may contribute to the development of sensitization and allergy during infancy, although causality cannot be proven.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Docosahexaenoic acid supplementation in mothers of preterm infants is associated with a reduced pro-inflammatory lipid mediators profile in breast milk

Hélène Fougère ORCID iD[1], Karine Greffard[1], Mireille Guillot[1], Iwona Rudkowska[1,2], Etienne Pronovost[1], David Simonyan[1], Isabelle Marc[1], Jean-François Bilodeau[1,2]

[1]CHU de Québec-Université Laval, Québec, Canada. [2]Faculté de Médecine, Université Laval, Québec, Canada

Abstract

Oxylipins are known to be involved in the inflammation process. The objective of the study was to characterize the breast milk oxylipins profile following a docosahexaenoic acid (DHA)-rich algae oil supplementation of mothers of preterm infants. Forty mothers who delivered before 29 weeks of pregnancy from the MOBYDIck cohort were randomly selected and stratified according to the supplementation received (supplemented in DHA (S-DHA) or placebo (PL)) and the DHA content quartiles (high or low). Breast milk samples, collected 14 days after birth, were analyzed in 4 groups as follows: PL-Low, PL-High, S-DHA-Low and S-DHA-High, by LC-MS/MS to determine the oxylipins content, expressed in ng/mL of milk. Ten oxylipins derived from DHA were higher in the S-DHA-High group compared to the 3 other groups ($p<0.001$). The 18-HEPE, was higher in the S-DHA-High group (0.11 ± 0.01) compared to the 3 other groups ($P=0.0001$). The prostaglandin PGF2α was lower in the S-DHA-High group (0.21 ± 0.45, $P=0.03$) compared to the PL-Low group (1.87 ± 0.44). Similarly, PGE2 was lower in the S-DHA-High group (0.33 ± 0.26, $P = 0.04$) compared to the PL-Low group (1.28 ± 0.25). In sum, the DHA supplementation favored an anti-inflammatory oxylipins profile characterized by higher precursors of resolvins and lower levels of pro-inflammatory prostaglandins than the placebo group. This profile could potentially affect neonatal outcomes and would require further investigation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Enriching the tissues with EPA and DHA in the omnivorous consumer: Several solutions are additive and even synergistic!

Dr Mathieu Guillevic PhD ORCID iD[1], Nathalie Kerhoas[2], Dr Pierre Weill PhD[2]
[1]Valorex, Combourtillé, France. [2]Association Bleu-Blanc-Coeur, Rennes, France

Abstract

Studies show a negative and dose-dependent relationship between Ω3 (EPA+DHA) tissue content and cardiovascular events. These contents are evaluated thanks to the Omega 3 Index (O3I) . In Framingham study, a low O3I is linked to a decrease in life expectancy identical to regular tobacco consumption. Our study measures O3I of a population aware about Ω3 intake in its feed.

The OmegaQuant self-test was used to determine O3I and consists of a lipid analysis of a drop of fasting blood. 43 of these users shared their Ω3 consumption: Products from Bleu-Blanc-Coeur (BBC) land animals, Fish, Oil and seeds, Food supplements.

The average O3I was 7.2 (3.9 - 10.8).

All volunteers consumed BBC animal products at different levels. In addition, 50% consumed Ω3 plant, 20% Ω3 capsules. Average fish consumption was 1.3/wk. Coupled with FAs, consumption data characterized 3 groups: (i) High input Ω3 plant & Capsules for high EPA DHA, Ω6/Ω3, ARA/EPA, C16:1/C16:0 low; (ii) Low input Ω3 plants & Capsules for ARA, ARA/EPA high, ALA EPA LA low; (iii) Low input Ω3 animals & plants for MUFA, C16:1/C16:0, Ω6/Ω3 high, EPA, DPAn3, DHA ARA low.

The additive consumption of different Ω3 sources; precursors (Oils, Seeds), long chains (land animals, fish); provides interesting O3I values but remain lower than Asian values (high fish consumption, overfishing). Land-based sources (BBC animals, plant sources) are therefore important.

While in Framingham cohort, top quintile is 6.8; our study shows that it is possible to reach it without drastically changing consumption habits and altering marine resource. This first study is to be continued on the general French population and to apprehend the possibilities of improvement of the O3I.

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Milk fat globule membrane modulates inflammatory pathways in human monocytes: a crossover human trial

Lei Deng PhD[1], Charlotte Michielsen PhD[1], Frank Vrieling MSc. ORCID iD[1], Guido Hooiveld PhD[1], Rinke Stienstra PhD ORCID iD[1], Anouk Feitsma PhD ORCID iD[2], Sander Kersten Prof ORCID iD[1], Lydia Afman PhD[1]
[1]Wageningen University, Wageningen, Netherlands. [2]FrieslandCampina, Amersfoort, Netherlands

Abstract

Intake of high-fat foods leads to a postprandial elevation in plasma triglycerides and inflammatory markers, which may be modulated by the type of fat ingested. Dairy products are commonly consumed but not much is known about the impact of milk fat and the milk fat globule membrane (MFGM) on postprandial inflammation. Here, we aimed to study the effect of milk fat with and without MFGM on post-prandial inflammation, with a focus on blood monocyte gene expression. To that end, we performed a randomized, double-blind cross-over trial in 37 middle-aged healthy male and female volunteers. The participants consumed a meal shake containing either a vegetable fat blend (VEGE), anhydrous milk fat (AMF), or cream (CREAM). Blood monocytes were collected at 0 hours and 6 hours postprandially and used for bulk RNA-sequencing analysis and ex vivo incubation with LPS.

Consumption of all three shakes led to a significant postprandial decrease in the percentage of classic monocytes and a significant increase in intermediate monocytes and non-classic monocytes. However, no significant differences were observed between the postprandial effects of the three interventions on monocyte subsets. Using a threshold of $P<0.01$, 787 genes were differentially regulated postprandially between the three shakes. 89 genes were differentially regulated postprandially between AMF and VEGE, while 373 genes were differentially regulated between AMF and CREAM and 667 genes between VEGE and CREAM, indicating that the effect of CREAM on monocyte gene expression was very distinct from AMF and VEGE. Pathway analyses showed that VEGE significantly activated inflammatory pathways, while this was less evident after AMF and oppositely after CREAM. CREAM significantly down-regulated energy metabolism-related pathways.

In conclusion, compared to acute consumption of a vegetable fat blend and anhydrous milk fat, cream significantly downregulated energy and inflammation-related pathways in blood monocytes, suggesting a potential anti-inflammatory effect of MFGM.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Effects of the long chain mono-unsaturated fatty acid, cetoleic acid, on omega-3 index and skin quality

Derek Tobin PhD ORCID iD[1], Lisa Kolden Midtbø PhD[2], Jennifer Mildenberger PhD[2], Harald Svensen PhD[1], Iren Stoknes PhD[1]
[1]Epax Norway AS, Ålesund, Norway. [2]Møreforsking, Ålesund, Norway

Abstract

Health benefits of mono-unsaturated fatty acids have been attributed to oleic acid in olive oil and usage in the Mediterranean diet. Less well known, is a body of work performed mostly by the US NIH focused on long chain mono-unsaturated fatty acids (LCMUFA) such as cetoleic acid (C22:1 n11), gadoleic acid (C20:1 n-11) and gondoic acid (C20:1 n-9). These fatty acids have been demonstrated in animal models to have beneficial effects on a range of metabolic parameters including blood cholesterol levels, insulin sensitivity and glucose tolerance. In addition, in vitro cell work with hepatocytes has demonstrated the ability of cetoleic acid to promote the conversion of a-linolenic acid to EPA and DHA.

There is an increased interest in the health benefits of these LCMUFAs which in many cases show different, but complementary, activities to EPA and DHA. North Atlantic fish, such as mackerel and herring, offer an alternative source of fish oil rich in LCMUFAs as well as traditional EPA and DHA.

Here we report the use of a marine based, cetoleic-rich oil in human intervention studies. Firstly, we report the omega-3 index after 2 months oral intervention and demonstrate similar increase as that obtained with a traditional EPA /DHA oil low in LCMUFA. Secondly, we provide data from a pilot study in skin health and demonstrate a statistically significant improvement of skin redness (a proxy for inflammation) after intervention with a cetoleic-rich oil for 3 months compared to a placebo. These results support further study of cetoleic-rich oils in inflammatory skin conditions.

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Impact of Milk fat on Postprandial Plasma Metabolomics:A Randomized Cross-over Human trial

Charlotte Michielsen PhD[1], Lei Deng PhD[1], Maaike den Os[1], Anouk Feitsma PhD ORCID iD[2], Sander Kersten Prof ORCID iD[1], Lydia Afman PhD[1]

[1]Wageningen University, Wageningen, Netherlands. [2]FrieslandCampina, Amersfoort, Netherlands

Abstract

Elevated postprandial lipids are associated with an increased risk of atherosclerotic cardiovascular disease. While numerous studies have examined the effect of different dietary fat sources on postprandial lipid levels, a more global analysis of postprandial plasma metabolites has been lacking. A common fat source in the Western-type diet is milk fat. Here, we aimed to investigate the acute effects of milk fat on postprandial metabolites, with a special interest in the specific properties of the milk fat globular membranes. To that end, a double-blind crossover human trial was performed in which 37 participants received in random order a high-fat shake composed of cream (CREAM), anhydrous milk fat (AMF), or vegetable fat (VEGE). Blood samples were drawn up to eight hours after consumption. At baseline, and 3 and 6 hours postprandially, plasma metabolites were quantified using NMR metabolomics. The changes in plasma fatty acids reflected the fatty acid composition of the shakes. AMF and CREAM consumption resulted in a faster postprandial increase and decrease in several fractions of VLDL and the inflammatory protein GlycA. Consumption of CREAM resulted in a more rapid increase in total triglycerides and branched chain amino acids at 3 hours and a faster decrease at 6 hours compared to the other shakes.

Overall, the consumption of shakes differing in fat sources led to altered postprandial dynamics of several metabolites. Specifically, consumption of milk fat and especially CREAM caused a steeper rise and more rapid return to baseline of numerous lipid metabolites and the inflammatory marker GlycA. Our study suggests a suppressive effect of milk fat and MFGM on postprandial lipemia and inflammation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

na

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Lower serum neurofilament light chain levels in infants developing retinopathy of prematurity after enteral arachidonic and docosahexaenoic acid supplementation

Ulrika Sjöbom[1,2], Annika Öhrfelt[3], Aldina Pivodic[2], Anders K. Nilsson[2], Kaj Blennow[4,5], Henrik Zetterberg[3,5,6], Ann Hellström[2], Chatarina Löfqvist[1,2]

[1]Learning and Leadership for Health Care Professionals At the Institute of Health and Care Science at Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden. [2]Department of Clinical Neuroscience At the Institution of Neuroscience and Physiology at Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden. [3]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. [4]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Göteborg, Sweden. [5]Clinical Neurochemistry Laboratory At the Sahlgrenska University Hospital, Mölndal, Sweden. [6]Department of Neurodegenerative Disease at the University College of London Institute of Neurology, London, United Kingdom

Abstract

Background: Early high serum levels of the brain injury marker neurofilament light (NfL) have been associated with the development of retinopathy of prematurity (ROP). In addition, infants born <28 weeks of gestation enrolled in a randomized controlled trial (RCT) investigating supplementation with enteral arachidonic acid (AA) and docosahexaenoic acid (DHA) found a 50% reduction of severe ROP. This secondary analysis of this RCT investigates AA+DHA supplementation's relationship with NfL concentrations.

Method: Serum collected at postnatal days 1, 3, 7, 14, and 28 were analyzed for NfL (SIMOA NF-Light Advantage kit, Simoa HD-X, Quanterix Corp) and phospholipid fatty acids by GC-MS. ROP screening was performed according to national guidelines, and ROP was defined as any stage of ROP. Mean daily levels were calculated with the area under the curve for the first month and compared with Mann-Whitney U-test. Data are presented as the median with a 95% confidence interval of the median.

Results The effect of the AA+DHA supplementation on NfL levels was investigated in 153 infants. Mean daily NfL the first month was in the AA+DHA group 44.2 [42.6-55.0] pg/mL (n=73) and standard nutrition: 64.1 [55.8-74.4] pg/mL (n=80) (p=0.065). Among infants developing any-ROP, the AA+DHA group had lower mean daily NfL (46.1 [42.6-56.1] pg/mL, n=44 vs. 73.9 [64.2-87.5] pg/mL, n=51, p=0.006). NfL levels were negatively associated with DHA during the first month (rs=-0.28 [95% CI: -0.43—-0.12], n=153, p<0.001).

Conclusion: In this study, AA+DHA supplementation was associated with lower NfL levels in infants developing ROP which might suggest improved neuronal health.

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Modification of serum fatty acids in preterm infants by parenteral lipids and enteral docosahexaenoic acid (DHA) + arachidonic acid (AA)

Ulrika Sjöbom[1,2], Mats X Andersson[3], Aldina Pivodic[1], Anna-My Lund[4], Mireille Vanpeee[5], Ingrid Ingrid Hansen-Pupp[4], David Ley[4], Dirk Wackernagel[6], Karin Sävman[7,8], Anders K Nilsson[1]

[1]Section for Ophthalmology, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [2]Learning and Leadership for Health Care Professionals at the Institute of Health and Care Science at Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. [3]Department of Biological and Environmental Sciences, University of Gothenburg, Gothenburg, Sweden. [4]Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Pediatrics, Lund, Sweden. [5]Department of Women's and Children's Health, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden. [6]Department of Neonatology, Karolinska University Hospital and Institute, Astrid Lindgrens Children's Hospital, Stockholm, Sweden. [7]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [8]Region Västra Götaland, Department of Neonatology, The Queen Silvia Children´s Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

Abstract

Background. LCPUFA deficiency is common among preterm infants. We determined longitudinal serum fatty acid profiles in preterm infants concerning lipid intake.

Methods. Secondary analysis of data from an RCT with infants born <28 weeks of gestation (n=204) receiving standard nutrition or daily enteral supplementation with AA+DHA from birth to postmenstrual age 40 weeks. Serum phospholipids fatty acids were determined by GC-MS and reported in relative (mol%) and absolute concentration (µmol/l) units.

Results. Higher parenteral lipid administration resulted in lower serum proportions of AA and DHA during the first 13 weeks of life ($p<0.001$, 25th vs 75th percentile). The absolute concentration of total phospholipid fatty acids changed rapidly in the first weeks of life, peaking at day 3, and was positively related to the intake of parenteral lipids. Overall, infants displayed common fatty acid trajectories over the study period. However, remarkable differences in fatty acid patterns were observed depending on whether levels were expressed in relative or absolute units. For example, the relative levels of many LCPUFAs, including DHA and AA, declined rapidly after birth while their absolute concentrations increased in the first week of life. For DHA, absolute levels were significantly higher compared to cord blood from day 1 until postnatal week 16 ($p<0.001$). For AA, absolute postnatal levels were lower compared to cord blood from week 4 throughout the study period ($p<0.05$).

Conclusions. Parenteral lipids aggravate the postnatal loss of LCPUFAs seen in preterm infants and serum AA available for accretion is below that *in utero*.

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Deep phenotyping and biomarkers of various dairy fat intakes in an 8-week randomized clinical trial and 2-year swine study

Dr Jean-Charles Martin PhD ORCID iD[1,2,3], Dr Claire Bal-dit-Sollier MD[4,5], Dr Jean-Marie Bard PhD[6,7], Dr Denis Lairon PhD[3,1], Dr Michel Bonneau PhD[8], Chantal Kang PhD[4], Catherine Tardivel master[2], Dr Corinne Marmonier PhD[9], Dr Pascale Leruyet PhD[10], Dr Ludovic Drouet MD[5,4]

[1]AMU, Marseille, France. [2]INRAE, Marseille, France. [3]INSERM, Marseille, France. [4]APHP, Paris, France. [5]INSERM, Paris, France. [6]Université de Nantes, Nantes, France. [7]CRNH Ouest, Nantes, France. [8]INRAE, Jouy-en-Josas, France. [9]CNIEL, Paris, France. [10]Lactalis R&D, Retiers, France

Abstract

Health effects of dairy fats (DF) are difficult to evaluate due to poor intake evaluation in epidemiology and heterogeneous compositions influencing biological responses. We set out to find biomarkers of DF intake and assess biological response to a summer DF diet, a winter DF diet without or with added calcium, and compared to a plant-fat-based diet in a randomized clinical trial (n = 173) and a 2-year study in mildly metabolically disturbed downsized pigs (n = 32). Conventional clinical measures were completed by LC/MS plasma metabolomics/lipidomics. The omics response was modeled as biological functions to facilitate interpretation. Twelve lipid species repeatably predicted DF intakes in pigs and were validated in humans (6.6% errors). DF intakes in pigs rewired metabolism to close to its initial healthy status after a one-year turnaround. In pigs, quality of DF modulated the time-related biological response (summer fat: 30 regulated functions, primarily at 6 months; winter fat: 26 regulated functions, mostly at 6–12 months; winter+calcium: 43 regulated functions, mostly at 18 months). Despite this heterogeneity, 9 functions overlapped under all 3 DF diets and in both species, related to a restricted area of amino acids, cofactors, nucleotides and xenobiotic pathways and the microbiota. In conclusion, over the long-term, DF reprograms metabolism to close to its healthy biological status in metabolically-disrupted pigs. Quality of the DF modulates its metabolic influence, although some effects were common to all DF. A resilient signature of DF consumption found in pigs was validated in humans.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Plasma and rectal mucosal oxylipin levels during aspirin and eicosapentaenoic acid treatment in the seAFOod polyp prevention trial

Dr Harriett Fuller[1], Ms Amanda Race[2], Dr Hayley Fenton[1], Ms Lauren Burke[2], Dr Amy Downing[1], Dr Elizabeth Williams[3], Professor Colin Rees[4], Professor Louise Brown[5], Professor Paul Loadman[2], Professor Mark Hull[1]

[1]University of Leeds, Leeds, United Kingdom. [2]University of Bradford, Bradford, United Kingdom. [3]University of Sheffield, Sheffield, United Kingdom. [4]Newcastle University, Newcastle, United Kingdom. [5]University College, London, United Kingdom

Abstract

Background: Aspirin and eicosapentaenoic acid (EPA) have colorectal polyp prevention activity, alone and in combination. We measured levels of plasma and rectal mucosal oxylipins in participants of the randomised, placebo-controlled 2x2 factorial seAFOod polyp prevention trial, who received aspirin 300 mg daily and EPA 2000 mg free fatty acid daily, alone and in combination, for 12 months.

Methods: Resolvin (Rv) E1, 15-epi-lipoxin (LX) A_4 and respective precursors 18-HEPE and 15-HETE (with chiral separation) were measured by ultra-high performance liquid chromatography-tandem mass spectrometry in plasma taken at baseline, 6 months and 12 months, as well as rectal mucosa obtained at trial exit colonoscopy at 12 months, in 401 trial participants.

Results: Despite detection of *S*- and *R*- enantiomers of 18-HEPE and 15-HETE in ng/ml concentrations, RvE1 or 15-epi-LXA_4 were not detected above a limit of detection of 20 pg/ml in plasma or rectal mucosa, even in individuals randomised to both aspirin and EPA. We have confirmed in a large clinical trial cohort that prolonged (12 months) treatment with EPA is associated with increased plasma 18-HEPE concentrations (median [inter-quartile range] total 18-HEPE 0.51 [0.21-1.95] ng/ml at baseline versus 0.95 [0.46-4.06] ng/ml at 6 months [$P<0.0001$] in those randomised to EPA alone), which correlate strongly with respective rectal mucosal 18-HEPE levels ($r=0.82$; $P<0.001$), but which do not predict colorectal polyp prevention efficacy by EPA or aspirin.

Conclusion: Analysis of seAFOod trial plasma and rectal mucosal samples has not provided evidence of synthesis of the EPA-derived specialised pro-resolving mediator RvE1 or aspirin-trigged lipoxin 15-epi-LXA_4. We cannot rule out degradation of individual oxylipins during sample collection and storage but readily measurable precursor oxylipins argue against widespread degradation in the seAFOod trial biobank.

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N-3 polyunsaturated fatty acid-modified Fat-1 microbiota prevents the alteration of the colonic mucus layer through endoplasmic reticulum stress prevention in obesogenic conditions

Mrs Amina BOURRAGAT[1,2], Dr Sandrine BELLENGER PhD[1,2], Pr Michel NARCE PhD[1,2], Dr Jérôme BELLENGER PhD[1,2]
[1]INSERM U-1231, Dijon, France. [2]Université de Bourgogne, Dijon, France

Abstract

Aim

During the onset of dietary obesity, a dysbiosis of intestinal microbiota contributes to alteration of intestinal barrier function by increasing intestinal epithelium permeability and altering the colonic mucus layer.

In this context, we studied the impact of n-3 polyunsaturated fatty acids (n-3 PUFAs) on the colonic mucus layer in order to prevent alterations of the barrier function. The relative contribution of microbiota has been assessed.

Methods

Four groups of Wild Type (WT) and transgenic fat-1 mice (exhibiting a n-3 PUFA tissue enrichment) were fed a high fat (HFD) or control (CTL) diet for 12 weeks. Measurements of thickness and structure of the mucus layer were performed after alcyan blue staining and electron microscopy, respectively. Expression of MUC2 and potential contribution of ER stress have been evaluated.

Additionally, WT mice have been transplanted with either caecal content of fat1 or WT mice, and then fed HFD or CTL diet for 12 weeks. The impact of microbiome transfer has been evaluated on the mucus layer thickness. Expression of MUC2 and of ER stress markers have been analyzed.

Results

We evidenced that WT HFD mice exhibit thicker and altered structure of the mucus layer, whereas fat-1 HFD mice (protected against dietary obesity and intestinal permeability) present a mucus layer as thick as the one of controls and a highly stratified outer mucus layer, keeping bacteria away from epithelial cells. Similar protection was observed by transferring microbiome of fat-1 to WT. We evidenced that such prevention occurred mainly through ER stress alleviation.

Conclusion

These new findings highlight a novel feature of the preventive effects of n-3 PUFA against intestinal permeability occurring in obesity-related conditions. It remains to decipher how n-3-modified microbiome influences the formation process, the structure and the functionality of the mucus layer via the identification of bacteria and metabolites of interest.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

no

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The confusing state of omega-3 status testing in US clinical laboratories

Dr Kristina Jackson PhD, RD
OmegaQuant Analytics, Sioux Falls, SD, USA. University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA

Abstract

A lack of standardization of omega-3 status testing in the clinical laboratory space hinders its acceptance and use by medical professionals. The purpose of this presentation is to compare the omega-3 status tests reported by various laboratories in the US (Lab Corps; Quest Diagnostics; Boston Heart Lab; OmegaQuant Analytics). All the labs report different metrics and reference ranges due to the sample types analyzed, analytical instruments used, and fatty acids included in the combined metrics. The following are specific examples of confusion from each laboratory. 1) Lab Corps, Quest, Cleveland Heart Lab: It is unclear if the OmegaCheck® metric (EPA+DPA+DHA/total fatty acids) is measured in plasma phospholipids or whole blood. 2) Boston Heart Diagnostics: The Omega-3 Fatty Acid Index is not defined, and the ratio reported is an Omega-3/Omega-6 ratio instead of Omega-6/Omega-3 ratio and is also undefined. 3) OmegaQuant: The erythrocyte-equivalent of the Omega-3 Index (EPA+DHA/total fatty acids) is converted from the dried whole blood levels for reporting, but all other fatty acids and ratios are based on whole blood levels. While the omega-3 status tests are likely all highly correlated with each other, the differences in reporting and analysis make omega-3 status testing too complicated for many medical professionals. Standardizing omega-3 status testing is essential for the translation of omega-3 research into clinical practice.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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High fat diet feeding of mothers during lactation durably alters the transcriptome of adipose stem cells in the mouse male offspring

Camille LEFEVRE PhD ORCID iD, Emmanuelle MEUGNIER PhD ORCID iD, Hubert VIDAL PhD ORCID iD, Marie-Caroline MICHALSKI PhD ORCID iD, Anne MEY PhD ORCID iD
CARMEN Laboratory, Lyon, France

Abstract

Obesity promotes the development of metabolic complications, like type 2 diabetes, preceded by a period of adaptation during which changes in life habits may restore normal metabolism. This prediabetes period varies with individuals and non-genetic susceptibilities for complications have been observed, independently of the body weight. Exposure to high fat diet during the youth or the early life have been associated with complications in adulthood but mechanisms are poorly understood. We made the hypothesis that adipose stem cells (ASC) may represent vectors in the long-term memory of high fat diet exposure. Indeed, ASC are adipocytes progenitors emerging during early life and exerting regulating functions that are relevant for adipose tissue homeostasis. Using a kinetic study of high fat diet induced obesity starting after weaning, we showed previously that ASC aquired improved immunosuppressive properties, long before the emergence of insulin resistance and inflammation making the proof that ASC are early sensors of metabolic changes. To test the relevance of ASC in the delayed effects of high-fat diet during lactation, ASC isolated 6 weeks after weaning from the male offspring, were cultivated and analyzed. RNA sequencing revealed changes in the transcriptome of these cells that were associated with the mother’s high-fat diet and differences between ASC isolated from distinct adipose depots were observed. Comparisons with the transcriptome of ASC isolated from mice fed high fat diet after weaning only revealed similarities for genes associated with innate immunity. These results show that after a recent or distant exposure to high-fat diet, ASC acquire a new basal state that precedes the shift towards altered functions in morbid obesity. Therefore, ASC represent a new marker for adipose tissue health in obesity and a relevant player in the delayed effects of obesity.

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Circulating Omega-3 Levels and Risk of Stroke:A Pooled/Harmonized Analysis of 183,291 Subjects from 29 Prospective Studies

Dr James O'Keefe MD ORCID iD[1], Nathan Tintle PhD[2], Dr Evan O'Keefe MD[1], William Harris PhD[2]
[1]Saint Luke's Mid America Heart Institute, Kansas City, USA. [2]Fatty Acid Research Institute, Sioux Falls, USA

Abstract

Higher omega-3 fatty acid blood levels are associated with lower coronary heart disease risk, but possibly an increased risk of atrial fibrillation. However, the relationship between omega-3 and risk of stroke remains unclear. Via the FORCE consortium, we investigated associations between omega-3 blood levels and incident stroke (total, ischemic, and hemorrhagic stroke) in 29 international prospective cohorts. Each site conducted a de novo individual-level analysis using a pre-specified analytical protocol with defined exposures, covariates, analytical methods, and outcomes; the harmonized data from the 29 studies were then centrally pooled. Among 183,291 study participants, there were 10,561 total strokes, 8220 ischemic strokes and 1142 hemorrhagic strokes recorded over a median of 14.3 years follow-up. Multivariable adjusted hazard ratios and 95% confidence intervals (CI) across omega-3 quintiles were computed for each stroke outcome. Across quintiles, risk of ischemic stroke was 16% lower for docosahexaenoic acid, and 19% lower for eicosapentaenoic acid ($p<0.001$ for both). Comparing quintile 5 (highest) to quintile 1 (lowest) for docosahexaenoic levels, there was a 13% lower risk for total stroke (0.87, CI 0.79-0.95; $p<0.0001$) and a 16% lower risk for ischemic stroke (0.84, CI 0.76-0.93; $p<0.0001$) without any significant association with risk for hemorrhagic stroke (1.08, CI 0.8-1.46; $p=0.317$). Neither baseline history of atrial fibrillation nor prevalent cardiovascular disease significantly modified these relationships. Conclusion: Higher omega-3 blood levels were strongly associated with lower risk for total and ischemic stroke, with no increased risk of hemorrhagic stroke.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

no

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Association Between Oxidation-Modified Lipoproteins And High-Risk Coronary Plaque Features In Cardiovascular Disease Patients

Dr Alexander Sorokin MD, PhD ORCID iD[1], Christin Hong[1], Angel Aponte[1], Elizabeth Florida[1], Jingrong Tang[1], Martin Playford[1], Marcus Chen[1], Kazuhiko Kotani[2], Alexander Bocharov[1], Alan Remaley[1]
[1]NHLBI, NIH, Bethesda, USA. [2]Jichi Medical University, Shimotsuke, Japan

Abstract

Background: Oxidized LDL (oxLDL), along with other oxidation-modified lipoproteins (OMLs), such as oxidized HDL (oxHDL), are known pro-atherogenic factors. However, its prognostic value for assessing high-risk coronary plaque features has not been fully elucidated.

Methods: In a prospective, observational study, 306 subjects with known cardiovascular disease (CVD) had extensive lipoprotein profiling, including plasma OMLs and HDL function measured. Proteomics analysis was performed on oxHDL isolated by anti-oxApoA-I antibody. Atherosclerotic plaque assessment was accomplished by quantitative coronary computed tomography angiography (QAngio, Medis). Cohort stratification was based on 50thpercentile oxLDL/oxHDL plasma values.

Results: Patients were white overweight males (58.5%) on statin therapy (43.5%). Significant increase in LDL-C, ApoB, LDL-TG, sdLDL-C ($P<0.001$ for all) and TGs ($P=0.03$) was observed in high oxLDL group, accompanied byelevated markers of systemic inflammation (hsCRP and GlycA), and less efficient HDL function measured by cholesterol efflux capacity and CETP activity. Opposite effects were discovered under high oxHDL levels. Additionally, high oxLDL was significantly positively associated with coronary plaque burden, which was evident for fibro-fatty burden (FFB) ($\beta=0.15$) and necrotic burden (NB) ($\beta=0.20$) ($P<0.001$) after multivariate adjustment. Low oxHDL had significant reverse association with these plaque characteristics. Moreover, oxHDL better predicted FFB and NB after adjustment (2.31, 1.16-4.59) (ORs, 95% CIs) compared to oxLDL and HDL-C. Interestingly, oxHDL was associated with fibrous burden (FB) change over 3.3 years follow-up in a limited number of CVD patients ($rho=0.535$; $P=0.033$), when compared to oxLDL. Finally, combined Met(136) monooxidation and Trp(132) dioxidation showed the most significant positive correlation with CAC score ($r=0.786$; $P<0.001$) and FB ($r=0.539$; $P=0.012$) in high oxHDL patients, whereas Met(136) monooxidation had significant association with high-risk plaque features in low oxHDL.

Conclusions: Our findings suggest that the investigated OMLs are associated with high-risk coronary plaque features and its progression over time in CVD patients.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Specificity of Each Phospholipase A2 Toward AA/EPA/DHA Regulates Production of Downstream PUFA-Derived Mediators

Edward Dennis Ph.D.
University of California San Diego, La Jolla, USA

Abstract

We found that enzymes that release free fatty acids from phospholipids can discriminate between phospholipids containing AA, EPA, or DHA in their sn-2 fatty acyl position. Thus, these enzymes regulate which downstream pro-inflammatory and pro-resolution metabolites are produced. We demonstrated that membranes interact allosterically with phospholipase A2 (PLA2) enzymes to regulate cell signaling, membrane remodeling and lipid mediator production by their specificity at the molecular species level. We recently developed substrate lipidomics using UPLC/MS coupled with molecular dynamics simulations revealing enzyme specificity linked to highly specific hydrophobic binding sites for specific sn-2 fatty acyl chains released in membrane phospholipid substrates [Mouchlis et al (2018) *JAmChemSoc*]. We now discovered unexpected head-group and acyl chain specificity for each of the 4 major types of human PLA2's that explains observed specificity at a new atomic level. A unique hydrophobic binding site, not each enzyme's catalytic residues or polar head-group binding site — dominates each enzyme's specificity. Each PLA2 shows unique specificity for its required sn-2 fatty acyl with cPLA2 favoring pro-inflammatory omega-6 arachidonic acid (AA) and sPLA2 favoring anti-inflammatory fish oil omega-3 DHA [Hayashi et al (2021) J Lipid Res]. Others like iPLA2 favor omega-3 EPA and membrane remodeling linolenic acid, while LpPLA2/PAFAH favors oxidized FAs in LDL [Mouchlis et al (2022) *ProcNatlAcadSciUSA*]. Furthermore, plasmalogens or alkyl ethers in the sn-1 acyl chain can affect the sn-2 fatty acyl selectivity [Hayashi et al (2022) *BiochimBiophysActa, MolBioLipids*]. We found that each PLA2 releases a specific FA after the enzyme associates allosterically with membranes and extracts a single phospholipid substrate into its catalytic site [Review: Dennis (2022) *JBiolChem*]. We can now correlate PLA2 specificity with physiological function using a novel lipidomics platform that provides a paradigm for the selectivity for pro-inflammatory or anti-inflammatory/pro-resolving lipid mediator production in macrophages in vivo.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Unknown

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Associations between maternal fish intake, maternal or cord polyunsaturated fatty acids (PUFA) with prevalence of asthma at 7 years in a high fish-eating population.

Mr Cealan O Henry[1], Dr Philip J Allsopp[1], Dr Alison J Yeates[1], Dr Toni Spence[1], Dr Maria S Mulhern[1], Dr Emelyn Shroff[2], Dr Conrad F Shamlaye[2], Dr Edwin van Wijngaarden[3], Professor J J Strain[1], Dr Emeir M McSorley[1]
et al
[1]Ulster University, Coleraine, United Kingdom. [2]Ministry of Health, Mahé, Seychelles. [3]University of Rochester, Rochester, USA

Abstract

Background: Associations between prenatal polyunsaturated fatty acids (PUFAs), in particular the anti-inflammatory n-3 PUFAs, with the development of childhood asthma, have yielded conflicting results with limited information from high fish-eating populations.

Methods: Serum PUFAs (linoleic acid [LA; C18:2 n-6], alpha-linolenic acid [ALA; C18:3 n-3], arachidonic acid [AA; C20:4 n-6], eicosapentaenoic acid [EPA; C20:5 n-3] and docosahexaenoic acid [DHA; C22:6 n-3]) were quantified in maternal blood collected at 28-weeks' gestation and in cord blood (n=1265) from the Seychelles Child Development Study. Information on asthma in children at 7 years of age was collected using the validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (n=1098). Using multivariable logistic regression, we examined associations between maternal fish intake, maternal and cord PUFA with prevalence of childhood asthma.

Results: A total of 10.3% of children were asthmatic (n=97). The prevalence of asthma was not associated with maternal fish intake or maternal PUFA. Cord DHA (p=0.005) and total n-3 PUFA (p=0.03) were significantly higher in asthmatic children compared to non-asthmatic children. Higher concentrations of cord DHA were predictive of asthma in these children (OR, 1.67; 95% CI, 1.08-2.57; p=0.02), adjusting for maternal age, maternal body mass index, gestation age, birth weight and socioeconomic status.

Conclusion: Within this high fish-eating cohort, higher cord DHA was associated with the presence of asthma in children. Preferential transfer of DHA across the placenta to the foetus may be enhanced in mothers of asthmatic children in order to regulate inflammation. Further research is needed to confirm this possibility.

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Blood Omega-3 Levels Inversely Associated with Hematological Measures in UK Biobank Cohort

Dr Michael McBurney PhD ORCID iD[1,2,3], Dr Nathan Tintle PhD ORCID iD[1,4], Dr William Harris PhD ORCID iD[1,5]
[1]Fatty Acid Research Institute, Sioux Falls, USA. [2]University of Guelph, Guelph, Canada. [3]Tufts University, Boston, USA. [4]University of Illinois, Chicago, USA. [5]University of South Dakota, Sioux Falls, USA

Abstract

Background: High neutrophil-lymphocyte ratio (NLR) is a biomarker of systemic inflammation and innate-adaptive immune system imbalance, and red blood distribution width (RDW) is associated with decreased red blood cell deformability. Both RDW and NLR are predictors of chronic disease risk and mortality. In a US study of healthy individuals, omega-3 index (O3I) values were inversely associated with NLR and RDW levels.

Objective: To determine if plasma long chain omega-3 fatty acids were associated with RDW and NLR values in the UK Biobank cohort, a population-based cohort of 502,639 individuals aged 40-69y recruited between 2007-2010.

Methods: Total long chain omega-3 fatty acids (Omega3%) and DHA (DHA%) were measured in plasma by nuclear magnetic resonance in 117,351 individuals and reported as percent of total fatty acids. Of these, 109,191 individuals had data on NLR, RDW, age, sex, BMI, high-sensitivity C-reactive protein (CRP), and hemoglobin (Hb).

Results: Mean age (SD) was 57.1y (8.1) and 58% female. Multivariable regression models were constructed to predict NLR and RDW values by cubic splines of Omega3% and DHA% alone and after further adjustment of NLR-models for age, sex, BMI and CRP and RDW-models for age, sex, BMI, CRP and Hb. NLR- and RDW- relationships were inversely correlated with Omega3% (all models $p<0.0001$) and DHA% (all models $p\leq0.0003$).

Conclusions: These cross-sectional associations confirm previous findings that low omega-3 fatty acid levels are associated with higher NLR and RDW values. The hypothesis that RDW and/or NLR values can be reduced in individuals with less-than optimal long chain omega 3 values need to be tested in randomized controlled intervention trials using EPA and/or DHA.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Abstract has not been published.

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Role of the Stearoyl-CoA Desaturase-1 in the formation of very-low density lipoproteins

Alexandre Légiot PhD student[1,2,3], Simon Pogu AgroFood Engineer[4], Dre Catherine Mounier PhD[1,2,3]
[1]Université du Québec à Montréal, Montréal, Canada. [2]Centre d'Excellence en Recherche sur les Maladie Orphelines, Montréal, Canada. [3]Cardiometabolic Health, Diabetes and Obesity Research Network, Montréal, Canada. [4]L'institut agro Rennes Angers, Rennes, France

Abstract

Background: ApolipoproteinB100 (ApoB100) is the major lipoprotein of the very low-density lipoprotein (VLDL). The palmitoylation of ApoB100 in the reticulum prevent his degradation by the proteasome promoting VLDL formation. Saturated fatty acid, palmitate and stearate can be mono-desaturated into palmitoleate and oleate by the Stearoyl CoA-desaturase-1 (SCD1) in the reticulum. SCD1 could make available oleate and palmitoleate for ApoB100 acylation.

Methods: Our study was performed in hepatocarcinoma cells and liver specific SCD1 KO (LKO) mice fed with a high saturated fat high sugar diet (HFHS). We evaluated the SCD1 interactome by mass spectrometry and determined by immunofluorescence the subcellular localization of SCD1 and ApoB100. We also evaluated the expression levels of several proteins implicated in lipoprotein formation, the hepatic lipids storage and the level of plasmatic lipids.

Results: Using MS and immunofluorescence, we identified a functional link between SCD1 and ApoB. When the hepatoma cells were exposed to a specific SCD1 inhibitor, the concentrations of intra and extracellular ApoB100 decrease. This is reversed by addition of oleate but not by stearate. Stearate treatment can partially prevent the degradation of ApoB100 compared to a cotreatment with stearate and SCD1 inhibitor. Stearate treatment also increases ApoB100 localization to the Golgi. In vivo, we showed that the livers of LKO mice fed with HFHS diet are more steatotic than the livers of WT mice. Interestingly, compared to WT mice, the visceral adipose tissue is decreased in LKO mice while the plasmatic level of ApoB-100 is increased. This may be explained, at least in male by the reduction of LDL receptor expression.

Conclusion: SCD1, mostly through its product oleate, may stabilize intracellular ApoB100 increasing its excretion and subsequently, the synthesis of VLDL by the hepatocytes. This stabilization could be due to the acylation of ApoB100 by oleate.

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Compound-specific isotope analysis as a method to analyze omega-3 and omega-6 polyunsaturated fatty acid metabolism

Daniel Chen[1,2], Adam Metherel[1], Kimia Rezaei[1], Camilla Parzanini[1], Chuck Chen[1], Christopher Ramsden[3], Keturah Faurot[4], Daisy Zamora[4], Beth MacIntosh[4], Richard Bazinet[1]
et al
[1]University of Toronto, Toronto, Canada. [2]University of Alberta, Edmonton, Canada. [3]National Institute on Aging and National Institute on Alcohol Abuse and Alcoholism, Baltimore, USA. [4]University of North Carolina, Chapel Hill, USA

Abstract

Natural variations in the ^{13}C:^{12}C ratio (carbon-13 isotopic abundance [$\delta^{13}C$]) of the food supply have been used to determine dietary origin and metabolism of fatty acids, especially in the n-3 polyunsaturated fatty acid (PUFA) biosynthesis pathway. However, n-6 PUFA metabolism following linoleic acid (LNA) intake remains under-investigated. Here, we sought to use natural variations in the $\delta^{13}C$ signature of dietary oils to analyze n-3 and n-6 PUFA metabolism following dietary changes in LNA and eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) in adult humans. We hypothesized that plasma $\delta^{13}C$- EPA and -DHA shift towards the dietary $\delta^{13}C$-EPA and -DHA signature in diets with increased EPA and DHA consumption, and that the plasma $\delta^{13}C$-arachidonic acid (ARA) and -LNA change towards the dietary $\delta^{13}C$-LNA signature in diets with increased LNA intake. Participants with migraine (aged 38.6 ± 12.8 y) were randomized to one of three dietary groups for 16 weeks: 1) low omega-3, high omega-6 (L3H6, n=10), 2) high omega-3, high omega-6 (H3H6, n=10), or 3) high omega-3, low omega-6 (H3L6, n=10). Blood was collected at baseline, 4, 10, and 16 weeks. Plasma PUFA concentrations and $\delta^{13}C$ were determined for total lipids and fractions – phospholipids, cholesteryl esters, triacylglycerides, and free fatty acids. Lipid fraction data is currently being analyzed and will be available for the presentation. Plasma from L3H6 intervention participants exhibited increases in total lipid plasma $\delta^{13}C$-LNA signature while LNA concentrations were unchanged. No changes in plasma $\delta^{13}C$-ARA or concentration were observed in any intervention. Plasma DHA and EPA concentration increased in the H3H6 and H3L6 interventions. Plasma $\delta^{13}C$-EPA increased in the H3L6 intervention compared to baseline. Compound-specific isotope analysis has the potential to track dietary intake patterns and provide insight into n-3 and n-6 PUFA metabolism, provided that the isotopic signature of the dietary source is sufficiently different from plasma $\delta^{13}C$ signatures.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not currently published, but is being prepared for submission.

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Polymorphism in the FADS gene locus influences arachidonic acid content in human milk extracellular vesicles

Dr. John Miklavcic Ph.D. ORCID iD[1], Ms. Natalie Paterson M.S.[1], Dr. Jennifer Hahn-Holbrook Ph.D.[2], Dr. Laura Glynn Ph.D.[1]
[1]Chapman University, Orange, USA. [2]UC Merced, Merced, USA

Abstract

The WHO recommends six months of exclusive feeding with human milk for newborns. Human milk contains many bioactives, including lipid membrane-enclosed extracellular vesicles (EVs), which may in part be responsible for promoting growth and development processes. SNPs in the *FADS* gene locus have been shown to impact the concentrations of polyunsaturated fatty acids in human milk and other tissues. As integral components of the lipid membrane, the composition of LCPUFAs may impact the bioavailability of EVs in newborns consuming human milk. The objective of this study was to investigate how SNPs in the *FADS* gene locus affected LCPUFA content of EVs from human milk. Maternal demographics, human milk, and saliva were collected from mothers (n=33) from clinics in Orange County, California at 2-weeks of lactation. Saliva samples were analyzed with pyrosequencing for SNPs in rs174546 (*FADS1*) and rs174575 (*FADS2*). Extracellular vesicles were isolated from human milk using a precipitation-based method with guidance from the Minimum Information for Studies of Extracellular Vesicles (ISEV, 2018). The fatty acid content (%w/w) of EVs was analyzed using gas chromatography-mass spectrometry high sensitivity quantitative lipidomic analysis. The rs174546 genotype was an independent predictor of the arachidonic acid (AA) content in EVs from human milk ($p < 0.01$) after adjusting for income-to-needs ratio and education (>/< high school) in regression modelling. The lower content of AA in EVs may be due to lower fatty acid desaturase activity in mothers who are A allele carriers in rs174546. The decrease in AA status in EVs associated with this SNP may indicate a reduced capacity to form AA-derived oxylipins and impaired vascular permeability of EVs. Whether reduced AA content of EVs alters EV bioavailability or downstream functions requires further investigation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Dietary supplementation with ω-3 very-long-chain polyunsaturated fatty acids enhances retinal function and reduces cardiometabolic risk factors in mice

Dr. Zhihong Yang PhD ORCID iD[1], Aruna Gorusupudi[2], Todd Lydic[3], Anupam Kumar Mondal,[1], Jingrong Tang[1], Krishna Vamsi Rojulpote[1], Anna Lin[3], Hannah Decot[3], Hannah Koch[3], Daniel Brock[1]

[1]National institutes of health, Bethesda, USA. [2]John A. Moran Eye Center, ,Salt Lake City, USA. [3]Michigan State University, East Lansing, USA

Abstract

N-3 very-long-chain polyunsaturated fatty acids (VLCPUFA; C≥24), which are found primarily in retina and a few other select tissues, are known to play critical roles in specific biological systems. Although n-3 PUFA, such as EPA and DHA, may confer cardiovascular benefits, they did not improve age-related macular degeneration (AMD), a leading cause of blindness worldwide, in clinical trials. The activity of ELOVL2, an enzyme that converts EPA into C24 VLCPUFA, is known to decrease in the retina with age due to promoter methylation. We, therefore, hypothesized that dietary VLCPUFA may delay or prevent AMD, by bypassing the ELOVL2-mediated lipid elongation step.

Fish oils contain vanishingly small amount of VLCPUFA, but we have produced a new fish oil that contains ~40% (w/w) of VLCPUFA normally produced by ELOVL2. Our mouse diet supplementation studies showed not only was this new fish oil well tolerated but also that VLCPUFA in the diet was incorporated into eyes and improved retinal function and vision. Furthermore, like EPA and DHA, we also observed favorable cardiometabolic changes (decreased plasma lipids and glucose) due to dietary VLCPUFA. Lipidomic analysis indicated that dietary VLCPUFA-oil caused significant shifts in the lipid metabolic profiles. Transcriptome analysis revealed that VLCPUFA-enriched fish oil favorably regulated genes involved in nuclear receptor signaling pathways and in lipid metabolism. Overall, our multi-omics studies revealed for the first time several potential health benefits for our new VLCPUFA-enriched fish oil in several age-related diseases and support its future development as a new dietary supplement.

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Circulating Omega-3 Levels and Risk of Total and Cause-Specific Mortality: A Pooled/Harmonized Analysis of 160,404 Subjects from 18 Prospective Studies

Dr Evan O'Keefe MD[1], Nathan Tintle PhD[2], Dr James O'Keefe MD ORCID iD[1], William Harris PhD[2]
[1]Saint Luke's Mid America Heart Institute, Kansas City, USA. [2]Fatty Acid Research Institute, Sioux Falls, USA

Abstract

Omega-3 fatty acids' long-term effects on all-cause, cardiovascular (CV), and cancer mortalities remain uncertain. To address this issue, we analyzed data from UK Biobank, which included 117,702 subjects with omega-3 blood levels and 12.7 years follow-up. Comparing the lowest to the highest quintiles of circulating DHA levels, there was 21% lower risk of all-cause mortality (HR 0.79, 95%; 95% CI 0.74-0.85; p<0.001); 21% lower risk of CV mortality (95% CI 0.67-0.93; p<0.001); 21% lower risk of in cancer mortality (95% CI 0.71-0.88; p<0.001), and a 21% reduction in all other mortality (95% CI 0.69-0.91; p<0.001). To confirm these findings, we merged UK Biobank data with findings from a recent FORCE consortium study that was a pooled and harmonized analysis using data from 17 prospective cohort studies. Each site conducted a de novo individual-level analysis using pre-specified analytical protocol with defined exposures, covariates, analytical methods, and outcomes; harmonized data from the 18 studies (including UK Biobank) were then centrally pooled and analyzed. The cumulative sample population included 160,404 individuals and 24,342 deaths during a median of 14 years of follow-up. After multivariable adjustment for relevant risk factors, comparing the lowest to the highest quintiles of DHA, the HR (95% CI) for all-cause mortality = 0.83 (0.79, 0.87 p<0.001), for CV mortality = 0.79 (0.73, 0.87; p<0.001), for cancer mortality = 0.83 (0.77, 0.89; p<0.001) and for all other mortality = 0.85 (0.79, 0.91; p<0.001). Conclusion: Higher DHA levels were significantly associated with lower risks for total, CV, cancer, and other mortality.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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Fatty acid composition, Level of oxidation and Nutritional indices of Palm oil recovered from Yellow Garri

Otu Okogeri PhD, Abigail Ekeh Nwali BSc
Department of Food Science and Technology, Ebonyi State University., Abakaliki, Nigeria

Abstract

Garri is the most popular cassava food in West African countries, and is produced by grating cassava roots into a mash, dewatering and fermenting the mash, and roasting (garifying) mash to a granular form. Crude palm oil (CPO) is typically added to cassava mash prior to fermentation stage or during garifying, to give garri its characteristic appealing yellow color. However, at garifying temperature, edible oils can undergo heat-induced oxidation with possible formation of complex mixtures of compounds such as cyclic monomers which have been implicated in the development of certain chronic diseases. In this work level of oxidation and potential health implications of CPO extracted from yellow garri were studied. Fresh CPO was added to cassava mash prior to dewatering and fermentation or during garifying, to obtain two samples of yellow garri (GF and GG respectively). Both samples were then subjected to oil extraction, and the oils extracted (samples GFO and GGO respectively) were evaluated for Level of oxidation (Peroxide value (PV) and Iodine value (IV)); Fatty acid composition; and Nutritional indices (Hypocholesterolemic/Hypercholesterolemic (HH) ratio; Polyunsaturated Fatty Acid/Saturated Fatty Acid (PUFA/SFA) ratio; Index of Atherogenicity (IA); and Index of Thrombogenicity (IT)). Fresh CPO served as control (FCPO). Addition of CPO led to decrease in PUFA and increase in MUFA of samples. Higher PV (10.40 meq/kg) and lower IV (46.50g I_2/100g) were recorded for GFO compared to GGO (7.52 meq/kg and 48.30g I_2/100g) and FCPO (6.11 meq/kg and 50.80g I_2/100g), suggesting that addition of CPO prior to fermentation resulted in higher level of oxidation. Increase of ≤2% in atherogenic and thrombogenic potentials of FAs and decrease of up to 4% in PUFA/SFA and HH ratios were recorded for samples. Addition of CPO during garifying negatively impacted nutritional indices more than addition prior to fermentation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

None

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Effect of milk fat globule membrane supplementation on psychological health: a randomized clinical trial in healthy adults with moderate stress

Naom Davies[1], Christopher Frampton[2], Dr Maher Fuad ORCID iD[3], Caroline Gunn[3], Rebecca Slykerman[1]
[1]Department of Psychological Medicine, The University of Auckland, Auckland, New Zealand. [2]Department of Medicine, University of Otago, Christchurch, New Zealand. [3]Health and Nutrition Science, Fontarra, Palmerston North, New Zealand

Abstract

Mental health issues are an increasing global health problem and the one of the top health concerns in New Zealand. High and sustained levels of psychological stress can impair cognitive function and contribute to anxiety and depression. Given the prevalence of stress in modern life, we need to investigate nutritional interventions to help improve psychological well-being.

Polar lipids are integral to nervous system health and function and are implicated in cognitive performance and psychological responses to situational stress. The milk fat globule membrane (MFGM), surrounding the milk fat globule, is a rich source of phospholipids, gangliosides, and proteins. Due to its unique properties, research has attributed the MFGM and its phospholipids with properties of health promotion and maintenance across the lifecycle.

The current study tested the effect of MFGM supplementation at two different doses on stress, anxiety, and depression. Healthy adults (n=122) enrolled in a randomized, double-blind, placebo-controlled trial received either 600 mg or 1200 mg MFGM (containing 300 or 600 mg milk phospholipids, respectively) or a placebo daily for 12 weeks. Questionnaires were given at baseline, six and 12 weeks assessing psychological outcomes.

Participants supplemented with MFGM had significantly lower stress scores than the placebo group after six weeks (p=0.0004) and 12 weeks (p=0.002). There was a trend for MFGM supplementation to reduce anxiety after 12 weeks (p=0.06). These results suggest that MFGM supplementation may improve general psychological health beyond situation-specific improvements in stress. Further trials investigating potential psychological health benefits associated with MFGM will advance the field of nutritional interventions for mental health.

Keywords: Milk fat globule membrane, phospholipids, stress, anxiety, psychological well-being

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Whole-body tissue distribution in rats after a single dose of 14C-labelled eicosapentaenoic and docosahexaenoic acids in either lyso-phosphatidylcholine, phosphatidylcholine or triglyceride forms

Dr Nils Hoem PhD, Dr Lena Burri PhD, Dr Petter-Arnt Hals PhD
Aker BioMarine Antarctic AS, Lysaker, Norway

Abstract

Lyso-phosphatidyl choline (LPC) is now known to be an important factor in the distribution of the long-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for their delivery to specific target organs. The aim of the present study was to investigate and map out how the LPC form given both orally and intravenously influences the tissue delivery of these fatty acids in comparison to oral phosphatidylcholine (PC) or triacylglycerol (TG). LPC is the form required to bind to the membrane bound lipid sodium-dependent LPC symporter (Mfsd2a) that is responsible for most of the fatty acid transport across the blood-brain and -retina barriers. Hence, the study tried to elucidate, if and how tissue accumulation of 14C-radiolabelled LPC-bound EPA and DHA was preferentially elevated in MFSD2A-expressing as compared to other organs. By using multiple quantitative whole-body autoradiography from baseline to 0.5 to 336 hours after a single dose administration and simultaneous analysis of more than 40 individual organs, it was found that administration of either EPA- or DHA-LPC was well-distributed throughout the body, with higher concentrations generally associated with the brain/spinal cord (especially in the long-term), liver, fat (both brown and white), myocardium, and several glandular tissues, i.e. the preputial, adrenal and pituitary glands. Moreover, the intravenous application of LPC provided additional differences over its oral administration with rapid distribution to some tissues, especially the brain and neuronal tissue. Concomitant frequent sampling in blood and plasma provided data that was used to create a compartmental kinetic model by which detailed long-term dynamic simulations of multiple organ EPA and DHA distribution could be made.

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Krill oil supplementation’s effect on school grades in typically developing adolescents.

Dr Inge van der Wurff[1], Prof. Dr. Clemens von Schacky[2], Dr. Trygve Bergeland[3], Prof.Dr. Maurice Zeegers[4], Prof.Dr. Paul Kirschner[1], Prof.Dr. Renate de Groot[1]

[1]Open University of the Netherlands, Heerlen, Netherlands. [2]Omegametrix, Martinsried, Germany. [3]former employee of Aker BioMarine Antarctic AS, Lysaker, Norway. [4]Maastricht University, Maastricht, Netherlands

Abstract

Introduction: Long-chain polyunsaturated fatty acids (LCPUFA) are important for brain development and functioning, and possibly also for school performance. Cross-sectional studies have shown significant positive associations between fish consumption (LCPUFA source) and school grades. The effect of LCPUFA supplementation on school grades remains unstudied.
Aim: To investigate (I) the associations between the Omega-3 Index (O3I) of students at baseline and after 12 months, and school grades (II) the effect of 1-year krill oil supplementation on school grades in adolescents with a low O3I at baseline.
Methods: Double-blind placebo controlled RCT. Participants received 800 mg EPA + DHA per day or a placebo. O3I was assessed at baseline, three, six and twelve months. Grades for English, Dutch and math were collected, a standardised math test (SMT) was executed at baseline and twelve months. Data were analysed with (I) linear regression for associations at baseline and follow-up (II) mixed model analyses for supplementation effect.
Results: The krill oil group had a small significant increase in O3I at all time points. However, very few participants achieved the intended target O3I of 8-11%. At baseline a significant association between O3I and English grade was found along with a trend towards an association with Dutch grade. After 12 months no significant associations and no significant effects of supplementation on grades or SMT score were found.
Conclusion: There was no significant effect of krill oil supplementation on grades or SMT performance. However, many participants dropped out and/or were non-adherent, results should be interpreted cautiously.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

The manuscript is currently under review at PLEFA.

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Soy protein reduces hepatic delta-6 desaturase activity compared to dairy protein independent of changes in Fads2 gene expression

Melissa Gonzalez Soto MSc ORCID iD[1], Siobhan Woods MSc[1], Ruxandra Rotarescu[2], Adam Metherel PhD[2], David Mutch PhD[1]
[1]University of Guelph, Guelph, Canada. [2]University of Toronto, Toronto, Canada

Abstract

Endogenous production of long-chain polyunsaturated fatty acids (LC-PUFA) is regulated by delta-6 desaturase (D6D). Dietary factors, such as protein, can regulate D6D activity. We recently demonstrated that young adults who consumed soy containing foods had lower estimated D6D activity compared to those who consumed dairy containing foods. The aim of this study was to investigate the underlying mechanism of action by which soy protein suppresses omega-3 LC-PUFA synthesis in comparison to dairy protein. C57BL/6 male mice (n=12 per diet) were fed a Western diet (35%/50%/15% kcal from fat/carbohydrate/protein) containing 1% kcal of alpha-linolenic acid (ALA). Protein content corresponded to either dairy (skim milk powder, SMP) or soy protein isolate (SPI). After 8 weeks of feeding, liver tissues were collected. Hepatic fatty acid content was quantified by gas chromatography-flame ionization detection (GC-FID) and compound-specific isotope analysis (CSIA) by GC-isotope ratio mass spectrometry (IRMS). To assess D6D activity, microsomes were isolated from perfused livers and treated with ALA. Fads2 (which encodes D6D) gene and protein expression were quantified by qPCR and Western Blot, respectively. Hepatic ALA content was not different between SPI and SMP groups; however, significantly lower ($p=0.0002$) levels of eicosapentaenoic acid (EPA) were observed in the SPI group compared to the SMP group. IRMS revealed a more complete turnover of the ALA pool with SMP compared to SPI but similar turnover in the EPA pool. Microsomal D6D activity was lower in mice fed SPI compared to those fed SMP. D6D protein expression did not differ between groups, while Fads2 gene expression was significantly higher ($p<0.05$) in mice fed SPI compared to those fed SMP. Collectively, these results suggest that the lower levels of hepatic EPA in mice fed SPI stems from lower D6D activity which is independent of changes in gene or protein content.

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EPA and DHA can modulate Protein arginine methyltransferase 4 in Alzheimer’s disease

Dr. Cristiane Citadin PhD, Dr. Mariana Udo PhD, Garrett Clemons Bachelor, William Carr, Dr. Vesna Tesic PhD, Dr. Yin Chieh Wu PhD, Christina Acosta Master, Dr. Hung Wen (Kevin) Lin PhD
LSU Health Science Center, Shreveport, USA

Abstract

Alzheimer’s disease (AD) has been correlated with lack of dietary polyunsaturated fatty acids omega-3, characterized by the low content of docosahexaenoic acid (DHA) in the brain. Clinical trial results suggest improvement in mild to medium cognitive impairment with fish/fish oil supplementation. We recently discovered that protein arginine methyltransferase 4 (PRMT4) was enhanced in 1) patients with AD and related dementias (ADRD), 2) in post-mortem ADRD brain and the 3xTg-AD mouse brain. In the 3xTg-AD mouse model, this was further characterized by cognitive deficits and attenuated cerebral blood flow but was reversed upon PRMT4 inhibition. Additionally, treatment with fish oil rich in eicosapentaenoic acid (EPA, 70 %) or (DHA (50 %) reduced PRMT4 protein expression in brain endothelial cells, in vitro. This led us to investigate if EPA can regulate PRMT4, which is thought to be important in ADRD.

We treated 3xTg-AD mice with an equivalent of a daily human dose of 500 mg of fish oil containing 70 % EPA for 5 weeks (P.O.). The results suggest that this fish oil (70 % EPA) can: a) prevent (-12.37 % ± 2.93) AD-associated weight loss in 3xTg-AD mice v sham, b) improve spatial learning and memory function, with (39.32 % ±14.68) alternation rate increase measured by T-maze behavioral test, in mice before and after treatment, c) increase concentration of EPA (82 ± 11.59 ηmol/g) and DHA (14,242 ± 1236.59 ηmol/g) in the 3xTg-AD mouse brain v. sham (37 ± 3.005 ηmol/g and 10,898 ± 667.56 ηmol/g respectively). Overall, these results suggest that fish oil with 70 % EPA prevented AD-associated weight loss, improved memory function, and leads to increased brain DHA. Additionally, fish oil rich in DHA or EPA can modulate the expression of PRMT4 enzyme in mouse brain endothelial cells

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Differentiating exogenous EPA and DHA from endogenously synthesized EPA and DHA by compound specific isotope analysis: A secondary analysis of a clinical trial.

Amy Symington PhD ORCID iD[1], Melissa Gabbs MSC ORCID iD[2], Dr. Peter Zahradka PhD ORCID iD[2], Dr. Carla Taylor PhD ORCID iD[3], Dr. Harold Aukema PhD ORCID iD[2], Dr. Richard Bazinet PhD ORCID iD[1]
[1]University of Toronto, Toronto, Canada. [2]University of Manitoba, Manitoba, Canada. [3]University of Manitoba, Manitboa, Canada

Abstract

Precise biomarkers which measure n-3 PUFAs deserve attention given their use in measuring fish intake, an important source of n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are vital for cell membrane structure, and brain and eye health. Delta Carbon 13 (δ13C) is a measure of the 13C:12C isotope ratio (milliUrey, mUr). Plants vary in fixed C13, allowing tracing of fatty acid δ13C by isotope ratio mass spectrometry (IRMS) possible. This is a cost effective, and non-invasive tool to validate contributions of exogenously consumed and endogenously synthesized EPA and DHA in humans.

Methods: A secondary analysis of a crossover study with 12 healthy subjects aged 19-34 was executed. Subjects were supplemented 4g/d of either alpha linolenic acid (ALA) from flax oil or EPA and DHA from fish oil for 28 days with 6-week wash in and wash out phases. Supplements and plasma (baseline and day 28) were analyzed by gas chromatography-IRMS to determine δ13C signatures.

Results: δ13C n-3 PUFA signatures of the ALA and DHA supplements are -33.247 and -25.3991 mUr respectively. Baseline plasma signatures of EPA and DHA between supplement groups were not statistically different. However, at day 28, δ13C signatures of EPA and DHA diverged toward the isotopic signature of the DHA supplement ($p<0.01$).

Conclusion: By using IRMS we differentiated EPA and DHA obtained from fish oil versus flaxseed. This will better improve our understanding of n-3 PUFA metabolism in humans.

Future analysis: Days 3, 7 and 14 will be analyzed and n-3 PUFA turnover assessed.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Vitamin D and Omega-3 fatty acid supplementation in patients with type 2 diabetes mellitus.

Prof. Roxana Valdes-Ramos DSc ORCID iD, Dr. Ana Laura Guadarrama-López DSc ORCID iD, Dr. Beatriz Elina Martínez-Carrillo PhD ORCID iD
Facultad de Medicina, Universidad Autónoma del Estado de México, Toluca, Mexico

Abstract

Type 2 diabetes mellitus (T2DM) is a pandemic associated with obesity. Evidence suggests that low-grade inflammation is a risk factor for T2DM, and its progression. However, the mechanisms for this association are still being studied. Proinflammatory cytokines are higher in T2DM. Omega 3 and 6 fatty acids facilitate the action of insulin through various metabolic pathways, such as the suppression of hepatic lipogenesis, decrease in liberation of triglycerides from liver, improvement in ketogenesis and oxidation of fatty acids in liver and skeletal muscle, all of which favor glucose uptake and decrease insulin resistance. The evidence indicates that vitamin D is also associated with chronic inflammation in T2DM. Vitamin D may improve insulin sensitivity and promote the survival of pancreatic beta-cells, by modulating proinflammatory cytokines and nuclear transcription factors such as NF-kB. To evaluate the effect of vitamin D and PUFA in patients with T2DM, we undertook a 6-month supplementation trial with 2295 mg of EPA/720 mg of DHA and 3000 IU of Cholecalciferol (n=24), vs placebo (n=25). Anthropometry, glucose metabolism, lipid profile, adipokines and cytokines were measured in adults with T2DM in Mexico before and after supplementation. The protocol was approved by our institutional review board and all subjects signed an informed consent. In the supplemented group, we observed significant reductions in waist and hip circumferences, Hb1ac, leptin, IL-1β, IL-8, IL-6, TNFα and IFNγ. The combined supplementation of vitamin D and polyunsaturated fatty acids may help modulate the negative effects of low-grade chronic inflammation in patients with T2DM.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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The enzyme involved in 20:4n-6 biosynthesis and incorporation into phospholipids is high in the human triple-negative breast cancer MDA-MB-231 cells

Chen-Ling Lan MS, Associate Professor Hui-Min Su Ph.D. ORCID iD
National Taiwan University, Taipei, Taiwan

Abstract

Fatty acids are presented in phospholipids which are the major component of cell membranes. This study was to examine the fatty acids levels and the enzymes involved in the fatty acid biosynthesis and incorporation into phospholipids in human breast cancer cells from less aggressive estrogen receptor-positive MCF-7 followed by BT474, then aggressive HER2-enriched Sk-BR-3, to the most aggressive triple-negative MDA-MB-231 as well as human mammary epithelial cells MCF-10A to find out the key fatty acids and enzymes for the aggressiveness of breast cancer cells. The cells were cultured in 10% FBS DMEM medium, and MCF-10A was in 5% horse serum DMEM medium as maintained by most studies. We found that the enzymes involved de novo lipogenesis FASN and SCD1 protein expression and its metabolites of 16:0 and 18:1n-9 were much higher in MCF-7, BT-474, and SK-BR-3 and then in MDA-MB-231 followed by MCF-10A. The 20:4n-6 levels were significantly higher in human breast cancer cells, especially in MDA-MB-231, than MCF-10A. In contrast, the main n-6 PUFA were 18:2n-6 in MCF-10A. The FADS2 and ELOVL5 mRNA and protein expression were significantly higher in MDA-MB-231 and BT-474 than in MCF-10A, MCF-7 and SK-BR-3. The mRNA and protein expression of ACSL4, ACSL5, and LPEAT2 were significantly higher in MDA-MB-231 than other 3 human breast cancer cells. LPCAT1 protein expression was significantly higher in human breast cancer cells than MCF-10A. It was concluded that the most aggressive MDA-MB-231 showed higher 20:4n-6 levels, and had more enriched enzymes involved in 20:4n-6 biosynthesis and incorporation into phospholipids including FADS2, ELOVL5, ACSL4, ACSL5, and LPEAT2 than other human breast cancer cells.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

no

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N-acyl ethanolamine involvement in the permeability barrier through epidermal tight junction formation

Prof Anna Nicolaou PhD ORCID iD, Dr Anggit Sunarwidhi PhD, Prof Catherine O'Neill PhD, Dr Alexandra Kendall PhD
University of Manchester, Manchester, United Kingdom

Abstract

The epidermal permeability barrier maintains skin hydration and electrolyte flux supported by the formation of tight junctions (TJ), intercellular structures that control the trafficking of ions, and immune cells. As environmental and inflammatory stimuli alter production of bioactive lipids essential for barrier function, we have explored the role of N-acyl ethanolamines (NAE) on the maintenance of epidermal TJ.

Normal human epidermal keratinocytes (NHEK) were grown in culture, differentiated and treated with UVR, histamine and NAE. Intracellular and secreted levels of NAE were measured by ultraperformance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS. Transepithelial electrical resistance (TEER) and fluorescein isothiocyanate (FITC)-dextran trans-epithelial permeability were used to assess the integrity of TJ. Expression of claudin-1, claudin-4, occludin and ZO-1 mRNA and protein were assessed by PCR and immunoblotting, respectively, while immunofluorescence was used to assess their localisation.

Proliferating and differentiating NHEK produced a range of NAE including AEA, OEA, SEA and PEA. While treatment with histamine stimulated NAE production, exposure to UVR at doses that did not affect cell viability, did not alter NAE in NHEK. Of the NAE tested, PEA and OEA increased TJ functionality via the charge-selective pathway and protected TJ leakage induced by histamine, but not UVR-induced damage. While PEA increased claudin-1 and -4 mRNA expression in differentiated NHEK, AEA, OEA and SEA reduced protein expression and cellular localisation of claudins. These findings demonstrate the differential impact of NAE on epidermal TJ formation, suggesting a potential role in inflammatory skin disorders characterised by barrier dysfunction.

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Vegan diet in children and adults is associated with lower serum DHA status than mixed diet

Topi Hovinen ORCID iD[1], Riitta Freese ORCID iD[2], Elina Kettunen ORCID iD[2], Nicola Zamboni ORCID iD[3], Liisa Korkalo ORCID iD[2], Anu Suomalainen ORCID iD[1,4,5]

[1]Research Programs Unit, Stem Cells and Metabolism, University of Helsinki, Helsinki, Finland. [2]Department of Food and Nutrition, University of Helsinki, Helsinki, Finland. [3]Institute of Molecular Systems Biology, ETH Zürich, Zürich, Switzerland. [4]HUSLAB, Helsinki University Hospital, Helsinki, Finland. [5]Neuroscience Center, HiLife, University of Helsinki, Helsinki, Finland

Abstract

Docosahexaenoic acid (DHA, 22:6 n-3) is needed for optimal cognitive development, neuronal signalling and vision as well as resolution of inflammation. We have previously reported that vegan diet not supplemented with DHA in children (n=6) was associated with lower status of DHA when compared with children on a mixed diet (Hovinen EMBO Mol Med 2021). The present larger cross-sectional study investigated the associations of vegan, vegetarian and mixed diets with nutritional status and metabolism among daycare-aged (2 to 7 y) children and their caregivers. Fasting serum samples were obtained from 68 children (of whom 26, 16 and 26 followed vegan, vegetarian and mixed diets, respectively) and from 91 caregivers (n = 33, 22 and 36 for vegan, vegetarian and mixed diet, respectively).

Untargeted MS metabolomics analysis indicated that children on vegan diets had significantly higher alphalinolenic acid (ALA, 18:3 n–3, Benjamini-Hochberg (BH) adjusted $p < 0.0001$) and lower DHA (BH-adjusted $p < 0.0001$) concentrations than children on mixed diets. No differences in eicosapentaenoic acid (EPA, 20:5 n–3) were seen in children. When comparing caregivers, ALA concentrations did not differ between the diet groups while serum EPA (BH-adjusted $p < 0.0001$) and DHA (BH-adjusted $p < 0.0001$) levels were lower in vegans than in the mixed diet group. Targeted analyses of serum total fatty acids by GC-FID are under way.

The results show that serum DHA concentrations were lower in children and adults following vegan diet. Strategies to increase preformed DHA intake in vegan diets may be warranted.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Maternal overweight-induced changes in the plasma phospholipidome are associated with altered immune cell frequencies in cord blood

Sebastian Graute[1], Perniyan Seyed-Abbaszadeh[1], Marceline Manka Fuh[1], Anna Worthmann[1], Petra Arck[2], Anke Diemert[3], Ludger Scheja[1], Joerg Heeren[1]

[1]Department of Biochemistry and Molecular Cell Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [2]Division for Experimental Feto-Maternal Medicine, Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [3]Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Abstract

Maternal obesity is linked to adverse health outcomes for the offspring during pregnancy and beyond. The basis of many complications is related to an insulin-resistant state, accompanied by an abnormal plasma metabolic profile and signs of chronic subclinical inflammation. So far, several studies focused on metabolic consequences for offspring of maternal obesity, but associations between maternal lipidome and fetal immunometabolism are largely undiscovered. In the current study, we investigate the effects of obesity on maternal plasma lipidome in each trimester of pregnancy and compare it with that of fetal cord blood. In addition, we associate maternal and fetal lipidomic patterns with the frequency of immune cell subsets in cord blood.

Using SelexION differential mobility mass spectrometry of the Lipidyzer™ platform and liquid chromatography coupled to mass spectrometry, we quantified more than 1,000 lipid species from 14 lipid classes in plasma samples of 170 healthy pregnancies and the corresponding cord blood plasma. According to pre-pregnancy BMI, the cohort was categorized into lean (BMI <25 kg/m2) and overweight (≥25 kg/m2) females. Circulating immune cells were analyzed using fluorescence-activated cell sorting.

Lipidomic analyses revealed increased gestational levels of phosphatidylethanolamines and triacylglycerides, especially ones containing arachidonic acid, in plasma of overweight women. In contrast, polyunsaturated phosphatidylcholine (PC) species displayed lower levels in plasma of overweight mothers during pregnancy as well as in cord blood. Notably, cord blood from neonates born by overweight women showed decreased levels of hydrophilic bile acid species compared to lean controls. Importantly, both obesity-associated PCs and bile acids correlated with the fetal immune cell profile.

These data imply that maternal obesity impairs fetal bile acid metabolism, which possibly affects the immunomodulatory properties of the fetal bile acid pool. In addition, our data suggest that polyunsaturated PCs are transplacentally transported and thus contribute to the immunometabolic crosstalk between mother and fetus.

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Genetic regulation of fatty acids in adipose tissue and their link to cardio-metabolic health

Miss Xinyu Yan PhD student ORCID iD[1], Mr Sergio Villicaña PhD student ORCID iD[1], Dr Maxim Freidin PhD ORCID iD[2], Dr Amy Roberts PhD ORCID iD[1], Dr Julia El-Sayed Moustafa PhD ORCID iD[1], Dr Jordana Bell PhD ORCID iD[1], Dr Kerrin Small PhD ORCID iD[1]
[1]King's College London, London, United Kingdom. [2]Queen Mary University of London, London, United Kingdom

Abstract

Fatty acids (FA) are essential to life and reflect the metabolic state of the human body. Adipose tissue (AT) serves as a critical endocrine organ that plays a central regulatory role in energy balance, glycolipid metabolism, cardiometabolic health, and immune response. AT lipolysis is the only source of plasma free FAs under postabsorptive conditions. To increase our understanding of the regulation and health impact of FAs in AT, levels of 18 FAs were measured in subcutaneous AT from 569 female twins from TwinsUK cohort, and FA ratios were calculated as proxies for enzymatic activities. The heritability of FAs ranged from 0.17 to 0.59, suggesting substantial genetic regulation of adipose FA levels. To identify genetic loci associated with FAs in adipose tissue, we performed genome-wide association studies for 36 heritable FAs. Thirteen distinct genome-wide significant loci (SCD, MKRN2/TSEN2, FADS1/FADS2, ZBTB41, EXOC6B, ACSL3, SNTB1/MTBP, PIEZO2, HAPLN1, RTL4) were associated with 13 FAs ($P<5\times10\text{-}8$). Moreover, these variants were also associated with type 2 diabetes, dyslipidemia, and coronary artery disease. To identify whether genes and epigenetic markers mediate SNP and adipose FAs, we conducted colocalization and mendelian randomization analyses using concurrent measures of adipose FAs, expression, and methylation data. Our findings indicated that the associations of SNPs with the levels of SFA and MUFA were mediated by one CpG and SCD expression, and n-6 PUFAs were intermediated through FADS1/FEN1 expression and two methylation probes. We next validated the links between FAs and cardio-metabolic markers in our study and found saturated FAs to be positively associated with LDL-C and TAG, but negatively associated with insulin resistance and β cell function, yet polyunsaturated FAs showed opposite effects. Discovering genetic variants and potential mediators of FA metabolism in AT and highlighting their associations with cardiometabolic health could open new opportunities for developing precise therapy strategies.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Influences of gender, diet, cigarette smoking and alcohol use on the metabolism of n-6 fatty acids in human subjects

Dr Robert Pawlosky Ph.D., Dr. Joseph Hibbeln MD, Dr. Yuhong Lin Ph.D., Dr. Norman Salem Jr. Ph.D.
National Institute on Alcohol and Alcoholism, Bethesda, MD, USA

Abstract

Plasma fatty acid (FA) profiles and in vivo n-6 FA metabolism were studied in subjects who either smoked (S) or did not smoke (NS) cigarettes when maintained on self-select, a fish- and a beef- based diet. A separate group of subjects with alcohol use disorder (AUD) were studied on self-select diets.

In a cross-over design, S and NS subjects subsisted on each of three diets for 3 wk. Beginning the final wk of each dietary period subjects consumed an oral dose of pentadeuterated (d5)-18:2n-6 ethyl ester. AUD subjects consumed a dose of the d5-ethyl ester. Plasma was sampled for FA and (d5) -18:2n-6, -20:2n-6, -20:3n-6, and -20:4n-6 over 168 h and analyzed using gas chromatography (GC) and GC-mass spectrometry. Time course data for the n-6 and d5- n-6 FA was fit to a compartmental model and the rate constants coefficients for the synthesis, utilization, and turnover of individual n-6 FAs were determined.

Results: Plasma concentrations of 20:5n-3 and 22:6n-3 were elevated on the fish diet compared to the beef diet in all subjects. Compared to NS men, smokers had higher concentrations of plasma 22:4n-6 and 22:5n-6 on the beef and self-select diets. Men who smoked also had higher concentrations of plasma 18- and 20- carbon n-6 FA compared to NS men. In all subjects synthesis of d5-20:4n-6 was greater on the fish- compared to the beef- diet and S men had the highest rates of synthesis. Men with AUD had elevated plasma n-6 FA compared to women with AUD.

Conclusions: Dietary fats, gender, smoking, and alcohol use distinctly influenced the metabolism of n-6 FA in humans. Dietary FA had a major impact on remodeling plasma n-6 FA and their in vivo metabolism. Men who smoke had heighten responses in the synthesis of 20:4n-6 and overall metabolism of n-6 FA.

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N-3 polyunsaturated fatty acid intake and status in Swiss pregnant women in association with antenatal depressive symptoms

Dr Jeannine Baumgartner PhD ORCID iD[1,2], Dr. Maria Andersson PhD ORCID iD[3], Dr. Isabelle Herter-Aeberli PhD ORCID iD[2]
[1]King's College London, London, United Kingdom. [2]ETH Zurich, Zurich, Switzerland. [3]University Children's Hospital Zurich, Zurich, Switzerland

Abstract

Maternal n-3 polyunsaturated fatty acid (PUFA) intake and status during pregnancy have been associated with a variety of pregnancy, maternal and child outcomes, including perinatal depression. The objectives of this study were to assess the n-3 PUFA intake and status in Swiss pregnant women and to explore associations with antenatal depressive symptoms. This study formed part of a cross-sectional national iodine survey in 500 Swiss pregnant women conducted in 2021-2022. We determined intake of n-3 PUFA using an abbreviated quantitative food frequency questionnaire and the n-3 PUFA status by measuring fatty acid composition (% of total fatty acids) in dried blood spots. We assessed antenatal depressive symptoms by using the Edinburg Postnatal Depression Scale (EPDS). In a preliminary sample of 304 pregnant women, the mean n-3 index was 4.59±1.03. The n-3 index was higher in women taking an antenatal supplement containing n-3 PUFA (43%) than in their non-supplemented counterparts (4.91±1.09% vs. 4.27±0.84%, P<0.001). Furthermore, the n-3 index was significantly higher in women who consumed fish ≥1x/week (25%) and 1-3x/month (42%) than in women who consumed fish <1x/month (33%) (5.05±1.18% and 4.71±0.96% vs. 4.29±0.94%). The median (IQR) EPDS score was 4 (2,8) and 13% of the women had an EPDS score ≥11 indicative of depression. We observed a negative correlation between the n-3 index and EPDS scores (r=-0.14, P=0.025). Our preliminary results indicate that Swiss pregnant women have a low n-3 PUFA status. Even though the n-3 PUFA status was higher in the women who reported taking a supplement containing n-3 PUFA or consumed fish ≥1x/week than in their respective counterparts, the n-3 PUFA remained low in these groups. The association between n-3 PUFA status and depressive symptoms further highlights the need for public health measures to optimize the n-3 PUFA status in Swiss pregnant women.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Impact of dairy fat supplementation on cognition during aging in a primate model, the grey mouse lemur (*Microcebus murinus*)

Yohann Chaudron[1], Constance Boyer[2], Corinne Marmonier[2], Mélanie Plourde[3,4], Annick Vachon[3,4], Bernadette Delplanque[5], Mohammed Taouis[5], Fabien Pifferi[1]

[1]UMR CNRS MNHN 7179, Brunoy, France. [2]Centre national interprofessionnel de l'économie laitière, Paris, France. [3]Centre de Recherche sur le Vieillissement, CIUSS de l'Estrie – CHUS, Sherbrooke, Canada. [4]Département de Médecine, Université de Sherbrooke, Sherbrooke, Canada. [5]Institut NeuroPSI - UMR9197 CNRS Université Paris-Saclay Campus CEA Saclay, Saclay, France

Abstract

Even if the consumption of dairy products is recommended at all ages for the general population, very little is known about their specific impact during aging. Since dairy fat could be a good source of short- and medium-chain fatty acids and a favourable n-6/n-3 polyunsaturated fatty acids ratio, we hypothesised that it could sustain brain functioning at different stages of life. The MiCo program, is currently testing the impact of dairy fat on cognitive functions during aging in a non-human primate, the grey mouse lemur (*Microcebus murinus*). This species is an omnivorous, easy to breed, lemuriform primate and a useful model for nutritional studies.

We designed two experimental diets: a dairy fat-based (DF, n=25) and a vegetal fat-based (VF, n=25) diet that have been implemented in 2 cohorts of aged mouse lemurs (~6 y.o.) and for 18 months. Different cognitive functions have been assessed, such as learning, working and long-term memory but also exploration and emotion-related behaviour.

There were strong differences in medium-chains saturated fatty acids and n-3 polyunsaturated fatty acids in the plasma supporting differences between dietary fatty acid intake. If long-term memory was not significantly different between DF- and VF-fed animals after 18 months of supplementation, we observed a significant improvement in learning in older DF-fed animals. In addition, we identified the presence of strong cognitive bias in VF-fed animals, that significantly increase with age compared to DF-fed animals. Brain imaging and function studies (PET-scan, MRI and EEG) will help decipher the mechanisms behind behavioural observations. In addition, miRNA expression, an important epigenetic marker, will be investigated to explore potential mechanistic hypotheses.

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Impact of dairy fat supplementation on brain functions during development and aging in a primate model, the grey mouse lemur (*Microcebus murinus*)

Yohann Chaudron[1], Constance Boyer[2], Corinne Marmonier[2], Mélanie Plourde[3,4], Annick Vachon[3,4], Bernadette Delplanque[5], Mohammed Taouis[5], Fabien Pifferi[1]

[1]UMR CNRS MNHN 7179, Brunoy, France. [2]Centre national interprofessionnel de l'économie laitière, Paris, France. [3]Centre de Recherche sur le Vieillissement, CIUSS de l'Estrie – CHUS, Sherbrooke, Canada. [4]Département de Médecine, Université de Sherbrooke, Sherbrooke, Canada. [5]Institut NeuroPSI - UMR9197 CNRS Université Paris-Saclay Campus CEA Saclay, Saclay, France

Abstract

Even if the consumption of dairy products is recommended at all ages for the general population, very little is known about the implication of dairy lipids in brain functioning during development and aging. Since dairy fat could be a good source of short- and medium-chain fatty acids and a favourable n-6/n-3 polyunsaturated fatty acids ratio, we hypothesised that it could sustain brain functioning at different stages of life. The *MiCo program* is currently testing the impact of dairy fat on cognitive functions during development and aging in a non-human primate, the grey mouse lemur (*Microcebus murinus*). This species is an omnivorous, easy to breed, lemuriform primate and a useful model for nutritional studies.

We designed two experimental diets: a dairy fat-based (DF, n=25) and a vegetal fat-based (VF, n=25) diets that have been implemented in 2 cohorts of animals. A cohort of new-born animals was supplemented from mother's pre-conception to 15 months old, and a cohort of aged animals (>5.5 y.o.) was supplemented for 18 months. Different cognitive functions have been assessed, such as learning, working and long-term memory, balance performance and exploration, at different stages of life

We showed that DF positively impacted the psychomotor performances in new-borns 8 days after birth, compared to VF. Learning and long-term memory were also improved at 3 months old and after. In aged animals' impact of DF was weaker than in young animals with a significant improvement in learning in older DF-fed animals.

The differences of effects between young and aged animals will be further explored using complementary approaches such as brain imaging and functioning lipids analysis in central and peripheral tissues but also metabolic outcomes. It will be completed by the analysis of epigenetic markers, to explore some mechanistic hypotheses

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Associations of n-3 polyunsaturated fatty acid status and intake with depression in Swiss adolescents with and without diagnosed paediatric major depressive disorder: a case-control study

Dr Ester Osuna PhD[1], Dr Isabelle Herter-Aeberli PhD[1], Dr. Klaus Schmeck[2], Prof. Susanne Walitza[3], Prof. Martin Hersberger[4], Prof. Michael Zimmermann[1], Dr. Isabelle Häberling[3], PD Gregor Berger[5], Dr. Jeannine Baumgartner PhD ORCID iD[6,1]
[1]ETH Zurich, Zurich, Switzerland. [2]Psychiatric University Hospitals Basel, University of Basel, Basel, Switzerland. [3]Psychiatric Hospital, University of Zurich, Zurich, Switzerland. [4]University Children's Hospital Zurich, Zurich, Switzerland. [5]Psychiatric Hospital University of Zurich, Zurich, Switzerland. [6]King's College London, London, United Kingdom

Abstract

Major depression, a leading cause of disability worldwide, often emerges during adolescence. The aetiology of depression is poorly understood and likely multifactorial. Observational studies suggest a link between n-3 polyunsaturated fatty acid (PUFA) intake, PUFA status, and depression in adults, but studies in adolescents are scarce. We determined associations of n-3 PUFA status and intake with paediatric major depressive disorder (pMDD) in Swiss adolescents.

We conducted a matched case-control study in 95 adolescents diagnosed with pMDD and 95 healthy controls aged 13 to <18 years. We analysed red blood cell (RBC) fatty acid (FA) composition (% of total FA). n-3 PUFA intake was assessed using a focused food frequency questionnaire and depression severity was assessed by the Children's Depression Rating Scale-Revised (CDRS-R).

Mean RBC EPA and DHA were lower in cases than controls (EPA: 0.41±0.11 vs 0.46±0.12, p<0.001; DHA: 4.07±1.04 vs 4.73±1.04, p<0.001). Subsequently, the mean RBC n-3 index was lower (4.51±1.10 vs 5.20±1.11, p<0.001). RBC ARA was lower in cases than controls (13.5±1.38 vs 14.2±1.01, p<0.001), but the n-6/n-3 PUFA ratio remained higher in cases than controls (5.51±1.25 vs 4.96±1.08, p<0.001). Adolescents with a higher n-3 index had lower odds for depression (OR=0.49 [95%CI:0.32-0.71]). In contrast, the n-6/n-3 ratio was associated with higher odds for depression (OR=1.58 [95%CI:1.14-2.25]). Higher RBC EPA and DHA were associated with lower odds for depression (EPA: OR=0.00 [95%CI:0.00-0.14]; DHA: OR=0.47 [95%CI:0.30-0.70]). However, intake of ALA, EPA and DHA did not differ between cases and controls.

Our results suggest that a higher n-3 PUFA status during adolescence is associated with a lower risk for pMDD, whereas a higher n-6/n-3 ratio is associated with a higher risk for pMDD. Differences in n-3 PUFA intake did not explain the observed differences in n-3 PUFA status.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Attenuation of lipid peroxidation and inflammation with low n6/n3 ratio diet in high fructose-fed rats

Prof Tomislav Masek PhD, Mrs Petra Roskaric PhD, Prod Kristina Starcevic Prof
University of Zagreb, Faculty of Veterinary medicine, Zagreb, Croatia, Zagreb, Croatia

Abstract

Herein, we investigated whether dietary intervention with DHA/EPA supplementation would attenuate lipid peroxidation and inflammatory markers in the liver and adipose tissue of rats fed a high-fructose diet. Male rats were divided into three groups: a control group (CON) (n6/n3 ratio ~7), a high fructose group (HF) (n6/n3 ratio ~7) and the DHA-HF group (n6/n3 ratio ~1, with the addition of docosahexaenoic (DHA) and eicosapentaenoic (EPA) acid). The CON group received plain water while the HF groups received 15% fructose in drinking water. Fructose overconsumption during five months significantly induced higher fasting blood insulin levels in all treated groups. A decrease in the content of EPA and DHA as well as EPA/ARA ratio was observed in the fructose treated rats. Moreover, the expression of inflammatory gene markers TGFβ, TNFα and IL6 was significantly increased in both tissues in the HF group. The decreased EPA/ARA ratio and the increase in the expression of inflammatory genes, are characteristics of the low-grade inflammation caused by fructose treatment. Decrease in the expression of antioxidant gene marker NRF2 was observed in both tissues in fructose fed rats. In addition, fructose treatment also increased malondialdehyde (MDA) and 4-hydroxynonenal (HNE) content in the liver and adipose tissue. DHA/EPA supplementation attenuated oxidative stress by increasing NRF 2 gene expression and decreasing the level of HNE and MDA. Moreover, DHA/EPA supplementation also decreased the expression of inflammatory gene markers in both tissues. Overall, this study showed that observed negative influence of fructose overconsumption in rat liver and adipose tissue could be ameliorated by dietary intervention consisting of DHA/EPA supplementation and lowering the n6/n3 ratio.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Age, sex and dietary fiber content influence on the liver fatty acids composition and desaturation in the high-sucrose rat model of obesity

Prof Tomislav Masek PhD, Mrs Petra Roskaric PhD, Prof Kristina Starcevic PhD
University of Zagreb, Faculty of Veterinary medicine, Zagreb, Croatia, Zagreb, Croatia

Abstract

This study evaluated the long-term effects of high-sucrose intake on the changes in the hepatic fatty acid metabolism. In particular, the effects of aging, sex and dietary fiber content on these parameters were evaluated.

Male and female Wistar rats were assigned to the control groups (normal or high fiber content), or experimental groups (normal or high fiber content). The control groups were provided with tap water and experimental groups with the solutions of sucrose in water (30%). Liver fatty acid profile was measured using GC-MS at the 2nd, 12th and 24th month. Desaturase activity was verified using quantitative PCR and Western Blotting.

Overconsumption of sucrose caused significant changes in the liver fatty acid profile. The most pronounced changes related to sucrose were increase in the content of palmitoleic and oleic acid due to the high increase in the Δ9 desaturation. In contrast sucrose treatment decreased the content of linoleic, arachidonic, and docosahexaenoic acid. All sex related differences that were visible in the 2nd month (increased stearic, arachidonic, and docosahexaenoic acids in females) were not visible at the 24th month probably due to the decreased desaturation during aging. The supplementation with the high fiber-low calory diet did not improve changes in the fatty acid profile caused by sucrose treatment. Interestingly, in the high fiber-low calory control group the content of liver docosahexaenoic acid content decreased at the 24th month to the level of sucrose treated rats, while the control group with normal fiber content maintained constant docosahexaenoic acid values.

Aging and chronic sucrose consumption show synergistic effects resulting in the alterations in the content of liver fatty acids and desaturation activity. High fiber-low calory diet failed to improve sucrose related changes. Initial positive effect of female sex on the content of polyunsaturated fatty acids is not visible in the aged rats.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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The skin lipid profile changes as we age, with consequences for the epidermal barrier and skin health

Dr Alexandra Kendall PhD ORCID iD, Rayed Alqahtani ORCID iD, Dr Kate Fisher PhD, James Horn, Professor Rachel Watson PhD ORCID iD, Professor Anna Nicolaou PhD ORCID iD
The University of Manchester, Manchester, United Kingdom

Abstract

The cutaneous epidermal barrier is maintained by a complex and unique profile of lipids, both in the stratum corneum and on the skin surface. We sought to investigate the impact of ageing on the epidermal lipidome, as this can directly affect the quality of the physical and immunological barriers, contributing to aged skin's impaired ability to resist and repair damage.

Adhesive tapes were used to sample the forehead (a sebaceous site), armpit (moist) and buttock (dry, photoprotected) of male (n=46) and female (n=52) healthy volunteers aged 18-40 and 70+. Ceramides (902 species) and oxygenated products of polyunsaturated fatty acids (11 species) were analysed using ultra-high performance liquid chromatography with tandem mass spectrometry. Free fatty acids (FFA; 60 species), triacylglycerols (TG; 97 species) and diacylglycerols (DG; 51 species) were analysed using ultra-high performance supercritical fluid chromatography with quadrupole time-of-flight mass spectrometry. Cholesterol was analysed using gas chromatography.

Lipid profiles were significantly altered in aged skin, with decreased FFA, TG, DG, and ceramides, and increased cholesterol; women showed more pronounced changes than men. Lipids varied by anatomical site, with FFA, TG and DG highest in forehead > armpit > buttock, and cholesterol the reverse. FFA, TG and DG demonstrated negative correlations with skin pH (which increased with age), whilst cholesterol demonstrated positive correlations with pH and transepidermal water loss. These show age-related changes in skin lipids that are more profound in females, potentially weakening the skin's defensive acid mantle and impairing barrier function, with significant detriment to skin health.

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Compound-specific analysis provides further insights into the association between dairy fatty acid biomarkers (15:0, 17:0) and dairy intake

Dr. Camilla Parzanini PhD ORCID iD[1], Miss Marisa Soo[1], Miss Shirley Vien[1], Dr. Bohdan Luhovyy PhD[2], Dr. Harvey Anderson PhD[1], Dr. Richard Bazinet PhD[1]

[1]University of Toronto, Toronto, Canada. [2]Mount Saint Vincent University, Halifax, Canada

Abstract

Increasing evidence suggests that dairy consumption may decrease the risk of type II diabetes. However, this association remain unclear, due to methodology limitations. Among these, the use of 15:0 and 17:0 as fatty acid (FA) biomarkers of dairy consumption is questioned as these FA may be found in food items other than dairy (e.g., meat, fish). Moreover, there is evidence for endogenous synthesis of 15:0 and 17:0. As a part of a secondary analysis, we used compound specific isotope analysis with the goal to increase the accuracy of the information provided by dairy FA biomarkers, considering that each food item holds a unique stable C isotope ($\delta^{13}C$) signature. Healthy, overweight to obese adults were randomly assigned to one of 3 dietary treatments in a controlled multi-site (Toronto, Halifax) clinical trial for 12 weeks: i) calorie-restricted (CR) diet; ii) dairy-rich (DR) diet, consisting of 3 servings of full-fat milk, cheese, and yogurt per day; and iii) dairy-rich and calorie restricted (DCR) diet. The $\delta^{13}C$ signatures of 15:0 and 17:0 were measured in dairy, collected prior to delivery to the participants, and plasma samples, drawn at baseline and every 4 weeks. Preliminary results, based on 187 plasma samples, indicated that the plasma isotopic signature overall varied between sites, suggesting intrinsic differences in the diet between these groups. Furthermore, the $\delta^{13}C_{15:0}$ and $\delta^{13}C_{17:0}$ ratios measured in the plasma of participants from Halifax consuming dairy increased ($p < 0.05$) towards the signature of dairy (δ13C15:0, -21.4 ± 0.9; δ13C17:0, -25.0 ± 0.8) in 12 weeks (D-$\delta^{13}C_{15:0}$, -27.5 ± 2.9 to -25.1 ± 0.1mUr, DCR-$\delta^{13}C_{15:0}$, -26.8 ± 3.2 to-24.6 ± 0.6; D-$\delta^{13}C_{17:0}$, -26.6 ± 1.9 to -25.9 ± 0.1mUr, DCR-$\delta^{13}C_{17:0}$, -27.0 ± 2.0 to -25.8 ± 1.5), reflecting dairy consumption. This study will contribute to refining and improve the use of biomarkers of dairy intake.

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Effect of vegetarian and vegan diet on fatty acid composition in blood and spermatozoa in young men

Dr. Rodrigo Chamorro PhD, Mss. Rut Farías Bachelor, Mss. Paulina Allende Bachelor, Mss. Camila Farías MSc., Dr. Rodrigo Valenzuela PhD.
University of Chile, Santiago, Chile

Abstract

Introduction: There is an growing interest in vegetarian and vegan diets but both diets can potentially affect tissue fatty acids (FA) composition. We aimed to evaluate the effect of vegetarian diets on plasma, erythrocytes, and sperm n-3 polyunsaturated fatty acids (PUFAs) status in healthy young men. Methods: Four groups were studied: i) men consuming a regular omnivore diet (OMV-1, n=35); men consuming an omnivore diet but without fish and seafood (OMV-2, n=34); men consuming a vegetarian diet (including dairy, eggs, fish, and seafood) (VEG-1, n=36); and men following a strict vegan diet (VEG-2, n=35). Participants in each group should follow their diet for at least the previous 12 months. Diet evaluation included a structured food frequency questionnaire (FFQ) and one 24-hour recall (24hR). FA composition was measured in plasma, erythrocyte phospholipids, and spermatozoa by gas-liquid chromatography, expressed as a mole percentage of the total FA content. Results: Main findings showed higher alpha-linolenic fatty acid (ALA) and total PUFAn-3 dietary intake in the VEG-2 group. In plasma, arachidonic (AA) and eicosapentaenoic (EPA) acids were higher in OMVs and VEG-1 groups whereas docosahexaenoic acid (DHA) level was lower in VEG-2. Higher ALA but reduced DHA and total PUFAn-3 levels were found in erythrocytes and spermatozoa in the VEG-2 group. Conclusion: Higher dietary ALA intake was found in vegetarians and vegan men. However, the higher ALA intake was not reflected in higher DHA content in the evaluated tissues. PUFA assessment and dietary supplementation with DHA is necessary to improve PUFA status in vegan men.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Contents and activities of desaturase and elongase enzymes in liver, brain, testicle and kidney from mice: Dependency of substrate

Dr. Rodrigo Valenzuela PhD.[1], Dr. Adam Metherel PhD[2], Dr. Giulia Cisbani PhD.[3], Mss. Mackenzie Smith Msc.[2], Dr. Raphaël Chouinard-Watkins PhD[2], Mss. Brinley Klievik MSc.[2], Professor Luis Videla Msc.[2], Dr. Richard Bazinet PhD[2]
[1]University of Chile, Santiago, Chile. [2]University of Toronto, Toronto, Canada. [3]University of Toronto, Toronto, Chile

Abstract

Objectives: The synthesis rates of n-3 and n-6 polyunsaturated fatty acids (PUFAs) in rodents and humans are not agreed upon and depend on substrate availability independently of the capacity for synthesis. Therefore, we aimed to assess the activities of the enzymes for n-3 and n-6 PUFA synthesis pathways in liver, brain, testicle, kidney, heart and lung, in relation to their protein mass levels. Methods: Eight-week-old Balb/c mice were fed a standard chow diet (6.2% fat, 18.6% protein and 44.2% carbohydrates) until 14 weeks of age, anesthetized with isoflurane and tissue samples were collected (previously perfused) and stored at -80 oC. The protein mass of the enzymes (D-6D, D-5D, Elovl2 and Elovl5) were assessed by ELISA kits; their activities were assayed using specific PUFA precursors and measuring the respective PUFA products as fatty acid methyl esters by gas chromatographic analysis. Results: The liver had the highest capacity for PUFA biosynthesis, with limited activity in the brain, testicles and kidney while we failed to detect activity in the heart and, lung. The protein content and activity of the enzymes were significantly correlated. Furthermore, D-6D, D-5D and Elovl2 have a higher affinity for n-3 PUFA precursors compared to n-6 PUFA. Conclusion: The capacity for PUFA synthesis in mice mainly resides in the liver, with enzymes having preference for n-3 PUFAs.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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A Study on the Portuguese Population Shows Which Factors Affect The Omega 3 Index, a Key Cardiovascular Health Indicator

Dr Narcisa Bandarra PhD ORCID iD, Dr Carlos Cardoso PhD, Romina Gomes Master, João Francisco Master, Maria Sapatinha Master, Dr Cláudia Afonso PhD
IPMA, Lisbon, Portugal

Abstract

A pioneer study on the relationship between lifestyle habits, diet, and health, as predictive factors, and the omega-3 index (sum of eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acid contents in the red blood cell membrane), as key parameter for the assessment of cardiovascular disease risk, was carried out in the Portuguese population. For this purpose, a representative sample of the Portuguese population (1,126 individuals) had blood sampled for the determination of the omega 3 index and a questionnaire answered. Participants were asked to indicate their consumption frequencies, the average meal portion, and other relevant data: gender, age, geographical location, lifestyle habits, and some health condition factors. The average omega 3 index of the population was 4.82 ± 2.30%, a value not too different from those of other Western populations and unexpected, given the high seafood consumption in Portugal. There was an increasing trend of the omega 3 index with higher amounts of consumed seafood, determining three or more weekly meals an omega 3 index of almost 6%, higher than the 3-5% level for lower consumption frequencies (below three weekly meals). Age was a major determinant, presenting 50-79 year old males higher omega 3 index values than 18-49 and >80 year old males, an effect of dietary patterns. Participants performing regular physical activity had a higher omega 3 index than the other ones, 5.05 ± 2.39% vs 4.64 ± 2.21%, and smokers had a lower omega 3 index than non-smokers, 4.38 ± 1.97% vs 4.89 ± 2.34%. Results showed that the effect of physical activity upon the index was not observed in the population with low seafood consumption levels. There was also a reduction of omega 3 index levels in elderly (>70 year old) with high blood pressure, from 5.57 ± 2.53% to 5.03 ± 2.27%.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Production and characterization of DHA-rich phospholipids extracts suitable for the prevention of Alzheimer disease

Dr Ana Bispo PhD[1,2], Romina Gomes Master[1], Inês Mendes Master[1], Prof. Paula Duarte PhD[3], Dr Carlos Cardoso PhD[1], Dr Cláudia Afonso PhD[1], Dr Narcisa Bandarra PhD ORCID iD[4,2]
[1]IPMA, Lisbon, Portugal. [2]CIIMAR, Porto, Portugal. [3]FCT, LIsbon, Portugal. [4]IPMA, LIsbon, Portugal

Abstract

Docosahexaenoic acid (DHA) is a key constituent of brain tissues membranes, being required for multiple physiological functions. Low levels of this fatty acid (FA) are related with cognitive decline and neurological disorders, like Alzheimer Disease (AD). Considering DHA is not produced by neurons, it must be provided by the diet. As lysophosphatidylcholine (LPC) is the preferred carrier form of DHA into the brain, its ingestion might be the straightest way to ensure the uptake of the required amounts of DHA.

Since most of the DHA found in pelagic fish, like Atlantic mackerel (Scomber scombrus), is found in phospholipids (PL) fraction, this abundant and cheap species was used to produce extracts rich in LPC-DHA for AD prevention. Oil was extracted with ethyl acetate and then with ethanol (to obtain the PL fraction), and phosphatidylcholine (PC) was converted into LPC through enzymatic hydrolysis with Rhizomucor miehei lipase. The extract was characterised in lipid classes and FA profile.

In the hydrolysed extract, PL corresponded to 21.2±2.7% of total lipid classes, and non-polar lipids (NL) accounted 78.8±2.7%. Among PL, LPC corresponded to 25.2±3.4% and PC to 21.7±4.1%. Lysophosphatidylethanolamine (LPE) and phosphatidylethanolamine (PE) were also identified, corresponding to 14.9±3.7% and 38.2±4.5%, respectively. In NL group, free FA and triacylglycerols (TAG) were the most abundant with 46.0±2.4% and 26.8±1.2% of total lipid classes, respectively. The FA profile of lipid classes showed that DHA represented in average 73.5% of total FA of LPC and LPE, 53.8% for PL and PE, and 18.6±1.0% in TAG fraction. These promising results demonstrate that the production of LPC-rich extracts suitable for supplementation may provide an innovative strategy to improve DHA brain uptake and AD prevention. It is also intended to contribute to the circular blue economy by upgrade of undervalued fish species.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Lipid profile of erythrocyte membranes as a novel inflammatory biomarker to distinguish metabolically healthy obesity in children for more precise nutritional recommendations

Dr Sara Arranz PhD ORCID iD[1], Iker Jauregibeitia[1], Itxaso Rica[2], Itziar Tueros[3], Olaia Velasco[2], Gema Grau[2], Luis Castaño[2], Carla Ferreri[4]
[1]AZTI, Food Research, Basque Research and Technology Alliance (BRTA)., Derio-Bizkaia, Spain. [2]Biocruces Bizkaia Health Research Institute, Barakaldo, Spain. [3]AZTI, Food Research, Basque Research and Technology Alliance (BRTA), Derio - Bizkaia, Spain. [4]National Research Council, Bologna, Italy

Abstract

Background: Metabolically Healthy Obesity (MHO) has been described as obese people, without traditional obesity-associated complications. Consensus to define MHO in children is required and continues being a challenge since nutritional stategies in MHO individuals should be personalized. Biomarkers of inflammation have been proposed as suitable candidates to describe MHO. Objective: The lipid profile of mature erythrocyte membranes (LPMEM) is proposed as a biomarker of inflammatory conditions with a strong relationship with metabolic and nutritional status that can differentiate children with MHO. Methods: An observational study was carried out in 194 children (76 with obesity and 118 with normal weight) between 6 and 16 years old. LPMEM was analysed by gas chromatography-flame ionization detector (GC-FID). Dietary habits were evaluated using validated food frequency questionnaires (FFQ). An unsupervised hierarchical clustering method was conducted on the LPMEM from children with obesity to identify clusters with MHO. Results: The MHO cluster showed a LPMEM similar to children with normal weight, characterised by lower values of arachidonic acid, total ω-6 fatty acids (FA), ω6/ω3 FA ratios and higher values for EPA, DHA and total ω-3 FA ($p \leq 0.01$) compared to the rest of the children with obesity. The MHO cluster also presented higher Δ-9-desaturase activity and lower SFA/MUFA ratio compared to the rest of children with obesity. Conclusions: The LPMEM, together with clustering techniques, provides an excellent biomarker to identify MHO children. Differences observed are relevant for the follow-up of patients, also in view of personalized protocols providing tailored nutritional recommendations for the intake of essential fatty acids. Monitoring the LPMEM can be extended to other population studies and validate it as a biomarker to differentiate, for example, subjects who are of normal weight but metabolically unhealthy.

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Analytical characterization of chemically oxidized highly unsaturated neural phospholipids via GC-MS/MS and LC-MS/MS

Secilia Garza Analytical chemistry ORCID iD[1], Genevieve James Nutrition[1], Dr Hikyu Park Food science[2], Dr Paul Baker Analytical chemistry[3], Dr J. Thomas Brenna Analytical chemistry[1,2]
[1]University of Texas, Austin, USA. [2]Dell Medical School, Austin, USA. [3]SCIEX, Redwood City, USA

Abstract

Phospholipid (PL) oxidation is likely to be a shared characteristic in neurodegenerative diseases. Specifically, reactive oxygen species attack highly unsaturated fatty acids (HUFA) on a PL at the bis-allylic C-H bond due to the weak bond dissociation energy (75 kcal/mol). Docosahexaenoic acid (DHA; 22:6) performs critical roles in the nervous system and is particularly susceptible to oxidation at its five bis-allylic positions. We demonstrate proof-of-principle in which oxidized HUFA on intact PLs are detected in complex neural tissue extracts (bovine retina and rat brain tissue). Lipid extracts are subjected to mild chemical oxidation (likely in the form of hydroxyls, epoxides, peroxides, or hydroperoxides) in ambient air conditions. GC-MS provides a full quantitative profile of the fatty acids that compose the neural PLs. The fatty acid profile is referenced to build multiple reaction monitoring (MRMs) of expected PLs in neural tissue for LC-MS/MS analysis via the Sciex 7500 Triple Quadrupole/Qtrap system. We primarily focus on monitoring the oxidation of phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs), particularly those with DHA. Tandem mass spectrometry revealed the extent of oxidation on intact neural PLs. With the use of independent data acquisition (IDA) MRMs, we have confirmed the detection of unoxidized (native; chemically unaltered) PCs and PEs in neural tissue as well as their damaged, oxidized counterparts after oxidation in our model system. MS/MS analysis of di-22:6 (di-DHA) species unique to retina shows that both O are on a single 22:6 chain, suggesting addition as a hydroperoxide. Quantitative estimates of oxidation products will be presented.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Neuroblastoma cells in culture are severely essential fatty acid deficit.

Dr Hui Gyu Park PhD, Dennis Sheeter, Secilia Martinez Garza, Niharika Badi, Erika Espinosa, Kumar Kothapalli PhD, James Thomas Brenna PhD, John Powers PhD
University of Texas at Austin, Austin, USA

Abstract

Background.

Neuroblastoma (NB) is a devastating cancer of childhood affecting the extra-cranial nervous tissue, usually originating in the neural crest cells of the adrenal. NB can progress rapidly to death or, remarkably, arise asymptomatically and spontaneously go into remission with lesions. We cultured several NB initial and relapse cell lines under standard conditions to check whether fatty acid profiles change.

Methods

Fibroblasts served as non-neural controls. Four NB paired cell lines (diagnosis and relapse) were studied: SK-N-BE(1) and SK-N-BE(2), SMS-KAN and SMS-KANR, SMS-KCN and SMS-KCNR, and CHLA-15 and CHLA-20. Culture conditions were RPMI 1640, 10% FBS, 5% CO2, 37ºC. RNA-Seq confirmed by qPCR for selected genes in the PUFA metabolism pathway were analyzed. Kaplan-Meyer (KM) plots were generated using R2, an online datamining platform to indicate whether any particular gene expression changes are known to be associated with NB pathology.

Results

Fibroblast fatty acids were strikingly different from NB cells. Under normal physiological conditions, the essential fatty acid deficiency indicator Mead acid (20:3n-9) should be close to 1% of ARA (20:4n-6), however in NB cells, they were comparable in intensity. The elongation product of Mead acid, 22:3n-9, was similarly elevated and thus confirmed the finding. The C18 precursors of ARA and DHA, linoleic acid and alpha-linolenic acid as well as all intermediates were at very low levels. These results indicate that PUFA levels in the media are insufficient to support the demand of NB cells for HUFA, and imply that the cells respond by upregulating synthesis of Mead acid (20:3n-9) which can be synthesized de novo. KM plots showed expression of most of the fatty acid synthetic genes were upregulated in NB.

Conclusions

Standard culture conditions induce dramatic essential fatty acid deficiency in NB cell lines. KM data indicate that NB pathology is tied to fatty acid synthesis.

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Physicochemical properties of liposomal solutions of marine, dairy, and egg lecithin for the encapsulation of vitamin D

Fatoumata CONDE, Maureen GERLEI, Dr Cyril KAHN, Dr Elmira ARAB-TEHRANY, Dr Michel LINDER
Université de Lorraine, Nancy, France

Abstract

Vitamin D is a liposoluble molecule, which has many biological properties, such as calcium homeostasis regulation for optimal growth and the maintenance of proper bone mineralization throughout life. Its low solubility in water strongly reduces its bioavailability. This leads to a generalized deficiency of this vitamin, which is a worldwide public health problem. Thus, vitamin D supplementation in encapsulation systems, which increases its stability, biological functions, and bioavailability, remains essential. The most viable method to encapsulate vitamin D remains the nanostructured lipid carriers. These nanoliposomes are characterized by a high loading capacity and low toxicity, facilitating the transport and the controlled release of lipophilic molecules such as liposoluble vitamins. Indeed, phospholipids, which are amphiphilic molecules composed of a hydrophilic part and a lipophilic part, give them the capacity to encapsulate molecules of different hydrophilicity. The objective of this study was to study vitamin D_3 encapsulation with different liposomal solutions elaborated from marine lecithin rich in eicosapentaenoic and docosahexaenoic acids, egg lecithin rich in essential fatty acids such as linoleic and alpha linolenic acids, and mainly phosphatidylcholine, and dairy lecithin rich in sphingolipids and ceramides. The evaluation of these nanoliposomes was carried out according to their physicochemical characteristics (fatty acid composition, size, electrophoretic mobility, structure), as well as their stability over time and their encapsulation efficiencies, to determine the best carrier for this vitamin. The nanoliposomes composed of marine lecithin showed better properties in size, electrophoretic mobility, structure, stability, and encapsulation efficiency compared to those formulated from egg and milk lecithin.

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Hepatic and intestinal de novo lipogenesis after a high sucrose and high fat diet

Professor Jean-Marc Schwarz PhD[1,2], Dr. Sally Chiu PhD[1], Assoc. Professor Grace Jones PhD[1], Researcher Sergiu Palii PhD[1], Researcher Krishna Barakoti PhD[1], Researcher Ewan Sinclair PhD[1], Professor Susan Noworolski PhD[2], Professor Morrie Schambelan MD[2], Professor Kathleen Mulligan PhD[2]

[1]Touro University CA, Vallejo, USA. [2]University of California San Francisco, San Francisco, USA

Abstract

Hepatic de novo lipogenesis (hDNL) is increased by consumption of fructose-containing sugars and is associated with hyperlipidemia, hepatic steatosis, and insulin resistance. In a randomized, crossover study in nine overweight/obese participants, we compared the amount of newly synthesized fat (hepatic and intestinal, iDNL), and lipid and metabolic profiles after 12 days of a high-sucrose (HS) vs. a high-fat (HF) isocaloric diet. Both hDNL and iDNL, fasting triglycerides, and total cholesterol (C) to HDL-C and triglyceride to HDL-C ratios were significantly higher with the HS diet. In a separate, randomized study focused on meal pattern, ten overweight/obese participants consumed the isocaloric HS or HF diets as small, frequent meals (eight meals/day) or two large meals/day. There were no significant differences between meal patterns in DNL or lipid profiles. Overall, a short-term HS vs. HF diet was associated with adverse lipid markers of cardiometabolic risk, an effect not mitigated by consuming the diets as small, frequent meals.

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Optimizing the Synergistic Action of Medium-chain Triglycerides and Omega-3 Fatty Acids for Preserving Cellular Metabolic Homeostasis and Inhibiting LPS-induced Pro-inflammatory Responses

Benjamin Frank MS, Camila Isern MS, Yao Chen MS, Roni Touboul BS, Shuchen Hu BS, Dr Chuchun Liz Chang PhD
Columbia University, New York, USA

Abstract

Objectives: Bioactive omega-3 fatty acids (n-3 FA) exhibit pro-healing and anti-inflammatory characteristics. Our previous studies have shown that a model triglyceride (TG)-rich lipid emulsion (TGRP) containing both medium-chain TG (MCT) and n-3 TG (8:2, wt/wt) was rapidly cleared from the blood and readily available for organ uptake in experimental animal models. Our goal was to define the optimal ratio of MCT to n-3 that would maximize cellular uptake and enrichment of n-3 FA to enhance its anti-inflammatory effects and mitigate adverse pathophysiological responses.

Methods and Results: We measured cellular TG uptake and deposition of model TGRP comprising pure MCT, n-3 and mixed MCT: n-3 TG in different ratios (8:2, 6:4 and 2:8, wt/wt) using a non-metabolizable radioactive tracer - [^{3}H]CEt in vitro and in vivo. Metabolic and inflammatory phenotypes were analyzed using qRT-PCR, Seahorse-based bioenergetics and lipidomics. Our data show that 4-h incubation of murine macrophages with MCT:n-3 6:4 or 2:8 TGRP (200 g TG/ml) led to 2-fold increases in TG uptake compared to other TGRP ($p<0.05$). IV Injection of mixed MCT/n-3 TGRP (0.4 mg TG/25 g BW) also accelerated blood clearance and fractional catabolic rates and was readily available for organ uptake ($p<0.05$). n-3-containing TGRP suppressed LPS-induced expression of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6) in a dose-dependent manner, while MCT TGRP had little effect. MCT:n-3 8:2 TGRP notably enhanced mitochondrial respiration and glycolytic capacity in resident and LPS-stimulated macrophages ($p<0.05$). Pro-inflammatory lipid species - ceramides and diglycerides were reduced in macrophages treated with MCT:n-3 2:8 and n-3 only TGRP.

Conclusion: MCT and n-3 FA cooperatively preserve metabolic activity and demonstrate anti-inflammatory effects. The optimal composition of MCT and n-3 TG to maximize cellular enrichment of n-3 FA will inform the design of more effective therapeutic agents aimed at ameliorating adverse inflammatory responses.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Detection of epoxides and vicinal diols of bis-allylic deuterated docosahexaenoic acid in rat retinas by LC/MS/MS

Genevieve James MS, Nutrition ORCID iD[1], Secilia Garza[1], Dr. Hikyu Park[1,2], Dr. Paul Baker[3], Dr. Mikhail Shchepinov[4], Dr. J Thomas Brenna[1,2]

[1]The University of Texas at Austin, Austin, USA. [2]Dell Medical School, Austin, USA. [3]Sciex, Framingham, USA. [4]Biojiva, Los Altos, USA

Abstract

Background: Retina is rich in docosahexaenoic acid (DHA), an oxidatively labile fatty acid required for retinal response to light. In a mouse model of retinal degeneration, we recently showed that feeding mice bis-allylic deuterated DHA (D-DHA) prior to intraocular iron injections completely protected the retina from iron-catalyzed oxidative damage. Epoxy and vicinal diol products of DHA derived from the cytochrome P450 (CYP450) pathway have been linked to retinal disease pathogenesis. We searched in retinal tissue to discover whether these products from D-DHA and natural DHA (H-DHA) could be detected.

Experimental Approach: Rats were fed a D-DHA diet for two months and sacrificed. Fatty acid profiles for single eyecups containing retinas were generated with GC-MS. A Sciex® ExionLC® coupled to a model 7500 triple quadrupole ion trap was used to identify oxylipins from both H-DHA and D-DHA, including the target epoxy and vicinal diols.

Results: GC-MS analysis showed that an array of D-DHA isotopologues, bis-allylic D8-D13 DHA, were present in the eyecup tissue. D-DHA comprised over 50% of all DHA in the tissue. LC-MS/MS analysis revealed the presence of epoxides (EpDPA) and vicinal diols (DiHDPA) at the 7-8, 10-11, and 19-20 positions for the H-DHA and D-DHA parent molecules. The relative abundance of the H versus D peaks showed differences, with some dominated by the H isotopologue and others by the D isotopologues within one compound class. For metabolites related by a hydrolysis event, e.g., 19,20-EpDPA → 19,20-DiHDPA, relative abundances differ implying different rates of enzyme-driven hydrolysis.

Conclusion: D-DHA shows great promise as a therapeutic for retinal diseases driven by oxidative stress. This is the first time D-DHA derived bis-allylic deuterated oxylipins generated from the CYP450 pathway have been reported. D-DHA is metabolized to these oxylipins, illuminating a potential mechanism of action for D-DHA as a retinal disease therapeutic.

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Lysophosphatidyl choline Docosahexaenoic acid (LPC-DHA) is a novel therapeutic approach for the prevention and treatment of Alzheimer's disease

Dr Sugasini Dhavamani PhD ORCID iD
University of Illinois at Chicago, Chicago, USA

Abstract

Alzheimer’s disease is the most common cause of dementia which accounts for 60 to 80% of cases. One safe and cost-effective preventive approach is to increase the brain DHA levels through the diet, because of the well-known beneficial effects of DHA on brain function. Moreover, high habitual DHA consumption is associated with a low incidence of AD. However, currently available dietary supplements have yielded disappointing results in both humans and experimental animals.Recent studies demonstrated the specific transporter (Msfd2a) that selectively transports LPC-DHA through BBB. Our aim is to identify the most efficient dietary carrier of DHA for enriching brain DHA and to determine whether such enrichment can prevent Alzheimer’s disease. We tested that enriching brain DHA by dietary LPC-DHA prevents or delays the development of AD in mouse models of 5XFAD mice. LPC-DHA was blended with rodent chow to yield the final DHA concentration of 0.35 g/kg diet and fed to 5XFAD mice for 6 months, starting at the age of one month. The control group was fed algal DHA oil containing DHA at the same dose in the form of triacylglycerol (TAG) Our results showed that LPC DHA significantly increased brain DHA in female 5XFAD mice, whereas the TAG DHA showed a much lower effect Dietary LPC DHA markedly decreased Aβ42 levels as compared to 5XFAD control and 5XFAD TAG. These results suggest that dietary LPC DHA could be protective against Amyloid βeta production and accumulation. More importantly, mice treated with LPC DHA showed significantly improved spatial learning and memory in the Morris water maze test, and increased brain BDNF levels, compared to TAG DHA-treated 5XFAD mice and WT mice. This study could lead to a novel nutraceutical approach for the prevention and treatment of Alzheimer's disease and related dementia as well as other neuro-inflammatory diseases.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Nutritional value and fatty acid profile of fermented products as a vitamin K dietary sources

Associate Professor Magdalena Franczyk-Żarów dr hab. inż. ORCID iD[1], PhD Student Barbara Czosnowska mgr inż.[1], Research Assistant Agnieszka Kij dr ORCID iD[2], Associate Professor Marek Sady dr hab. inż. ORCID iD[1], Associate Professor Kinga Topolska dr hab. ORCID iD[1], Professor Renata B. Kostogrys prof. dr hab. dr n. med. ORCID iD[1]
[1]University of Agriculture in Krakow, Krakow, Poland. [2]Jagiellonian Centre for Experimental Therapeutics (JCET), Krakow, Poland

Abstract

The term vitamin K refers to a group of several lipophilic chemical compounds, among which we can distinguish vitamin K1 (of plant origin) and vitamin K2, which contains several forms depending on the length of the isoprene chain. Until recently vitamin K was associated with the regulation of the coagulation system. The interest in the biological activity of these compounds increased when it was discovered that vitamin K2 affects the processes of calcification of both bones and soft tissues. Due to the fact that vitamin K2 (except for the MK-4) is produced as a result of bacterial synthesis, the products that are the richest source of these compounds may be fermented food products such as fermented soybean *natto* or cheese.

The aim of the study was to determine the basic composition, fatty acid profile and forms of vitamin K in fermented products. Dry matter, ash and fiber content were determined by standard methods (AOAC), fat content using the TFE 2000 analyzer, and protein - TruSpec N. The fatty acid profile was analyzed using GC-MS. Determination of the content of phylloquinone and menaquinones was performed by HPLC.

Fermented products show significant differences in basic composition and fatty acid profile depending on the origin and can be considered a source of vitamin K in the human diet. The best source of phylloquinone was sauerkraut, while the highest content of menaquinones, especially MK-7, was found in *natto*, while cheeses contained the most vitamin K2 in the form of long-chain menaquinones.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not applicable.

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Effects of basil seed meal (rich in dietary fiber and alpha-linolenic acid) against insulin resistance and hepatic steatosis induced by a high-fat diet in mice

Mss. Camila Farias Bachelor[1], Mss. Camila Cisternas Bachelor[1], Mss. Angie Caicedo Msc.[1,2], Mss. Lorena Mercado Bachelor[1], Dr. Loreto Muñoz PhD.[3], Dr. Rodrigo Valenzuela PhD.[1]
[1]University of Chile, Santiago, Chile. [2]University of Antioquia, Medellin, Colombia. [3]Universidad Central de Chile, Santiago, Chile

Abstract

Introduction: Currently there is an increase in the incidence of insulin resistance (IR) and hepatic steatosis in the population. Dietary fiber and alpha-linolenic acid (C18:3n-3, ALA) have a protective role against these metabolic alterations. Despite this, the average intake of dietary fiber and alpha-linolenic acid is very low (compared to what is recommended). Basil (Ocimum basilicum L.) is a plant that is consumed all over the world. However, the nutritional characteristics of the basil seed have not been widely studied. Objective: To determine the effects of basil seed meal rich in dietary fiber and alpha-linolenic acid against IR and hepatic steatosis induced by a high-fat diet in mice. Methods: Mice were fed a control diet or a high-fat diet (HFD) for 10 weeks, then HFD-fed animals received a diet supplemented with basil seed meal (HFD-B), for 4 weeks (14 weeks of age). intervention). Results: The HFD diet induced IR, hepatic steatosis, a proinflammatory state, and a significant decrease in the production of short-chain fatty acids (CCFA). In contrast, the HFD diet supplemented with HFD-B achieved a protective effect through a lower IR, attenuation of hepatic steatosis, decreased inflammatory state, an increase in n-3 polyunsaturated fatty acids (ALA, EPA and DHA) in liver, adipocytes and erythrocytes, and increase in CCFA production. Conclusions: The supplementation with HFD-B exerted a protection against the injury generated by the HFD, for which the basil seed meal could be considered as a potential therapeutic line for the management of IR and the reversal of hepatic steatosis.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Associations between *FADS* and *ELOVL* genetic variants with EPA or DHA levels in human blood pools: A scoping review.

Insaf Loukil[1,2], David Mutch[3], Melanie Plourde[4,2]

[1]Department of Medicine, Faculty of Medicine and health sciences, University of Sherbrooke, Sherbrooke, QC J1H 5N4, Canada., Quebec, Canada. [2]Research Center on Aging, Health, and Social Sciences Center – Sherbrooke University Geriatrics Institute, Department of Medicine, University of Sherbrooke, Sherbrooke, QC J1G 1B1, Canada., Quebec, Canada. [3]University of Guelph | UOGuelph · Department of Human Health and Nutritional Sciences (HHNS), Ontario, Canada. [4]Department de Medicine, Faculty of Medicine and health sciences, University of Sherbrooke, Sherbrooke, QC J1H 5N4, Canada., Quebec, Canada

Abstract

Omega-3 fatty acids play a significant role on general health. Among the most important are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which can be synthesized from alpha-linolenic acid (ALA). However, the conversion rate is still debated. The synthesis of EPA and DHA requires fatty acid desaturase and elongation enzymes which are encoded by the *FADS* and *ELOVL* genes, respectively. Although it is well known that there are genetic variations in the *FADS* and *ELOVL* genes, the extent to which they modify the conversion of ALA to EPA and DHA is unclear.

This scoping review aims to evaluate the current evidence regarding whether *FADS* and *ELOVL* polymorphisms change the level of EPA and DHA in human serum/plasma/RBC.

Research articles were identified using PubMed, Cochrane, and Scopus databases.

A total of 47 different SNPs in FADS were reported across 41 peer-reviewed papers. Only 7 SNPs were reported in 7 studies for *ELOVL* polymorphisms. *FADS*1-rs174537 was the most studied SNP. EPA and DHA levels were associated with this SNP where those carrying the minor allele (T) had lower levels compared to those carrying the major allele (C). EPA was more correlated with genetic variations in *FADS* and *ELOVL* than DHA. Considering the large number of SNPs investigated in *FADS* and the few studies investigating SNPs in *ELOVL*, the functional SNP (s) yet haven’t been clearly identified. Whether these SNPs are really involved in the levels of omega-3 remain to be established.

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Benefits of a chia by-product in the reversal of hepatic steatosis and other metabolic disturbances induced by a high-fat diet in mice

Miss Camila Cisternas Bachelor[1], Miss Camila Farias Bachelor[1], Miss Angie Caicedo Msc.[1], Mr. Hector Calderon Bachelor[2], Miss Lorena Mercado Bachelor[1], Miss. Alejandra Espinosa PhD.[1], Miss. Loreto Muñoz PhD[2], Dr. Rodrigo Valenzuela PhD.[1]
[1]University of Chile, Santiago, Chile. [2]Universidad Central de Chile, Santiago, Chile

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide. In NAFLD, increased liver triglycerides (steatosis), insulin resistance, oxidative stress, inflammation and decreased n-3 polyunsaturated fatty acids are observed. Dietary fiber and alpha-linolenic acid (C18:n-3,ALA) play a fundamental role in the regulation of these parameters. Chia (Salvia hispanica L.) is a seed that has a high content of dietary fiber (predominantly insoluble) and ALA. Objective: To evaluate the effects of consuming a chia by-product rich in dietary fiber and ALA on the development of hepatic steatosis and other metabolic alterations induced by a high-fat diet in mice. Methods: Male C57BL/6J mice were randomly assigned to control diet (10% fat) (CD) or high-fat diet (60% fat) (HFD) for 10 weeks. Subsequently, they were fed with CD or HFD containing 20% (w/w) chia seed rich in dietary fiber and ALA (HFD-Ch) for 4 weeks (14 weeks of intervention). Parameters of steatosis and liver damage, insulin resistance, inflammation, lipid profile and liver fatty acids were evaluated. Results: HFD feeding induced hepatic steatosis and metabolic alterations. The intake of HFD-Ch significantly protected against HFD in i) hepatic steatosis; ii) inflammatory and oxidative stress parameters, iii) triglyceride levels and liver fat content, and iv) increased n-3 PUFA (ALA, EPA and DHA) content. Conclusion: The intake of HFD-Ch generated protection against the damage caused by HFD, for which it could be considered as a therapeutic potential for the management of hepatic steatosis and other metabolic disorders in mice.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Sex dependent changes in tissue and serum n-3 PUFA levels of liver-specific *Elovl2*-KO mice fed an ALA-only or ALA+DHA diet

Kuorosh Rezaei Bachelor of Science, Ashley Bejoy, Brinley Klievik Master of Science, Dr. Adam Metherel Doctor of Philosophy
University of Toronto, Toronto, Canada

Abstract

Docosahexaenoic acid (DHA, 22:6n-3) must be consumed from diet or synthesized from polyunsaturated fatty acid (PUFA) precursors, such as a-linolenic acid (ALA, 18:3n-3). Elongase 2 (*ELOVL2* gene) catalyzes two elongation reactions in the PUFA biosynthesis pathway and may be important in regulating the observed sex differences in n-3 PUFA levels. Therefore, the aim of the present study was to determine how the targeted knockout of liver *Elovl2* affects tissue and blood n-3 PUFA levels in male and female mice. Twenty-eight-day old male (M) and female (F) liver *Elovl2*-KO and control (CTL) mice were placed onto one of the two dietary protocols (4–8 mice per genotype, per diet, per sex): 1) an 8-week 2% ALA diet or 2) a 4-week 2% ALA diet followed by a 4-week 2% DHA + 2% ALA diet. At 12 weeks of age, mice were sacrificed and liver, brain, heart, plasma and erythrocytes were collected and fatty acid levels measured. Generally, liver-specific *Elovl2*-KO increased n-3 PUFA substrates and decreased n-3 PUFA products of *Elovl2*. There were significant interaction effects ($p < 0.05$, sex x genotype) for DHA levels in liver and heart. In liver, DHA levels were significantly different ($p<0.01$) between all groups with F-CTL > M-CTL > F-KO > M-KO, and in the heart F-CTL = M-CTL > F-KO > M-KO ($p<0.001$). However, F-KO mice had significantly higher DHA levels in the heart compared to M-KO mice. The addition of DHA to diet removed the interaction effects on DHA levels in the liver and heart, yielding a significant sex effect (F > M, $p<0.01$) in liver and genotype effect (CTL > KO, $p<0.05$) in the heart. Liver-specific knockout of *Elovl2* results in significantly lower DHA in the liver, serum, heart, and brain, with potential sex dependent differences in the liver and heart.

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Regulation of SREBP1c transcriptional activity by oleate

Tania Guillemette Msc, Antoine Jutras-Carignan PhD, Catherine Mounier
Université du Québec à Montréal, Montréal, Canada

Abstract

BACKGROUND: The transcription factor sterol regulatory element-binding protein 1c (SREBP1c) is the main regulator of lipid homeostasis. It is regulated by various nutritional and hormonal stimuli. However, the molecular mechanisms underlying these adaptive responses remain to be elucidated. Preliminary results have shown that a decrease in intracellular oleate concentration leads to a decrease in SREBP1c transcriptional activity and that SREBP1c is labeled when cells are incubated with radiolabeled oleate. These results suggest that SREBP1c may be acylated by oleate, or by one of its metabolites. Acylation, a post-translational modification of a protein by a lipid, increases the hydrophobic character of a protein allowing to regulate its cellular localization, its stability, and its interactions with other proteins. OBJECTIVES: To characterize the molecular mechanisms involved in the regulation of SREBP1c transcriptional activity by oleate. METHODS AND RESULTS: Using bioinformatics analysis, we identified a cysteine on SREBP1c that could be acylated. Mutation of this cysteine by an alanine completely prevents SREBP1c proteolytic cleavage and reduce the mRNA level of his target gene Stearoyl-CoA desaturase-1 (SCD1) and Fatty acid synthase (FAS) in cultured hepatocarcinoma cells. Furthermore, using a mass shift technique that exploits the cysteine-specific chemical property, it was shown that mature SREBP1c was present in three different acylation states at the cysteine residues in mouse liver, namely: no acylation, 1 or 2 acylations. Acylated forms of SREBP1c are more present in the livers of mice fed an obesogenic, high oleate diet as opposed to a non-obesogenic, low-fat diet. CONCLUSION: The characterization of a new mechanism of regulation of SREBP1c activity would constitute a major advance in the field of lipid metabolism and in the understanding of several diseases associated with metabolic disorders.

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Novel Insights Into the Role of Very Long Chain Fatty Acids In Neuronal Function.

Dr Martin-Paul Agbaga PhD ORCID iD[1,2], Dr Gyening Kofi Yeboah PhD ORCID iD[1,2], Dr Neeraj K Chauhan PhD ORCID iD[1,2], Madison Tytanic B.SC ORCID iD[2], Vicki Ea MS ORCID iD[2], Richard S Brush MBA ORCID iD[2]

[1]Dept. of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, USA. [2]Dept. of Ophthalmology & Dean McGee Eye Institute, OUHSC, Oklahoma City, USA

Abstract

Elongation of Very Long Chain Fatty Acid-4 (ELOVL4) enzyme mediates tissue-specific biosynthesis of both Very Long Chain PUFA (VLC-PUFAs) and VLC-Saturated FA (VLC-SFAs) that play critical roles in neuronal function, and in maintenance of the skin permeability barrier. While some ELOVL4 mutations cause blindness in Autosomal Dominant Stargardt-like Macular Dystrophy (STGD3), other heterozygous ELOVL4 point mutations, such as L168F and W246G, affect the brain and/or skin, leading to Spinocerebellar Ataxia-34 (SCA34) and Erythrokeratodermia (EKV). The mechanisms by which these ELOVL4 mutations alter VLC-PUFA and VLC-SFA biosynthesis to cause the different tissue-specific pathologies are not well understood. To understand how the different ELOVL4 mutations alter VLC-PUFA relative to VLC-SFA biosynthesis to cause neurodegenerative disorders including STGD3 and SCA34, we used *in vitro* studies and animal models of STGD3 and SCA34 to interrogate how the different mutant ELOVL4s affect very chain fatty acids (VLC-FA: VLC-PUFA and VLC-SFA) biosynthesis to contribute to disease pathology. We showed that L168F and W246G mutants were capable of VLC-PUFA biosynthesis relative to VLC-SFA biosynthesis. W246G synthesized and accumulated 32:6n3, while L168F exhibited gain of function of VLC-PUFA biosynthesis and made 38:5n3, which we did not detect in WT-ELOVL4 or W246G-expressing cells. However, compared with WT-ELOVL4, both L168F and W246G mutants were deficient in VLC-SFA biosynthesis, especially the W246G, which showed negligible VLC-SFA biosynthesis. The STGD3 causing mutant ELOVL4 lacks both VLC-PUFA and VLC-SFA biosynthesis. These results suggest VLC-PUFA biosynthetic capabilities of L168F and W246G in the retina may explain the lack of retinal phenotype in SCA34 patients, while the retinal pathology in the STGD3 may be due to loss both VLC-PUFA and VLC-SFA. We propose that defects in VLC-SFA biosynthesis by L168F and W246G variants contribute to the pathogenic mechanisms underlying age-related cerebellar neurodegeneration in SCA34, and the skin defects in EKV.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

https://pubmed.ncbi.nlm.nih.gov/36464075/

Gyening YK, Chauhan NK, Tytanic M, Ea V, Brush RS, Agbaga MP. ELOVL4 Mutations That Cause Spinocerebellar Ataxia-34 Differentially Alter Very Long Chain Fatty Acid Biosynthesis. J Lipid Res. 2023 Jan;64(1):100317. doi: 10.1016/j.jlr.2022.100317. Epub 2022 Dec 1. PMID: 36464075; PMCID: PMC9823237.

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Measuring the turnover of docosahexaenoic acid (DHA) in mouse brain, liver, and plasma tissues using compound specific isotope analysis

Brinley Klievik, Dr Adam Metherel, Dr Rodrigo Valenzuela, Dr Giulia Cisbani, Dr Richard Bazinet
University of Toronto, Toronto, Canada

Abstract

The brain is rich in DHA, which plays important roles in regulating neuronal function. Recently, using compound-specific isotope analysis (CSIA) that takes advantage of natural differences in carbon-13 content ($^{13}C/^{12}C$ ratio or $\delta^{13}C$) of the food supply, we determined brain DHA half-lives in mice. However, due to methodological limitations, we were unable to capture DHA turnover rates in peripheral tissues. In the current study, we applied CSIA via high-precision gas chromatography combustion isotope ratio mass spectrometry (GC/C/IRMS) to determine half-lives of brain, liver, and plasma DHA in mice following a dietary switch experiment. To model DHA tissue turnover rates in peripheral tissues, we added earlier timepoints within the diet switch study, took advantage of natural variations in the $\delta^{13}C$-DHA of algal and fish DHA sources to maintain DHA pool sizes and used an enriched (uniformly labeled ^{13}C) DHA treatment. Mice were fed a fish-DHA diet (control) for 3 months, then switched to an algal-DHA treatment diet, the ^{13}C enriched-DHA treatment diet, or they stayed on the control diet for the remainder of the study time course. In mice fed the algal and ^{13}C enriched-DHA diets, the brain DHA half-life was 47 and 46 days, the liver half-life was 5.6 and 7.2 days, and the plasma half-life was 4.7 and 6.4 days respectively. By using improved methodologies, we calculated DHA turnover rates in the liver and plasma, and our study for the first time, by using an enriched DHA source (very high $\delta^{13}C$), validated its utility in diet switch studies. Future work will examine the turnover of DHA in the remaining tissues (adipose, skin, muscle, heart, and RBCs).

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Impact of high linoleic acid intake and/or maternal obesity on n-3 polyunsaturated fatty acids metabolism in liver and brain rats in newborn and prepuberty

Dr. Rodrigo Valenzuela PhD[1], Miss. Lorena Mercado Bachelor[1], Miss Camila Farias Bachelor[1], Miss. Camila Cisternas Bachelor[1], Miss. Angie Caicedo Msc.[1,2], Dr. Alexies Dagnino PhD[3], Mr. Robinson Carrasco Bachelor[3], Dr. Alejandra Espinosa PhD.[3,1]
[1]University of Chile, santiago, Chile. [2]Universidad de Antioquia, Medellin, Colombia. [3]Universidad de Valparaiso, Valparaiso, Christmas Island

Abstract

Introduction: n-3 polyunsaturated fatty acid (n-3 PUFA) especially α-linolenic acid (C18:3n-3, ALA) and docosahexaenoic acid (C22:6n-3, DHA) shown to have a relevant role in the fatty acid metabolism in liver and brain. But, several factors can limit the bioavailability of n-3 PUFAs (ALA and DHA) and impact the PUFA metabolism in liver and brain in newborn and prepuberty. Aim: The high linoleic acid (C18:2n-6, LA) intake and/or maternal obesity during pregnancy and breastfeeding impair ALA's ability to DHA in liver and brain in rats in newborn and prepuberty. Methodology: Female rats 12 weeks before pregnancy, during pregnancy and lactation, and pups 7 days after weaning were fed the following diets: i) control diet (CD: 10% energy as fat: ALA 2% + LA 8%, ii) CD-rich in LA (ALA < 1% + LA 10%), iii) high fat diet (HFD: 60% energy as fat: ALA 2% + LA 8%, iv) HFD-rich in LA (ALA < 1% + LA 10%). We evaluated i) the content of n-3 and n-6 PUFAs in brain (cortex), erythrocytes, liver and adipose tissue, ii) hepatic parameters of oxidative stress, and iii) activity of delta-6 and delta-5 desaturase enzymes in liver and brain of newborn and prepubertal rats. Results: HFD-rich in LA generated a significant reduction in content of n-3 PUFA (ALA, EPA and DHA) in all tissues studied. Followed by CD-rich in LA and HFD , compared to CD. Regarding the n-3 PUFA, the significant reduction of DHA content in cerebral cortex and liver was notable. Liver and brain of offspring of rats fed with HFD-rich in LA, a significant reduction in activity of desaturase enzymes (delta-6 and delta-5), and significant increase in the hepatic parameters of oxidative were observed. Conclusion: These results demonstrate the adverse effect of obesity and low ALA intake on n-3 PUFA metabolism during pregnancy, lactation, and prepuberty.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Effects of omega-3 polyunsaturated fatty acids on human brain structure and function in anxiety and depression: A systematic review and hierarchical narrative synthesis

Mr Christos F. Kelaiditis MSc ORCID iD, Dr E. Leigh Gibson PhD ORCID iD, Prof Paul Allen PhD ORCID iD, Dr Simon C. Dyall PhD ORCID iD
University of Roehampton, London, United Kingdom

Abstract

Anxiety and depression are characterised by aberrant prefrontal cortex metabolite concentrations and emotion-generated corticolimbic network functional connectivity. Randomised controlled trials (RCTs) have utilised neuroimaging techniques to explore the underlying treatment-related effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in anxiety and depression. However, in our recent meta-analysis, we identified that significant reductions in the severity of depressive symptoms were only produced with supplementation with EPA-enriched regimes comprising EPA doses at a ratio of ≥60% of total EPA+DHA (Kelaiditis et al., 2022). We therefore utilised a hierarchical approach to review the literature, firstly summarising all neuroimaging RCTs investigating omega-3 PUFA interventions in depression, and secondly summarising only those that achieved this level of supplementation (PROSPERO ID: CRD42022345553).

The literature was searched systematically for human interventions administering omega-3 PUFAs regimes, while employing measures of anxiety and/or depression and neuroimaging techniques comprising functional magnetic resonance imaging, magnetic resonance spectroscopy and diffusion tensor imaging. The findings are presented in a two-level hierarchical narrative synthesis, with results grouped into meaningful concepts relative to neuroimaging findings comprising subjects supplemented with omega-3 PUFAs at various degrees of anxious and/or depressive states. Level 1 comprised studies administering any oral supplemental form of omega-3 PUFAs and placebo preparation, where seven articles, comprising five studies and 160 participants, were identified. At level 2, where EPA was provided at doses ≥60% of total EPA+DHA, with placebo regimes free of bioactive compounds, such as olive oil, two studies with a total of 65 participants were identified.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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EPA at proportions of ≥60% of total EPA and DHA is associated with reductions in the severity of depressive symptoms

Mr Christos F. Kelaiditis MSc ORCID iD, Dr E. Leigh Gibson PhD ORCID iD, Dr Simon C. Dyall PhD ORCID iD
University of Roehampton, London, United Kingdom

Abstract

Mounting preclinical and mechanistic evidence suggests that the omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic (EPA), docosahexaenoic (DHA) and docosapentaenoic (DPAn-3) acids may be promising therapeutic options against affective disorders. However, meta-analyses (MAs) of randomised controlled trials (RCTs) consistently produce mixed findings, attributed to methodological inconsistencies in RCTs. This MA assesses for the first time the efficacy of omega-3 PUFA against the severity of anxious and depressive symptoms, measured by validated scales, with specific consideration of methodological issues encountered in the field.

The literature was searched systematically on PubMed, CINAHL, PsycINFO, Cochrane Library and Web of Science for eligible RCTs administering omega-3 PUFA against anxiety and/or depression. This systematic review and meta-analysis (SR/MA) adopts the PRISMA guidelines. Ten RCTs comprising 1509 participants were included in the quantitative synthesis. The main finding of this SR/MA is that EPA-enriched interventions comprising EPA proportions ≥60% of total EPA+DHA are associated with a modest, but statistically significant reduction in depression severity, compared to placebo (SMD:−0.32;95% CI: −0.59,−0.06;p=0.02); however, EPA doses of ≥2000 mg/day are not (SMD:−0.11;95% CI:−0.43,0.20;p=0.48).

There are some concerns regarding bias and population heterogeneity amongst the eligible studies, highlighting the lack of high-quality RCTs in this area. Our findings indicate that EPA at proportions ≥60% of total EPA+DHA, and doses between of 1000 mg and 2000 mg, reduces depression scores. Further high-quality RCTs are needed, with specific methodological consideration for this field, to elucidate the therapeutic potential of EPA, DHA and DPAn-3.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Effects of high-eicosapentaenoic acid multinutrient supplementation on brain structure and function in young adults; Preliminary findings from NeuroMOOD

Mr Christos F. Kelaiditis MSc ORCID iD, Dr E. Leigh Gibson PhD ORCID iD, Prof Paul Allen PhD ORCID iD, Dr Simon C. Dyall PhD ORCID iD
University of Roehampton, London, United Kingdom

Abstract

Poor omega-3 PUFA status is associated with aberrant brain function and structure and anxious and depressive symptomatology. Dietary enrichment with omega-3 PUFAs has been shown to improve these outcomes. NeuroMOOD is a two-centre, 12-week, randomised, placebo-controlled, proton magnetic resonance spectroscopy and functional magnetic resonance imaging trial exploring the effects of a high-EPA multinutrient supplement on brain function and structure in young adults. This is a nested study within the NutriMood Study (ClinicalTrials.gov Identifier: NCT04844034).

University students (18-29 years) without a diagnosis of anxiety and/or depression, but with Generalised Anxiety Disorder Assessment-7 (GAD-7) score ≥ 5, and Patient Health Questionnaire (PHQ-8) depression score ≥ 4 were randomised to active treatment (1125 mg EPA, 441 mg DHA, 330 mg magnesium and 7.5 mg vitamin E per day), or placebo, for 12 weeks. The primary outcomes were changes from baseline in choline and myo-inositol concentrations in the dorsolateral prefrontal cortex and the anterior cingulate cortex, and changes from baseline in seed-to-voxel functional connectivity using bilateral orbitofrontal cortex and amygdala seeds at week 12. The correlations between changes in neurometabolite levels and functional connectivity and measures of anxiety and depression, assessed with GAD-7 and PHQ-8 respectively, were also investigated. Resting-state fMRI and ^{1}H-MRS images were acquired on a 3-T Siemens Magnetom TIM Trio scanner using a 32-channel head coil. Resting-state fMRI data was analysed on SPM-12 and Conn Toolbox in MATLAB, and ^{1}H-MRS data was analysed on LCModel and GABA Analysis Toolkit (Gannet).

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Effects of high-EPA supplementation on stress, anxiety and depression in young adults: Preliminary findings from NutriMOOD

Mr Christos F. Kelaiditis MSc ORCID iD, Dr E. Leigh Gibson PhD ORCID iD, Dr Simon C. Dyall PhD ORCID iD
University of Roehampton, London, United Kingdom

Abstract

Anxiety disorders affect nearly 20% of young and are highly comorbid with depressive disorders. Our recent systematic review and meta-analysis suggests that supplementation with EPA and DHA, comprising EPA proportions of ≥60% of total EPA and DHA, is associated with statistically significant reductions in the severity of depressive symptoms. However, the effects in those with sub-clinical anxiety and depression, who may not otherwise be eligible for pharmacological or cognitive behavioural therapy interventions, have not been well explored. Results presented are a non-final analysis of the NutriMood Study ("Effects of a High EPA Multinutrient Supplement on Negative Affect in Young Adults", ClinicalTrials.gov Identifier: NCT04844034).

Young adults (18-29 years) without a diagnosis of anxiety and/or depression, but with a Generalised Anxiety Disorder Assessment-7 (GAD-7) score ≥ 5, and Patient Health Questionnaire (PHQ-8) depression score ≥ 4, were randomised to active-treatment (1125 mg EPA, 441 mg DHA, 330 mg magnesium and 7.5 mg vitamin E per day), or placebo, for 12 weeks. The primary outcome was change in anxiety symptoms, compared to placebo, assessed with the GAD-7 scale. Secondary endpoints were depression assessed with PHQ-8, anxiety and stress on the 21-item Depression, Anxiety and Stress Scale (DASS-21), and a battery of Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive function tests sensitive to mood, including Emotional Bias Task, Rapid Visual Information Processing, Spatial Working Memory, and Stop Signal Task. Dietary intake, whole-blood fatty acid content, and a range of polymorphisms thought to influence omega-3 polyunsaturated fatty acids metabolism were also assessed.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Omega-6 and Omega-3 Fatty Acids in Metabolism, Inflammation and Pathogenesis of Type-2-Diabetes

Professor Laurence Harbige PhD ORCID iD[1], Professor Efosa Oghagbon MBBS[2], Mr Mohamed Ahmed PhD Candidate[1], Professor Roxana Valdes-Ramos PhD[3]

[1]London Metropolitan University, London, United Kingdom. [2]College of Health Sciences, Benue State University, Makurdi, Nigeria. [3]Universidad Autonoma del Estado de Mexico, Toluca, Mexico

Abstract

Worldwide there are 537 million people living with type-2-diabetes (DM2) and is predicted to increase to 783 million people by 2045 (IDF 2021). In many DM2 studies the *n*-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:6*n*-3) and *n*-6 PUFA linoleic acid (LA, 18:2*n*-6) show negative epidemiological associations whilst other studies show beneficial effects of these PUFA on metabolic and inflammatory biomarkers in DM2. These and experimental and molecular findings appear to be direct or indirect effects of these PUFA on insulin sensitivity via, e.g., GLUT transporters, kinases, free fatty acids, blood lipids, transcription factors (e.g., PPAR), and inflammatory cytokines/adipokines. In a comparative study of plasma phospholipid fatty acids of DM2 and healthy controls from Mexican and West African (Nigerian) populations we found significant intra- and inter-population similarities and differences. Both Mexican and West African DM2 had significantly lower dihomogammalinolenic acid (DGLA, 20:3*n*-6), arachidonic acid (AA, 20:4*n*-6), Adrenic acid (22:4*n*-6) and Osbond acid (22:5*n*-6) compared with the corresponding healthy controls. This could indicate an *n*-6 conversion problem in DM2. In contrast both Mexican DM2 and their corresponding healthy controls had higher LA compared with their West African counterparts whilst West African DM2 and their corresponding healthy controls had higher EPA and DHA than their counterpart Mexican DM2 and healthy controls. This suggests differences in dietary intake of LA, EPA, and DHA between Mexican and West Africans and/or the known 18:2*n*-6/22:6*n*-3 relationship. Mexican and West African fatty acid findings are further discussed in relation to metabolic and inflammatory biomarkers.

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Fatty acid profiles of the lipid classes from the muscle tissue of European anchovy (Engraulis encrasicolus, Lineus 1758).

Dr Grigorios Krey PhD ORCID iD
Fisheries Research Institute, Nea peramos, Greece

Abstract

Small pelagic fish, such as the European anchovy (Engraulis encrasicolus), being omnivorous planktivores, play a crucial role in the transfer of EPA and DHA between lower and higher trophic levels and therefore, constitute an important intermediary source for these fatty acids in human nutrition. Herein, the fatty acid profiles of the lipid classes in the polar and neutral fractions from the muscle (filet) fat of European anchovy were determined through a combination of Thin Layer and Gas Chromatography methods. Analyses were performed on day-fresh fish, as well as on 4-days post-harvest fish stored in slurry ice containing 3,5% NaCl. In the day-fresh fish, the polar fraction of the fat is rich in poly-unsaturated fatty acids with DHA being the most abundant, representing >30% of the total fatty acids. In contrast, saturated fatty acids, and particularly palmitic acid, dominate in the neutral fraction of the fat. The lipid classes within the polar and neutral fractions exhibited fatty acid profiles corresponding to those of their respective fractions, with the exception of the phosphatidyl inositol and phosphatidyl serine classes, where the saturates are more abundant. The same pattern, with non-significant variations, was observed in the polar and neutral fractions of the 4-days post-harvest fish, indicating that the high levels of n-3 PUFAs are preserved during storage. However, a significant quantitative shift from TGA towards the free fatty acids appears to be associated with storage time.

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Development of fluorescent tool compounds to investigate endocannabinoid metabolism in tissue preparations and intact cells

Thomas Lange ORCID iD[1], Tim Depmeier[1], Timo Strünker[2], Matthias Lehr[1]
[1]Institute of Pharmaceutical and Medicinal Chemistry, University of Münster, Münster, Germany. [2]Centre of Reproductive Medicine and Andrology, University Hospital Münster, University of Münster, Münster, Germany

Abstract

Endocannabinoids play an important role in many physiological and pathophysiological processes. The two most prominent representatives of these are the monoacylglycerol 2-arachidonoylglycerol (2-AG) and the ethanolamide anandamide (AEA). Both their biosynthesis and degradation can in principle be catalyzed by different enzymes, whose respective relevance varies depending on the cell type or tissue. To study the metabolism of 2-AG and AEA, as well as the influence of hormones or other compounds on it, fluorescent substrates that behave like the corresponding natural substrate can serve as a powerful tool. We have therefore synthesized novel fluorescent analogs for 2-AG and AEA and their major precursors 1,2-diacylglycerol (DAG) and *N*-acyl phosphatidylethanolamine (NAPE), respectively. In these probes, the arachidonoyl residue of the natural compound was replaced by a fluorescent 4-(pyren-1-yl)butanoyl group. The derivatives thus obtained were used to monitor the activity of enzymes involved in endocannabinoid metabolism, such as *N*-acyl phosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD), 1,2-diaylglycerol lipase (DAGL), fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), in various tissue homogenates (rat liver preparations and brain microsomes) and in intact cells (human sperm) using HPLC with fluorescence detection. In addition, the fluorogenic substrates can be employed to evaluate inhibitors of these enzymes.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Lipid mediator response following unaccustomed resistance exercise in healthy males is dietary fatty acid intake dependant

Dr Arista Nienaber PhD Dietetics ORCID iD, Mr Victor Akerele MSc Dietetics ORCID iD, Dr Lizelle Zandberg PhD Biochemistry ORCID iD, Dr Cornelia Conradie PhD Nutrition ORCID iD, Prof Lize Havemann-Nel PhD Exercise Science ORCID iD, Prof Linda Malan PhD Nutrition ORCID iD
North-West University, Potchefstroom, South Africa

Abstract

In exercise, the inflammatory response is stimulated by muscle injury and oxidative stress. Inflammation is essential for recovery, but non-resolving inflammation can have detrimental consequences. Inflammation and resolution are, therefore, equally important and influenced by n-6 and n-3 PUFA. The relationship between dietary PUFA intake and post-exercise inflammation is unknown. This study aimed to determine the association of dietary n-6 and n-3 essential and LCPUFA intake with the lipid mediator response following a bout of unaccustomed resistance exercise in apparently healthy males.

This longitudinal study included 33 healthy males aged 18 to 35 years subjected to an unaccustomed exercise challenge. Dietary fatty acid intake over 3 days before exercise and a longer period was measured with 3-day dietary records and quantified food frequency questionnaires (QFFQ), respectively. Blood samples were collected before and directly, 1, 2, 24 and 72 hours after exercise to measure lipid mediators and fatty acid status. Data were analysed with linear mixed models.

Higher AA and total n-6 LCPUFA intake over 3 days before exercise were associated with a higher 15-HETE response (P=0.017 and P=0.009) and higher longer-term LA intake was associated with higher 5-HETE (P=0.010). A higher 3-day intake of ALA and DHA were associated, and total n-3 LCPUFA tended to be associated, with higher 17-HDHA post-exercise (P=0.026, P=0.017, and P=0.069). Similarly, with a higher longer-term EPA and total n-3 LCPUFA intake, higher 18-HEPE was evident post-exercise (P=0.017 and P=0.005). Resolvin D1 was not associated with dietary intake, but higher longer-term EPA and total n-3 LCPUFA intake were associated with lower resolvin E1 (P=0.001 and P=0.49).

A higher dietary n-6 and n-3 essential and LCPUFA intake in the 3 days before exercise, and over a longer term may both mediate the post-exercise pro-inflammatory and inflammation-resolving lipid mediator intermediate response in healthy males.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Effects of MFGM-providing ingredients on intestinal functions using an *in vitro* quadricellular model of intestinal epithelium

Gwenal Broudic[1,2], Marion Lemaire[1], Julie Pourprix[3], Benjamin Choque[1], Latifa Bousarghin[2], Isabelle Le Huërou-Luron[2], Sophie Blat[2]
[1]SODIAAL, Research and Innovation Center, Rennes, France. [2]NUMECAN, INRAE, INSERM, Univ Rennes, Rennes, France. [3]SODIAAL, Eurosérum, Port-sur-Soaône, France

Abstract

Intestinal digestive, barrier, endocrine and immune functions are modulated by the nature of the food bolus. We hypothesized that dairy ingredients providing milk fat globule membrane (MFGM) could modulate these functions.

Our objective was to investigate the effects of four dairy ingredients (A, a non-enriched source of MFGM and B to D, enriched MFGM-ingredients) on gut functions in both physiological and inflammatory environments using a quadricellular (Caco-2, HT29-MTX, NCI-H716 and RajiB) model of the human intestinal epithelium.

Enriched ingredients were standardized at 1.34 mg/mL phospholipids whereas ingredient A was used at a lower concentration (0.51 mg/mL) to investigate dose-dependent effects. Inflammation was induced using TNFα. Cytoxicity was evaluated by lactate-dehydrogenase release and barrier integrity by trans-epithelial electrical resistance (TEER). Expression of genes of interest was quantified by RT-qPCR.

All MFGM-ingredients significantly decreased cytotoxicity and improved barrier integrity compared to culture medium alone in the physiological state. An MFGM-dose dependent effect on TEER was observed, with the strongest effects for enriched ingredients. Ingredients B and C, both enriched in MFGM but differing in protein fraction, induced more changes in gene expression (barrier, digestive, endocrine and proliferative functions).

In the inflammatory state, all four ingredients had no effect on cytotoxicity but maintained barrier integrity. Ingredient B up-regulated several genes involved in gut barrier (claudins, mucins, occludin, ZO-1), digestive function (lactase) and induced a stronger immune response. Ingredient A, closer to ingredient B in terms of protein fraction, also modulated the expression of genes involved in digestive and immune functions, suggesting that components other than MFGM, such as proteins, could be involved in the observed effects.

These results add to the body of evidence of MFGM benefits. Further analysis is being conducted to investigate the effects of these ingredients incorporated within a model matrix and subjected to an *in vitro* digestion.

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PUFA content in maternal diet modifies inflammation in neonatal mouse cerebral microvessels, blood and brain.

Tetyana Chumak[1], Maryam Ardalan[1,2], Joakim Ek[1], Pernilla Svedin[1], Zinaida Vexler[3], Carina Mallard[1]
[1]Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [2]Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, Denmark. [3]Department of Neurology, University California San Francisco, San Francisco, USA

Abstract

The content of PUFAs in the maternal diet can affect offspring brain development, angiogenesis and inflammatory response early in life. To explore the possible mechanisms of these effects, we performed an extensive analysis of the cerebral microvessel transcriptome and cytokine/chemokine profile in neonatal plasma and brain after initiation of inflammation in the offspring of mothers fed balanced (soybean oil-based), n-3 (fish oil-based) or n-6 (corn oil-based) PUFA enriched diets.

Female mice were fed one of the three diets from the first day of mating. On postnatal day (P) 9 pups received an intraperitoneal injection of LPS (1mg/kg) or saline solution. RNA sequencing was performed on brain microvessel samples extracted from P10 pups. Blood plasma and brain tissue were collected from P10 and P12 pups, and cytokine/chemokine levels were measured using the Mouse Cytokine Standard 31-Plex (Bio-Rad).

LPS affected the microvessel expression of 791 genes in balanced, 742 genes in n-3 and 677 genes in n-6 diet; 379 of them were common for the three diets. Genes involved in defense response and cytokine production were upregulated by LPS to a greater extent in the cerebral microvessels of pups fed n-3 diet, while inflammation affected the expression of fewer genes related to angiogenesis, tight junctions and extracellular matrix in n-3 diet compared to the other two diets. The effect of treatment on the blood level of 16 cytokines in balanced, 12 in n-3 and 14 in n-6 enriched diet was found, 8 of these cytokines were common to all diets. In contrast, more brain cytokines were regulated in pups fed n-3 (16) and n-6 (14) than balanced (8) diet 1 day after LPS injection.

Maternal diet impacts the inflammatory response in neonatal cerebral microvessels, blood and brain.

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The abstract has not been published

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Unveiling how temperature and salinity affect the lipid composition of the microalga *Tetraselmis striata* CTP4 using lipidomic approaches

Tiago Conde[1,2,3], Dr Susana Aveiro[4], Dr Tânia Melo[1,2], Tamára Santos[5], Professor Dr Bruno Neves[3], Professor Dr Pedro Domingues[2,4], Professor Dr João Varela[5,4], Dr Hugo Pereira[4], Professor Dr M. Rosário Domingues[1,2,4]

[1]CESAM - Centre for Environmental and Marine Studies, Aveiro, Portugal. [2]Mass Spectrometry Centre, LAQV-REQUIMTE, Aveiro, Portugal. [3]Department of Medical Sciences and Institute of Biomedicine—iBiMED, Aveiro, Portugal. [4]GreenCoLab - Associação Oceano Verde, Faro, Portugal. [5]CCMAR–Centre of Marine Sciences, Faro, Portugal

Abstract

Tetraselmis striata CTP4 is a euryhaline, eurythermal microalga, rich in lipids, including omega-3 polyunsaturated fatty acids (PUFAs). However, little is known about how salinity and temperature affect its fatty acid profile and distribution of the membrane polar lipids and reserve neutral lipids across this microalga lipidome. Thus, this work sought to evaluate the plasticity of the fatty acid profile and the lipidome of *T. striata* CTP4 grown under different combinations of salinity (5, 20 and 35 ppt) and temperature (10, 20, 30 and 40°C) by gas-chromatography (GC-MS) and liquid-chromatography coupled to mass spectrometry (LC-MS). *Tetraselmis striata* biomass produced under all combinations of salinity and temperature showed a high abundance of PUFAs, especially omega-3 PUFAs. Temperature was the variable that mostly affected the FA composition of *T. striata* CTP4, while little to no changes were observed under different salinities, for the same temperature. The cultures grown under the condition T30-S20 achieved the highest accumulation of PUFA (biomass of 108.0±19.4 mg FA.g-1), and omega-3 PUFA (biomass of 66.3±12.2 mg FA.g-1). The content in omega-3 PUFA decreased in cultures at 20°C when compared to 10°C, and accompanied by an increase in the omega-6/omega-3 ratio. Fatty acids from *T. striata* were distributed across different polar and neutral lipids which were altered by salinity and temperature. Lipid species up-regulated at 30°C and at all salinities appear to correspond to less unsaturated species, while at 10°C and 20°C the up-regulated lipid species appeared to be more unsaturated. *Tetraselmis striata* CTP4 grown at 40°C had higher monounsaturated FA and triacylglycerol productivity, although imposing severe limitations on its survival. Overall, the different combinations of salinity and temperature allowed the production of biomass with dissimilar lipid composition and nutritional value with promising biotechnological applications.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

The abstract has not been published yet. However, till the date of February 13th 2023, a work containing the results herein described is under evaluation in the Journal *Algal Research*.

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Lipophenols as a new pharmaceutical solution against carbonyl stress in Alzheimer’s disease

Léa OTAEGUI[1,2], Jordan Lehoux ORCID iD[1], Théo Urgin[2], Mathieu Vitalis[2], Dr Laurent Givalois ORCID iD[2], Dr Thierry Durand ORCID iD[1], Dr Catherine Desrumaux[2], Dr Céline Crauste ORCID iD[1]

[1]Institut des Biomolecules Max Mousseron (IBMM), Pôle Recherche Chimie Balard, UMR5247, Université de Montpellier, CNRS, ENSCM, , 1919 rte de Mende, Montpellier, France. [2]Molecular Mechanisms in Neurodegenerative Dementia Laboratory, University of Montpellier, EPHE-PSL, INSERM U1198, Montpellier, France

Abstract

Alzheimer’s disease (AD) accounts for 80% of dementia cases worldwide, with a prevalence correlated with the aging of population. AD patients become entirely dependent due to memory loss, motor dysfunction, and disorientation. The major histopathological marker of AD is the accumulation of extracellular senile plaques composed of aggregated beta amyloid peptides. At the biochemical level, amyloid accumulation leads to increased oxidative stress, which through lipid peroxidation induces the apparition of another type of stress called carbonyl stress. Carbonyl stressors (small reactive aldehydes as malondialdehyde, glyoxal or acrolein) form adducts with proteins, lipids and nucleic acids and disturb their functions. Oxidative and carbonyl stress (COS) are thereby therapeutics targets to fight AD progression.

Polyphenols and omega-3 polyunsaturated fatty acids (PUFAs) are two types of natural compounds known to reduce COS and neuroinflammation. However, their efficacy in vivo is limited by the low bioavailability of polyphenols and the oxidation susceptibility of PUFAs. Lipophenols are hybrid molecules composed by a polyphenol (anti-oxidant) and a PUFA (DHA; anti-inflammatory). In a previous work, alkyl-lipophenols, having isopropyl group (IP) on one polyphenol function, showed ability to reduce COS in both in vitro and in vivo models of age-related macular degeneration.

In this work, an in vitro methodology was developed to evaluate the potential of three different DHA-containing alkyl-lipophenols with resveratrol, phloroglucinol or quercetin as polyphenol part, to reduce COS in a neuroblastoma cell line, using acrolein as carbonyl stressor. Quercetin-7-IP-3-DHA showed the best protection against toxic concentrations of acrolein and was selected for further in vivo assays to evaluate its therapeutic potential in a transgenic mouse model of AD. Thus, to produce a sufficient amount of quercetin-7-IP-3-DHA for in vivo evaluation, a new synthetic methodology (gram scale up) was developed using a chemoenzymatic pathway.

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Maternal obesity programs liver lipidomic alterations in offspring

Juan Antonio García Santillán PhD[1], Carla Elena Mezo González PhD[1], Mathilde Gourdel PhD[2,3,4], Mikaël Croyal PhD[2,3,4], Francisco Bolaños Jiménez PhD[1]

[1]UMR Physiologie des Adaptations Nutritionnelles, INRAE— Nantes Université, Nantes, France. [2]CRNH-O Mass Spectrometry Core Facility, Nantes, France. [3]Nantes Université, CNRS, INSERM, L'institut du Thorax, Nantes, France. [4]Nantes Université, CHU Nantes, Inserm, CNRS, SFR Santé, Inserm UMS 016, CNRS UMS 3556, Nantes, France

Abstract

Human epidemiological and experimental animal studies show that individuals born to obese mothers develop hepatic steatosis. However, it is unknown whether the quality, in addition to the quantity, of cumulated lipids in the liver of the offspring is impacted by maternal obesity. To address this issue, here the liver lipidomic profile of male adult rats born to obese dams was determined. Female Wistar rats were fed either standard chow or rendered obese by exposure to a high-calorie diet from weaning. At adulthood, they were mated with control male rats to form two first generation (F1) experimental groups: control mother/control father (CM/CF); obese mother/control father (OM/CF). At weaning, F1 animals were fed either a standard or a high-calorie diet for 16 weeks. Rats born to obese mothers fed standard diet, displayed no differences in body weight or fat mass compared to their control counterparts. However, they exhibited a higher concentration of triglycerides in the liver than control animals. In addition, they gained more weight and accumulated more triglycerides in liver in response to the high-calorie diet. OM/CF offspring, also showed increased expression of genes involved in de novo lipogenesis and this expression was exacerbated by consumption of the high-calorie diet. All of these metabolic alterations were correlated with an increased abundance of diacyl and triacylglycerols synthesized from saturated and monounsaturated fatty acids. These results indicate that maternal obesity exacerbates the adverse effects of a high-calorie diet on the liver of the offspring by promoting the synthesis of diacylglycerols and triacylglycerols.

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Orally administered Very Long Chain Fatty Acids are taken up by meibomian glands. Potential importance in Dry Eye Disease.

R&D Scientist Harald Svensen Dr, R&D PhD Fellow Martina Torrissen MSc, Clinical Science Manager Derek Tobin Dr., R&D Manager Iren Stoknes Dr
Epax Norway, Alesund, Norway

Abstract

There are several causes of dry eye disease, a common irritation of the eye, including aberrant lipid composition of meibomian lipids and tears. Tear fluid is composed of an inner mucin layer, a watery layer and an outer lipid layer that prevents evaporation. Lipidomic studies of the tear fluid lipid layer show the presence of very long chain lipids, which may be disturbed in dry eye disease.

Very-long-chain fatty acids (VLC-FA) are fatty acids with a chain length of ≥24 carbon atoms. They are synthesized in tissues expressing the ELOVL4 enzyme, which mediates the biosynthesis of these fatty acids from shorter chain precursors. These tissues include the retina, skin, testis, and brain. Mutations in ELOVL4 leads to different conditions dependent on the target tissue, suggesting VLC-FAs play important roles in these tissues.

After identifying VLC-FAs in fish oil and developing a method for concentrating n-3 VLC-PUFAs, we have conducted a feeding trial in mice, where the VLC-PUFA enriched fish oil was included in the feed and administered for 33 days. At the end of the feeding trial, tissue containing meibomian glands were extracted and analyzed with GC-MS for detection of VLC-FAs. Results show that VLC-FAs given as an oral supplementation are taken up by meibomian gland tissue, and the lipid profile reflects the fatty acids present in the supplemented oil. Based on these findings, it is of interest to further investigate in intervention trials whether tear fluid composition can be altered in a manner beneficial to dry eye disease.

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The manufacturing process of dairy products affects the integrity of milk fat globule membrane proteins and their beneficial effects as determined by proteomic analysis

PhD student Veronica Gallo Food Science ORCID iD, PhD student María Señoráns Food Science ORCID iD, Dr. Calvo María Visitacion ORCID iD, Dr. Javier Fontecha ORCID iD
Instituto de Investigación en Ciencias de la Alimentación (CIAL), Madrid, Spain

Abstract

Milk fat globule membrane (MFGM) proteins have been associated with various health-promoting properties, including beneficial effects on neurodevelopment, the cognitive system, the immune system, and the gastrointestinal tract. However, the severe conditions applied during the dairy processing and subsequent MFGM isolation can significantly compromise the integrity of MFGM proteins and thus their beneficial effects. In this work, we performed a comprehensive characterization of the MFGM protein fraction of all products involved in butter and butter oil production (from raw milk to the corresponding by-products) and that of the relative MFGM extracts obtained by ultracentrifugation. Characterization of MFGM proteins included evaluation of protein concentration by Bradford assay, protein profile by SDS-PAGE and protein identification by MALDI-TOF/TOF/MS. In addition, protein bands were quantified by densitometry, while the interaction of MFGM proteins with other milk proteins was investigated by non-reducing SDS-PAGE. The results showed that most by-products of butter and butter oil production can be optimally used for the isolation and purification of bioactive MFGMs. Indeed, these MFGM extracts exhibited high protein concentrations (53-66%) and high band density, suggesting that cream churning may promote fat globule degradation and consequent release of membrane fragments. In contrast, MFGM isolated from the mixture of buttermilk and butter serum powder exhibited the lowest protein content and band density, possibly due to the harsh conditions during the spray drying and evaporation process. Finally, SDS-PAGE showed the presence of non-MFGM proteins (casein and whey proteins) under reducing and non-reducing conditions, which inevitably reduced the yield of MFGM proteins.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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A comprehensive lipid profile of MFGM from dairy products and by-products from butter and butter oil production

PhD student María Señoráns Food Science ORCID iD, PhD student Veronica Gallo Food science ORCID iD, Dr. María Visitación Calvo ORCID iD, Dr. Javier Fontecha ORCID iD
Food Science Research (CIAL, CSIC), Madrid, Spain

Abstract

Consumption of milk fat globule membrane (MFGM) has been associated with beneficial health effects, particularly on neuronal and cognitive development, as well as immune and gastrointestinal health in infants and the elderly. MFGM is found in dairy products and by-products of butter and butter oil production. In addition, MFGM is released into the aqueous phase after mechanical treatments such as agitation, homogenization, or churning. Therefore, buttermilk and butter serum by-products are important sources of polar lipids contained in MFGM. This study allowed the selection of suitable dairy by-products for the isolation and purification of MFGM by their characterization using a lipidomic approach. Lipid classes characterized by HPLC-ELSD, triacylglycerides (TAG) and fatty acid methyl esters (FAMEs), determined by GC-FID of several dairy by-products obtained during the production of butter and butter oil from raw and pasteurized milk were studied. The featured profiles in polar lipids indicated that buttermilk (BM), butterserum (BS) and their mixture (BM-BS) are the most suitable by-products to be used as starting materials for the isolation and purification of MFGMs, thus obtaining MFGM-enriched extracts for their use as ingredients in food formulations with high biological activity. Finally, an enriched MFGM extract was obtained from BM containing more than 55% polar lipids.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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A dietary supplement enriched in polar lipids could prevent age-related mild cognitive impairment

Dr JAVIER FONTECHA PhD ORCID iD, Dr María V. Calvo PhD ORCID iD
Institute of Food Science Research (CIAL, CSIC-UAM). 1Food Lipid Biomarkers and Health Group, MADRID, Spain

Abstract

Polar lipids (PL), widely distributed in all tissues, play an important role in metabolism due to their structural function, as cell signaling molecules, or to generate precursors. Dietary intake of polar lipids is frequently associated with the prevention and amelioration of cardiovascular disease, liver disease, immune responses, and cognitive disorders. Although PL are widely found in foods, milk and dairy products have significant amounts (0.2-1 g PL /100 g fat) and, unlike vegetable lecithins, contain a variety of phospho- and sphingolipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol, and sphingomyelin. Our group pioneered the development and evaluation of a milk-fat globule membrane (MFGM)-enriched dietary supplement for the prevention of age-related mild cognitive impairment through preclinical studies in aged rats and adults over 65 years of age. This dietary supplement exhibited high bioavailability as determined by lipidomic analysis and behavioral changes related to emotional memory. The results suggest that the intake of a dietary supplement rich in MFGM, in combination with a balanced diet and physical activity, can be considered a non-pharmacological preventive and therapeutic intervention for mild cognitive impairment in the elderly. However, these studies are a first step for future work where the dosage of intake and its effects on behavior need to be determined.

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Hydroxylated fatty acids as therapeutic approaches to neuropathic pain

Mr. Marc Miralles[1,2], Mr. Joan Cabot[1,2], Mr. Sebastià Parets[1,2], Dr. Marta Salvador-Castells[1,3], Dr. Antonio Oliviero[4], Dr. Paula Fernandez-García[1,2], Dr. Victoria Lladó[1,5], Dr. Pablo Vicente Escribá[1,2], Dr. Manuel Torres[1]

[1]Laboratory of Molecular and Cellular Biomedicine, Biology Department, University of Balearic Islands, Palma, Spain. [2]Laminar Pharmaceutics, S.A, Palma, Spain. [3]Fundación Marathon, Palma, Spain. [4]National Hospital for Paraplegics, SESCAM, Toledo, Spain. [5]Laminar Inc., Boston, Massachussets, USA

Abstract

Finding viable therapeutic approaches to neuropathic pain (NP) is one of the biggest challenges of modern medicine. Produced by multitude of causes, from physical trauma, to diabetes, to the herpes zoster virus, it affects millions of people every year. The chemotherapeutic treatment with vincristine can cause NP by destabilizing afferent nerve fibbers due to its ability to inhibit the polymerization of microtubules. In this work, we developed an animal model based on chemotherapy-induced peripheral neuropathy (CIPN) with Wistar rats by administering vincristine intraperitoneally to Wistar rats at a dose of 0.1mg/Kg/day for 10 days. We then tested this model with 2-hydroxyoleic acid (NFX88, 2OH-C18:1), an hydroxylated monounsaturated fatty acid which indeed has already shown a great therapeutic potential to treat spinal-cord-injury (SCI)-associated neuropathic pain in Wistar rats. In these previous studies, NFX88 has demonstrated a reduction in mechanical and thermal hypersensitivity in this SCI-based model of NP. Also, the NFX88 is under research in clinical trials and points towards a good safety profile and potential for NP therapy in humans. Similarly, we also observed such a reduction of thermal and mechanical hypersensitivity in our model of CINP, after being orally treated with NFX88 for 28 days at a dose of 400mg/Kg/day. On the other hand, we also introduce in this work we also tested 2-hydroxy-docosahexaenoic acid (DHA-H, 2OH-C22:6), an hydroxylated polyunsaturated fatty acid, as a novel molecule for NP therapy. Using the same conditions as with NFX88, we observed similar changes with the treatment with DHA-H to those induced by HOA in our CINP model. Overall, our results show potential therapeutic approaches for NP arising from both physical and non-physical causes.

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Adaptation of cellular lipid metabolism of Caco-2 cells to food matrices supplemented with milk fat globule membrane.

Victoria Martínez-Sánchez[1,2], María Visitación Calvo[1], Javier Fontecha[1], Antonio Pérez-Gálvez[2]
[1]Instituto de Investigación en Ciencias de la Alimentación (CSIC-UAM), Madrid, Spain. [2]Instituto de la Grasa (CSIC), Sevilla, Spain

Abstract

Food supplementation with bioactive ingredients has become an efficient strategy to provide society with benefits for health. One of those ingredients is the milk fat globule membrane (MFGM), to which growing research attention is focussed considering evidence for improvement of immune and gut system, brain functions or cardiometabolic health. However, before exerting any of these health benefits, the MFGM and the food matrix in which is formulated must be digested and assimilated, processes that can modify efficiency of functionality. This is why bioaccessibility studies based on the use of in vitro models are currently on the rise. In this study, it has been determined how the bioaccessibility of MFGM components changes depending on the food matrix characteristics, when it is subjected to a standardised digestion protocol. Likewise, the use of Caco-2 cells as a model of intestinal absorption has allowed to determine how cells are capable of sensing dietary lipids and adapt the cellular lipid metabolism accordingly. In fact, food matrices with higher content of polar lipids, related to MFGM supplementation, showed a clear tendency to the accumulation of triacylglycerols (TAGs) after the postprandial period. This effect indicates the activation of important metabolic routes critical for production of lipoproteins, signalling molecules or membrane synthesis as CDP-choline pathway. This provides further insights into how food formulation can be improved to enhance the beneficial effects of compounds such as MFGM.

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Mechanisms for the interaction of the milk fat globule membrane lipids with the plasma membrane of gut epithelial cells

Victoria Martínez-sánchez[1,2], Julio Girón-Calle[2], María Visitación Calvo[1], Javier Fontecha[1], Antonio Pérez-Gálvez[2]
[1]Instituto de Investigación en Ciencias de la Alimentación (CSIC-UAM), Madrid, Spain. [2]Instituto de la Grasa (CSIC), Sevilla, Spain

Abstract

Milk is a natural oil in water emulsion where lipids are structurally organized as milk fat globules. These globules have a triacylglycerol core surrounded by a tri-layer biological membrane called milk fat globule membrane (MFGM). The unique compositional profile and arrangement of lipids in such structure, with the characteristic lateral segregation of polar lipids and cholesterol in the MFGM, and its specific composition in membrane proteins and glycoproteins, represent a challenge to understand a number of related processes. The aim of this study was to draw on the arrangement of lipids in the MFGM and their involvement in membrane-membrane fusion, to explore whether MFGM could fuse with the plasma membrane of gut epithelial cells. The experimental approach was labelling of milk lipids using lipid fluorochromes, measurement of Förster resonance energy transfer and the application of microscopy techniques. Our results point to a transfer of the lipid fluorochromes from the MFGM, either forming part of the complete milk matrix or previously isolated, to the plasma membrane of the cell culture. Several mechanisms may be responsible for such effect, including endocytosis, dissociation of the lipid fluorochromes from the MFGM followed by diffusion and partitioning into cell, or fusion/aggregation of the MFGM with the apical membrane of the cells.

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Acute or Delayed Treatment of Rat Cervical Contusion Spinal Cord Injury with Fortasyn® Connect Promotes Neuroplasticity

Dr Isabell Nessel PhD ORCID iD[1], Dr Patrick N. Pallier PhD[1], Maria Helena Gonzales-Ortiz MSc[1], Rebecca Maguire MSc[1], Dr Oscar Seira PhD[2], Prof Adina T. Michael-Titus PhD ORCID iD[1], Dr Wolfram Tetzlaff MD, PhD[2]

[1]Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom. [2]International Collaboration on Repair Discoveries, University of British Columbia, Blusson Spinal Cord Centre, Vancouver, Canada

Abstract

Spinal cord injury (SCI) is a leading cause of disability. Damage to descending tracts, such as the corticospinal tract (CST), can lead to paralysis of limbs and trunk. Fortasyn® Connect (FC) is a medical multi-nutrient containing phospholipid precursors and co-factors for membrane synthesis. We hypothesized that acute or delayed administration of FC will be neuroprotective and promote neuroplasticity of motor tracts after cervical contusion SCI.

Following injury, adult Sprague-Dawley rats were treated with either 1) a control diet (control group (CG)) or 2) a FC-supplemented diet for 18 weeks, followed by a control diet for 14 weeks (acute treatment group (AG)), or 3) a control diet for 18 weeks, followed by a FC-supplemented diet for 14 weeks (delayed treatment group (DG)). At 30 weeks post-injury, biotinylated dextran amine (BDA) was injected into the motor cortex contralateral to the lesion for BDA staining analysis 2 weeks later. Synaptic proteins at the epicentre and rostral/caudal to injury were analysed by western blotting.

AG animals showed increased sparing of CST tracts, and increased CST sprouting was seen into the denervated spinal cord in both treatment groups, but there was no increased neuronal survival or decreased lesion size or cavitation. The mean expression of synaptic proteins synaptophysin and syntaxin-3 was higher in tissues of FC-treated groups compared to CG tissues, but this was not significant.

Therefore, FC treatment significantly promoted CST reorganisation but in the absence of neuroprotection, suggesting that FC can modulate neuroplasticity following cervical contusion SCI, even with delayed treatment.

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Dietary low polyunsaturated /saturated fatty acids (PUFA/SAFA) ratio improves glucose and lipid metabolism in obese Zucker rats fed a normolipidemic diet

Professor Gianfranca Carta PhD ORCID iD[1], Elisabetta Murru PhD ORCID iD[1], Claudia Manca PhD ORCID iD[1], Giovanna Trinchese PhD[2], Gina Cavaliere PhD[3], Maria Pina Mollica PhD[2], Sebastiano Banni PhD[1]

[1]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy. [2]Department of Biology, University of Naples Federico II, Napoli, Italy. [3]Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy

Abstract

The amount of fat recommended for young growing laboratory rats has been determined to be 7%, with a PUFA/SAFA ratio 4:1, mostly because high proportion of dietary SAFA at expenses of dietary PUFA has been linked to a deranged lipid metabolism and insulin resistance (IR).

Most of the experimental animal studies on SAFA, have been conducted using diets with exceedingly high fat content that cannot be considered for translational nutritional studies on the effects of dietary fatty acids (FA).

Based on these premises we aimed at investigating the impact of dietary low or high PUFA/SAFA ratio on IR and FA deposition and metabolism, in lean and obese Zucker rats, an animal model of obesity and IR.

Zucker rats were fed diets containing 7% of total fat with low PUFA/SAFA ratio 1:2 (SAFA-diet), where palmitic acid (PA) represented 70% of total SAFA, or a control diet with high PUFA/SAFA ratio 4:1 (CTRL diet) for 8 weeks. We determined tissue FA profile, their N-acylethanolamine bioactive metabolites, liver and muscle mitochondrial function and plasma lipid glucose and insulin levels.

Our results showed an increase of PA only related to obese condition irrespective of the diet, suggesting an endogenous biosynthesis via de novo lipogenesis related to metabolic impairment rather than to its dietary intake. Feeding SAFA-diet reduced plasma lipids, glucose and insulin levels. We also found improved muscle mitochondrial function and increased muscle N-palmitoylethanolamine (PEA), a bioactive lipid derived from PA able to modulate lipid metabolism and metabolic flexibility.

In conclusion, a relatively long term low dietary PUFA/SAFA ratio did not significantly influence PA tissue concentration and improved glucose and lipid metabolism, probably by an enhanced metabolic flexibility favored by a higher PEA biosynthesis. Our data suggest that dietary PA may play a crucial nutritional role in overnutrition-induced obesity.

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Maternal dietary Conjugated Linoleic Acid and DHA influence positively fetal brain metabolism

Elisabetta Murru PhD ORCID iD[1], Gianfranca Carta PhD ORCID iD[1], Claudia Manca PhD ORCID iD[1], Asgeir Saebo[2], Michele Santoni PhP[1], Marco Pisti PhP[1,3]

[1]Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy. [2]Innolipid AS, Ålesund, Norway. [3]Neuroscience Institute, Section of Cagliari, National Research Council of Italy, Cagliari, Italy

Abstract

There are no studies available on possible synergistic actions on brain metabolism of conjugated linoleic acid (CLA), a group of positional and geometric isomers of linoleic acid present in ruminant meat and dairy products and endogenously synthesized in non-ruminants and humans, and DHA. We have previously shown that CLA modulates the biosynthesis of endogenous PPARα ligands in brain tissue and DHA the biosynthesis of N-docosahexaenoylethanolamine, (DHEA), which has been shown to favor synaptogenesis.

We therefore aimed to evaluate whether maternal intake of CLA and DHA in phospholipid form, crosses the placental barrier and is able to influence the profile of fetal brain fatty acids (FA) and the biosynthesis of bioactive lipid mediators derived from FA, the N-acylethanolamines (NAE) involved in different neurophysiological functions.

We fed rat dams, during the first 2/3 of their pregnancy, CLA and DHA in phospholipid form at a dietary concentration of 0.5% and 0.2%, respectively. FA and NAE profiles were analyzed in the maternal and fetal liver and brain.

We found that CLA crosses the placenta and was readily incorporated into the fetal liver and brain. CLA metabolites were found abundantly in fetal tissues, particularly the conjugated 16:2, the product of partial peroxisomal beta oxidation of CLA, in fetal brain. Changes in the profile of FAs modulated the biosynthesis of NAE derived from arachidonic acid (ARA; N-arachidonoylethanolamine, AEA) and increased DHEA, deeply involved in brain development.

Therefore, the administration of CLA and DHA in phospholipid form could be considered a promising dietary treatment during pregnancy to promote brain development during the critical prenatal period.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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The effect of alpha-aminobutyric acid (AABA) supplementation on a high fat diet (HFD)-induced liver diseases in mice model

Felicianna - ORCID iD[1], Dr. Kwun Kwan Emily Lo ORCID iD[1], Dr. Hani El-Nezami ORCID iD[1,2]
[1]University of Hong Kong, Hong Kong, Hong Kong. [2]University of Eastern Finland, Kuopio, Finland

Abstract

Non-alcoholic fatty liver disease (NAFLD) refers to a chronic disorder characterized by the excess accumulation of lipids in the liver in individuals who rarely consume alcohol. This disorder has recently come to be one of the most common type of liver disease globally. Metabolomic profiling of NAFLD subjects has been increasingly used to not only identify novel biomarkers, but to also identify mechanisms of disease manifestation and metabolic signatures related to improved therapeutic outcomes. In a human study involving the treatment of NAFLD, our collaborators have identified that serum alpha-aminobutyric acid (AABA) is negatively correlated with intrahepatic triglyceride (TG) content and serum TG levels which is characteristic of NAFLD manifestation. AABA is a non-proteinogenic amino acid produced as a metabolite produced by out gut microbiome. Our preliminary in-vitro study suggests that AABA was able to downregulate de novo lipogenesis related genes in HepG2 cells and potentially reduce fatty acid uptake. In this study, we aim to investigate whether AABA could alleviate NAFLD hepatic steatosis and its associated metabolic parameters in a high-fat diet (HFD) induced NAFLD mice model. Supplementation of AABA was found to attenuate HFD-induced hepatic steatosis. A significant decrease in intrahepatic triglyceride content, serum triglycerides, fasting insulin levels and NAFLD activity score were observed, and further analysis revealed that the gene expression of lipogenic enzymes in the liver were decreased, while those involved in fatty acid oxidation were upregulated. Moreover, signalling pathways of bile acid metabolism were found to be modulated. Altogether, these findings suggest that AABA could be a potential therapeutic option for the treatment of NAFLD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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The endocannabinoidome lipid mediator oleoylethanolamide as a therapeutic approach for obesity and insulin resistance: modulation of body composition, mitochondrial bioenergetics and gut microbiome

Fabiano Cimmino ORCID iD[1], Giovanna Trinchese[1], Lidia Petrella[1], Gina Cavaliere[1,2], Angela Catapano[1], Jyoti Sihag[3], Cristoforo Silvestri[3], Vincenzo Di Marzo[3], Maria Pia Mollica[1]

[1]Department of Biology, University of Naples Federico II, Naples, Italy. [2]Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy. [3]Canada Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health (CERC-MEND), Université Laval, Quebec city, Canada

Abstract

The endocannabinoidome (ECBome) is a complex lipid signaling system composed of more than 100 fatty acid-derived mediators and their receptors. Oleoylethanolamide (OEA), which is part of this system, was first described as a satiety hormone synthesized in the jejunum, and later recognized as an important player in the regulation of body weight and eating behavior. However, its involvement in metabolic and inflammatory regulation is still partially unknown. This study aims to evaluate the effect of OEA administration on metabolic and inflammatory profiles in a mouse model of diet-induced obesity, focusing on its efficacy in the modulation of hepatic mitochondrial function, ECBome mediators and microbiome composition.

C57BL/6J mice were divided in two groups receiving, for 18 weeks, standard diet or high fat diet (HFD). Afterwards both groups were subdivided to receive, via intraperitoneal injection, vehicle or OEA for further 4 weeks. During the whole experimental period, body weight and food intake were monitored. Energy balance, body composition, metabolic and inflammatory parameters, hepatic mitochondrial function and oxidative stress were evaluated together with LC-MS/MS analysis of ECBome mediators and 16S sequencing for gut microbiota composition.

In HFD mice, OEA decreased body weight, food intake and the inflammatory state in both serum and liver and decreased hepatic and body lipid accumulation. At the hepatic level, OEA modulated mitochondrial oxidative capacity reducing lipid accumulation and oxidative stress. OEA treatment also affected the levels of some ECBome lipid mediators and the composition of the gut microbiota.

These findings identify OEA as a viable candidate in the treatment of obesity through the modulation of mitochondrial function, and affecting both metabolic and inflammatory profiles, thereby reducing the damage induced by lipid overload. OEA-induced changes in ECBome mediator and gut microbiota composition might participate in these effects, although further studies are required to investigate this possibility.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

These findings have not yet been published

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Metabolism of odd chain fatty acids *in vivo* in mice and *in vitro* in Fao rat hepatoma cells.

Vincent Ciesielski[1,2], Julia Mwenge Wambel[1,2], Manuel Vlach[1,2], Daniel Catheline[1,2], Philippe Legrand[1,2], Vincent Rioux[1,2]
[1]Institut Agro, Rennes, France. [2]Institut NuMeCan, INSERM, INRAE, Univ Rennes, Rennes, France

Abstract

Pentadecanoic (15:0) and heptadecanoic acids (17:0) are two main odd chain fatty acids (OCFAs), mainly found in dairy products. Their physiological effects are still unknown, yet some evidences suggest they might be beneficial to human health. We tested *in vitro* the desaturation of 15:0 and 17:0 in Cos7 cells producing recombinant SCD1, FADS1 or FADS2 proteins to observe if the OCFAs are substrates of the Δ9, Δ5 or Δ6 desaturases. We investigated the conversion of OCFAs in mice with a 4 months diet supplementation (4% energy intake of high fat diet at 4.8 kcal/g) and *in vitro* with 24h incubations in Fao cells. Total fatty acids were extracted from mice liver or cells and analysed by gas-chromatography and mass spectrometry.

In Cos7 cells, 15:0 and 17:0 were found substrates of the Δ9 and Δ6 desaturases. However only 17:0 was detected to be directly desaturated by the Δ5 desaturase.

In mice liver and in Fao cells, OCFAs were found both elongated and desaturated by the Δ9 desaturase. Two metabolites were produced by the main metabolic pathways: (i) 17:0 and 17:1 n-8. Secondaries metabolic pathways resulted in the formation of (ii) 19:0 and 19:1 n-10 (iii) 15:1 n-6 and 17:1 n-6.

Thus, *in vitro* and *in vivo*, OCFAs appear to be preferential substrates of the Δ9 desaturase, resulting in the formation of monounsaturated OCFAs (n-8, n-10 and n-6). 15:0 is mainly metabolised into 17:0 and 17:1 n-8. Further investigations are needed to decipher OCFAs' and their monounsaturated OCFAs metabolites physiological effects.

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Interactions lipids-proteins of oilseeds: impact on *in vitro* digestibility

Lina Toutirais[1], Carole Vaysse ORCID iD[1], Stephane Walrand ORCID iD[2], Leslie Couëdelo ORCID iD[1], Corentin Bouju[1], Hélène Abrous[1], Ikram Chamekh[1]

[1]Iterg : Nutrition Health and Lipid Biochemistry Department, Bordeaux, France. [2]UMR-1019 Equipe alimentation, santé musculaire et sarcopénie (ASMS), Clermont-Ferrand, France

Abstract

Demand for animal protein-based products is high and expected to increase over the next decade due to strong global population growth. The limited resources and the ecological impact of animal protein production have led to a rise of plant-based diets. The oilseed proteins, generally present into the animal feed market, could have a potential application in Human nutrition. They offer a double nutritional interest in providing proteins and lipids, including PUFA. However, the nutritional quality and value of oilseed proteins are not well-known.

The aim of this study was to determine the *in vitro* digestibility and to assess the nutritional potential of different protein-lipid formulas from oilseeds according to the sourcing of plant proteins, production processes and amino acid and fatty acid composition.

INFOGEST protocol was applied to determine the *in vitro* digestibility of the different formulas: cake, concentrate, isolate of soy, sunflower, rapeseed with or without rapeseed oil. Pea was used as reference. In vitro digestates were characterized by the degree of protein and lipid hydrolysis.

The *in vitro* digestibility of proteins from oilseeds was improved by the addition of lipids in the reaction medium (+30% in average, according the nature of oilseed proteins). Moreover, the higher the amount of added lipid in the medium, the higher the digestibility of the proteins (DH% of BSA is 59% without oil, 69% with 0.2g of oil and 79% with 0.6g of oil). Inversely, the *in vitro* lipid digestibility is not impacted by the presence of proteins.

The increase in proteolysis in the presence of rapeseed oil during *in vitro* digestibility of oilseed protein-lipid formulas, could suggest that these nutrients interact together. In addition, the magnitude of hydrolysis activation by rapeseed oil depends on the nature of proteins. These results are new data on the *in vitro* digestibility of proteins and lipids.

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Upregulated vasoactive lipid mediators in systemic lupus erythematosus contribute to endothelial dysfunction

Dr. Maria Dolores Camacho Muñoz[1], Dr. Sophie, N. Saxton[2,3], Prof. Anthony, M. Heagerty[2,3], Prof. Anna Nicolaou[1,3]
[1]Laboratory for Lipidomics and Lipid Biology, Division of Pharmacology and Optometry, The University of Manchester, Manchester, United Kingdom. [2]Division of Cardiovascular Sciences, The University of Manchester, Manchester, United Kingdom. [3]The Lydia Becker Institute of Immunology & Inflammation, The University of Manchester, Manchester, United Kingdom

Abstract

Systemic lupus erythematosus (SLE) is considered an independent risk factor for endothelial dysfunction, contributing to premature cardiovascular disease risk. Our pilot clinical studies suggest that circulating levels of the arachidonic acid-derived epoxyeicosatrienoic acids (EETs) were found increased in the blood of SLE patients compared to healthy controls, whereas their diol derivatives (DHETs) had similar concentrations. EETs and DHETs have vasoactive properties, and pathological concentrations could damage the microvascular endothelium. Here, we investigate their effects on endothelium-dependent vasodilation in the microvasculature.

Wire myography was used to assess the vasoactive effect of 11(12)-EET and 11,12-DHET in mouse mesenteric resistance arteries (<250 µm). The effect of both lipids on all major pathways of endothelium-dependent vasodilation were studied using a nonselective nitric oxide synthase (NOS) inhibitor, a cyclooxygenase (COX) inhibitor or a selective TRPV4 antagonist.

Endothelium-dependent vasodilation was suppressed by both lipids. NOS inhibition abolished vasodilation. This response was not affected by 11(12)-EET but was attenuated by 11,12-DHET. COX inhibition had no effect on vasodilation or the reduced vasodilator response observed in the presence of 11(12)-EET. However, it reduced the effect of 11,12-DHET on vasodilation. Blockage of TRPV4 signalling pathway had no effect vasodilation in the presence or absence of both lipids.

Our results show that 11(12)-EET and 11,12-DHET at concentrations found in SLE patients reduce endothelial function in small resistance arteries, and this may be due to the contribution of nitric oxide and endothelium-derived hyperpolarisation factor via TRPV4 signalling. Upregulation of vasoactive lipid species in SLE could predispose to endothelial and vascular dysfunction.

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A probiotic supplementation prevents lipid metabolism alterations and limits weight gain possibly via inhibition of intestinal FXR activity in mice fed a high fat diet

Alice Beau[1], Bérengère Benoît PhD[1], Mélanie Le Barz PhD[1], Catherine Calzada PhD[1], Emmanuelle Meugnier PhD[1], Armelle Penhoat PhD[1], Sophie Holowacz PhD[2], Elsa Jacouton PhD[2], Marie-Caroline Michalski PhD[1], Hubert Vidal PhD[1]

[1]CarMeN laboratory, Inserm U1060, INRAE UMR1397, Université Claude Bernard Lyon 1, Université de Lyon, Pierre-Bénite, France. [2]PiLeJe Laboratoire, Paris, France

Abstract

Obesity and metabolic syndrome are major health issues without proper medical solutions. Probiotics have emerged as promising therapeutic tools although their underlying mechanisms of action remain unclear. Lipid metabolism is strongly altered in these pathologies, with defective absorptive and postprandial metabolisms, and an orientation of their fate towards excessive storage in tissues. We investigated the protective effects of a mix of *Bifidobacterium animalis* subsp. *lactis* LA804 and *Lactobacillus gasseri* LA806 in mice fed a high-fat diet (HF). These strains were previously selected for their beneficial action on obesity and inflammation. The results showed that supplementation with probiotics (HF-Pr2) prevented weight gain, decreased fat mass, lowered hepatic lipid accumulation and maintained normal glucose homeostasis. Importantly, the postprandial rise of plasma triglycerides was lowered during an oral lipid tolerance test in HF-Pr2 compared to HF mice. At the molecular level, probiotics lowered mRNA levels of genes related to lipid absorption, metabolism and storage in liver and adipose tissue, and strongly decreased mRNA levels of genes related to inflammation in white adipose tissue and to oxidative stress in liver, likely as a consequence of reduced lipid accumulation in these tissues. Finally, analysis of bile acids (BAs) in the caecum revealed that probiotics modified intestinal BA profile leading to a significant increase in the Farnesoid-X-Receptor (FXR) antagonist/agonist ratio between BA species. Consistently, HF-Pr2 mice exhibited a strong inhibition of the FXR/FGF15 signaling pathway in the ileum. Inhibition of intestinal FXR activity has been reported as a potent mechanism to overcome insulin resistance and metabolic disorders. Altogether, our results demonstrate that the selected probiotics could limit obesity and associated lipid metabolism disorders and inhibit FXR signaling in the intestinal tract when provided as a preventive strategy to HF-fed mice.

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DIETARY STEARIDONIC ACID-RICH BUGLOSSOIDES ARVENSIS OIL ALLEVIATES INFLAMMATORY ARTHRITIS IN THE K/BxN SERUM TRANSFER MOUSE MODEL

Melina Doucet MSc[1,2], Angela Laevski MSc[1,2], Paskale Pineau BSc[1,2], Audrée LeBlanc BSc[1,2], Luc Boudreau PhD ORCID iD[1,2], Marc Surette PhD ORCID iD[1,2]

[1]Université de Moncton, Moncton, Canada. [2]New Brunswick Centre for Precision Medicine, Moncton, Canada

Abstract

Background: N-3 PUFA from marine sources are linked to beneficial effects in rheumatoid arthritis (RA) patients. However, the questionable sustainability of fish oils (FO) warrants the investigation in inflammatory arthritis of renewable sources of dietary n-3 PUFA such as the stearidonic acid-rich *Buglossoides arvensis* seed oil.

Methods: C57BL/6 mice consumed diets based on human western diets providing 34% of energy from lipids, 50% from carbohydrates and 16% from protein for 5 weeks. Treatment groups consumed control diets in which 3.3% or 10% of energy was from *B. arvensis* oil, or 3.3% was from FO. After 3 weeks, inflammatory arthritis was induced by injections (days 0 and 2) of autoreactive K/BxN mouse serum. Clinical index, ankle thickness and locomotor activity using Smart Cages™ were then measured over 14 days. Liver fatty acid composition was measured by GC-FID and paw homogenates were prepared for cytokine (panel by flow cytometry) and lipid mediator analyses (LC-MS/MS).

Results: Liver n-3 PUFA content was greater in *B. arvensis* and FO groups compared to controls ($p<0.05$). Changes in ankle thickness were smaller in the low dose *B. arvensis* and FO groups compared to controls ($p<0.05$). No significant differences in clinical index were measured between groups. Locomotor activities were significantly different during baseline (day 0), peak (day 8) and resolution (day 14) phases and tended to be greater in the low dose *B. arvensis* and FO groups compared to controls. Cytokine profiles changed significantly with disease progression, but with limited effect of diets.

Conclusions: On a western diet background, low dose *B. arvensis* and FO alleviated joint inflammation and positively impacted on mobility in this inflammatory arthritis model. This study suggests that the clinical investigation of *B. arvensis* oil on RA severity may be warranted. Planned lipid mediator analyses may reveal mechanisms of action of this intervention.

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A mix of dairy fatty acid supplementation reduces some metabolic syndrome disorders in high fat diet fed mice.

Vincent Ciesielski[1,2], Julia Mwenge Wambel[1,2], Manuel Vlach[1,2], Daniel Catheline[1,2], Gaëlle Boudry[2], Isabelle Luron[2], Philippe Legrand[1,2], Constance Boyer[3], Sophie Blat[2], Vincent Rioux[1,2]

[1]Institut Agro, Rennes, France. [2]Institut Numecan, INRAE, INSERM, Univ Rennes, Rennes, France. [3]French Dairy Interbranch Organization (CNIEL), Paris, France

Abstract

The consumption of dairy products is often associated with a lower incidence of metabolic syndrome (MS) disorders. Minor dairy fatty acids (FA) like odd-chain FA (OCFAs, 15:0 and 17:0) and trans-palmitoleic acid (TPA) are biomarkers of dairy consumption. A rising hypothesis is that they might modulate physiological functions and could protect against MS.

During 4 months, mice were fed high fat diet (HFD, 4,8 kcal/g) supplemented with either 15:0, 17:0, TPA (each at 4% energy intake) or a mix of the 3 of them (MIX diet, 1.5% of both 15:0 and 17:0 and 1% of TPA). Two control diets were implemented, a healthy control (normocaloric, 3,8 kcal/g) without FA supplementation and a MS positive control (4,8 kcal/g) supplemented with palmitic acid (4% energy). Physiological parameters were measured at the end of the experiment.

All HFD mice slowly developed an obesity syndrome. Interestingly, only 17:0 and 15:0 supplemented mice's body weights weren't significantly increased compared to control. MIX diet mice's subcutaneous adipose tissues weren't significantly different from control unlike the 4 others HFD which were increased. Only HFD+C16:0 supplemented mice weren't able to decrease their blood glucose level 2 hours after oral glucose tolerance test, compared to control.

A mix of dairy FA, 15:0, 17:0 and TPA, in HFD seem to prevent some MS disorders in mice. Individually, OCFAs and TPA at 4% energy did not reduce all MS parameters, they might be efficient at smaller concentrations, as there are in dairy products.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Palmitic acid methyl ester induced CA1 hippocampal neuroprotection is independent of neuronal electrophysiological alterations

Dr Jake Neumann PhD ORCID iD, Ms Melissa Bakowski BS
West Virginia School of Osteopathic Medicine, Lewisburg, USA

Abstract

Cerebral ischemia is a leading cause of death and disability in the USA. Clinically, there are distinguishing neurological deficits secondary to cerebral ischemia that are apparent within minutes of disease onset. These neurological deficits illustrate how rapidly neurons in the brain deteriorate under ischemic conditions. Due to the rapid tissue brain damage, we investigated mechanism of palmitic acid methyl ester (PAME; a known neuroprotectant) induced CA1 region of the hippocampus. The main goal of this study was to investigate if PAME elicits neuroprotective effects in the CA1 by altering the time to anoxic depolarization and modifying neuronal conductance. We hypothesized that PAME induces neuroprotection by alter neuronal electrophysiological properties. Our studies used either organotypic or acute hippocampal slices that were treated with either vehicle or PAME for 1-hour prior to an ischemic event or prior to recording electrophysiological parameters. In addition, we also investigated if the treatment of PAME to organotypic hippocampal cultures modulates neuronal firing properties or inhibitory synaptic currents (IPSPs) following PAME administration. Our results suggest that PAME induced neuroprotection does not occur through delaying anoxic depolarization of CA1 neurons in the hippocampus and that PAME does not modulate neuronal firing properties or inhibitory signaling. Overall, these data suggest that PAME induces neuroprotection without altering neuronal function and that additional studies are required to determine the mechanism of PAME induced CA1 neuroprotection. All of the protocols were approved by the West Virginia School of Osteopathic Medicine Institutional Animal Care and Use Committee.

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Molecular species of sphingomyelins and ceramides in dairy products vary according to cow diet

David Cheillan[1,2], Emmanuelle Meugnier[1], Bruno Martin[3], Matthieu Bouchon[4], Isabelle Verdier-Metz[5], Gwenaël Jan[6], Anne Ferlay[3], Céline Delbes[5], Benoît Graulet[3], Marie-Caroline Michalski[1]

[1]INRAE, UMR1397, CarMeN laboratory, Inserm, U1060, Univ-Lyon, Université Claude Bernard Lyon 1, Pierre-Bénite, France. [2]Service de Biochimie et de Biologie Moléculaire, Centre de Biologie et de Pathologie Est, Hospices Civils de Lyon, Bron, France. [3]INRAE, UMR1213 Herbivores, VetAgroSup, Université Clermont Auvergne, Saint-Genès-Champanelle, France. [4]INRAE, UE1414 HerbiPole, Marcenat, France. [5]INRAE, Université Clermont Auvergne, VetAgroSup, UMR545 Fromage, Aurillac, France. [6]INRAE, UMR1253 STLO, Rennes, France

Abstract

Context: High plasma levels of different species of ceramides (Cer) and sphingomyelins (SM) are associated with cardiometabolic diseases. A supplementation with milk polar lipids, a dietary source of SM and Cer, can decrease circulating atherogenic SM and Cer species in at-risk subjects. However, composition of SM and Cer species in milk and dairy products remains to be further explored, notably according to cow diet, a known regulator of milkfat composition.

Methods: Raw whole milks were obtained from cows fed either corn-silage-based diets or pasture-based diets. Cantal cheeses were processed therefrom. Polar lipids were extracted from lyophilized products (chloroform/methanol 1:2). Molecular SM and Cer species were analyzed by tandem mass spectrometry (API 4500 QTRAP) and concentrations quantified over dry matter (DM) (mean±SD of triplicate products).

Results: Total SM amount (nmol/gDM) was in the range 746±108–1081±293 in milks and 749±54–953±84 in cheeses, while Cer amount (nmol/gDM) was 36±6–46±16 in milks and 55±5–77±12 in cheeses. The most abundant molecular SM species (nmol/gDM) were d18:1/C16:0 (milks: 110±11–140±42; cheeses: 118±10–129±11), d17:1/C23:0 (milks: 103±15–152±41; cheeses: 104±8–128±8), d18:1/23:0 (milks: 80±6–108±27; cheeses: 88±6–100±7) and d18:1/24:0 (milks: 53±3–73±21; cheeses: 58±5–66±5). These species were also the most abundant within Cer. Several SM species were present in higher amounts from pasture diets vs corn-silage diets, the most affected being d17:1/26:1, d18:1/23:1, d18:2/21:0 in milks (~2-fold; Anova-$p_{value}<0.005$) and d17:1/26:1, d18:1/23:1, d18:2/21:0, d18:1/26:1 in cheeses (Anova-$p_{value}<5.10^{-5}$). No major diet impact on Cer composition was observed.

Conclusion: Corn silage-based diet results in lower amounts of several SM species in milk DM, which can persist after cheesemaking. Potential metabolic impacts remain to be studied.

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Application of microbial mixture in management of HFD-induced non-alcoholic fatty liver disease in mice model

miss zhang fangfei
University of Hong Kong, hong kong, Hong Kong

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide. Gut microbial dysbiosis have been found to contribute to the manifestation of chronic liver diseases including NAFLD. In the last decade, more studies attempted to use probiotic or other gut microbiota modulators in preventing and treating liver diseases through targeting gut-liver axis. Prohep is a microbial mixture that were developed and previously shown to be effective on treating hepatocarcinoma carcinoma (HCC) in our laboratory. However, its effect on NAFLD was yet to be evaluated. Here, we studied effect of probiotic mixture supplementation on NAFLD development and gut microbiome changes in a High-fat high cholesterol diet (HFD)-induced NAFLD mice model. HFD or normal chow (NC) diet were given to 8-week-old C57BL/6J male mice for 16 weeks. In the meantime, probiotic mixture was given daily during the period of feeding. Through metagenomic DNA analysis, we identified the gut microbiota shifts after HFD feeding but reversed when treated with daily probiotics. Also preliminary results demonstrated that the supplementation of microbial mixture could significantly ameliorate the progression of NAFLD probably through increased short chain fatty acids (SCFAs) production in the gut. Pathway enrichment analysis also revealed the activation of SCFA biosynthesis.

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Dietary intake varying in n-6 and n-3 PUFA regulate unique gene signatures in response to ethanol between male and female mice

Dr. Chuck Chen PhD ORCID iD[1,2], Mr. Matthew Yu[1], Ms. Mackenzie Smith ORCID iD[1], Mr. Chiraag Gohel[3,2], Ms. Sophie Haven[2], Dr. Joseph Hibbeln[2], Dr. David Goldman MD[2]

[1]University of Toronto, Toronto, Canada. [2]National Institute on Alcohol Abuse and Alcoholism, North Bethesda, USA. [3]George Washington University, Washington DC, USA

Abstract

Background: Increase in female alcohol use is associated with earlier development of alcohol-related heart disease and brain damage. In mouse models for alcohol use, it is established that female mice would voluntarily consume higher levels of alcohol as compared to male mice. In addition to sex, modifiable intake of dietary fatty acids may affect brain transcriptomic response to ethanol exposure in males. To-date, no study has examined the interaction between dietary fatty acid intake and sex in response to alcohol use.

Methods: Time-pregnant C57BL/6J dams were randomized to one of four dietary interventions: modern (8 energy% LA; 0 en% n-3 PUFA), evolution (1 en% LA; 0 en% n-3 PUFA), fish oil pill (8 en% LA; 0.5 en% n-3 PUFA), and combo (1 en% LA; 0.5 en% n-3 PUFA). 15-week-old male and female offspring were subjected to a daily ethanol gavage of 2.5 g/kg (9 days) and 5 g/kg (final day). Prefrontal cortex (PFC), hippocampus, and cerebellum were collected for next generation RNA sequencing.

Results: Transcriptome t-SNE clusters by brain regions and sex implied that the transcriptomic response to ethanol are distinct by brain region and between the sexes. PFC exhibited significantly more sex differences in response to ethanol treatment across all dietary interventions as compared to hippocampus and cerebellum. Differential gene expression analysis found that amino acid and fatty acid metabolism, specifically prostaglandin synthesis, were differentially affected between the sexes exposed to ethanol. However, upon subgrouping by dietary interventions, modern, evolution, fish oil pill, and combo diet resulted in modulations of different pathways: dopamine signaling, cell adhesion and migration, histone acetylation, and damaged DNA binding, respectively.

Conclusions: This study confirms that male and female PFC significantly differ in transcriptomic response to ethanol exposure. Furthermore, the response is unique and dependent on dietary fatty acid intake.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Lipid profile and fatty acid signatures from certain lipid classes of the muscle tissue of deep-water fish species from the Irminger Sea

Viktor Voronin ORCID iD[1], Dmitrii Artemenkov ORCID iD[2], Alexei Orlov ORCID iD[3,4], Svetlana Murzina ORCID iD[1]
[1]Institute of Biology of the Karelian Research Centre of the Russian Academy of Sciences, Petrozavodsk, Russian Federation. [2]Russian Federal Research Institute of Fisheries and Oceanography, Moscow, Russian Federation. [3]A.N. Severtsov Institute of Ecology and Evolution of the Russian Academy of Sciences, Moscow, Russian Federation. [4]Shirshov Institute of Oceanology of the Russian Academy of Sciences, Moscow, Russian Federation

Abstract

Fish of the Stomiidae are diverse and common deep-sea aquatic organisms living in extreme conditions. Multifunctional and metabolically active lipid molecules are aimed to maintain the homeostasis of metabolic processes in particular in such conditions as deep-water. The lipid and fatty acid (FA) profiles of muscles of fish species - *Chauliodus sloani*, *Stomias boa*, *Malacosteus niger*, *Borostomias antarcticus* (Stomiidae) collected at different depths of the Irminger Sea were studied. The storage of waxes in *B. antarcticus* was found, which a particular for vertically migratory species. For other species, the prevalence of triacylglycerols was revealed, indicating a different strategy of compensatory response during daily vertical migrations. A low percentage of similarity (up to 40%) was established for phospholipid classes among the studied species. Two fish species – *C. sloani* and *S. boa* – had a relatively similar accumulation of neutral lipids, but showed different deep-vise change of polar lipids. The dominance of monounsaturated FA (up to 60% of the total FA) in the muscles was detected mainly due to food consumption (certain species of crustaceans). The physicochemical state of the biomembrane maintained by deep-vise change in the spectra and content of polyunsaturated FAs (cis20:4(n-6), cis20:5(n-3), cis22:6(n-3)) in phospholipids in fish. Also, the accumulation of saturated FA in phospholipids was noted at relatively shallow depths. Differences in the FA composition in cholesterol esters and waxes in *B. antarcticus* and *S. boa* were established, but such differences were not noted for *C. sloani*, which may indicate differences in the mechanisms for maintaining proper buoyancy in these vertically migratory species. This study was carried out at the Laboratory of Ecological Biochemistry and using the equipment of the Core Facility KarRC RAS. This research was funded by the Presidential Grant for Young Doctors of Science MD-5761.2021.1.4 and the State Order to KarRC RAS FMEN-2022–0006.

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Patterns of early life fatty acids exposure in mother-infant pairs from the EDEN birth cohort

Aline Abou Assi[1], Barbara Heude[1], Catherine Sarté[2], Muriel Tafflet[1], Wen Lun Yuan[1,3], Marie-Aline Charles[1,4], Martine Armand[2], Jonathan Y. Bernard[1]

[1]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, INRAE, Centre for Research in Epidemiology and StatisticS (CRESS), F-75004 Paris, France. [2]Aix Marseille Univ, CNRS, CRMBM, Marseille, France. [3]Singapore Institute for Clinical Sciences, Agency for Science, Technology, and Research (A*STAR), Singapore, Singapore. [4]Unité mixte Inserm-Ined-EFS ELFE, Ined, Aubervilliers, France

Abstract

Background

Offspring's exposure to omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) over the first 1,000 days has been assessed using biomarkers from different biofluids (maternal or cord blood, or breastmilk) generally examined separately. Our aim was to characterize this exposure using a more holistic approach combining PUFAs data from multiple perinatal biofluids.

Methods

We used data from 735 mother-child dyads enrolled in the EDEN birth cohort. Thirty-four n-3 and n-6 PUFAs levels were measured in erythrocytes membranes from maternal (24-28 weeks of gestation) and cord blood, and in colostrum. Principal component analysis was performed to identify perinatal patterns of n-3 and n-6 PUFAs exposure.

Results

Five components explaining 53% of the total variance were identified. Pattern A referred to higher levels in n-3 long-chain PUFAs (LC-PUFAs) combined with lower levels in n-6 LC-PUFAs concurrently in erythrocytes and colostrum. Pattern B was characterized by higher levels of n-6 LC-PUFAs in all matrices associated with lower levels of n-3 LC-PUFAs in erythrocytes, but not in colostrum presenting specifically higher levels of ETA (C20:4 n-3) and DPA (C22:5 n-3). Pattern C depicted a contrast between maternal erythrocytes with higher levels of n-3 precursor (ALA (C18:3 n-3)), and cord erythrocytes with lower n-3 (especially ALA) and n-6 PUFAs. Pattern D was driven by higher levels of n-6 precursor (LA (C18:2 n-6)) in all biofluids. Finally, pattern E was defined by higher levels of ALA and LA in colostrum exclusively.

Conclusion

Five patterns were identified highlighting relevant variations concomitantly between PUFAs species (n-6 vs n-3, precursors vs LC-PUFAs) and between exposure periods. This provides a more comprehensive assessment of early life exposure to n-3 and n-6 PUFAs for further studies examining the genetic determinants of those specific patterns and their associations with child health outcomes.

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The effect of EPA/DHA supplementation or ibuprofen with TB medication, in lung-specific immune and inflammatory responses of Mtb-infected C3HeB/FeJ mice

Ms Simone King MSc Dietetics[1], Dr Arista Nienaber PhD Dietetics ORCID iD[1], Prof Robin Dolman PhD Dietetics ORCID iD[1], Dr Frank Ekow Atta Hayford PhD Dietetics ORCID iD[2], Prof Cornelius Marius Smuts PhD Biochemistry ORCID iD[1], Prof Linda Malan PhD Nutrition ORCID iD[1], Dr Lizelle Zandberg PhD Biochemistry ORCID iD[1]
[1]North-West University, Potchefstroom, South Africa. [2]University of Ghana, Accra, Ghana

Abstract

Background: Tuberculosis (TB) remains a major global public health threat. Host-directed therapy has become a valuable area of research where adjunctive TB treatments are applied to modify inflammation and shorten drug treatment periods. The potential of n-3 LCPUFA and ibuprofen as adjunct TB therapies were demonstrated recently in C3HeB/FeJ mice, but the underlying molecular mechanisms of the immune response pathways remain largely unknown.

Aim: Here we aim to characterize and elucidate the underlying molecular relationships and functional network interactions in lung-specific immune and inflammatory responses provoked by n-3 LCPUFA supplementation or ibuprofen treatment provided adjunct to TB medication.

Methodology: We used in silico predictive functional network modelling to predict underlying molecular relationships and functional network interactions associated with inflammatory and immune response pathways in the lung tissue of *Mtb*-infected C3HeB/FeJ mice receiving TB medication with or without n-3 LCPUFA supplementation or ibuprofen. Targeted gene expression profiling using relative qPCR and commercial assays was conducted to confirm predicted gene targets and bio-signaling pathways.

Results: We found significantly more free alveolar space in the ibuprofen group than in the EPA/DHA group at the initial stage (4 days) ($p=0.05$). However, long-term (14 days) EPA/DHA supplementation resulted in more free alveolar space and lower lung bacillary loads compared with the control group ($p<0.05$). In silico pathway analysis of the Th1, Th2, and Th17 immune activation pathways showed that short-term adjuvant ibuprofen treatment resulted in a balanced Th1, Th2, and Th17 immune response pathways. Contrasting to this, short-term EPA/DHA supplementation resulted in an activation of the Th1, Th2, and Th17 immune response. However, with long-term adjuvant EPA/DHA supplementation a balanced Th1, Th2, and Th17 immune response was restored.

Conclusion: Therefore EPA/DHA supplementation as an adjuvant TB treatment shows promise in restoring a balanced immune profile in the long term.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Alterations of mitochondrial function and epithelial homeostasis by saturated fatty acids according to their nature on the *in vitro* model of enterocyte IPEC-J2

Thomas Guerbette ORCID iD[1], Mégane Bostoën[1], Marine Buraud[1], Vincent Rioux[2,1], Annaïg Lan ORCID iD[3,1], Gaëlle Boudry ORCID iD[1]
[1]NuMeCan Institute, Rennes, France. [2]L'Institut Agro, Rennes, France. [3]AgroParisTech, Palaiseau, France

Abstract

Obesity is characterized by a low-grade inflammation associated with disturbances of small intestine permeability. The latter notably relies on mitochondrial function of intestinal epithelial cells (IEC). Yet changes in lipid metabolism of IEC induced by high fat diet (HFD) might alter mitochondrial function of IEC. We thus wondered whether saturated fats alter mitochondrial function of IEC and intestinal permeability.

The in vitro model of enterocyte IPEC-J2 was treated for 3 days with lauric (C12:0), myristic (C14:0), palmitic (C16:0) and stearic (C18:0) acids, abundantly found in HFDs, alone at 250 µM or in mix with 250 µM each. Mitochondrial function was assessed by the Seahorse technology while epithelial permeability was evaluated by measuring the transepithelial electrical resistance.

Treatment with the mix of fatty acids induced enterocyte steatosis and oxidative stress concomitant to antioxidant machinery activation but decreased β-oxidation activity during the first hours of treatment, indicating enterocyte metabolic adaptation. Mitochondrial function was altered after 3 days of treatment with marked decreased respiration and lower mitochondrial ATP production rate linked with increased epithelial permeability compared to control cells. Although 3 days of treatment with each fatty acid provoked enterocyte steatosis, C12:0 and C14:0 induced greater lipid storage than C16:0 and C18:0. Only C16:0 decreased mitochondrial respiration of IPEC-J2 while C16:0 and C18:0 lowered the mitochondrial ATP production rate and increased epithelial permeability.

In conclusion, chronic treatment with a mix of fatty acids simulating HFD, induced alterations of enterocyte metabolism and increased permeability likely due to the effect of C16:0 and/or C18:0.

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The effect of duration of supplementation period on plasma omega-3 polyunsaturated fatty acid levels in children with high functioning autism.

Dr Beata Joanna Kozielec-Oracka MD[1], Prof Kebreab Ghebremeskel PhD ORCID iD[2], Yoeju Min PhD[3], Amritpal S Bhullar PhD[4], Barbara Stasiak[5]

[1]The Children's Memorial Health Institute, Warsaw, Poland. [2]London Metropolitan University, London, United Kingdom. [3]Lipidomics and Nlutrition Research Centre School of Human Sciences London Metropolitan University, London, United Kingdom. [4]Division of Human Nutrition, Department of Agricultural, Food and Nutritional Science, University of Alberta,, Edmonton, Canada. [5]Masovian Neuropsychiatry Center, Warsaw, Poland

Abstract

Background: High-functioning autism is a neurodevelopmental disorder characterised primarily by social and communication skill deficits, sensory difficulties and obsessive adherence to routines. Findings of studies of the beneficial effects of omega-3 fatty acid, primarily eicosapentaenoic acid, supplementation on cognition and behaviour of children with the syndrome have been inconclusive. The inconsistency has been attributed to factors such as the dosage used and the duration of the supplementation time.

Aim: To investigate the effect of the duration of the supplementation period on plasma fatty acid levels in children with high-functioning autism. Procedure: Twenty-three children (n=23) with high-functioning autism (HFA), aged 9.8±3.0 years, were recruited from the Diagnostic and Therapeutic Centre for Children with Autism (Warsaw, Poland). The children were supplemented daily with 558 mg EPA, 174 mg DHA and 60 mg GLA for six months. Blood samples were collected at baseline and months 3 and 6.

Results: The levels of plasma choline phosphoglycerides EPA (0.9 ± 0.5 vs 2.8±1.2, p = 0.000), omega-3 DPA (0.9 ± 0.2 vs 1.5±0.4, p=0.000) and DHA (3.6 ± 1.0 vs 4.8± 1.1, p=0.001) were lower and linoleic (LA, 22.7±3.0 vs 19.8±2.1, p=0.000) and arachidonic (AA, 10.5 ± 1.7 vs 9.9 ± 1.5, p>0.05) acids higher at baseline compared to month 3. The month 6 plasma choline phosphoglycerides EPA (2.7 ± 1.0), omega-3 DPA (1.5 ± 1.3), DHA (4.5 ± 1.2), LA (19.9 ± 2.3) and AA (9.2 ± 2.1) were not significantly different from that of month 3.

Conclusion: The findings of this study suggest that extending the supplementation period from three to six months does have a significant effect on the e levels of the main plasma omega-6 and -3 fatty acids. However, further investigation is required to establish if this is the case with blood cells.

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Upregulated Hepatic Lipogenesis from Dietary Sugars Supplies Palmitic Acid to the Developing Brain of Mice fed Low Palmitic Acid from Birth

Ms Mackenzie E Smith ORCID iD[1], Dr Chuck T Chen PhD ORCID iD[1], Mr Chiraag Gohel[2], Dr Giulia Cisbani PhD ORCID iD[1], Mr Daniel K Chen ORCID iD[1], Ms Kimia Rezaei ORCID iD[1], Dr Richard P Bazinet PhD[1]

[1]University of Toronto, Department of Nutritional Sciences, Toronto, Canada. [2]George Washington University, Department of Biostatistics and Bioinformatics, Washington, USA

Abstract

Background: Palmitic acid (PAM) can be obtained from the diet or synthesized via *de novo* lipogenesis (DNL). Previous techniques investigating brain PAM origin were limited to acute interventions with labelled PAM ($^{14}C/^{2}H$-PAM). Accordingly, our laboratory demonstrated brain PAM carbon isotope ratios (CIRs; $^{13}C/^{12}C$; $\delta^{13}C$) are responsive to levels of dietary PAM in adult mice. However, brain PAM origin utilizing CIRs during development in addition to genetic pathways maintaining brain PAM have not yet been investigated.

Objective: To determine the origin of brain PAM utilizing CIRs and identify genetic pathways maintaining brain PAM by RNA sequencing during development in response to low dietary PAM.

Methods: Dams were fed isocaloric diets low (<2%), medium (47%) or high (>95%) in PAM prior to breeding. Dietary PAM was depleted in $\delta^{13}C$, while dietary sugars were enriched. Offspring stayed on the dam diet and were euthanized at postnatal day 0, 10, 21, and 35. Pup brain and liver lipids were quantified by gas chromatography (GC)-flame ionization detection, after which tissue $\delta^{13}C$-PAM was measured by GC-combustion-isotope ratio mass spectrometry. Postnatal day 35 tissue RNA was sequenced on a NovaSeq S4 Flowcell.

Results: Total PAM was maintained in the brain, but not the liver across diet groups at all timepoints. Brain $\delta^{13}C$-PAM was enriched overall revealing DNL from dietary sugars maintains the majority of brain PAM, augmented in mice fed low PAM from birth. Importantly, gene sets involved in DNL containing Acaca, Acly, Mlycd, etc. were upregulated in mice fed low compared to high PAM in the liver, but not the brain.

Conclusions: We demonstrate a feasible technique to study brain PAM origin during development and show hepatic lipogenesis from dietary sugars is a compensatory mechanism to maintain total brain PAM in response to low dietary PAM, suggesting an importance of PAM regulation during development.

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Docosahexaenoic Acid Intake Recommendations and Early Preterm Birth in a Clinical Setting

Dr. Danielle Christifano PhD ORCID iD, Dr. Gene Lee MD, Dr. Sharla Smith PhD, Sarah Crawford MS, Dr. Byron Gajewski PhD, Dr. Susan Carlson PhD
University of Kansas Medical Center, Kansas City, USA

Abstract

Docosahexaenoic acid (DHA) supplementation is effective for the prevention of early preterm birth (EPTB; <34wks). Women consuming <150mg DHA/day according to a 7-question food frequency questionnaire (DHA-FFQ) benefit most from high dose DHA supplementation for prevention of EPTB. The objectives of this project are to describe DHA intake via the DHA-FFQ and to determine the frequency at which DHA supplementation is recommended by a provider among a large sample of pregnant women in a clinical setting, including women who have EPTB. The DHA-FFQ was sent to all women who initiated prenatal care at our University Health System OB/GYN clinic with an automated recommendation to take DHA based on their responses. A follow-up survey was sent to determine provider recommendations surrounding DHA and weeks of gestation at birth (<34wks, 34-37wks, >37wks). Herein, we report descriptive statistics. Final results will incorporate survey data through June 2023. As of January 2023, 1,071 women received the DHA-FFQ, 974 women completed the DHA-FFQ, and 320 completed the follow-up survey. Mean DHA intake was 249 ± 237mg/day, with 38% consuming <150mg/day and 62% consuming ^{3} 150mg/day. Of those that completed the follow up survey, 37% reported their provider recommended a DHA supplement. Of those with low DHA intake, 35% received a provider recommendation to take a DHA supplement. All women who reported EPTB (n=3) had intake <150mg DHA/day and none received a provider recommendation to take DHA. The DHA-FFQ is a simple, low-cost tool that can be used in clinical practice to identify women most at risk for EPTB. Provider education surrounding DHA supplementation recommendations warrants future attention.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Prophylactic Effect of Omega-3 Polyunsaturated Fatty Acids (N-3 PUFAs) Monotherapy to Prevent Recurrent Major Depressive Disorder (MDD): A Randomized Control Trial

Ikbal Andrian Malau MSc[1,2], Doctor Jane Pei-Chen Chang MD, PhD[2,3], Doctor Wei Che Chiu MD, PhD[4,5], Prof. Kuan-Pin Su MD, PhD[2,1,6]
[1]Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan. [2]Mind-Body Interface Laboratory (MBI-Lab) and Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan. [3]College of Medicine, China Medical University, Taichung, Taiwan. [4]Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan. [5]School of Medicine, Fu Jen Catholic University, Taipei, Taiwan. [6]An-Nan Hospital, China Medical University, Tainan, Taiwan

Abstract

Background: Major depressive disorder (MDD) is a prolonged illness in consequence current psychopharmacological prescriptions are consistently associated with treatment-resistant with severe adverse effects. Omega-3 polyunsaturated fatty acids (N-3 PUFAs) have been proven as a complementary treatment against MDD and hinder recurrence with fewer adverse effects. This study aimed to assess the prophylactic effect of N-3 PUFAs monotherapy against recurrent MDD.

Method: We conducted a 6-month randomized controlled trial (RCT) of 3 mg N-3 PUFAs supplementation to assess the effect of N-3 PUFAs in preventing recurrent MDD. We assigned 60 remitted MDD patients to N-3 PUFAs group (n=30) and placebo group (n=30). Later, we assessed the difference in depression severity and MDD recurrence using the 21-item Hamilton Rating Scale for Depression (HRSD) at months 1, 2, 3, 4, and 6 between groups. Furthermore, erythrocyte fatty acids level was assessed as the secondary outcome.

Results: There was no significant difference in the HRSD score between the omega-3 and placebo groups at each time point. MDD patients in N-3 PUFAs group had a lower recurrence rate compared to placebo group at month 6 ($p=0.035$). ON-3 PUFAs supplementation was superior in preventing recurrent MDD than placebo analyzed using Kaplan-Meier survival analysis ($p=0.034$). In comparison, erythrocyte eicosapentaenoic acid (EPA) level in N-3 PUFAs group after treatment was significantly higher than in placebo group ($p=0.023$), but not with erythrocyte docosahexaenoic acid (DHA) level ($p=0.119$).

Conclusion: This study concluded that N-3 PUFAs monotherapy had a prophylactic effect on recurrent MDD events and contributed to a better survival rate of MDD patients.

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Using a machine learning algorithm to predict the DHA content of nervous tissue in rat pups from the fatty acid profiles of red blood cells

Dr Jean-Charles Martin PhD ORCID iD[1,2,3], Dr Nacima Aidoud PhD[1], Dr Pascale Leruyet PhD[4], Dr Bernadette Delplanque PhD[5]
[1]Aix-Marseille Université, Marseille, France. [2]INRAE, Marseille, France. [3]INSERM, Marseille, France. [4]Lactalis R&D, Retiers, France. [5]INSERM, Paris, France

Abstract

Predicting DHA in brain or retina of human newborns from an easily accessible sample could be advantageous in designing formulas to optimize DHA dietary intake.

We evaluated how to predict DHA content in nervous tissues from red blood cell (RBC) fatty acids (FA) using an artificially gastroctomized reared rat pup model by the mean of a machine learning (ML) technique (partial-least square).

Formula-fed pups and the gastroctomized sham pups were used as the ML training set to select the most appropriate combination of FA to predict DHA in nervous tissues. Six RBC fatty acids (including DHA) select by ML explained 60% of the brain DHA variability at the individual level (39% with the sole RBC DHA), and 78% at the group level (92% with RBC DHA). The robustness of the prediction was validated externally by predicting brain DHA using data obtained in another rat study performed 4 years earlier. At the individual level, the external prediction of ML as 45% with the composite predictor, nil with the sole RBC DHA. We also extended our finding to eye lipids and calculated a new ML model including 7 RBC FA achieving 55 and 98% of the eye DHA variability prediction explained at the individual and group levels, respectively, vs 18% and 83% with the sole RBC DHA. In conclusion using a multiplex RBC FA biomarker generated by ML could improve the prediction of nervous tissues DHA content in the newborn.

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Novel *n*-3 Very-Long-Chain Polyunsaturated Fatty Acids and Their Potential Role in Skin Functions and Integrity

Martina Torrissen ORCID iD[1,2,3], Elisabeth Ytteborg[3], Harald Svensen[2], Iren Stoknes[2], Tone-Kari Østbye[3], Gerd Berge[3], Marta Bou[3], Bente Ruyter[3]

[1]Norwegian University of Life Sciences, Ås, Norway. [2]EPAX AS, Ålesund, Norway. [3]NOFIMA, Ås, Norway

Abstract

Very-long-chain fatty acids (VLC-FAs) have a chain length of ≥24 carbon atoms and are generally not provided through dietary sources. They are synthesized in tissues expressing the enzyme responsible for their condensation reaction (Elongase of Very Long Chain Fatty Acids-4, ELOVL4), such as retina, skin, testis, and brain, and emerging evidence suggest they play critical important roles in these tissues. After identifying VLC-FAs in fish oil and developing a method for concentrating *n*-3 VLC-PUFAs in kg scale, feeding trials have been conducted to investigate their biological effect *in vivo.* Juvenile Atlantic salmon *(Salmo salar)* were fed different dietary levels of *n*-3 VLC-PUFAs, and fatty acid composition and histological samples of different organs were analyzed. The results demonstrate promising health beneficial effects, like improved skin quality, with increasing levels of *n*-3 VLC-PUFAs in the feed. Skin from VLC-PUFA fed fish had a more mature morphology, with better recruitment of scale precursor cells, and in general more mature scales, factors all believed to provide the fish with a more robust skin at an earlier life stage. Furthermore, we carried out *in vitro* experiments with primary Atlantic salmon keratocytes and human dermal fibroblasts, where we have observed promising effects by supplementing these cells with the *n*-3 VLC-PUFA concentrate in scratch assay and cell migration trials. The *in vitro* results are in line with the *in vivo* findings, indicating a potential beneficial effect of *n*-3 VLC-PUFAs in wound healing. Understanding the incorporation of VLC-PUFAs in the body, and how it is involved in the body tissue functions, is important, as is can potentially lead to improvements in cell and tissue function. Data from follow-up feeding trials are currently being processed and will also be presented.

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The Future of Sustainable Aqua Feeds? Assessment of Genetically Modified, Plant Based Oils on the Phospholipid Composition of Atlantic Salmon.

Dr. Richard Broughton[1], Prof. Douglas Tocher[1], Prof. Johnathan Napier[2], Dr. Monica Betancor[1]
[1]University of Stirling, Stirling, United Kingdom. [2]Rothamsted Research, Harpenden, United Kingdom

Abstract

Aquaculture is tasked with fulfilling the demands of a growing population, owing to the constraints on capacity of traditional fisheries. To meet the demands of a growing population, aquaculture will need to provide the additional capacity by which sustainable and nutritious seafood is produced. Salmon are known to be a rich source of omega-3 (n-3) long chain polyunsaturated fatty acids (LCPUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are usually biotrophically accumulated within the fish. However, traditional aquaculture diets typically blend vegetable oils, rich in 18 carbon fatty acids, to supplement fish oils, typically reducing the overall feed content of LCPUFAs. To address the fact that LCPUFAs are a limited resource, genetically modified oilseeds have been developed which are capable of producing these LCPUFAs, with one of their target markets being aquaculture.

Owing to the synthetic approach by which these fatty acids are biosynthesised, the parity of these oils needs to be established. Due to the complexity of lipid synthesis, and the various substrate pools in which the fatty acids reside, the variation in lipid isomers, both acyl and potential stereospecific numbering (sn) isomers, was explored in addition to the standard lipid classes. Two diets were used for this study, one typical of industrial feed, rich in vegetable oil, whereas the other contained the EPA and DHA rich oil from the modified oilseed Camelina sativa. Trends were discovered both relating to the fatty acid composition, characteristic of both terrestrial and modified oils, as well as tissue specific dietary responses. Preliminary findings also suggest alterations within sn-like isomers, indicating potential lipid fingerprints which remain intact throughout the digestive process.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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The effect of oral 2-aminoadipic acid administration on the development of early NAFLD in mice

Marsena Jasiel Ismaiah, Dr. Hani El-Nezamy, Dr. Jetty Chung-Yung Lee, Dr. Kwun Kwan Lo
School of Biological Sciences, The University of Hong Kong, Hong Kong, Hong Kong

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the leading form of chronic liver disease worldwide, affecting around a quarter of the global population. It is a spectrum of comorbidities ranging from simple fat accumulation in the liver cells (steatosis) to inflammatory non-alcoholic steatohepatitis (NASH). The development of NAFLD is a complex process systemically involving multiple pathways including lipid accumulation in the liver (steatosis), insulin resistance, and oxidative stress.

Preliminary in-vitro studies in our laboratory showed that AAA-treated liver cells increased expression of genes involved in de-novo lipogenesis and lipid uptake, as well as increased oxidative stress marker. AAA is a non-proteinogenic amino acid formed via the saccharopine pathway of lysine degradation. Previous literatures have also suggested the role of AAA in inducing oxidative stress in-vitro, altering energy metabolism, insulin signalling and glucose metabolism. Even so, its effect in-vivo is still largely unknown. With this, we hypothesise that AAA participate and potentially exacerbate the development of NAFLD from steatosis to NASH in mice fed with high-fat diet.

In this study, we found that oral administration concurrent with high-fat feeding for 8 weeks potentially worsen the development of early NAFLD through increased steatosis, increased hepatic total cholesterol, alteration of bile acid and cholesterol metabolism as well as the depletion of hepatic antioxidant capacity.

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Plant lecithins in high-fat diets preserve the gut microbiota diversity of mice in relation with specific faecal lipids

Chloé Robert[1], Armelle Penhoat[1], Leslie Couëdelo[2], Magali Monnoye[3], Emmanuelle Meugnier[1], Stéphanie Chanon[1], Nicolas Guillot[1,4], Philippe Gérard[3], Carole Vaysse[2], Marie-Caroline Michalski[1]

[1]CarMeN laboratory, INRAE, UMR1397, INSERM, U1060, Université Claude Bernard Lyon 1, Université de Lyon, Pierre-Bénite, France. [2]ITERG, Equipe Nutrition, Santé et Biochimie des Lipides, Canéjan, France. [3]Micalis Institute, Université Paris-Saclay, INRAE, AgroParisTech, Jouy-en-Josas, France. [4]LIBM, INSA-Lyon, Université Claude Bernard Lyon 1, Villeurbanne, France

Abstract

Context: Synthetic emulsifiers are reported to promote metabolic syndrome and considerably alter gut microbiota. Yet, data is lacking regarding the effects of natural emulsifiers such as plant lecithins, a source of plant n-3 PUFA, on gut and metabolic health.

Methods: Male Swiss mice were fed for 13 weeks a Chow diet, or a 25%-fat semi-synthetic high-fat diet (HFD) rich in SFA and n-6 PUFA (Western control-HFD, no lecithin), or different 25%-fat semi-synthetic HFDs replete in α-linolenic acid (ALA, 4.7% of total fatty acids) with identical fatty acid profile but different lecithin contents within fat: 0% (lecithin-free control-HFD), 10 or 20% rapeseed lecithin (RL) or 10% soy lecithin (SL).

Results: Lecithins did not enhance HFD-induced adipose tissue mass nor inflammation, and did not alter gut barrier markers (colonic mucin and expression of some tight-junction proteins). Gut microbiota diversity was overall improved with lecithins. While both Western control-HFD and lecithin-free control-HFD significantly decreased the microbial α-diversity (observed richness) compared to Chow ($P_{ANOVA}<0.0001$), α-diversity was preserved similar to Chow when HFD included 10% RL ($P_{ANOVA}\leq0.01$ *vs* both Western and lecithin-free control-HFDs). Different operational taxonomic units (OTUs) were impacted by lecithins at the genus level, including increase of specific groups of *Lachnospiraceae*, *Lactobacillus* and *Ruminococcaceae*, parallel to a decrease of OTU of the *Blautia* genus. The abundance of most lecithin-enhanced microbiota OTUs was correlated to the amount of faecal polar lipid-bound ALA (positively) and unesterified palmitic acid (negatively) ($P_{Spearman}<0.001$).

Conclusion: Altogether, SL or RL within ALA-replete HFD did not exacerbate HFD-induced weight gain, metabolic nor inflammatory outcomes and contributed to n-3 PUFA status. Plant lecithins beneficially affected the gut microbiota in association with changes in lipid residues in the distal gut.

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Higher hepatic DHA synthesis rates in female compared to male mice fed an ALA only diet

Ruxandra Rotarescu, Ashley Bejoy, Adam Metherel
University of Toronto, Toronto, Canada

Abstract

Young women have higher DHA levels than men which may arise from higher DHA synthesis rates in women from the nutritionally essential n-3 PUFA, ALA; however, this remains to be assessed. Here, we use compound specific isotope analysis – with potential for translation to humans – to determine sex differences in DHA synthesis and turnover rates in mice. Male and female C57BL/6 mice were allocated to one of three 12-week dietary interventions with constant n-3 PUFA content: 1) 4-week low carbon-13 (δ13C)-ALA diet → 8-week high δ13C-ALA diet, 2) 4-week low δ13C-EPA diet → 8-week high δ13C-EPA diet or 3) 4-week low δ13C-DHA diet → 8-week high δ13C-DHA diet (n=4 per diet, per time point, per sex). On days 0, 1, 3, 7, 14, 28, 56 post-diet-switch blood was collected from the left ventricle, animals were perfused with cold saline and liver, heart, brain, adipose and whole bodies were collected to determine DHA synthesis and turnover rates. Mean liver DHA concentrations were 32, 31 and 23% higher in the ALA, EPA and DHA fed females, respectively, compared to males ($p < 0.05$). Hepatic DHA synthesis rates were 83% higher in ALA-fed females (1.7 µmol/g/day) compared to males (0.93 µmol/g/day), as determined by non-overlapping 95% confidence intervals. Conversely, mean plasma DHA concentrations were significantly higher ($p < 0.05$) in EPA and DHA-fed males compared to females. In plasma, the DHA turnover rate was 73% higher in EPA-fed males (100.6 nmol/mL/day) compared to females (58.1 nmol/mL/day). Higher hepatic DHA synthesis in the ALA-fed females compared to males may explain the higher DHA status in females and encourages further work on sex-specific differences on DHA synthesis from ALA. However, mouse plasma does not appear to match hepatic synthesis, potentially due to faster tissue DHA turnover in females and necessitates further investigation.

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Land-based sources of LC-PUFA as ingredients for salmon feed: Impact on smoltification and lipid inflammatory mediators

Doctor Mónica Betancor PhD[1], Dr Daniel Gonzalez-Silvera PhD[1], Mr Abdalla Salah MSc[1], Dr Richard Broughton Broughton PhD[1], Prof Johnathan Napier PhD[2]

[1]University of Stirling, Stirling, United Kingdom. [2]1. Rothamsted Research, Harpenden, United Kingdom

Abstract

The use of terrestrial vegetables as a source of protein and lipid in aquaculture has led to a reduction of n-3 long-chain polyunsaturated fatty acids (LC-PUFA) in salmon fillets. Genetic modification of oilseed crops such as Camelina or rapeseed has allowed the production of land-based sources of LC-PUFA with the potential to take the pressure off fish oil supplies, which mainly come from wild-caught oily fish – a finite resource. The aim of the present trial was to assess the impact of different novel lipid sources on Atlantic salmon performance, composition and readiness to migrate to sea water (smoltification). Additionally, the production of lipid inflammatory mediators (LIM) was tested after a challenge in marine water. Consequently, eight diets were tested in triplicate, including two GM-camelina oils (high EPA and high EPA+DHA), a canola GM oil (high DHA), a microalgal oil (high EPA and DHA), a northern- and southern-hemisphere oil (reference feeds), krill oil (positive control) and sunflower oil (negative control). Fatty acid content of several tissues, fish health status and the smoltification index will be assessed, together with the circulating levels of LIM. The results will help us to define the possibilities of these new sources of EPA and DHA in salmon farming through their impact on health markers, and will also be useful information to define new policies on the use of GM oils in animal feeds.

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INHIBITION OF STEAROYL-COA DESATURASE-1 DECREASES LYMPHOCYTIC CELL PROLIFERATION AND INCREASES THE BIOSYNTHESIS OF N-10 AND N-12 MONOUNSATURATED FATTY ACIDS

Philippe-Pierre Robichaud PhD[1,2], Jérémie Doiron MSc[2,3], Christy Gnagbo MSc[2], Marc Surette PhD ORCID iD[2,3]
[1]Vitalité Health Network, Dr. Georges-L.-Dumont University Hospital Centre, Moncton, Canada. [2]Université de Moncton, Moncton, Canada. [3]New Brunswick Centre for Precision Medicine, Moncton, Canada

Abstract

The inhibition of stearoyl-CoA desaturase-1 (SCD1) blocks the proliferation and survival of several different carcinoma cell types. However, SCD1 inhibition in lymphocytic leukemia cells or normal human T cells has not been investigated. In the current study the impact of SCD1 inhibition on fatty acid metabolism, cell proliferation and apoptosis was measured in Jurkat T lymphocytic leukemia cells and in CD3/CD28-activated T cells from human blood. Incubation of cells with the SCD1 inhibitor A939572 (0 to 1µM) reduced cell proliferation in 10% serum, which was exacerbated in serum free media. This was accompanied by a significant reduction ($p<0.05$) in cellular SCD1 products 16:1n-7, 18:1n-7 and 18:1n-9. GC-MS/MS analysis of fatty acid methyl esters following dimethyl disulfide derivatization revealed that A939572-treated cells accumulated 16:1n-10, 18:1n-10 and 18:1n-12 which was more pronounced in reduced serum (0% or 2%) conditions. Remarkably, these accounted for over 40% of Jurkat cell fatty acids in serum free + SCD1 inhibition conditions. Similar results were obtained in monocytic THP-1 and MM6 cell lines. Production of these unusual fatty acids was prevented in the presence of the delta-6 desaturase (D6D) inhibitor SC-26196 (2µM). Reduced serum conditions, but not SCD-1 inhibition, induced significant ($p<0.05$) increases in mRNA coding for SCD1, fatty acid synthase (FASN) and D6D measured by qPCR. This was accompanied by significantly increased SCD1 and FASN protein content measured by western blot. Dual inhibition of SCD1 and D6D in Jurkat or THP-1 cells induced significant apoptosis (Annexin V/PI) that was prevented by the addition SCD1- or D6D-derived fatty acids. Altogether, these results indicate that SCD-1 inhibition and/or reduced serum conditions induce the biosynthesis of unusual D6D-derived fatty acids as a compensation mechanism in lymphoid cells. Care should also be taken when assessing anti-cancer effects of test compounds that is often performed under serum-free conditions.

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Cholesterol metabolism, oxysterols and retinal integrity

Elodie Masson ORCID iD[1], Jeanne Urban[1,2], Elise Léger-Charnay[1], Lucy Martine[1], Bénédicte Buteau[1], Ségolène Gambert[1], Georges Alves[2], Yael Grosjean[2], Niyazi Acar[1], Lionel Bretillon[1]

[1]Eye and Nutrition Research Group, Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAE, Institut Agro, Université de Bourgogne Franche-Comté, Dijon, France. [2]Sensory perception, glia-neuron interaction Research Group, Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAE, Institut Agro, Université de Bourgogne Franche-Comté, Dijon, France

Abstract

The retina, as a part of the central nervous system, is particularly rich in lipids. Free cholesterol is found in plasma membranes where it participates in maintaining a structural organization required for proper visual transduction. Lack or excess of cholesterol has been shown to be neurotoxic in the brain and evidence indicate that it might also be the case in the retina. The retina exhibits a unique cholesterol metabolism based on endogenous synthesis and transport as well as on exchange with the systemic circulation via lipoproteins. Excess of cholesterol can also be eliminated after conversion into oxysterols, via CYP enzymes. In the retina, CYP46A1, that produces 24S-hydroxycholesterol (24S-OHC), is expressed in a specific type of neurons, targeted during glaucoma. Using primary cell cultures, we have shown that Müller cells, the major glial cells of the retina, were able to adjust their cholesterol metabolism in response to 24S-OHC exposure, highlighting the signaling role of 24S-OHC in neuron-glia communication. In addition, we have reported that the expression of CYP27A1, another retinal CYP enzyme, was modulated in a rat glaucoma model, along with the expression of other major actors of cholesterol metabolism. This was associated with a transient cholesterol overload in the retina. Drosophila making a powerful genetic model to study nervous tissue functionality, we have undertaken the retinal characterization of flies with a downregulated CYP27A1 ortholog mainly expressed in the drosophila retina and observed that they exhibit reduced eye size. Altogether, these data suggest that cholesterol conversion into oxysterols is crucial for cholesterol homeostasis and integrity of the retina.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Some results mentioned in the abstract have been published:

Léger-Charnay et al., Experimental Eye Research, 189:107857 (2009)

Léger-Charnay et al., PLoSOne, 17(3):e0264787 (2022)

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FADS variants and associations with red blood cell fatty acid composition, patterns and estimated desaturase activities in pregnant woman from African descent: The NuPED study

Dr Lizelle Zandberg PhD Biochemistry ORCID iD[1], Dr Elizabeth A Symington PhD Nutrition ORCID iD[2], Mrs Anika Prinsloo Msc Dietetics[1], Mrs Amanda Kuit Msc Nutrition ORCID iD[1], Dr Cornelia Conradie PhD Dietetics ORCID iD[1], Ms Ester Osuna[3], Prof Cristian Ricci[1], Dr Jeannine Baumgartner PhD Nutrition ORCID iD[4], Prof Linda Malan PhD Nutrition ORCID iD[1], Prof Cornelius M Smuts PhD Biochemistry ORCID iD[1]
[1]North-West University, Potchefstroom, South Africa. [2]Department of Life and Consumer Sciences, University of South Africa, Johannesburg, South Africa. [3]ETH Zurich, Zurich, Switzerland. [4]King's College London, London, United Kingdom

Abstract

Biosynthesis of LCPUFA are partially dependent on the genetic characteristics of the fatty acid desaturase. Here, the genetic characteristics of the FADS1/2/3 gene cluster variants and their association with red blood cell total phospholipid fatty acid composition, patterns and estimated desaturase activities of pregnant women from African descent living in Johannesburg, South Africa are described. In the NuPED study, RBC total phospholipid fatty acid composition was assessed in 250 pregnant women at <18 weeks gestation using GCMSMS. RBC phospholipid fatty acid were determined using principal component analysis. LCPUFA ratios were used as estimated desaturase activities. In a subset, the FADS1/2/3 gene cluster were sequenced using Ion Torrent amplicon panel sequencing. Variants of interest were genotyped using the iPLEX® MassARRAY system.

The mean n-3 index was 5.92 ± 1.39. 55% of women had low n-3 index (<6%) and 5% had a very low n-3 index (<4%). Four RBC phospholipid fatty acid patterns were apparent, i.e., a high saturated FA (Pattern 1); low DHA and n-6 PUFA, and high trans FA (Pattern 2); high ALA, EPA, n-3 DPA and n-6 GLA (Pattern 3); and high n-3 PUFA (Pattern 4). A novel variant, rs78678033(G/A) associated with lower DGLA and fourteen more common variants were associated with higher estimated D5D and lower estimated D6D independent of dietary intake. Minor allele carriers for rs6591665(G/A) had higher total saturated fatty acid composition (Pattern 1), whereas minor allele carriers for rs174547(T/C), rs147549(G/A), rs174634(G/C) and rs174635(T/G) had higher ALA, EPA, n-3 DPA, and n-6 GLA (Pattern 3). Minor allele carriers for rs174555 and rs11245493 had lower total n-3 PUFAs (Pattern 4).It is evident that genetic variants of the FADS 1/2/3 gene cluster alter the n-3 LCPUFA status women of African descent independent of diet.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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Can LC-PUFA levels be boosted in Atlantic salmon through nutritional programming? A long term study

Miss Karla Fernandez MSc[1], Dr Stuart McMillan PhD[1], Dr Matthew Sprague PhD[1], Dr Laura Martínez-Rubio PhD[2], Dr Ashie Norris PhD[3], Dr Ingunn Stubhaug PhD[4], Dr Monica Betancor PhD[1]

[1]University of Stirling, Stirling, United Kingdom. [2]Mowi AS, Bergen, Norway. [3]Mowi Genetics, Bergen, Norway. [4]Skretting ARC, Stavanger, Norway

Abstract

Due to availability and sustainability issues, there has been a change in the formulation of farmed fish feeds in recent years, generally resulting in a decrease in the long chain polyunsaturated fatty acid (LC-PUFA) – rich ingredients. This has led to lower LC-PUFA contents in farmed fish, but also detrimentally in terms of consequences for health for the human consumer. A potential way to boost the levels of these health-beneficial fatty acids in fish could be the application of early nutritional intervention (“stimulus”) where fish are fed a predominantly vegetable-based (V) diet for a short period, to induce more efficient uptake and utilization of nutrients from a similar diet when fed at a later period in a concept referred to as “nutritional programming”. This concept has been previously tested in Atlantic salmon, resulting in physiological adaptations at the molecular level, as well as an enhanced tolerance to “terrestrial” diets. It is unknown whether these benefits are extended in the long term (eg in the seawater stage) or if a “booster” is needed. The aim of the present study was to validate the long-term effect of nutritional programming and the possible interactions of nutrition with the genotype (high and low pigment deposition). Results related to fish growth performance, feed efficiency, biochemical composition, nutrient retention and tissue gene expression are presented.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

NA

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Higher n-3 LCPUFA status associates positively with blood pressure in pregnant African women: The NuPED cohort

Prof Linda Malan PhD ORCID iD[1], Dr Lizelle Zandberg PhD ORCID iD[1], Dr Arista Nienaber PhD ORCID iD[1], Ms Katlego Kekana MSc ORCID iD[1], Dr Amy Wise MBBCh, MMed, FCOG, Dip HIV Man ORCID iD[2], Dr Elize Symington PhD ORCID iD[3], Dr Jeannine Baumgartner PhD ORCID iD[4], Prof Marius Smuts PhD ORCID iD[1]

[1]North-West University, Potchefstroom, South Africa. [2]University of the Witwatersrand, Johannesburg, South Africa. [3]University of South Africa, Johannesburg, South Africa. [4]King's College, London, United Kingdom

Abstract

Background: Adequate intake and status of n-3 LCPUFA have been linked to improved endothelial function and reduced blood pressure. In South Africa pregnant women receive routine iron supplementation. High iron intake has been associated with oxidative stress which may increase blood pressure.

Aim: The Nutrition during Pregnancy and Early Development (NuPED) study assessed the relationship of n-3 PUFA status with blood pressure in pregnant African women receiving routine iron supplementation and in their 12-month-old infants.

Methods: 250 pregnant women were recruited at <18 weeks gestation in clinics in Gauteng province, South Africa. Red blood cell total phospholipid fatty acid composition and blood pressure were measured at <18-, 22- and 36-weeks' gestation and blood pressure in their 12-month-old infants.

Results: At 22 weeks' gestation n-3 LCPUFA correlated positively with systolic ($r=0.213$, $p=0.001$) and diastolic ($r=0.210$, $p=0.001$) blood pressure and EPA with pulse pressure ($r=0.133$, $p=0.045$). EPA, DHA and n-3 LCPUFA were higher (all $p<0.05$) in prehypertensive than normotensive women after adjusting for multiple factors including dietary intake. Maternal ALA at <18 weeks' gestation correlated negatively ($r=-0.334$, $p=0.028$) and EPA at 22 weeks' gestation borderline negatively with infant blood pressure ($r=-0.299$, $p=0.057$). Women with the G allele of FADS2-rs2072114 showed weak evidence of higher ALA and EPA at <18 ($p=0.063$ and $p=0.067$ one sided) and 22 weeks' gestational age ($p=0.045$ and $p=0.082$) and higher systolic blood pressure at 36 weeks' ($p=0.077$).

Conclusion: Higher n-3 LCPUFA composition in pregnant women of African descent was associated with higher blood pressure in the context of routine iron supplementation, independent of dietary n-3 LCPUFA intake. We hypothesize that the higher n-3 LCPUFA may be a genetically driven metabolic response to the physiological circumstances in this predominantly black African study population.

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Bioavailability of docosahexaenoic acid [22:6(n-3)] from regio- and stereospecifically structured triacylglycerols

Professor Baoru Yang PhD ORCID iD[1], Ms Amruta Kulkarni MSc[1], Ms Yuqing Zhang MSc[1], Professor Gudmundur Haraldsson PhD[2], Professor Kaisa Linderborg PhD[1], Professor Emeritus Heikki Kallio PhD[1], Professor Yumei Zhang PhD[3]
[1]University of Turku, Turku, Finland. [2]University of Iceland, Reykjavik, Iceland. [3]Peking University, Beijing, China

Abstract

Long chain n-3 polyunsaturated fatty acids (n-3 PUFAs) have a wide range of health promoting effects and are considered essential components of diet. However, there is limited on the importance of stereospecific position in dietary triacylglycerols (TAG) on the bioavailability of n-3 PUFAs. In this research, we investigated the effects of positional distribution of docosahexaenoic acid [22:6(n-3), DHA] in TAG molecules on the absorption and tissue accumulation of DHA in rats, using regio- and stereospecifically structured TAGs. Mildly n-3 deficient rats were fed daily with 360 mg structured TAGs containing DHA at sn-1, 2 or 3 position and stearic acid in other two positions for 5 days (Study I). Rats of normal n-3 status received DHA from structured TAGs containing one DHA and two palmitic acid moieties (500 mg/kg body weight per day) for four weeks (Study II). Groups receiving tristearin (Study I), tripalmitin (Study II), or standard feed AIN-93G (Study I & II) were also included. At the end of feeding, fatty acids were analysed from plasma, feces, liver, visceral fat, brain, eyes, testis, kidneys. Overall, the bioavailability of DHA was high despite the position of DHA, resulting in significant increase in DHA levels in all the tissues compared to the groups fed with n-3 deficent diet containing tripalmitin or tristearin. Compared to sn-3 DHA feeding, feeding with sn-1 DHA resulted in significantly higher DHA level in TAG of the liver (trial I) and plasma (trial II), whereas sn-3 DHA feeding led to highest DHA accumulation in visceral fat among the DHA groups (trial II). Our results indicate a possible difference also between the bioavailability of DHA between the two primary positions of dietary TAGs. This is the first study on the bioavailability of DHA from regio- and enantiopure TAGs.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Neonatal Ischemic Brain Injury: Omega-3 Fatty Acid Diglyceride Emulsions as a Novel Injectable Acute Therapeutic

Hylde Zirpoli PhD[1], Estela Area Gomez PhD[2], Denny Joseph Manual Kollareth PhD[3], Sergey A. Sosunov PhD[3], Vadim S. Ten PhD, MD[3], Richard J. Deckelbaum MD, CM, FRCP(C)[1], Tilla S. Worgall MD[4]

[1]Institute of Human Nutrition, Department of Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, USA. [2]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, USA. [3]Department of Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, USA. [4]Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, USA

Abstract

We previously reported that n-3 FAs carried by triglyceride (TG) emulsions provide neuroprotection after neonatal hypoxic-ischemic (HI) injury. Our recent findings of higher incorporation of n-3 diglycerides (DG) into model membranes and higher lipolysis of n-3 DG vs TG emulsions led us to question if this novel DG molecule would improve effectiveness of n-3 FAs in reducing infarct size after brain HI compared to TGs, and whether DGs might affect brain lipid profiles and membrane structure.

Using the Vannucci neonatal mouse model of HI brain injury followed by injections of n-3 rich DG or TG emulsions vs saline controls we measured infarct size at 24h by TTC staining. HPLC–MS/MS analysis measured brain sphingolipid profiles. We characterized lipid rafts (LRs) in cell membranes by filipin staining microscopy, and inflammatory markers by rt-PCR after DG administration in a microglia cell culture model (BV2).

n-3 DG emulsions provided 3-fold more robust neuroprotection than TGs in reducing infarct size. n-3 DG rapidly changed sphingolipid profiles in brain. Levels of ceramide (C18) and dihydroceramides (C16, C18, C18:1) were significantly downregulated (1 to 1.5-fold decrease) at 2h and 18h after n-3 DG emulsion administration compared to controls. n-3 DG increased by 1.5-fold brain levels of sphingosine-1-phosphate, known to have neuroprotective properties. n-3 DGs disrupted LR structure and distribution, by displacing endogenous cholesterol from microglia plasma membranes to the cytosol. In vitro n-3 DG treatment in BV2 increased expression of TREM2 receptor (1.6-fold) and downstream anti-inflammatory markers (IL-1 and IL-4, 2-fold).

Thus, the neuroprotective effects of n-3 DG emulsions involve the modification of membrane LR dynamics in microglia, via major changes in sphingolipid content, and the boosting of anti-inflammatory responses. n-3 DG emulsions represent a novel and far more efficient modality than TG for treating ischemic brain injury after HI.

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A plasma phospholipid signature as a possible biomarker of the acute phase of traumatic brain injury

Dr Isabell Nessel PhD ORCID iD[1], Dr Simon C. Dyall PhD ORCID iD[2], Dr Luke Whiley PhD ORCID iD[3], Prof Adina T Michael-Titus PhD ORCID iD[1]

[1]Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom. [2]School of Life and Health Sciences, London, United Kingdom. [3]Health Futures Institute, Murdoch University, Murdoch, Australia

Abstract

Traumatic brain injury (TBI) triggers complex neurochemical and metabolic changes, including membrane phospholipid (PL) breakdown. We investigated plasma PL changes in the first 3 days post-TBI, to assess whether such changes could become a marker of human acute TBI.

Patients with TBI (Abbreviated Injury Scale (AIS)3 indicating serious injury, n=5; AIS4 indicating severe injury, n= 8), and controls (n= 13), were selected from the QMUL Trauma-Biobank. Plasma samples were analysed for PLs by LC-MS. Neurofilament light (NFL) and pro-inflammatory cytokines were measured using electro-chemiluminescence. Red blood cell omega-3 index was calculated after fatty acid analysis by gas chromatography.

NFL levels were significantly increased at 24 and 72 h after injury in AIS4 TBI cases, vs. controls. IL-6 was significantly elevated 24 h after injury in AIS4 patients. LPC (18:0/0:0) and (16:0/0:0) and PC (40:8) and (36:4) were significantly decreased 24 h after TBI and were still significantly lower 72 h after injury in AIS4. Similar changes were seen for LPE, PE and SM. Furthermore, orthogonal projections to latent structures discriminant analysis revealed specific lipid patterns, separating AIS4 TBI samples at 24 and 72 h from controls. Over the first 3 days post-injury, the omega-3 index did not change significantly; notably, baseline levels were low in all patients (controls: 4.3±1.1% and TBI: 4.0±2.1%).

We have identified a range of changes affecting various PLs in the acute phase post-TBI. After confirmation in larger patient cohorts, this could inform the development of new lipid biomarker panels and also new therapies in TBI.

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Male and female FAT1 offspring are protected from hippocampal fatty acid composition and memory alterations triggered by maternal exposure to a n-3 PUFA deficient diet

Flore Marchaland[1], Moïra Rossitto[1], Maud Martinat[1], Stéphane Grégoire[2,3], Jing Xuan Kang[4], Corinne Joffre[1], Niyazi Acar[2,3], Charlotte Madore-Delpech[1], Jean-Christophe Delpech[1], Sophie Layé[1]

[1]Univ. Bordeaux, Bordeaux INP, NutriNeuro, INRAE UMR 1286, Bordeaux, France. [2]Univ. Bourgogne, CNRS UMR 6265, Centre des Sciences du Goût et de l'Alimentation, Dijon, France. [3]Univ. Bourgogne, INRAE UMR 1324, Centre des Sciences du Goût et de l'Alimentation, Dijon, France. [4]Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA

Abstract

Long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) are mainly provided to the offspring's brain by the mother. Previous studies reported that offspring from mother fed with a n-3 PUFA deficient diet display decreased level of LC n-3 PUFA in hippocampal synaptosomes, as well as hippocampal neuronal networks impairments and spatial memory alterations, at weaning age. We further identified a microglia contribution to memory and neuronal networks alterations in n-3 PUFA deficient offspring, induced by an impairment of its function. However, it is still unknown whether the restoration of n-3 PUFA levels in the offspring protect them from the deleterious effects induced by a n-3 PUFA maternal deficiency and whether this is sex-dependent.

For this purpose, we took the opportunity of the transgenic FAT1 mice that convert n-6 PUFA into n-3 PUFA *in vivo*. We found that at weaning age, FAT1 pups, but not WT pups - both from WT mothers fed with a n-3 PUFA deficient diet - did not exhibit neurobiological and behavioral alterations. In addition, PUFA profile was restored in the hippocampus of both male and female FAT1 pups.

Our results show that the deleterious effects of early-life exposure to a n-3 PUFA deficient diet on brain PUFA profile and memory affect both male and female WT pups at weaning age. They also reveal that the brain correction of n-3 PUFA profile in FAT1 pups protect them against these deleterious effects. We are currently exploring the underlying mechanisms of this protection, in particular the contribution of microglia.

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Introduction of Different Lighting and Feeding Modes in the Atlantic Salmon Salmo Salar L. Aquaculture Technology: Changes in the Lipid and Fatty Acid Composition

Dr. Svetlana A. Murzina Dr. ORCID iD, Dmitry Provotorov, Dr. Maria Kuznetsova Dr., Dr. Anton Kyritsyn Dr., Prof. Nina N. Nemova Dr.
Institute of Biology of the Karelian Research Centre of the Russian Academy of Sciences (IB KarRC RAS), Petrozavodsk, Russian Federation

Abstract

The parameters of lipid metabolism, along with other biochemical characteristics, are stable and genetically determined cumulative indicators of the smoltification of Atlantic salmon in nature and aquaculture. It is known that the manipulations with the photoperiod stimulate the transformation of “underyearlings to smolts”, contribute to reduce the duration of rearing of juveniles in freshwater, to obtain smolts at the 0+ age. Coordinating the smoltification is of significant interest to Atlantic salmon breeding in terms of increasing commercial production. A comparative study of the lipid and fatty acid (FA) composition of Atlantic salmon fingerlings reared under natural and continuous light (24LD) in commercial aquaculture in the summer-autumn and winter period in the North Ossetia-Alania was carried out. In the winter period from mid-November to early April – 24LD was stopped; the parr and smolts were collected in March and August. The decrease of the total lipids due triacylglycerols and phospholipids as a stable trend of lipid metabolism reconstruction during the smoltification in fingerlings under 24LD and feeding regime, and 24LD and daytime feeding was revealed. Such trend was detected in salmon parr in March until smolt transformation. A change in FA indicators was established: an increase in the content of PUFAs due to (n-3) PUFAs, and in them FA of the "marine" type - 22:6(n-3), high values of the ratios (n-3)/(n-6) PUFA, 18:3(n-3)/18:2(n-6), 22:6(n-3)/18:3(n-3). The "flesh lipid quality" index, which is based on the content of physiologically significant and essential 20:5(n-3) and 22:6(n-3), and determines the quality of fish products, in underyearlings, parrs and smolts grown under 24LD was preferable. This study was carried out at the Laboratory of Ecological Biochemistry and using the equipment of the Core Facility KarRC RAS. The study was financially supported by the Russian Science Foundation project № 19-14-00081.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No.

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Milk Fat Globule Membrane dietary supplementation in *Drosophila melanogaster* affects lipid metabolism and fecundity.

PhD student Víctor Mendoza-Grimau Food Science ORCID iD[1,2], Dr. Antonio Perez-Galvez ORCID iD[3], Dr. Ana Busturia ORCID iD[2], Dr. Javier Fontecha ORCID iD[1]

[1]CIAL (CSIC-UAM), Madrid, Spain. [2]CBM-SO (CSIC-UAM), Madrid, Spain. [3]IG (CSIC), Sevilla, Spain

Abstract

Although milk fat globule membrane (MFGM) has become an increasing focus of research interest due to demonstrated improvements in immune, gut, brain function, and cardiometabolic health in mammals, little is known about the mechanisms involved. We sought to investigate them using *Drosophila melanogaster* as a model system, a well-established and valuable model for lipid research that shares many similarities with the mechanisms controlling vertebrate lipid metabolism.

We performed a nutritional intervention by supplementing the fly's diet with different doses of MFGM to determine the physiological effects and their trans-generational inheritance. We have so far analyzed a) the effects on the lipidome, b) on female fecundity, and 3) on developmental cycle length. Our results show that consumption of MFGM induces significant and positive changes in the lipidome. For example, consumption of 2% MFGM increases the levels of linoleic acid, high molecular weight TAG fraction and phospholipids. In addition, we found that the intake of 2% MFGM increased the fecundity of females and accelerated the developmental cycle. Interestingly, the increase in fecundity and changes in the lipidome are inherited trans-generationally.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No

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Effect of a hyperlipidic diet enriched in linoleic acid on the liver in a C57BL/6J mouse model.

Youenn Launay PhD Student[1,2], Daniel Catheline Research Engineer[2], Manuel Vlach Project Engineer[2,1], Philippe Legrand Professor[2], Bernard Fromenty Research Director[1], Clemence Penhoat PhD Student[1], Karima Begriche Assistant Professor[1], Vincent Rioux Professor[2,1]
[1]NuMeCan Institute, Rennes, France. [2]Agro Institute, Rennes, France

Abstract

Introduction :

Excess dietary linoleic acid (LA) is associated with deleterious effects depending on the model studied. It increases the prevalence of adiposity and overweight in humans and has trans-generational pro-adipogenic roles in mice. Our study explores the effect induced by a hyperlipidic diet enriched in LA at the hepatic mouse level.

Materials and Methods:

C57BL/6J mice were fed with 3 different diets for a period of 17 weeks. The "CTRL" group was fed with a "chow diet" (10% total lipids including 24.7% LA), the "HPL" group was fed with a hyperlipidic diet (45% lipids including 24.7% LA) and the "HPL LA" group was fed with a hyperlipidic diet enriched in LA (45% lipids including 52.1% LA). After euthanasia, liver lipids were extracted and analyzed by GC-MS (Gas Chromatography Mass Spectrophotometry).

Results:

A significant increase in total lipids for the HPL group is shown compared to the CTRL group but not for the HPL LA group. Unexpectedly, the n-6 family was not increased in the liver of the HPL LA group compared to the HPL group despite the LA supplementation. Within the n-6 family, LA was increased in the HPL LA group but not differently from the HPL group compared to the control.

Conclusion:

All the results show that lipids do not seem to be accumulate in mice livers fed with an HPL LA diet compared to a more traditional HPL diet even at the n-6 family level. We can therefore hypothesize a strong regulation of LA in mice at the hepatic level.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Study of hepatic steatosis induced by an excess of linoleic acid in the human hepatoma cell line HepaRG

Youenn Launay PhD Student[1,2], Manuel Vlach Project Engineer[2], Daniel Catheline Research Engineer[2], Philippe Legrand Professor[2], Bernard Fromenty Research Director[1], Karima Begriche Assistant Professor[1], Vincent Rioux Professor[2,1]
[1]NuMeCan Institute, Rennes, France. [2]Agro Institute, Rennes, France

Abstract

Introduction :

Excess dietary linoleic acid (LA) is associated with deleterious effects depending on the model studied, in particular, LA is pro-steatotic in the HepaRG model. This study aimed to better understand this LA effect induce directly, or indirectly by 4 LA derived metabolites of interest including 2 Oxlams (Oxidized linoleic acid metabolites): 9-HODE (9-HydroxyOctaDecadienoic Acid) and 13-HODE, as well as 2 CLAs (Conjugated Linoleic Acids): c9,t11-C18:2 (rumenic acid) and t10,c12-C18:2.

Materials and methods :

HepaRG cells were cultured for 35 days then incubated for 1 week with the 5 identified molecules of interest (LA / 9-HODE / 13-HODE / c9,t11-C18:2 / t10,c12-C18:2) at different concentrations and compared to a control condition. After treatments, triglyceride assays and cell viability tests were performed. Gene’s expressions were quantified by RTqPCR.

Results :

Cells developed steatosis marked by the accumulation of intracellular triglycerides for LA/c9,t11-C18:2 and to a lesser extent t10,c12 C18:2 treatments at 150µM each, without associated cellular toxicity. The MTTP expression is more strongly decreased for c9,t11-C18:2. The expressions of DDIT3 and HSPA5 are respectively increased for t10,c12-C18:2 and decreased for LA whereas CPT1 is more strongly expressed for t10,c12-C18:2.

Conclusion : Our study shows a pro-steatotic effect of LA but also of the CLAs on HepaRG. Depending on the different molecules of interest, we observe a more marked impact on the VLDL secretion pathway for rumenic acid, whereas on the ER stress pathway for linoleic acid and t10,c12-C18:2, itself counterbalanced by an increase in mitochondrial beta oxidation.

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Study of the lipid metabolism of the hepatocellular model HepaRG.

Youenn Launay PhD Student[1,2], Lydie Hue Master 2 Student[3], Manuel Vlach Project Engineer[2], Iwan Jan Licence 3 Student[3], Daniel Catheline Research Engineer[2], Philippe Legrand Professor[2], Karima Begriche Assistant Professor[1], Vincent Rioux Professor[2]
[1]NuMeCan Institute, Rennes, France. [2]Agro Institute, Rennes, France. [3]University of Rennes, Rennes, France

Abstract

Introduction :

The HepaRG cell model is a human hepatocellular cell line model. This later is a bipotent progenitor model with a high proliferative potential capable of differentiating into hepatocytes and cholangiocytes. It is mainly used in toxicological studies, but also in NAFLD (Non-Alcoholic Fatty Liver Desease) studies because of the conservation of numerous metabolisms. Our study seeks to better describe the lipid and fatty acid metabolism in HepaRG cells.

Materials and Methods :

HepaRG cells were harvested at different growth stages: progenitor cells, after 14 days of proliferation, and after differentiation (35 days of total culture). Rat hepatocytes and human hepatocytes were used for comparison. The fatty acid composition of the cells was analyzed by GC-MS (Gas Chromatography Mass Spectrometry). Enzymatic activities, in particular desaturases, elongases (...) were determined. Quantitative analysis of gene expression was also performed.

Results :

Results show a strong decrease in FADS2 gene expression in differentiated HepaRG cells compared to rat and human hepatocytes. Consistently, results from enzyme activity assays show a significant decrease in delta 6 desaturase activity in HepaRG compared to rat hepatocytes. The expression of SCD1 encoding delta 9 desaturase is also strongly increased in the differentiated stage compared to the progenitor stage.

Conclusion :

The lack of expression of the FADS2 gene correlates well with the low enzymatic activity of delta 6 desaturase. The strong increase in SCD1 expression between the progenitor and differentiated stages could also become a marker of differentiation between these two stages in this model.

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Dietary n-3 Polyunsaturated Fatty Acids Improve Long-Term Neuropathological and Functional Outcome after Repeated Mild Traumatic Brain Injury

Dr. Abhishek Desai Ph.D., Dr. Huazhen Chen M.D., Mr. Karl Kevala MS, Dr. Hee-Yong Kim Ph.D.
NIAAA/NIH, Rockville, USA

Abstract

Repeated mild traumatic brain injury (TBI) can cause persistent neuropathological effects and is a major risk factor for chronic traumatic encephalopathy. In this study, we demonstrate positive effects of dietary n-3 PUFA on long-term neuropathological and functional outcome in a clinically relevant model of repeated mild TBI using the Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA). Adult mice, reared on n-3 PUFA adequate (higher n-3 PUFA) or deficient (lower n-3 PUFA) diets, were given a mild CHIMERA daily for 3 consecutive days. At 2 months after injury, visual function and spatial memory along with Glia cell activation and axonal damage were evaluated. Repeated CHIMERA (rCHIMERA)-induced gliosis and axonal damage was significantly suppressed in the brain of mice fed the n-3 PUFA adequate diet compared to the deficient diet group. rCHIMERA induced a drastic reduction in N1 amplitude of the visual evoked potential in both diet groups, however, the reduction was less severe in the adequate diet group. The Morris water maze probe test indicated a significant decrease in the number of platform crossings in the deficient diet group compared to the adequate group. These data support the neuroprotective potential of a higher n-3 PUFA diet in ameliorating the adverse outcome of repeated mild TBI.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Very long-chain saturated fatty acids, cardiovascular disease and mortality

Dr Rozenn N. Lemaitre PhD[1], Dr Amanda M. Fretts PhD[1], Dr Paul N. Jensen PhD[1], Dr Irena B. King PhD[2], Dr Dariush Mozaffarian MD, PhD[3]
[1]University of Washington, Seattle, USA. [2]Biomarker Consultant, Placitas, USA. [3]Tufts University, Boston, USA

Abstract

Very long-chain saturated fatty acids (VLSFAs) with 20 or more carbons and the lipids that carry them have received limited attention. We have studied circulating VLSFA, including arachidic acid (20:0), behenic acid (22:0) and lignoceric acid (24:0), in the Cardiovascular Health Study (CHS), a prospective cohort of older adults and in the Fatty Acids and Outcomes Research Consortium (FORCE), an international consortium of 30+ prospective studies. Independent of known risk factors, higher plasma phospholipid levels of VLSFA were associated in CHS with lower risk of incident heart failure (HF); lower risk of incident atrial fibrillation (AF); and lower total mortality. In pooled analyses in the FORCE Consortium, VLSFA were associated with lower risk of type 2 diabetes. In CHS, we also examined plasma ceramides (Cer) and sphingomyelins (SM) with acylated VLSFA and acylated palmitic acid (16:0). Both Cer and SM with a VLSFA were associated with lower risks of incident HF, incident AF and total mortality; in contrast, Cer and SM with 16:0 were associated with higher risks of incident HF, AF and total mortality. With regards to incident type 2 diabetes, all Cer, regardless of the acylated fatty acid, but none of the SM, were associated with higher risk. Further studies are needed to investigate the endogenous production of VLSFA and lipids that contain them, and ascertain whether dietary or other lifestyle factors can influence plasma levels of these fatty acids in order to promote better cardiovascular health.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

The abstract has not been published

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Relationship between maternal LCPUFA status and allergy in infants of African descent: The NuPED study

Prof Linda Malan PhD ORCID iD[1], Dr Arista Nienaber PhD ORCID iD[1], Dr Lizelle Zandberg PhD ORCID iD[1], Ms Ilse Gravett Msc ORCID iD[1], Dr Elizabeth Symington PhD ORCID iD[2], Dr Megan Burke MBChB, MMed (Paed)[3], Dr Jeannine Baumgartner PhD ORCID iD[4], Prof Cornelius Marius Smuts PhD ORCID iD[1]

[1]North-West University, Potchefstroom, South Africa. [2]University of South Africa, Pretoria, South Africa. [3]University of Witwatersrand, Johannesburg, South Africa. [4]Kings's College, London, United Kingdom

Abstract

Globally, allergy is a growing burden of disease. Maternal n-3 LCPUFA supplementation may protect infants from allergies. However, allergy protection among various ethnic groups is not fully understood and the relationship between LCPUFA status with allergy remains controversial and may depend on genetic variance in the fatty acid (FA) desaturation and elongation metabolism. This study aimed to determine the association of maternal n-3 and n-6 LCPUFA status at early pregnancy, and estimated desaturase activities, with allergic disease and sensitisation in urban African 6–12-month-old infants, residing in South Africa and if maternal allergy status and the genetic variance of maternal FADS2 rs2072114 modifies this relationship.

In the Nutrition during Pregnancy and Early Development (NuPED) African cohort associations of maternal LCPUFA status at early pregnancy (<18 weeks' gestation) with infant allergic disease (symptoms and/or sensitisation) at 6-12 months were assessed in 107 infant-mother pairs using logistic regression models. Desaturase activities estimated with FA ratios, maternal FADS2 rs2072114(A/G) genotype, and early pregnancy maternal allergic disease (symptoms or sensitisation) were also investigated.

42% of infants had allergy-like symptoms, 17% were sensitised and 41% had symptoms and/or sensitisation. The probability of allergy symptoms and/or sensitisation was 37% lower for each percentage increase in maternal DHA status (OR: 0.63; 95% CI: 0.41, 0.98). In infants with allergy-like symptoms, the maternal n-6:n-3 LCPUFA ratio was higher (p=0.039), and the AA: DGLA ratio lower (p=0.032) compared with non-symptomatic counterparts. Maternal allergy symptoms were a strong predictor of infant allergy symptoms, whereas FADS2 rs2072114(A/G) was not.

Higher maternal DHA status at early pregnancy was associated with lower allergy symptoms and/or sensitisation, implying that there may be a protective effect of maternal n-3 LCPUFA status on allergic disease manifestation in 6–12-month-old African infants.

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Impact of geographic origin of cocoa butter on composition and crystallization

Daniel KALNIN
Istom - Ecole Superieur d'agrodeveloppement international, Angers, France

Abstract

Cocoa butter (CB) is an essential ingredient of chocolate and has a direct influence on the consumer relevant characteristics of this globally consumed product. The crystallization properties of CB influence the tempering process, a necessary step in the production of quality chocolate. The composition and hence the hardness of CB can vary considerably depending on the geographic origin, particularly with the environmental temperature at the time of maturation of the beans. Additionally, aroma compounds such as they exist in fine cacao (eg. Colombia) can influence crystallization behavior. Besides, CB composition can influence the delivery of those aroma compounds in terms. Mastery of crystallization behavior is key for the process of tempering, which is necessary for high-quality chocolate.

We study the influence of the environmental temperature at the time of maturation of the beans on the crystallization of CB. We compare CB from three distinct locations in Ivory Coast, Peru, and Colombia with commercial-grade CB. Differential scanning calorimetry and X-ray diffraction were used to monitor and compare the crystallization behaviors of known origins obtained after different thermal treatments. The results show a notable physicochemical difference between the different CBs. Notably, they differ in their final melting points but we can follow different melting behavior indicating differences in composition, which we measure with a fatty acid profile and confirm with thermal analysis. We were able to compare composition data with physicochemical properties. The findings encourage further experimentation with the knowledge of the CB agronomic practices, which are perfectly identifiable, to understand precisely the influence of these agronomic parameters on the crystallization of CB.

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Lipidomics, a useful approach in the untargeted lipid analysis of human ocular tissues

Ms. Glenda Vasku PhD[1,2,3], Ms. Caroline Peltier PhD[4,2], Mr. Zhiguo He PhD[5], Mr. Gilles Thuret PhD[5], Mr. Philippe Gain PhD[6], Ms. Catherine P Creuzot-Garcher Doctor[7], Mr. Pierre-Henry Gabrielle Doctor[7], Mr. Alain M Bron Professor[1,7], Mr. Niyazi Acar Researcher PhD[1], Mr. Olivier Berdeaux Research engineer[4,2]

[1]Eye and Nutrition Research Group, Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAE, Institut Agro, Université de Bourgogne Franche-Comté, F-21000, Dijon, France. [2]INRAE, PROBE Research infrastructure, ChemoSens facility, F-21000, Dijon, France. [3]ye and Nutrition Research Group, Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAE, Institut Agro, Université de Bourgogne Franche-Comté, F-21000, Dijon, France. [4]ChemoSens Platform, Centre des Sciences du Goût et de l'Alimentation, Institut Agro, CNRS, INRAE, Université Bourgogne Franche-Comté, F-21000, Dijon, France. [5]Department of Ophthalmology, Biology, Imaging, and Engineering of Corneal Grafts, Faculty of Medicine,, Saint Etienne, France. [6]Department of Ophthalmology, Biology, Imaging, and Engineering of Corneal Grafts, Faculty of Medicine, Saint Etienne, France. [7]Department of Ophthalmology, University Hospital Dijon, Dijon, France

Abstract

Identification of lipid metabolites in dysregulated metabolic pathways relies mainly on the characterization of lipid profiles in human tissues and biofluids. Current analytical techniques, although vastly developed, cannot yet achieve single-run lipid analysis that includes all species ranging from polar to aploar lipids. This limitation is well illustrated in Age-related macular degeneration (AMD), which is the main cause of vision loss in Western countries. Numerous studies have identified lipid species that were discriminant for the disease, but most of these works were based on targeted approaches. In this study, we have used the complementary properties of hydrophilic interaction liquid chromatography (HILIC) and reversed-phase chromatography (RPC), coupled to high-resolution mass spectrometry (HRMS), to determine and identify approximately 500 lipid species in human ocular tissues, namely the retina and the retinal pigment epithelium (RPE).

Lipids were isolated from eyeglobes from 10 human donors, and lipidomic analysis was performed by alternating between HILIC and RPC analysis. While there was no signal of these compounds in HILIC, RPC demonstrated superior sensitivity in hydrophobicity-based lipid separation, detecting diacylglycerols (DAG), triacylglycerols (TAG), cholesterol (Chol), and cholesteryl esters (CEs). However, polar lipids such as phospholipids, which were well separated in HILIC in both ionization modes, were more challenging to be separated with RPC due to coelution processes. The detection and identification of lipids, which can offer unique insights into lipid metabolism and further into pathogenesis of AMD, depends on the complementary nature of these analytical methods.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Use of n-3 LCPUFA and ibuprofen as adjunct treatments for tuberculosis in a C3HeB/FeJ tuberculosis mouse model

Dr Frank Hayford PhD Dietetics ORCID iD[1], Dr Arista Nienaber PhD in Dietetics ORCID iD[2], Dr Mumin Ozturk PhD in Immunology of infectious diseases ORCID iD[3], Prof Renee Blaauw PhD Human Nutrition ORCID iD[4], Prof Du Toit Loots PhD Biochemistry ORCID iD[2], Prof Cornelius Marius Smuts PhD Biochemistry ORCID iD[2], Prof Frank Brombacher Ph.D. in Immunology of infectious diseases ORCID iD[5], Prof Suraj P Parihar PhD in Immunology of infectious diseases ORCID iD[5], Prof Robin C Dolman PhD, Dietetics ORCID iD[2], Prof Linda Malan PhD Nutrition ORCID iD[2]

[1]University of Ghana, Accra, Ghana. [2]North-West University, Potchefstroom, South Africa. [3]Radboud University, Nijmegen, Netherlands. [4]Stellenbosch University, Stellenbosch, South Africa. [5]University of Cape Town, Cape Town, South Africa

Abstract

Tuberculosis (TB) is still one of the most infectious diseases globally. The difficulty in effective treatment has led to efforts to develop host directed therapeutics to support current TB drug regimes. Hence, this study sought to administer adjunct ibuprofen and n-3 LCPUFA therapy, respectively, together with standard anti-TB drug treatment, in a C3HeB/FeJ mouse model of TB. Bacterial loads, lung pathology, lung cytokines/chemokines and lung lipid mediators were measured as outcomes at 4 and 14 days post-treatment (PT). Lung bacterial load on day 14 PT was lower in the n-3 LCPUFA, compared to the ibuprofen group ($p=0.039$), whereas it was higher in the ibuprofen group than the TB-drug-treated control group ($p = 0.0315$). TB-drug-treated control and ibuprofen groups had more free alveolar space 4 days PT ($p=0.0114$ and $p=0.002$, respectively) as compared to the n-3 LCPUFA group; however, significantly more alveolar space was present in the n-3 LCPUFA group compared to the ibuprofen group 14 days PT ($p = 0.035$). Interleukin 6 (IL-6) was lower in the ibuprofen group compared to the TB-drug-treated control, n-3 LCPUFA and untreated control groups at 4 days PT ($p=0.019$, $p=0.019$ and $p=0.002$, respectively). Notably, pro-resolving EPA derived 9-HEPE, 11-HEPE, 12-HEPE and 18-HEPE lipid mediators (LMs) were significantly higher in the n-3 LCPUFA group compared to the ibuprofen and TB-drug-treated control groups. This suggests that n-3 LCPUFAs do improve pro-resolving and anti-inflammatory properties during TB, and it may be safe and effective to co-administer as adjunct therapy with standard TB treatment, particularly longer-term. Also, hosts benefitted from short-term co-administration of ibuprofen, but not throughout the entire TB treatment course. Thus, ibuprofen and n-3 LCPUFA applications in human treatment as adjunct therapy may assist in improving the clinical outcome of TB infection.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Portions of the results from the bigger study was published in Frontiers in Immunology on the 28 April 2021, under the Section Vaccines and Molecular Therapeutics, Volume 12 - 2021 | https://doi.org/10.3389/fimmu.2021.659943. It contains some results of the abstract submitted.

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Prenatal EtOH reduces placental lipid droplet mobilization and n-3 fatty acids: A potential link with negative fetal developmental outcomes?

Bradley Feltham MSc ORCID iD[1,2], Joanna Candas BSc[1,2], Khuong Lee BSc[2], Michael Eskin PhD[1], Miyoung Suh PhD[1,2]
[1]University of Manitoba, Winnipeg, Canada. [2]St. Boniface Albrechtsen Research Centre, Winnipeg, Canada

Abstract

The placenta stores and transports lipids in the form of triglycerides (TG). It is unknown whether this plays a role in fetal development during prenatal EtOH exposure. We examined the impact of prenatal EtOH on placental lipid droplets, fatty acid composition and consequential fetal outcomes. Pregnant Sprague-Dawley rats were placed in control (n=11) or EtOH (20%, v/v in water, n=11) groups. At gestational day 20 (GD20), placentas (2/dam) were collected for morphometrics and lipid analysis. Prenatal EtOH significantly reduced maternal food intake ($P<0.05$) and pregnancy weight gain ($P<0.05$), while increasing both the placental labyrinth and junctional zone thickness ($P<0.05$). Relative to the control, EtOH-exposed placenta showed an increase in lipid droplets in the labyrinth zone (maternal-side) but a decrease in the junctional zone (fetal-side). EtOH decreased placental total saturated-, mono- and polyunsaturated fatty acids in all lipid classes ($P0<0.05$). Prenatal EtOH also reduced placental TG n-3 PUFA (-42%, $P<0.05$) and DHA (-37%, $P<0.05$) compared to control. Prenatal EtOH reduced litter size, fetal weights ($P<0.0001$), and increased fetal reabsorption points ($P<0.05$). The decreased fetal body weight and increased placental weight in the EtOH group led to a 17% reduction in placental efficiency ($P<0.0001$). This highlights that EtOH-induced morphological changes in the placenta play roles in lipid mobilization and the accretion of n-3 PUFA and DHA, impacting fetal development.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

No.

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Plant-based drinks as nutritional sources of fatty acids

Dr. Éva Szabó MD, PhD ORCID iD[1], Okba Hatem MSc[1,2], Dr. Zoltán Szabó PhD[3], Ibolya Madarászné Horváth MSc[4], Prof. Tamás Decsi MD, DSc[5], Tamás Marosvölgyi MSc ORCID iD[4]

[1]Department of Biochemistry and Medical Chemistry, University of Pécs, Medical School, Pécs, Hungary. [2]Doctoral School of Health Sciences, Faculty of Health Sciences, University of Pécs, Pécs, Hungary. [3]Institute of Nutritional Sciences and Dietetics, University of Pécs, Faculty of Health Sciences, Pécs, Hungary. [4]Institute of Bioanalysis, University of Pécs, Medical School, Pécs, Hungary. [5]Department of Paediatrics, University of Pécs, Medical School, Pécs, Hungary

Abstract

Objective: The use of plant-based drinks is worldwide on the rise, while their proper fatty acid (FA) composition cannot be found in the literature.

Methods: We investigated the FA composition of several commercially available, mono-ingredient plant-based drinks (almond, cashew, coconut, hazelnut, oat, rice, soybean, spelt) between chain length of C6:0-C26:0 on Perkin-Elmer Clarus 690 GC with FID detector.

Results: The FA composition of plant–based drinks in most cases was quite similar to that of the same plant seeds. Oleic acid was the main FA in the cashew drinks, while linoleic acid in the oat and soy drinks. By contrast, the FA composition of rice, almond and coconut drinks varied widely among the brands tested, and FAs otherwise not present in the seeds were also found.

There were also large differences between the sum of saturated fatty acid (SFA) contents (in w/w%) declared on nutritional label and the measured values in coconut and oat drinks (much lower on label), while in hazelnut and almond drinks the determined values were lower.

For quantification, odd-chain SFAs (C13:0-C21:0) are usually used as internal standards, but all the investigated plant-based beverages contained at least three of these FAs.

Conclusion: Although the product labels indicated that the plant-based drinks tested were mono-ingredient, in some cases significant differences were found in the values of several saturated and unsaturated fatty acids. These discrepancies may affect the FA supply of consumers, patients and the results of research studies on this topic.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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A DHA-Food Frequency Questionnaire: A pragmatic way to identify pregnancies that benefit from high dose DHA supplementation

Dr. Danielle Christifano PhD, Dr. Gene Lee MD, Dr. Sharla Smith PhD, Ms. Sarah Crawford MS, RD, Dr. Byron Gajewski PhD, Dr. Kathleen Gustafson PhD, Dr. Susan Carlson PhD
University of Kansas Medical Center, Kansas City, USA

Abstract

The recent ISSFAL statement “Omega-3 fatty acids during pregnancy to reduce preterm birth,” (doi.org/10.1016/j.plefa.2022.102495) highlights as a research priority “developing and validating novel, standardized omega-3 assessment tools and methodology that are robust, equitable and cost effective and can be widely implemented as a routine part of antenatal care.” We report here on the relationship between DHA intake at baseline and preterm birth assessed by a recently validated 7-question Food Frequency Questionnaire (DHA-FFQ) administered at baseline in two NICHD-supported clinical trials conducted between 2016 to 2021. The trials enrolled participants (n=1400) before 20 weeks gestation and randomly assigned them to either 200 mg/d of DHA, as suggested by several advisories, or a higher dose (800 or 1000 mg/d). Baseline DHA-FFQ results and birth data were available for 1310 participants. Gestational age modeled as a continuous time-to-event by dose (200 mg/d or a higher dose) identified an intake of <150 mg/d as a cut-point for benefit of the higher dose. Low DHA consumers (n=754, 57.6% of the cohort) had a lower risk of early preterm birth (EPTB) <34 wks if assigned to the higher vs the lower dose: 1.4% (CI 0.0, 2.9) vs 3.9% (CI 2.3,6.0) (pp=0.99). Their risk of PTB was also lower: 11.3% (CI 9.0, 13.8)vs 14.8% (CI 12.0, 18.0) (pp=0.97) (https://doi:.org/10.1016/j.clnesp.2022.12.004). The survey is validated for electronic use in pregnancy (https://doi:10.1016/j.plefa2022.102399). (https://redcap.kumc.edu/surveys/?s=XLP7DJDWF4). In conclusion, the DHA-FFQ identifies pregnancies in US women that could benefit from higher dose DHA supplementation. Because 3 of the DHA-FFQ questions ask about specific fish consumed in categories that are based on the DHA content of fish (low, medium and high), it could be used in other countries after modification for the types of fish available for consumption.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

I have provided the doi information for the results discussed here.

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Comparative analysis of the lipidomic and fatty acid profile of the prostate in lean and obese JCR:LA-*cp* rats consuming a flax enriched diet

Chelsey Walchuk MSc ORCID iD[1,2,3], Dr. Mihir Parikh PhD ORCID iD[4,3,5], Dr. Michel Aliani PhD ORCID iD[1,2,3], Dr. Grant Pierce PhD ORCID iD[4,3,5], Dr. Miyoung Suh PhD ORCID iD[1,2,3]

[1]Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, Canada. [2]Division of Neurodegenerative Disorders, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [3]Canadian Centre for Agri-Food Research in Health and Medicine, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [4]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [5]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada

Abstract

Benign prostatic hyperplasia (BPH) is the non-malignant growth of the periurethral prostate gland. The prevalence of BPH increases with metabolic syndrome (MetS), however, it is currently unknown how dietary lipids influence prostate growth. This study compared the lipidomic and fatty acid (FA) profile of the prostate after providing a flax enriched diet, using the JCR:LA-cp rat model of MetS. Male, lean and obese 12-week-old rats were fed a chow (Cont) or 10% ground flaxseed diet (Flax) for 12 weeks resulting in 4 groups: Lean-Cont, Obese-Cont, Lean-Flax and Obese-Flax (n=8/group). Lipidomic analysis was performed using HPLC-QTOF-MS and prostate total and glycerophospholipid (PL) FA distribution by GC. Obesity increased ventral prostate weight (%, body weight, $p<0.001$) with no effect of diet. Untargeted lipidomics detected 1939 and 2438 entities in ESI+ and ESI- mode, respectively. Following statistical analysis, 198 lipid metabolites were affected by genotype (n=145) and diet (n=76), consisting of PLs (37.9%), fatty acyls (18.2%), glycerolipids (17.2%), sphingolipids (14.1%), sterol lipids (8.1%) and prenol lipids (4.5%). Genotype (Lean-Cont vs Obese-Cont, Lean-Flax vs Obese-Flax) impacted prostate FAs by increasing ($p<0.0001$) total SFAs and MUFAs, while decreasing ($p<0.0001$) PUFAs in both obese groups. In PLs, SFAs increased ($p<0.0001$) and MUFAs decreased ($p<0.0001$) in both obese groups, while PUFAs decreased ($p=0.032$) in Obese-Cont only. Diet affected prostate FAs by increasing ($p<0.0001$) total MUFAs and PUFAs in both flax groups and decreasing ($p=0.028$) SFAs in Flax-Lean only. In contrast, PL SFAs increased ($p<0.0001$), PUFAs decreased ($p<0.0001$) and MUFAs remained unchanged in Lean-Flax and Obese-Flax groups. Overall, the lipid composition of the prostate is highly influenced by obesity and dietary lipids. Further research is warranted to examine the mechanisms in which these changes promote prostate growth, and whether alterations to dietary FAs could be used as a preventative strategy for BPH.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Comparing DHA synthesis rates in young women and men by the novel application of compound-specific isotope analysis (CSIA): a study design

Dr. Dandan Li PhD, Ruxandra Rotarescu PhD Candidate, Dr. Adam Metherel PhD
University of Toronto, Toronto, Canada

Abstract

Eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) status have been positively associated to fetal/infant development, and heart and brain function, and women have higher DHA levels than men. However, consumption of EPA and DHA in many countries is low, and we must rely on synthesis from the essential n-3 polyunsaturated fatty acid (PUFA), alpha-linolenic acid (ALA, 18:3n-3). Twenty-five years of research suggests that DHA synthesis from ALA in humans is very low. However, due to methodological limitations, invasive methods and costs of stable isotope tracers, DHA synthesis rates have not been adequately determined. Using a novel application for compound-specific isotope analysis (CSIA), the objectives of this study are to 1) measure DHA synthesis rates from dietary ALA in young adults, and 2) determine whether differences in DHA synthesis rates could explain the known sex differences in blood DHA levels. To achieve these objectives, healthy young (18 – 35 years of age) women and men (n =16 per sex), who are very low EPA/DHA consumers will be recruited. Each participant will be supplemented with 1 g/d of a vegetable oil spiked with 0.45 mg/day of 13C-ALA for 84 days (12 weeks). Whole blood, plasma and erythrocytes will be collected at baseline and on days 1, 3, 7, 14, 28, 56 and 84 days of supplementation, during which time participants will be instructed to maintain their normal dietary and lifestyle habits. Plasma DHA synthesis rates will be determined by one-phase exponential decay analysis, with differences ($p<0.05$) between women and men, as determined by independent t-test, being the primary outcome. This will be the first study to directly compare DHA synthesis rates in women and men, and will shed light on the mechanisms driving sex-specific differences in blood DHA levels.

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Gestational nutritional omega-3 polyunsaturated fatty acids deficiency induces cognitive deficits at adulthood

Ivan Marniquet, Liam Barry-Carrol, Moïra Rossitto, Sophie Layé, Jean-Christophe Delpech
Univ. Bordeaux, INP Bordeaux, INRAE UMR 1286, Nutrineuro, Bordeaux, France

Abstract

The consumption of omega-3 polyunsaturated fatty acids (n-3 PUFAs) is reduced in most of the developed countries compared to the recommendations. Western diet for example is known to have a low amount of n-3 PUFAs intake. Epidemiological data reported an association between n-3 PUFAs intake and cognitive decline. We thus investigated the link between n-3 PUFA consumption and cognitive abilities using a preclinical rodent model comparing n-3 PUFAs balanced diet to an n-3 PUFAs deficient diet introduced at gestation. We previously showed that n-3 PUFAs deficiency induced working spatial memory deficit at weaning associated with an altered neuronal arborization and microglia reactivity. Here, we examined at adulthood interconnected behavioural dimensions, including emotional, social and cognitive abilities in order to thoroughly evaluate the cognitive sphere in n-3 PUFAs deficient animals. In addition, we evaluate these parameters in both sexes. Our results show no alteration of the social dimension, an abnormal emotional behavior and working and associative spatial memory deficits in both sexes with some sexes specific effects.

Dorsal CA1 region of the hippocampus is known to play an important role in spatial memories both in human and rodents. We then conducted electrophysiological recording in order to assess hippocampal CA1 pyramidal neuron activity after gestational n-3 PUFAs deficiency compared to n-3 PUFAs balanced diet in both sexes. Our data show an alteration of intrinsic and/or network excitability properties depending on the sex in the pyramidal neurons of the hippocampus at adulthood. We are currently evaluating the transcriptomic signature of their hippocampus to better understand the pathways involved in the effect of n-3 PUFAs deficiency on cognitive abilities.

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Effect of various saturated fatty acids sources on oxidative stability and nutritional profile of docosahexaenoic acid-enriched infant follow-on formulas

Mrs Mathilde Cancalon ORCID iD[1,2], Dr Youna M. Hemery ORCID iD[3], Mrs Nathalie Barouh ORCID iD[2], Mr Bruno Barea[2], Dr Claire Berton-Carabin ORCID iD[4], Mrs Lucie Birault[4], Dr Erwann Durand ORCID iD[2], Dr Pierre Villeneuve ORCID iD[2], Dr Claire Bourlieu-Lacanal ORCID iD[1]
[1]UMR IATE,UM Montpellier, INRAE, Institut Agro, F34060 Montpellier, France. [2]CIRAD, UMR Qualisud, F34398 Montpellier, France. [3]IRD, CIRAD Qualisud, F34398 Montpellier, France. [4]INRAE, UMR BIA, Nantes, France

Abstract

Infancy is characterized by significant growth and development that leads to very specific nutritional requirements. During this period, lipids and more particularly long-chain polyunsaturated fatty acids play an important role. To comply with the recommendations, European regulation have recently evolved and now requires fortification of infant follow-on formulas (IFF) with docosahexaenoic acid (DHA) which strongly impacts their oxidative stability. The aim of this study was to improve the lipid profile and oxidative stability of DHA-enriched IFF by using structural and formulation lipid levers. To do so, a model IFF representative of marketed products was formulated and declined by varying the saturated fatty acids sources (refined (POM) or unrefined (RPOM) palm oil, coconut oil (COM), and dairy fat (DFOM)), the emulsifiers (soy lecithin or dairy phospholipids (DPL)) and the structure (droplet size). RPOM-IFF showed a higher stability than POM-IFF. This effect can be attributed to its content of provitamin A compounds (in the form of carotenoids) which act in synergy with tocopherols and have beneficial effects for infant nutrition. The combined use of DPL and DFOM led to a better oxidative stability with a peroxide value twice lower than POM (stabilized with lecithin) after 20 days of storage at 40°C and less important tocopherols degradation. This favorable effect was even reinforced for smaller droplet sizes. Dairy lipids also provide a complex lipid profile and high content of short and medium saturated chain fatty acids which is beneficial for infant nutrition. The introduction of dairy lipids and carotenoids in DHA-enriched IFF composition are interesting levers of stabilization against oxidation.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Eicosapentaenoic acid Prevents TBI-Mediated Neuropsychological Disorders

Nawajes Mandal PhD, Koushik Mondal PhD, Nobel Del Mar, Anton Reiner PhD
The University of Tennessee Health Science Centre, Memphis, USA

Abstract

Introduction: Traumatic brain injuries (TBI) may occur due to explosions or blunt trauma and cause chronic neurologic dysfunction, leading to diseases like depression, PTSD, and dementia. In previous studies, we found that mice with higher endogenous n-3 polyunsaturated fatty acid (n-3 PUFA) were protected from post-TBI behavioral deficits, and reduced levels of TBI-induced microglial activation, inflammatory and cell death factors and sphingolipid Ceramide (Cer), a lipid mediator of inflammation and cell death. The objective of this study was to test whether feeding n-3 PUFA (EPA and docosahexaenoic acid, DHA 2:1) can restrict the elevation of Cer in brain tissue and prevent TBI-mediated sensory-motor and behavioral deficits.

Methods: Wildtype C57/BL6 mice were gavage pre-fed with PUFA (EPA: DHA = 2:1) @ 500mg/kg body weight/week for two weeks before exposing to left side focal cranial air-blast (50 psi) TBI or sham-blast (0-psi). Saline-gavaged mice served as controls. PUFA feeding was continued for another four weeks after the blast; motor, cognitive and behavioral tests were conducted; and the brain tissues were collected for histological and biochemical assays.

Results: Lipidomics analysis confirmed a significant elevation of EPA in the plasma and brain tissue of PUFA-fed mice. TBI-blast was found to elevate Cer in the brain tissues in control mice but not in PUFA-fed mice. We found PUFA-fed mice were resistant to the decline in motor functions, depression, fear-producing effects of blast, degeneration of oculomotor nerves, and activation of microglia in the optic tract. Gene expression analyses confirmed decreases in TBI-mediated induction of Cer biosynthetic and inflammatory genes in PUFA-fed mice.

Conclusion: Our result demonstrates that EPA-mediated suppression of ceramide biosynthesis and inflammatory factors in PUFA-fed mice is associated with significant protection against the visual, motor, and emotional deficits caused by TBI.

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Targeted delivery of Piperine- curcumin-loaded marine-derived liposomes for breast cancer treatment

Professor Elmira Arab-Tehrany Ph.D
université de Lorraine, Nancy, France

Abstract

Female breast cancer is the most common cancer worldwide, with about 2.1 million newly diagnosed cases in 2018. Breast cancer (BC) occurs when there is abnormal growth or proliferation in breast cells. Higher consumption of dietary marine n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) is associated with a lower risk of breast cancer. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two n-3 LC-PUFAs found in fish and exert anticancer effects. In this study, natural marine-derived lecithin that is rich in various polyunsaturated fatty acids (PUFAs) was extracted from salmon heads and transformed into nanoliposomes.

In the present work, we investigated nanomechanical, biochemical and metabolic changes of BC cells such as of MCF-7 and MDA MB231 after direct exposure to curcumin and piperine and exposure to NL containing the active drugs.

To this end, we combine infrared spectroscopy (FTIR), atomic force microscopy (AFM), fluorescence microscopy, cell viability assay and cell life cycle analysis to decipher from the molecular to the cellular scale the impact of curcumin and piperine on mechanical and biochemical properties of MCF-7 and MDA MB231 cells.

The results showed that nanoliposomes decreased the proliferation and the stiffness of both cancer cell types. These results suggest that marine-derived lecithin possesses anticancer properties, which may have an impact on developing new liposomal delivery strategies for breast cancer treatment. Hence, the present study is focused on the production and multiscale characterization of negatively charged nanoliposomes from marine-derived lecithin rich in n-3 LC-PUFAs.

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Sexual dimorphism in the expression of long-chain acyl-CoA synthetase 3 (ACSL3) in Alzheimer’s disease

Assistant Professor Celeste Wu PhD, research associate Li Xu Ms, research associate Yulang Zhang BS, Post-doc Cristiane Citadin PhD, Associate Professor Hung Wen Lin PhD, Assistant Professor Reggie Lee PhD
LSUHSC-Shreveport, Shreveport, USA

Abstract

Alzheimer’s disease (AD) is a progressive neurodegenerative diseases which is the most common cause of dementia in the United States. Aged and gender are the major risk factors for AD. Women are more likely to develop a rapid progression of dementia than men with a greater risk of developing vascular dementia as compared to males. Cerebral blood flow derangements found in AD are thought to be the major cause of brain dysfunction and neurological deficits. AD-mediated hypoperfusion plays a vital role in vascular dementia-related neuroinflammation, mitochondrial dysfunction, neuronal cell death, and neurological deficits. Therefore, the major challenge is to alleviate the development and progression of vascular dementia. We previously discovered that expression of long-chain acyl-CoA synthetase 3 (ACSL3) in brain regions were significantly decreased with the aged AD mice. Specific agonist of ACSL3 enhanced neuronal survival and improved functional learning/memory. Our preliminary data suggest that decreased ACSL3 is detrimental in an aged 3xTg-AD mouse model (enhanced β-amyloid and tau aggregation and accumulation). Our central hypothesis is that ACSL3 is critical for age-related brain function to prevent learn/memory degradation. The present study can lead to novel therapies/targets against AD brain progression by investigating the pathophysiological role of ACSL3 in neuroprotection.

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Oxidative stability and nutritional profile of omega-3 enriched flours optimized for infant nutrition

Mrs Mathilde Cancalon[1], Dr Youna M. Hemery[2], Mrs Nathalie Barouh[3], Mr Bruno Barea[1], Dr Erwann Durand[1], Prof Valérie Micard[4], Dr Pierre Villeneuve[1], Dr Claire Bourlieu-Lacanal[4]

[1]CIRAD, UMR Qualisud, F34398 Montpellier, France. [2]IRD, CIRAD Qualisud, F34398 Montpellier, France. [3]CIRAD, UMR Qualisud, F, France. [4]UMR IATE, UM Montpellier, INRAE, Institut Agro, F34060 Montpellier, France

Abstract

Dietary diversification, which starts between 4 and 6 months, is a pivotal period in the infant development. After this diversification, complementary foods such as infant flours are therefore widely consumed throughout the world, particularly in southern countries. However, infant flours have often an unbalanced lipid profile in favor of omega 6 and overages in certain vitamins content (especially A and E). The aim of this study was to optimize the formulation of enriched infant flour in order to improve its nutritional profile and oxidative stability. For this purpose, the nutritional values and ingredient lists of 96 infant flours were analyzed to formulate model flours representative of the marketed products. The lipid profile of these model flours was then optimized by including flours with balanced omega 6/omega 3 ratios, i.e. teff and cowpea flours, and/or by adding long-chain polyunsaturated fatty acid (LC-PUFA) powder (DHA and ARA). After 3 months of storage, the optimized flour showed a quite good resistance to oxidation with a low evolution of peroxide values and a low tocopherols degradation. However, the inclusion of LC-PUFA significantly increased the oxidation sensitivity of the flours. In order to counteract this phenomenon, phenolic compounds were added via the addition of brown rice bran which did not seem to have a positive effect on stabilization regardless the particle size. Nevertheless, optimized omega 3 enriched and fortified infant flours could be proposed with fair stability over 3 months of storage.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Translational Pharmacology Considerations in Repurposing Nervonic Acid - a Dietary Monounsaturated Fatty Acid for Neurodegenerative Diseases

Ms. Chenxu Li MS[1], Dr. Marcia Terluk MS, PhD[1], Ms Ann Moser BS[2], Dr Troy Lund MD, PhD[1], Dr Gerald Raymond MD[1], Dr. Reena Kartha MS, PhD ORCID iD[1]

[1]University of Minnesota, Minneapolis, USA. [2]Kennedy Krieger Institute, Baltimore, USA

Abstract

Nervonic acid (NA, C24:1), is a naturally occurring monounsaturated fatty acid that is important in maintaining normal myelin function and is abundant in the white matter of the brain. It is increasingly being repurposed for the management of neurodegenerative diseases. NA has been found to activate the cellular antioxidant defense system and serves as a neuroprotective agent. We have shown NA has potential therapeutic benefits in a rare X-linked peroxisomal disorder called Adrenoleukodystrophy (ALD), caused by defective fatty acid transporter. This results in the abnormal accumulation of saturated very long chain fatty acids (VLCFA), predominantly hexacosanoic acid (C26:0), which causes tissue injury and leads to downstream mitochondrial dysfunction, cellular oxidative stress, and inflammation. Among the various phenotypes, boys with early neurological manifestations have a 50% mortality rate of <5yrs from symptom onset. Currently, there is no FDA-approved therapy for pre-symptomatic individuals. The current study aims to repurpose NA as a treatment to arrest or delay disease progression in all ALD phenotypes by normalizing VLCFA levels. Through a series of well-designed preclinical studies in ALD cell and mouse models, we aim to gain a better understanding of NA pharmacology. In ALD patient-derived fibroblasts, NA was found to decrease the levels of C26:0 and other VLCFAs in a concentration-dependent manner. Moreover, using fluorescence imaging and Seahorse assays, we show NA treatment to improve mitochondrial function. Our preliminary studies in ALD mice indicate the potential benefits of NA. Further research will characterize the exposure-response relationship of NA in these models to identify optimal dosages for first-in-human clinical studies. With a comprehensive understanding of its therapeutic potency, NA may be a promising treatment for neurological diseases such as ALD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Antibiotic-induced effects on the fatty acid composition of faeces in a rat model

Mr Tamas Marosvolgyi MSc ORCID iD[1], Ms Kitti Mintal MSc[2,3], Dr Nelli Farkas PhD ORCID iD[1], Dr Lilla Makszin PhD ORCID iD[1], Dr Eva Szabo PhD ORCID iD[4], Dr Attila Toth PhD ORCID iD[2,3], Dr Béla Kocsis PhD[5], Dr Zoltan Karadi DSc ORCID iD[2,3], Dr Anita Bufa PhD[1]
[1]Institute of Bioanalysis, Medical School, University of Pecs, Pecs, Hungary. [2]Institute of Physiology, Medical School, University of Pecs,, Pecs, Hungary. [3]Cellular Bioimpedance Research Group, Szentagothai Research Centre, University of Pecs, Pecs, Hungary. [4]Department of Biochemistry and Medical Chemistry, Medical School, University of Pecs, Pecs, Hungary. [5]Department of Medical Microbiology and Immunology, Medical School, University of Pecs, Pecs, Hungary

Abstract

In the present study, in total, 44 male Wistar laboratory rats were divided randomly into four groups: 1. Control group (control); 2. Antibiotics treated group (ABx); 3. Antibiotics and probiotic treated group (ABx + probiotic); 4. Probiotic treated group (probiotic). The rats of the antibiotics treated groups received broad-spectrum antibiotics mixture (5 components) for 4 weeks at adulthood (10 weeks old at start of treatment) to effectively deplete the gut microbiota. Stool samples were taken at specified intervals before and after treatment. The probiotic receiving groups were given our specific probiotics mixture, vial oral gavage every day for 2 weeks and it contained four beneficial bacterial species.

Wide spectrum of aliphatic saturated (C4:0-C26:0)-, mono-, and polyunsaturated fatty acid isomers, moreover branched- and trans fatty acid isomers too, were analysed as FAME after acidic transesterification with a Perkin-Elmer Clarus® 690 GC system with FID detector, on a Restek RT-2560 capillary column.

We measured not only the total fatty acid concentrations of wet stool, but we calculated the fatty acid weight/weight% values also.

Based on our results, we observed significantly reduced concentration and weight percent composition of short-chain-, trans-, and branched-chain fatty acids in response to antibiotic treatment. In addition, probiotic therapy following antibiotic treatment was able to restore the status close to baseline.

In conclusion, significant modification of the microbiota in the intestinal tract significantly affects both absolute and relative amounts of fatty acids in faeces.

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Effects of dietary whey protein phospholipid concentrate from milk on circulating lipid mediators and memory in rats

Ibuki Kusumoto[1,2], Duncan Sylvestre[1], Daniela Barile[1], Ameer Taha[1]

[1]Department of Food Science and Technology, College of Agriculture and Environmental Sciences, University of California, Davis, USA.

[2]Food Function Analysis Laboratory, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan

Abstract

Background

Whey protein phospholipid concentrate (WPPC) is a phospholipid-rich (~20%) by-product of milk whey protein processing. Prior studies have shown a link between milk phospholipid extracts (e.g. milk fat globular membranes) and brain development, leading us to hypothesize that WPPC may confer cognitive benefits in a high-fat diet model of cognitive impairment. We also explored the secondary hypothesis that potential cognitive benefits of WPPC may be linked to improvements in circulating pro-resolving lipid mediator lipid profile, in view of prior studies showing a positive association between pro-resolving lipid mediators and cognitive performance in both rats and humans.

Experimental procedures

Male rats were randomized to one of four diets starting at weaning (n=8-11 per group): (1) Low-fat diet (LF); (2) High-fat diet (HF); (3) High-fat diet with 1.6% of WPPC (HF-1.6); (4) High-fat diet with 10% of WPPC (HF-10). The object recognition test was used to measure cognitive function at 2 and 4 months after weaning. Serum was collected after euthanasia, at 4-5 months. Free oxylipins were extracted from 50-100 µL of serum and analyzed with liquid chromatography-mass spectrometry.

Results

The HF diet impaired cognition compared to the LF diet. The HF diet induced a few significant changes in circulating lipid mediators (both pro-resolving and pro-inflammatory) that were reversible by the HF-1.6% and HF-10% diets. In the HF-1.6% or HF-10% groups, circulating concentrations of pro-resolving 17-hydroxy-docosahexaenoic acid (17-HDoHE), Resolvin E1, and 14,15-dihydroxy-eicosatetraenoic acid (14,15-DiHETE) were positively associated with better memory ($P<0.05$).

Conclusion

This study provides new evidence of cognitive benefits of WPPC in a HF-diet model of cognitive impairment. The observed effects may be mediated by improvements in circulating pro-resolving lipid mediator profile following chronic WPPC intake.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

This abstract has not been published.

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Blood esterified fatty acids in a population of normotensive and hypertensive patients

Dr. Mikel De Uranga PhD ORCID iD, Dr. José Victor Calderón PhD ORCID iD
Cinvestav, Mexico City, Mexico

Abstract

Fatty acids (FA) are molecules that are found in different proportions in food and that in the body can be stored as energy, transmit intracellular and extracellular signals, be hormone precursors, and be esterified to form cell membranes. They are classified as saturated (SFAs), monounsaturated (MUFAs), and polyunsaturated (PUFAs). PUFAs such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), docosaexaenoic acid (DHA) are from the omega-3 (n-3) family, and arachidonic acid (AA) is from the omega-6 family. (n-6), all of them being precursors of pro-resolution mediators (SPMs) that are necessary for cellular homeostasis, regulation of the inflammatory process, and functioning of the immune and circulatory systems.

Trans fatty acids (TFA) can be found naturally in products of animal origin and also industrially processed. The consumption of TFA could favor the appearance of cancer, metabolic, and cardiovascular diseases, such as hypertension, which is a risk factor for more severe cardiovascular diseases. It has been shown that the consumption of EPA, DPA, and DHA benefits hypertensive patients.

In the present work, a comparison was made between the percentage of esterified FA in whole blood and the indicators O3-I, ΣTF, n-6:n-3, and AA:EPA in two groups of normotensive (n=29) and hypertensive patients. (n=29). A negative relationship was observed between the TFA and the n-3 in the total population studied, without finding a relationship with hypertension.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Extraction of *n*-3 and *n*-6 lipids from micro- and macroalgae, single or blended, using innovative food-grade and conventional methodologies

Francisca Marques[1,2], Marisa Pinho[1], Tiago Conde[1,2], Inês Guerra[1], Joana Silva[3], Helena Abreu[4], Rosário Domigues[1,2]
[1]CESAM—Centre for Environmental and Marine Studies, Department of Chemistry, University of Aveiro, Santiago University Campus, 3810-193 Aveiro, Portugal, Aveiro, Portugal. [2]Mass Spectrometry Centre, LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Santiago University Campus, 3810-193 Aveiro, Portugal, Aveiro, Portugal. [3]Allmicroalgae Natural Products S.A., R&D Department, Rua 25 de Abril 19, 2445-287 Pataias, Portugal, Leiria, Portugal. [4]ALGAplus—Production and Trading of Seaweed and Derived Products Ltd., 3830-196 Ílhavo, Portugal, Aveiro, Portugal

Abstract

Algae are sustainable sources of valuable compounds, including lipids. Traditional lipid extraction methodologies use solvents that are toxic to humans and the environment. Food-grade solvents are required to obtain extracts suitable for food, feed, and nutraceutical industries. However, these non-toxic solvents are associated with low extraction yields and, therefore, novel methodologies have emerged to address this disadvantage.

This study aims to explore the use of food-grade ethanol in combination with ultrasound (UAE) to obtain lipid extracts from *Chlorella vulgaris, Fucus vesiculosus, Ulva rigida*, and a blend of the four algae species, and evaluate the impact on the lipid yield (LY), fatty acid (FA) composition, and antioxidant potential, in comparison with the conventional extraction using chlorinated/methanol solvents (C) and extraction with ethanol (EtOH). LY, FA profiles, and antioxidant capacity were determined by gravimetry, GC–MS, and DPPH assay, respectively.

Only UAE extracts of *Chlorella* and blend had high lipid content (>60%), but in macroalgae the lipid content was low (≈40%). . All EtOH extracts showed very low LY, possibly due to the non-disruption of cells walls. The FA profile of the C and UAE extracts was comparable, while EtOH extracts were different in the case of blend. Lipid extracts from *Chlorella* presented higher content (%) in *n*-3 and *n*-6.

The extracts obtained by the different methods showed very dissimilar antioxidant activity. Comparing UAE with C, the best activity was achieved with UAE for *Ulva* and blend. However, the best antioxidant capacity was found in the EtOH extracts.

Overall, our results showed that UAE is a promising method to obtain extracts enriched in *n*-3 and *n*-6 lipids from *Chlorella* and blend for food, feed, and nutraceutical applications.

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Effects of complex milk lipids supplementation on secondary measures of metabolism including lipids and inflammatory markers.A 16-week double-blind, placebo randomised controlled trial in older adults

Ian Zajac[1], Naomi Kakoschke[1], David White[2], Maher Fuad[3], Caroline Gunn[3]
[1]CSIRO, Adelaide, Australia. [2]Swinburne University, Victoria, Australia. [3]Fonterra Research and Development Centre, Palmerston North, New Zealand

Abstract

Introduction: Complex milk lipids (CMLs) have been attributed with numerous health related properties including anti-inflammatory and cholesterol modulation. CMLs supplementation may support healthy ageing via roles in modifying lipids and inflammatory markers.

Objective: To evaluate whether increasing complex milk lipid intake (CMLs) in older adults exerts beneficial effects on a range of health-related outcomes. Body composition and metabolic markers including lipids and inflammatory measures were assessed in participants receiving increased CMLs compared to participants taking a placebo.

Method: A prospective multicentre, double blind, randomized placebo-controlled trial (CSIRO South Australia and Swinburne University, Victoria) in healthy subjects (male & female, N=240) aged 55 –75 years who consumed a low dose supplement delivering ~2.0g of total phospholipids or high dose delivering ~4.8g of total phospholipids or a rice starch placebo control. Outcomes included a range of body composition measures and haematological findings such as the metabolic markers for blood lipids and inflammation.

Results: Of the 236 participants randomised 149 (63%) completed the study with adherence to all protocol compliance measures. Body composition measures of weight, body fat mass and fat free mass and muscle mass were significantly different in the High Dose CMLs group compared to Placebo group with Body fat mass (kg and %) and weight significantly greater in the Placebo group than High Dose CMLs group, while muscle mass and fat free mass (%) were significantly greater in the High Dose CMLs group than Placebo group. Cholesterol was significantly reduced in the Low Dose CMLS group compared to Placebo group and marginally significant effects were found for triglycerides, high density lipoprotein and low density lipoprotein. There were no significant effects on inflammatory markers.

Conclusion: In healthy adults aged 55-75 years, daily consumption of supplementary complex milk lipids favourably modulates body composition and cholesterol levels.

Trial registration number ACTRN12620000270910

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Transcriptomic analyses of central effects of eicosapentaenoic acid in a diet-induced obese amyloidogenic mouse model of Alzheimer’s disease

Dr. Mahsa Yavari Ph.D.[1], Hamed Khedmatgozar[2], Dr. Latha Ramalingam Ph.D.[1,3], Dr. Breanna Harris Ph.D.[1], Dr. Chanaka Kahathuduwa M.D.,Ph.D.[4], Dr. Yujiao Zu Ph.D.[1], Micah Castillo[5], Dr. Preethi Gunaratne Ph.D.[5], Dr. Volker Neugebauer Ph.D.[2], Dr. Naima Moustaid-Moussa Ph.D. ORCID iD[1]

[1]Texas Tech University, Lubbock, USA. [2]Texas Tech Health Sciences Center, Lubbock, USA. [3]Syracuse University, Syracuse, USA. [4]Texas Tech health Sciences Center, Lubbock, USA. [5]University of Houston, Houston, USA

Abstract

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (Aβ) and phosphorylated tau tangles. Obesity is a risk factor for AD, and we previously reported that eicosapentaenoic acid (EPA) reduced adiposity, inflammation in diet-induced obese mice and also reduced serum Aβ in an obese amyloidogenic mouse model. Our objective here was to determine the mechanisms mediating effects of EPA in the brain of diet-induced obese amyloidogenic mice.

APPswePS1E9 transgenic (TG) and non-TG wild type (WT) male and female littermates were fed low fat (LF), high fat (HF), or HF diets supplemented with EPA (HF-EPA) from 2 to 10 months of age. We metabolically phenotyped the mice throughout the intervention, and then collected blood and various tissues including the brain. Cortex gene expression was analyzed using RNA-seq and qRT-PCR.

HF mice weighted more and were fatter than LF groups ($p < 0.001$). TG mice had higher human amyloid precursor protein (APP) mRNA levels in the cortex ($p = 0.0204$) compared to WT mice. EPA reduced APP mRNA level in the cortex of male and female TG mice ($p = 0.0168$ and 0.0030) compared to HF. Transcriptomic profiles revelated that in TG mice, amyloidosis, tauopathy and neuroinflammation pathways were significantly upregulated, compared to WT mice (including TLR2, and TREM2). Brain development and neuronal differentiation pathways were significantly upregulated by EPA compared to HF (including LHX1 and PRNP), while inflammatory pathways were significantly downregulated (including CCL3L3, CD14, CXCL10, and IL16). EPA downregulated mRNA levels for MCP1 ($p = 0.0226$) and NLRP3 ($p = 0.0205$) in male mice.

Overall, our results demonstrated protective effects of EPA in an AD mouse model, in part through reducing amyloid-beta, and neuroinflammation, and inducing brain neuroprotective pathways. These findings merit further mechanistic studies as well as exploring potential translation into humans.

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A 12-week Randomized Placebo-controlled Trial of Adjuvant Omega-3 Polyunsaturated Fatty Acids in the Treatment of Major Depressive Episode of Bipolar Disorder

Mr Halliru Zailani M.Sc.[1,2], Dr. Jane Pei-Chen Chang MD/PhD[3,4], Prof. Wei-Che Chiu MD/PhD[5,6], Prof. Kuan-Pin Su MD/PhD[3,7,8]
[1]Mind-Body Interface Laboratory (MBI-Lab) &; Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan. [2]Graduate Institute of Nutrition, China Medical University, Taichung, Taiwan. [3]Mind-Body Interface Laboratory (MBI-Lab) & Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan. [4]College of Medicine, China Medical University, Taichung, Taiwan. [5]Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan. [6]School of Medicine, Fu Jen Catholic University, Taipei, Taiwan. [7]Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan. [8]An-Nan Hospital, China Medical University, Tainan, Taiwan

Abstract

Background: Bipolar disorder (BD) is characterized by multiple depressive, manic, and hypomanic episodes, leading to increased morbidity and mortality. BD medications are associated with adverse effects, hence the need for alternative therapies with reduced side effects. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are safe and have been used in managing depression and other mood disorders. Moreover, n-3 PUFAs deficiency has been implicated in BD.

Methods: Thirty patients (n = 30) with depressive episodes of BD were randomized to receive either n-3 PUFAs or identical placebo capsules for 12 weeks. The main outcome was differences in depression severity based on 21-item Hamilton Rating Scale for Depression (HRSD-21) across time points. Other outcomes were differences in mania based on the Young Mania Rating Scale (YMRS), erythrocyte n-3 PUFAs levels, and routine biochemical parameters.

Results: N-3 PUFAs had no favorable effect on depression severity over placebo in the 1st (p=0.502), 2nd (p=0.249) 4th(p=0.096), 6th (p=0.148), and 8th (p=0.254) weeks. However, a superior effect of n-3 PUFAs on depression severity was seen in week 12 (p=0.022). N-3 PUFAs group was not superior to placebo on manic symptoms across all the study time points. A significant increase in docosahexaenoic acid (p=0.043) but not eicosapentaenoic acid (p=0.174) at endpoint was associated with n-3 PUFAs. No significant change in biochemical parameters was associated with n-3 PUFAs.

Conclusion: Adjunctive n-3 PUFAs therapy for 12 weeks has improved depression severity in patients with BD. Moreover, n-3 PUFA supplementation was well tolerated in this population. Therefore, this study supports the use of n-3 PUFAs as adjuvant therapy in depressive episodes of BD.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not published

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Effects of docosahexaenoic acid on fibrosis of kidney and heart in 5/6 nephrectomized kidney failure model rats.

Dr Masanori Katakura PhD ORCID iD, Dr Hiroki Muramatsu PhD, Mr Ryuki Hamajima
Josai University, Saitama, Japan

Abstract

Introduction: While CKD is a global problem, no adequate therapeutic strategies for treatment exist. We have reported that feeding diets containing arachidonic acid and docosahexaenoic acid prevented the increase in urinary albumin excretion. However, the detailed mechanism has not yet been fully elucidated. In the present study, docosahexaenoic acid feeding to 5/6 nephrectomized rats and examined its effects on oxidative stress and fibrosis in the kidney and heart. Methods: Sprague Dawley rats were randomly divided into Control group and docosahexaenoic acid (DHA) group. After two weeks feeding each diet, half of each group were removed 5/6 kidney and they were feed continuous for 8 weeks. Urine, plasma, heart, and kidney were collected 8 weeks after surgery. Oxidative stress, inflammation status, fibrosis, and indoxyl sulfate levels in kidney and heart. Results: After nephrectomy, urinary albumin excretion gradually increased with progression of renal failure. In the Control-Nx group, kidney and heart indoxyl sulfate levels, reactive oxygen species, and tumor necrosis factor-α were significantly increased compared to the Control group. These were significantly suppressed in the DHA-Nx group. Histology analysis confirmed that fibrosis in the kidney and heart was enhanced in the Control-Nx group compared to the Control group, while fibrosis was suppressed in the DHA-Nx group. Conclusion: Docosahexaenoic acid diet is effective in inhibiting the accumulation of indoxyl sulfate, increased oxidative stress, and fibrosis in the kidneys and heart of nephrectomy model animals, and in inhibiting the progression of chronic renal failure.

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Phosphatidic acid: a key lipid in normal and pathological neuronal function

Dr Nicolas Vitale PhD ORCID iD
INCI, CNRS UPR3212, Strasbourg, France

Abstract

Specific forms of fatty acids are well known to have beneficial health effects, but their precise mechanism of action remains elusive. Among them, poly-unsaturated omega-3 fatty acids have been proposed to prevent cognitive decline but how this achieved is not fully understood. Using pharmacological and genetic approaches, we described that phosphatidic acid (PA) synthesized by phospholipase D1 (PLD1) plays multiple crucial roles in regulated exocytosis including secretory vesicle biogenesis, transport, and recycling, revealing a very complex regulation of the entire life cycle of secretory vesicles by PA both in neuroendocrine cells and in neurons. Furthermore, lipidomic analysis, revealed that secretory vesicle and plasma membranes display a distinct and specific PA composition with over 40 distinct species. Exocytosis stimulation triggers the selective production of several PA species at the plasma membrane, located preferentially in the close vicinity of docked vesicles near the sites of active exocytosis. Restoration experiments identified that poly-unsaturated (DHA)-containing PA regulates fusion pore stability and expansion, whereas mono-unsaturated PA controls vesicle docking. This suggests that DHA-containing PA may plays an essential role in the speed of neurotransmitter release, which is probably necessary for optimal brain function. Altogether, our work also unravels unique roles of distinct subtype species of the same phospholipid family and opens for a better understanding of the key functions of polyunsaturated fatty acids in cognitive functions.

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A New Technology to Enhance the Bioavailability of Omega-3 Oil

Dr. Itay Shafat PhD[1], Mr. Rafael Ezra[2], Mrs. Naama Avidan Kanon[2]
[1]Capsoil FoodTech, Las Vegas, USA. [2]Capsoil, Shafayim, Israel

Abstract

A new technology called Solid Self-Nano Emulsifying System (S-SNES) is presented. The S-SNES technology converts oils and oil soluble ingredients into a self-emulsifying powder, and has the capability to convert most oils and lipophilic materials. Once the powdered oil meets a watery environment, such as the stomach, it self-creates a nano-emulsion. Among other attributes, this property is thought to increase the absorption and bioavailability of oils. To prove the concept, we conducted an absorption study in humans, comparing the absorption of an algae omega-3 oil to the absorption of the oil converted by the S-SNES technology. The human study involved 24 healthy adults who consumed a single dose of 1200mg EPA via a novel algae formulation, either as the oil itself or through material converted by the S-SNES technology, in a cross over design. Results of the study show that EPA levels in the blood of the participant increased following both treatments. Following consumption of the novel powder though, led to a significantly higher level of EPA in the blood of the participants. Moreover, analysis of questionnaires given to participants show that fewer of them suffered from the characteristic side effect of "fishy burps". The new technology is shown to increase the absorption of omega-3, and to reduce the side effect of fishy burps, which, together with the fact that the technology offers a solid phase solution, can lead to an increased usability of omega-3 solutions

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Absorption of Algal Oil and Solubilized Algal DHA Following Oral Intake in Rats

Mr Aidan Tyrrell BSc[1], Dr Chuck Chen PhD[1], Mr Stanley Leung BSc[1], Dr Itay Shafat PhD[2], Dr Richard Bazinet PhD[1]
[1]University of Toronto, Toronto, Canada. [2]Capsoil technologies Ltd, Los Angeles, USA

Abstract

Background: Docosahexaenoic acid (DHA) is the predominant omega-3 polyunsaturated fatty acid accreted in membrane phospholipids. In enriched tissues such as the brain and retina, DHA plays essential regulatory roles in neurogenesis, synaptogenesis, neuroinflammation, and mitochondrial oxidation. Since de novo DHA synthesis is low, tissue levels depend heavily on dietary intake. While the absorption of algal DHA has been characterized, it is unclear if increasing the solubility of algal DHA may alter absorption into the circulation and subsequently improve tissue uptake.

Objectives: Measure DHA concentrations in major neutral lipid pools in the plasma and tissues following a single oral dose of algal DHA as oil and solubilized powder.

Methods: Sprague Dawley rats received oral gavage of either water, algal DHA ethyl ester as oil, or solubilized algal DHA in water. Blood was sampled from the carotid artery over 24 hours, and tissues were collected following the final blood sampling. Total lipids extracts were isolated into five neutral lipid pools by thin-layer chromatography (TLC) and quantified by gas chromatography-flame ionization detection (GC-FID).

Results: Preliminary results may suggest differences between algal DHA and solubilized DHA plasma total phospholipid (TPL) levels, with area under the curve values of 68.53 and 53.04 umol*min/ml, respectively. These were both increased compared to saline control (36.8 umol*min/ml). Differences in TPL plasma levels may indicate the solubilization of DHA alters absorption, however measuring other plasma lipid fractions and tissue concentrations as well as increasing the sample size is underway and will be presented.

Significance: Results from this study will determine the efficacy of DHA solubilization as a means of improving DHA tissue uptake following oral supplementation and potentially provide further insight into the mechanism of DHA absorption.

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A randomized controlled trial of docosahexaenoic acid in preterm infants born <29 weeks' gestation and IQ and behavior at 5 years' corrected age

Dr Jacqueline Gould[1], Professor Maria Makrides[2], dr Thomas SUllivan[2], Jana bednarz[2], Professor Emeritus Robert Gibson[2], Dr Andrew McPhee[2], The N3RO Investigative Team[2]

[1]South Australian Health and Medical Research Institute, Adelaide, Australia. [2]south australian health and medical research institute, adelaide, Australia

Abstract

Background: Children born <29 weeks' gestation have full-scale intelligence quotients (FSIQ) ~12 points lower than term-born populations and are more likely to have cognitive impairments. This study aimed to determine whether supplementing infants born <29 weeks' gestation with the estimated in utero dose of DHA improves FSIQ.

Methods: 1273 infants born <29 weeks' gestation were randomised to receive enteral DHA (60 mg/kg/day of DHA) or a control emulsion (without DHA) from within 3 days of their first feed to 36 weeks' post menstrual age. 656 children were eligible and invited to undergo the Wechsler Preschool and Primary Scale of Intelligence (FSIQ, 4th edition) at five years' corrected age and parents of 952 children were invited to complete questionaries about behaviour, quality of life, symptoms of allergies, diagnosed health complications, and rehospitalizations.

Results: FSIQ was available for 480 (73%; 241 in the DHA group, 239 control group) and 731 parents completed the questionnaires (77% 361 in the DHA group, 370 control group). Following imputation, children in the DHA group (n=323) had a significantly higher FSIQ (mean 95.4, SD 17.3) compared with children in the control group (n= 333; mean 91.9, SD 19.1; adjusted mean difference 3.5, 95% confidence interval 0.4 to 6.5, P=0.03). Parent-rated results were comparable for the two groups.

Conclusions: Meeting estimated in utero DHA levels during the neonatal period is one of the few strategies to improve FSIQ for infants born <29 weeks' gestation. There were no indications of adverse effects of DHA supplementation in childhood.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Enrichment of neuronal cells with DHA, via AceDoPC, decreases the production of Abeta peptide by modulating membrane fluidity – a potential therapeutic strategy for Alzheimer disease

Adina-Nicoleta LAZAR PhD ORCID iD[1], Nathalie Bernoud-Hubac[1], Amanda Lo Van[1], Michel Lagarde[1], Ana-Maria Trunfio-Sfarghiu[1], André Schroder[1], Baptiste Fourmaux[1], Patricia Daira[1], Ofelia Maniti[2]

[1]Univ Lyon, INSA Lyon, CNRS, LaMCoS, UMR5259, Villeurbanne, France. [2]Univ. Lyon 1, ICBMS, Villeurbanne, France

Abstract

Alzheimer's disease is a multifactorial neurodegenerative disease. The fundamental pathological hallmarks are the senile plaques and neurofibrillary tangles accompanied by a severe brain atrophy. The main constituents of the senile plaques are extracellular deposits of Aβ aggregates. Aβ peptide is derived from the cleavage of Amyloid Precurseur Protein (APP) - a transmembrane protein –sequentially processes by beta-secretase and gamma-secretase.

Numerous studies showed altered levels of several lipids in the brain of AD patients: overload of cholesterol, depletion of phosphatidylethanolamines or accumulation of ceramides in the white matter. Depletion in the levels of docosahexaenoic acid (DHA/22:6w3), was also associated with cognitive impairment and AD. Several recent studies linked DHA to lower risk of developing AD, via different mechanisms such as modulating the activity of beta- and gamma-secretase or by tuning the location of APP within the plasma membrane.

We designed a structured phospholipid, 1-acetyl,2-docosahexaenoyl-glycerophosphocholine (AceDoPC), a stabilized form of the physiological carrier of DHA to the brain, sn-2-DHA-LysoPC. AceDoPC is neuroprotective in some models like experimental ischemic stroke. Giving the neuroprotective capacity of AceDoPC, we investigated its potential role in AD, using human neuroblastoma overexpressing or not the human APP gene. We demonstrated rapid integration of DHA within neuronal lipids. We also showed the capacity of AceDoPC to tune membrane fluidity and to regulate cellular cholesterol level, on biomimetic membranes as well as live, on neuronal cells. Subsequently we proved that, by modulating membrane fluidity, AceDoPC is able to modulate the processing of APP, reducing the level of Aβ production.

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African American Women with Cardiometabolic Complications of Pregnancy Have Decreased Serum Abundance of Specialized Pro-Resolving Lipid Mediators and Endocannabinoids

Kristal Maner-Smith ORCID iD[1], Erin Ferranti[1], Anne Dunlop[1], Elizabeth Corwin[2], Eric Ortlund[1]
[1]Emory University, Atlanta, USA. [2]Columbia University, New York, USA

Abstract

African American (AA) women experience higher rates of maternal morbidity and mortality compared to US women of other racial/ ethnic groups. Cardiometabolic complications of pregnancy (including gestational diabetes, gestational hypertension, and preeclampsia) are leading contributors to maternal morbidity and mortality. Marked changes in circulating lipids are known to accompany cardiometabolic complications of pregnancy. Serum concentrations of docosahexaenoic acid (DHA) have been shown to be inversely correlated with risk for preeclampsia. DHA is a biosynthetic precursor of a class of specialized pro-resolving mediators (SPMs), resolvins, that have anti-inflammatory properties and are also associated with hypertensive disorders of pregnancy. We employed targeted lipidomics to characterize the distribution of DHA-containing phospholipids and SPMs in maternal serum collected in early and late pregnancy (8–14 weeks and 24–30 weeks gestation, respectively) to identify key lipids that are dysregulated during pregnancy in AA women who develop cardiometabolic complications. We identified a lipid signature in early pregnancy serum samples of AA women that is predictive of cardiometabolic complications of pregnancy with 74% accuracy. These are Resolvin D1, Resolvin E1, 2-AG, PGE2-glyerol ester, and 36:6 PC. These findings suggest that there are blood-based markers detectable in early pregnancy that can potentially identify persons at risk and tailor clinical interventions.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

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Functional lipidomics: from prostaglandin E1 to docosahexaenoic acid, and beyond.

Professor Michel Lagarde PhD
INSA-Lyon (Université de Lyon), Lyon, France

Abstract

2023 Alexander Leaf Award Recipient

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Interactions of MCT with omega-3 fatty acids enhance efficacy of fish oil lipid emulsions in acute therapy – evidence from cells, animal models, and humans

Dr Yvon Carpentier MD[1], Dr Chuchun Chang PhD[2]
[1]Free University of Brussels, Brussels, Belgium. [2]Columbia University, New York, USA

Abstract

Our goal was to develop lipid emulsions for IV bolus injections to rapidly and efficiently incorporate omega-3 very long-chain fatty acids (n-3 VLCFA) in key organs of patients with acute conditions, aiming to reduce associated complications including severe inflammatory reactions, multiple organ dysfunction, and metabolic alterations like insulin resistance.

In vitro and in vivo studies comparing different ratios of fish oil (FO) and medium-chain triglycerides (MCT) demonstrated that the emulsion with 80% MCT and 20% FO was most efficient at increasing n-3 VLCFA content in cultured endothelial cells and facilitating rapid plasma TG clearance and membrane enrichment of n-3 VLCFA of different organs after IV injections. This emulsion has been branded as Prontomega^{R}, and found to be well tolerated in acute toxicity studies in mice and rats. In a phase 1 study on 12 human volunteers receiving a 50 mL Prontomega^{R} IV injection, plasma clearance was very rapid, and n-3 VLCFA enrichment substantially increased in membranes of platelets and white blood cells at 1h post-injection. No sign of toxicity was noted.

Pharmacokinetic studies in rats showed efficient plasma clearance for up to 40 mg injections without adverse effects. Repeated injections up to 4 times at hourly intervals did not affect plasma TG elimination kinetics. In cynomolgus monkeys, daily injection of Prontomega^{R} over 7 days induced a substantial rise of n-3 VLCFA in cell membranes without toxicity or tolerance problems. In a myocardial infarct (MI) model in cynomolgus monkeys, Prontomega^{R} injections at 133 and 400 mg/kg b.w. showed a substantial recovery of cardiac ejection fraction at 1 week post-MI, and a > 70% reduction in the infarcted myocardium compared to a saline-injected control group.

These studies support the feasibility of repeating small volume Prontomega^{R} injections at close intervals as new therapeutic approach for humans with acute conditions.

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Acute vs long term omega-3 therapies – Why and how for different organs?

Prof. Richard Deckelbaum MD,CM, Dr. Hylde Zirpoli PhD
Columbia University, New York, USA

Abstract

Still with some controversy, oral supplements of omega-3 (n-3) fatty acids(FA) and/or high dietary intakes of n-3 FA-rich fish have shown evidence for prevention and/or beneficial therapies for cardiovascular disease (CVD) and other adverse health conditions. Positive effects of n-3 FAs are usually linked to changes in cell membrane compositions accompanied by inhibiting cellular mechanisms associated inflammatory responses and cell death pathways and by promoting regenerative activities. However oral intake of n-3 FA requires weeks to months to substantially augment membranes with the bioactive n-3 FA (such as EPA, DHA, and others) and to exert their putative positive actions. In contrast we, and other groups, have shown that acute parenteral injection of n-3 FA as the FAs themselves (e.g., bound to albumin) or as n-3 FA rich lipid emulsions can increase n-3 FA cell membrane content within minutes to hours. Our initial reports showed that acute administration of n-3 rich triglyceride emulsions in rodent models of hypoxic ischemic heart and brain injuries blocking cell death pathways associated with mitochondrial failure, production of free radicals and other injury related mechanisms. Recent data demonstrates that acute delivery of DHA and/or EPA as diglycerides (DG) in a lipid emulsion after hypoxic injury in neonatal mouse and rat models provides superior neuroprotection that other n-3 FA injectable formulations. This “improved” protection is associated with both physical and biological advantages of the n-3 DG emulsions. We predict that these properties of n-3 DG emulsions will also result in improved outcomes for other organ injuries.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

Not published

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Acute omega-3 fatty acid therapy and neurological injuries – opening a new field

Professor Adina Michael-Titus PhD
Queen Mary University of London, London, United Kingdom

Abstract

Neurological injury can be an event with life-changing consequences. When injury occurs in the central nervous system, whether of vascular or traumatic origin, there are major obstacles to regenerative processes, therefore recovery of function is limited. There are no clinical interventions with high efficacy to support the patient through neuroprotection in the immediate aftermath of injury, or specific treatments in the chronic recovery period to restore disrupted neural connectivity. Data reported over the last two decades in models of traumatic and ischemic injury, and using acute parenteral modes of administration, have shown that long-chain omega 3 fatty acids such as docosahexaenoic acid (DHA), can reduce the impact of the injury and may support neural repair. Furthermore, the characterization of the complex metabolism of omega-3 fatty acids and the formation of bioactive lipid mediators, has strengthened the case for a new therapeutic class based on these lipids.

Our group has shown in several experimental models that administration of DHA significantly reduces neuronal loss after traumatic brain injury (TBI) and spinal cord injury (SCI), reduces glial activation and promotes neuroplasticity. The translation to the clinic of the findings reported in experimental models remains challenging, and key unresolved questions are awaiting answers: what is the best regime of administration, what are the cellular targets that need to be mobilized, and how much improvement could be achieved compared to the present standard of care? A successful clinical translation with omega-3 fatty acids will require these aspects to be addressed and elucidated.

If the Abstract has been published, please provide a link or indicate in what Journal and when the findings were published

N/A

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Probing cardiac and renal ketone metabolism in healthy adults: PET ketone imaging plus a ketone-nicotinamide riboside supplement in the fasted and fed state

Valérie St. Pierre[1], Etienne Croteau[2], Gabriel Richard[3], André Carpentier[2,4], Bernard Cuenoud[4,5], Stephen Cunnane[1,4]
[1]Research Center on Aging, sherbrooke, Canada. [2]Centre de recherche-CHUS, sherbrooke, Canada. [3]Centre de recherche-CHUS, Sherbrooke, Canada. [4]Dept of Medicine, Université de Sherbrooke, Quebec, Canada. [5]Nestlé Health Science, Lausanne, Switzerland

Abstract

Ketones (beta-hydroxybutyrate and acetoacetate) provided exogenously may be able to improve heart function in heart failure. Several nutritional strategies exist to increase blood ketones, but it remains unclear whether exogenous ketones could be significant metabolic fuels for the heart or kidney.

Cardiac and renal ketone metabolism was assessed in healthy participants using PET with the tracer – [1-11C]-acetoacetate. Ten healthy participants were evaluated, each under four conditions: fasted (water only), fed (Boost® liquid meal 20 min before imaging), fasted+supplement (fasted+S), and fed+supplement (fed+S). The supplement (S) provided 12 grams of D-beta-hydroxybutyrate salt plus 500 mg of nicotinamide riboside (D-BHB+NR) which was taken 30 minutes before the PET scan. Plasma ketones were measured and kinetic modeling provided heart and kidney metabolic rate of ketone consumption (MRketones). Conditions were compared with a one-way repeated measures ANOVA, with a significance threshold of $p < 0.05$.

With or without the liquid meal, D-BHB+NR 7-8 fold increased plasma ketones ([mean±SD]: fasted 0.2 ± 0.2 mM, fed 0.1 ± 0.4 mM, fasted+S 1.5 ± 0.8 mM, fed+S 1.5 ± 0.5 mM), without changing myocardial MRketones ([all µmol/100 g/min]: fasted 0.65 ± 0.12, fed 0.68 ± 0.12, fasted+S 0.65 ± 0.10, fed+S 0.69 ± 0.10). After D-BHB+NR with the liquid meal, end-systolic volume declined by 8% ($p < 0.05$). Preliminary data show that kidney MRketones was similar under all conditions (about 0.72± 0.08 µmol/100 g/min).

A single acute dose of D-BHB+NR increased plasma ketones 5-10 fold in the heart and kidney, an effect that was independent of feeding state. D-BHB+NR taken with food significantly lowered end-systolic volume; if sustained this effect could potentially be beneficial in the treatment of heart failure. Effects of D-BHB+NR supplementation in various conditions affecting heart and kidney function warrant further investigation.

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Brain energy metabolism during aging and in Alzheimer disease: recent developments with ketone and FDG PET, functional connectivity, and diffusion imaging

Stephen Cunnane[1,2], Valérie St-Pierre MSc[1], Mélanie Fortier MSc[1], Marie-Christine Morin RN[1], Christian Bocti MD[2], Tamas Fulop MD, PhD[2]
[1]Research Center on Aging, Sherbrooke, Canada. [2]Université de Sherbrooke, Sherbrooke, Canada

Abstract

BACKGROUND: We developed a ketone PET tracer – [1-11C]-acetoacetate (11C-AcAc) – to quantify brain ketone metabolism in healthy older people, Alzheimer disease (AD) and mild cognitive impairment (MCI), and to assess the brain's response to ketogenic interventions.

METHODS: In our protocol, 11C-AcAc is administered first, followed by a wash-out period, and then 18F-fluordeoxyglucose (FDG), with both scans completed with 120 min. Arterialized blood is collected to calculate the cerebral metabolic rate (CMRk) and influx rate or uptake capacity of ketones (Kketone) or glucose (CMRg and KFDG) expressed as mmol/100 g/min and min-1, respectively. Volumetric, resting state functional, and diffusion MR images are also acquired. PET images are analyzed using PMOD® software.

RESULTS: Based on n˃300 dual tracer PET scans over 15 years: (i) healthy aging is associated with 7-8% lower capacity to take up FDG (KFDG), primarily in the frontal cortex. (ii) MCI is associated with 9-10% lower KFDG, primarily in the cingulate cortex. (iii) AD is associated 15-20% lower KFDG in several cortical regions. (iv) No decline in KKetone regionally or globally in the brain has been observed in any of these studies. (v) CMRk increases linearly as plasma ketone concentration. (vi) While in nutritional ketosis, the additional ketones spare brain glucose uptake in young healthy adults, i.e., brain glucose uptake actually declines with higher ketone availability. (vii) While consuming a ketogenic medium chain triglyceride drink, myelin integrity and functional connectivity improve in MCI in relation to the brain uptake of ketones in specific white matter tracts and functional networks, respectively. Some of these results have been confirmed by other groups using PET and other methods.

DISCUSSION: Ketones improve cognition in MCI is because they bypass deteriorating brain glucose metabolism and rescue brain functional and structural connectivity.

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“One Health syncretism” and terrestrial biosynthesis of Omega 3 Fatty Acids.

Dr Pierre Weill
Bleu-Blanc-Coeur, Rennes, France. Rennes University, Rennes, France

Abstract

“One health” concept (Healthy soil makes healthy plants that make healthy animals on a healthy planet) is a syncretism (unlikely union of distant or antagonistic ideas). However, the fuzzy “One Health” concept can be supported by experimental demonstrations. The biosynthesis of n-3 polyunsaturated fatty acids (PUFA) all along terrestrial food chain provides a good example:

Only plants synthesize the n-3 precursor (ALA) which they need both for chlorophyll synthesis and for their defense mechanisms (via Jasmonic acid).

Essential for plants’ growth and defense, ALA is then consumed by animals. Ruminants hydrogenate ALA in their rumen. This bio-hydrogenation results in a measured decrease of methane (greenhouse gas) output, and produces totally or partially hydrogenated (most often in cis 9 and trans 11) C18 FA. Ingested by monogastric animals, ALA can be incorporated into the triglycerides of the animal's lipid reserves or elongated, desaturated into membranes’ phospholipids. People who consume products from animals fed with grass, flax or other ALA rich plants will therefore find an interesting contribution of ALA, EPA, DPA and DHA needs.

For 25 years, we measured the effects of increased production of ALA-rich plants to feed land animals. We measured positive impact of these changes on animals’ health and fertility.

We measured in human studies the impact of a "renewable” ALA-rich animal diet, in human regimen on the coverage of n-3 FA requirements, the improved composition of red blood cell in EPA, DPA and DHA. We measured positive impacts on health markers such as insulin resistance, weight gain, cardiovascular markers or milk composition of lactating women.

At the end, the increase of ALA intake in land animal diets is a good “evidence based” example of “One health” syncretism from healthy soils to healthy people.

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New understandings of the clinical roles for omega 3 fatty acids

Professor Robert Gibson PhD[1], Principal Research Fellow Robert Gibson[2]
[1]University of Adelaide, Adelaide, Australia. [2]South Australian Health and Medical Research Institute, Adelaide, Australia

Abstract

This talk is given in honour of Michel Chevreul a French chemist who is truly the father of lipid chemistry.

After many decades of intensive activity, fatty acid research is entering an amazing new phase. We now have the strongest evidence for a role for omega-3 fats in the prevention of premature birth and for preterm infants to attain their full neurological potential.

Omega 3 and pregnancy outcome: Following the early observations of increased gestation in high consumers of fish in the Faroe Islands, in 1986 it took another 35 years to prove that one of the causes of premature birth was low omega 3 fatty acid status in early pregnancy and that this could be overcome with appropriate supplementation primarily with DHA. To achieve this, randomised controlled trials that including thousands of women were necessary. The ORIP trial in Australia (n=5400) and the ADORE trial in the USA (n=1100) established that screening for omega 3 status and treating those who were low was an effective preventative strategy for preterm birth.

Omega-3 and infant development: 1986 also saw the seminal report of Martha Neuringer who demonstrated biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys. While these studies showed short term visual benefits long term neurological benefits could not be detected. It wasn’t until 2022 that we were able to prove that very preterm infants have a high DHA requirement, and if this is met through supplementation, long term benefits on IQ could be detected. Again, this require a clinical trial of over 1500 infants. The need for DHA supplementation of term infants remains debateable.

Despite these advancements we have no proven mechanism for preterm birth prevention or infant neurodevelopment by DHA.

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Using carbon 11, 12, 13 and 14 to study brain fatty acid metabolism. Highlights of a few fun findings along the way with an emphasis on translation.

Richard Bazinet PhD
University of Toronto, Toronto, Canada

Abstract

This talk will take a historical approach to our work in studying fatty acid metabolism. I first learned quantitative approaches to fatty acid metabolism with Stephen Cunnane (Chevreul Medal 2017) during my PhD, which was followed by kinetic approaches with my post-doctoral advisor Stanley Rapoport (Medal Chevreul 2007). Upon starting my research program in Toronto, we branched out with two major arms, one of which examined the role of fatty acids, especially DHA in neuroinflammation and another examining mechanisms by which fatty acids enter the brain. In this lecture I will highlight key findings throughout my career using a variety of isotopic techniques that have helped in our understanding of brain fatty acid metabolism. Highlights will include how understanding how DHA enters the brain improved estimates of brain DHA requirements, how EPA is maintained at low levels, and how new compound-specific isotopic analysis has led us to challenge some ideas on retroconversion and DHA synthesis.

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Full-fat dairy effects on blood lipids and CVD risk factors: towards a role of milk polar lipids

Marie-Caroline Michalski PhD
INRAE, CarMeN Laboratory, Lyon, France

Abstract

Recent literature highlights that dairy products can be associated with neutral to beneficial effects on cardiometabolic health despite their saturated fat content. Way beyond their fatty acid profile, milk fat globules are a unique supramolecular assembly surrounded by the milk fat globule membrane (MFGM). The MFGM is a source of milk polar lipids, with a specific composition including ~25% of sphingomyelin. This presentation focuses on recent advances on the possible benefits of milk polar lipid supplementation on different aspects of cardiometabolic health, including favourable effects of milk polar lipids on lipid digestion and absorption, reduction of lipid markers of cardiovascular risk and potential benefits on metabolic inflammation via modulations of the gut microbiota and barrier. The body of evidence in several in vivo studies and a few recent human studies is altogether consistent with significant impacts of the milk polar lipids and/or the whole MFGM. New perspectives include the metabolic importance of dairy sphingolipids and potential impacts of fermentation. Clinical trials are now warranted to further elucidate the role of polar lipids in full-fat dairy on different aspects of cardiometabolic health.

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New doors opening on the essential roles of dairy fatty acids in human nutrition

Vincent Rioux PhD
Institut Agro, INSERM, Rennes, France

Abstract

The fatty acid composition of milk fat is unique (more than 300 different fatty acid structures) but remains criticized for its richness in saturated fatty acids (60-65% of fatty acids) and for its relatively low content of essential polyunsaturated fatty acids, linoleic acid (2-3% of fatty acids) and a-linolenic acid (<1% of fatty acids). However, recent meta-analyses report lack of correlation between milk fat consumption and cardio-vascular disease, and lack of correlation between milk products consumption and the occurrence of diabetes. Inverse associations are now described between dairy product intakes and risk of type 2 diabetes and metabolic syndrome. Beyond epidemiological data and controversies, a growing number of studies suggests that, present in a balanced diet, many specific dairy fatty acids may play important and even essential biochemical and physiological roles, because they are not synthesized endogenously by humans (or at very low levels, potentially below their metabolic utilization) and only provided by the diet. Among these specific dairy fatty acids, we have previously shown that myristic acid (C14:0, 9-12% of milk fatty acids) and caprylic acid (C8:0, 1-2% of cow milk fatty acids), through their capacity to acylate different proteins, have important and specific roles which cannot be assumed by other fatty acids. Concerning trans fatty acids, although it represents only 0.04% of total fatty acids in bovine milk, trans-palmitoleic acid (trans-C16:1 n-7) was recently shown to improve adiposity and insulin sensitivity in mice fed a hypercaloric diet. We also recently questioned the potential essentiality of odd-chain saturated fatty acids, particularly pentadecanoic acid (15:0), because the metabolism of this fatty acid is still largely unknown, producing potential fatty acid members of the (n-6) family. All these results may contribute in the future to improve dietary guidelines and recommendations for the consumption of dairy fatty acids.

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Dairy foods, saturated fats, and cardiovascular diseases risk: an update.

Ian Givens PhD
University of Reading, Reading, United Kingdom

Abstract

Cardiovascular diseases (CVD) and related type 2 diabetes (T2D) are major causes of mortality and chronic morbidity. Whilst mortality from CVD has decreased, these remain the largest cause of death in Europe and the prevalence of T2D is increasing rapidly. A consistent component of public health advice is to reduce intake of saturated fatty acids (SFA) to reduce CVD in particular, which implies limiting consumption of dairy foods since they are often the largest source of SFA. Prospective studies and randomised controlled trials show that for dairy foods at least, SFA are not consistently associated with CVD or T2D risk. For CVD the association with dairy foods is generally neutral and for these foods at least, this creates considerable doubt concerning the validity of the traditional diet-heart hypothesis which positively relates SFA intake to increased serum LDL-cholesterol and subsequent increased CVD. There are however emerging findings that help explain this. These include the potentially counterbalancing effect of SFA-stimulated HDL-cholesterol and specific food matrix factors. In addition, SFA are generally associated with the less atherogenic large buoyant LDL particles and possible counterbalancing hypotensive effects of dairy proteins. Overall, dairy foods have either a neutral or beneficial association with CVD and T2D. Beneficial associations are seen for blood pressure and reduced T2D risk linked especially to yoghurt consumption, a subject that needs urgent attention given the sharp rise in T2D prevalence in many countries.